

Señor:

JUEZ TREINTA Y DOS (32) CIVIL DEL CIRCUITO DE BOGOTÁ.

E. S. D.

REFERENCIA: 2012-0094

DEMANDANTE: RICARDO ALEXANDER OVALLE LÓPEZ y OTROS.

DEMANDADO: CLÍNICA LA CAROLINA y OTRO.

ASUNTO: Aporto Dictamen Pericial

CARLOS ALBERTO CAMARGO CARTAGENA, mayor de edad, residente en la ciudad de Bogotá D.C., e identificado con la C.C. No. 79.318.915 de Bogotá, titulado e inscrito portador de la T.P. No. 168358 del C.S. de la J., en mi condición de apoderado judicial de la parte demandante, por medio del presente escrito me permito aportar a su despacho, Dictamen Médico Pericial elaborado por el Doctor Hernán Sepúlveda M.

Atentamente,



CARLOS ALBERTO CAMARGO CARTAGENA

C.C. No 79'318.915 de Bogotá.

T. P. No. 168.358 del C. S. de la J

Bogotá 5 de agosto de 2020.

Doctor:

CARLOS ALBERTO CAMARGO CARTAGENA

CAMARGO & CARTAGENA ABOGADOS EN SALUD

REFERENCIA: 2012-00094 - ORDINARIO

DEMANDANTE: RICARDO ALEXANDER OVALLE LOPEZ Y OTROS

DEMANDADO: CLINICA LA CAROLINA S.A. Y OTROS

Por la presente envío a usted el dictámen pericial en el caso de la señora MARIA INES LOPEZ SANABRIA QEPD. Se ha elaborado un análisis detallado del caso clínico, la descripción de las patologías que se presentaba la paciente y el análisis médico de las actuaciones de los diferentes profesionales en la atención hospitalaria y extrahospitalaria del caso.

El análisis fue elaborado por el por el médico Hernán Sepúlveda Martínez especialista en cirugía general de la Universidad Nacional de Colombia. Para los conceptos sobre anestesia y reanimación se contó con la colaboración del médico anestesiólogo Dr. Rodrigo Arturo Chaparro Espinosa especialista en anestesia y reanimación de la Universidad Militar Nueva Granada.

Los conceptos se ajustan a la juiciosa y objetiva revisión de las historias clínicas y documentos enviados, dentro de la lex artis y la experiencia profesional acumulada durante mis 31 años de ejercicio de la medicina, la cirugía, atención de urgencias y mi experiencia como perito en análisis de casos médicos legales.

DECLARACIONES DE LEY:

IDENTIDAD DE QUIEN RINDE EL DICTAMEN PERICIAL.

Hernán Sepúlveda Martínez cédula de ciudadanía 79.445.101 de Bogotá

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Médico General egresado de la Universidad Nacional de Colombia

Especialista en Cirugía General de la Universidad Nacional de Colombia

Especialista en Administración Hospitalaria en la Escuela de Administración de Negocios EAN

Docente adscrito la Hospital Universitario de la Universidad Nacional de Colombia

Especialista en Cirugía del Hospital Central de la Policía

EXPECIENCIA COMO PERITO

Mi experiencia como perito inicia en abril de 2018 desde cuando he emitido 13 conceptos periciales de los cuales tres se han presentado en contradicción en audiencia.

DESIGNACION COMO PERITO EN ESTE CASO

En este proceso he sido designado como perito por el apoderado de la parte demandante (Abogado Carlos Alberto Camargo Cartagena).

DECLARACIONES

Declaro que los métodos utilizados en la realización del presente dictamen, son los utilizados en el ejercicio regular de la medicina.

Declaro que no estoy incurso en las causales del artículo 50 del Código Penal Colombiano.

Declaro que las opiniones emitidas en este concepto, son independientes y corresponden a la real convicción profesional soportadas con revisiones bibliográficas imparciales de diversas publicaciones científicas.

DESCRIPCION DE LA METODOLOGIA EMPLEADA EN EL CONCEPTO PERICIAL

- a. DESCRIPCION DETALLADA DE LOS HECHOS CONSIGNADOS EN LAS HISTORIAS CLINICAS
- b. DESCRIPCION DE LAS PATOLOGIAS Y CONDICIONES MEDICAS DESCRITAS EN LA HISTORIA CLINICA
- c. ANALISIS DE LAS ACTUACIONES MEDICAS Y PARAMEDICAS DEL CASO
- d. CONCLUSIONES DE LOS PERITOS
- e. BIBLIOGRAFIA

DESCRIPCION DETALLADA Y CRONOLOGICA DE LOS HECHOS CONSIGNADOS EN LAS HISTORIAS CLINICAS

Se revisaron los archivos en PDF del caso debidamente foliados.

Historia Clínica de la Clínica la Carolina

Historia Clínica de la Fundación Santa Fe de Bogotá

Informe forense de la Necropsia del Instituto Nacional de Medicina Legal e Informe de ampliación de la misma

DESCRIPCION DE LAS PATOLOGIAS Y CONDICIONES MÉDICAS DESCRITAS EN LA HISTORIA CLINICA

Se describen la definición, etiología fisiopatología, diagnóstico y tratamiento de las principales patologías del caso,

ANÁLISIS DE LAS ACTUACIONES MÉDICAS Y PARAMÉDICAS DEL CASO

Se analiza según la información de la historia clínica, la revisión bibliográfica, la lex artis a la fecha del caso y la experiencia profesional de los peritos la calidad, idoneidad y oportunidad de las actuaciones de anestesia, cirugía plástica, personal paramédico, patología y emergenciológica.

CONCLUSIONES DEL PERITO.

Se resume los aspectos más relevantes del caso y explicarían los motivos de la muerte de la paciente.

BIBLIOGRAFIA

DESCRIPCION DETALLADA Y CRONOLOGICA DE LOS HECHOS CONSIGNADOS EN LAS HISTORIA CLINICA de la Clínica la Carolina, Ambulancia Médicas profesionales S.A., Clínica Fundación Santa Fe de Bogotá y Necropsia del Instituto de Medicina Legal

La señora MARIA INES LOPEZ SANABRIA (QEPD) era una paciente femenina de 47 años con cédula de ciudadanía 28.440.533 quien el 27 de noviembre de 2010 se sometió a una cirugía estética en la Carolina de Bogotá, posterior a la cual presentó complicaciones que condujeron a su muerte la noche del mismo día.

La revisión de la historia clínica de la Clínica La Carolina en orden cronológico describe a continuación:

El 25 noviembre 2010 se evidencia un registro de consulta del especialista en anestesia en hoja pro formato diligenciada a mano. En ella se hace la valoración previa a la cirugía “Pexia mamaria, minilipectomía, mas liposucción”, se da hora de la cirugía 7-12, se describen los antecedentes, el examen físico, peso 62 kg, talla 150 cm, valoración de la vía aérea, valores de hemoglobina, leucocitos, plaquetas, glicemia todos normales, Tiempos de coagulación (da valores de la paciente pero no anotan los valores de referencia). Hace un diagnóstico de Lipodistrofia y clasifica a la paciente con un riesgo anestésico ASA I (bajo riesgo anestésico) El anestesiólogo anota sus recomendaciones preanestésicas. En el borde inferior de la hoja aparece una nota a mano de 4

medios renglones que dice “continúa y se escribe unas recomendaciones de salida que se describirán en posteriormente.

Con fecha **de 25 noviembre 2010** se evidencia el consentimiento informado de anestesia, mencionando riesgos y complicaciones debidamente firmado.

Con fecha **de 27 noviembre 2010** se evidencia el consentimiento informado de cirugía, mencionando riesgos y complicaciones debidamente firmado.

El 27 noviembre 2010 se registra una nota: “NOMBRE DE LA CONSULTA: valoración preanestésica” Firmada por el Dr. Alejandro Chiappe Duarte Especialista en Cirugía Plástica. En la que refiere una paciente mujer de 44 años de edad “enfermedad actual”. Solo se anota: “lipodistrofia corporal y ptosis mamaria que se programa para procedimiento ambulatorio” .

En esta nota hay un lapsus de la información ya que la edad real de la paciente para esa fecha era de 47 años. En la nota no se dan detalles sobre la enfermedad actual. No se mencionan Antecedentes ni Revisión por sistemas, ni peso, ni talla, ni registro ni análisis de los paraclínicos, ni clasificación de riesgo.

El 27 noviembre 2010 se hace la “Descripción Quirúrgica” se anota Hora inicial **7:00** am Hora final **12:00** pm. Se describe Liposucción abdominal de 3.000 cc de grasa, minilipsectomía, lipoinyección en glúteos 320 CC en cada uno, pexia mamaria bilateral , técnica de Pitanguy en la que se describe “conización de la mama”

A las **12:45** hay registro en la historia clínica donde se escribe que: A las **12:30** finaliza el procedimiento quirúrgico, el Dr. Alfredo Rodriguez extuba la paciente y se traslada a recuperación (Enfermera Diana Carolina GomezCasallas)

A las **13:12** se anota Recomendaciones de Egreso con Signos de Alerta “Dolor no controlado con analgésicos, sangrado persistente por heridas.” No hay anotaciones sobre aparición de dificultad respiratoria, taquicardia ni fiebre. Se prescribe formulación de Bactrim F (antibiótico), Advil Max y Winadeine F (analgésicos compuestos), Firmada por el Dr. Alejandro Chiappe Duarte.

A las **14:30** en Registro de Signos Vitales se anota Presión arterial 120/78 frecuencia cardíaca 61, frecuencia respiratoria 17, saturación de oxígeno 97% (Valores dentro de rangos normales). Los registros previos de signos vitales de las 12:45,13:00, 13:15 y 13:30 se encuentran en valores normales.

A las **18:45** hay registro en la historia clínica donde se escribe en una sola nota que: A las **13:00** se retira al oxígeno y satura 95% al ambiente. A las **13:30** acepta y tolera la vía oral. A las **14:30** se entregan fórmulas, se entrega boleta de salida, se retira vía venosa se baja al sótano en silla de ruedas en compañía de familiar y se da egreso de la Clínica La Carolina (Enfermera Hayda Yazmin Aguirre)

A las **17:15** Existe una nota a mano en la hoja pro formato de registro de **anestesia** (folio 21 HC: Clínica La Carolina y ya mencionada al inicio) de siete medios renglones ubicada en un pequeño campo de la casilla "Analgesia" en la que el Dr. (nombre y registro medico no legibles) anota textualmente "Pte en adecuadas condiciones grales. Tolerando vía oral, diuresis positiva, Aldrete Kroulik 10 (La nota sigue a al reverso de la hoja en la página de la nota del la valoración y recomendaciones preanestésica del 25 de noviembre de 2010) Recomendaciones medidas antiembólica, Demabulación precoz, heparina bajo peso molecular, medias presoras. Continúa manejo por cirujano tratante." Esta anotación no quedó registrada en el sistema de información de la clínica la Carolina. Tampoco se anota frecuencia cardíaca, ni frecuencia respiratoria ni saturación de oxígeno, ni escala de dolor, ni tolerancia a la dieta.

A las **20:47** el Dr. Mauricio Rodríguez médico de turno de la Clínica La Carolina describe que a las **20:45** la paciente reingresa a la Clínica La Carolina por cuadro 2 horas de iniciode dificultad respiratoria y cianosis (coloración morada) de boca y extremidades, encontrando una tensión arterial de 140/78 una frecuencia respiratoria de 30 (normal de 16 a 20) frecuencia cardíaca de 140 por minuto (normal de 60 a 90) y saturación del 50% (normal mayor de 90%) iniciando oxígeno por mascarilla obteniéndose saturación de 80% (persistentemente baja). Se comunica con el Dr. Chiappe que se hace presente y por la alta probabilidad de un Trombo embolismo pulmonar se decide iniciar trámites de traslado a la clínica Palermo e inicia enoxaparina 40 mg subcutáneos.

A las **21:23** la Enfermera Cenaida Lucia Rincón describe que a las **20:20** reingresó la paciente por dificultad respiratoria con frecuencia cardíaca de 140 y saturación de oxígeno de 50% y que es atendida por el Dr. Mauricio Rodríguez.

A las **21:15** según nota de la enfermera Cenaida Lucía Rincón, llega la ambulancia y a las **21:20** sale la paciente con frecuencia cardiaca de 140 (muy alta) y saturación de 80% (baja) entregando paciente a los señores de la ambulancia con destino a la Clínica Palermo. El personal de la ambulancia describe paciente en mal estado general con cianosis generalizada.

A las **21:19** en la ambulancia se coloca máscara laríngea y luego describe uso de AMBU (Auto inflable Mascara-Bolsa para la vía Aérea) que se usa para apoyo ventilatorio. Se inicia reanimación básica y se decide ingreso a la Fundación Santa Fe por estado crítico de la paciente

A las **21:28** el personal de la ambulancia describe ingreso a la sala de reanimación de la Fundación Santa Fe.

A las **21:34** se evidencia la Hoja de ingreso a la Fundación Santa Fe. El Dr. Eliecer Cohen médico urgenciólogo de la Fundación Santa Fe (FSFB), describe en su nota que se trata de una paciente a quien se le realizó una cirugía estética en la Clínica la Carolina, fue dada de alta a la casa aproximadamente a las 15:00 y consultó por dificultad respiratoria y disnea en la tarde, la atienden de nuevo en La Carolina y sin mayor información a la familia deciden remitir a la Clínica Palermo. Durante el traslado en ambulancia básica y por información del personal de la ambulancia la paciente presentó "paro cardio respiratorio en el ascensor de la Carolina y continúan traslado, hasta que la presión de la hermana de la paciente logra desviarla a urgencias

de esta institución". Añade que "dicen llevar aproximadamente 10 - 15 minutos en paro, por lo que benéficamente y en consideración a paro no presenciado se inicia Reanimación Cardio Pulmonar inmediata". Anota también que a la FSFB la ambulancia llega sin sirena, ingresando como Triage Rojo prioridad 1 a la sala de reanimación, en mal estado general sin signos vitales y en coma profundo, cianosis y frialdad, midriasis no reactiva, no movimientos oculares no reflejos corneanos, abundante secreción espumosa rosada por la boca con máscara laríngea desinflada y llama la atención sobre "ausencia de compresiones torácicas y actitud de reanimación del caso". El Dr. Cohen inicia masaje cardíaco externo e intubación orotraqueal realizando maniobras de reanimación cardiopulmonar avanzada por 20 minutos tras de los cuales no hay repuesta y la paciente fallece a las 21:50.

El 28 noviembre 2010 a las 09:36, aparece una "Nota de evolución" firmada por " ENF ALEJANDRO CHIAPPE DUARTE CC 80413619 Especialidad Cirugía Plástica" Hace referencia a hechos acaecidos el **27 noviembre 2010 a las 19:30** y que describe que recibe llamada telefónica de esposo de la paciente informando que la señora presenta dificultad respiratoria. Ordena retirar la faja y trasladarse a la Clínica La Carolina. De inmediato el doctor dice dirigirse hacia la Clínica, habla con el Dr. Mauricio Rodríguez que le informa paciente desoxigenada con 50% de saturación, ordena aplicar oxígeno, iniciar trámites de remisión. A las 20:30 el Dr. Chiappe llega a la clínica, ordena aplicación de Heparina pero por no disponibilidad del fármaco en la Clínica aplica enoxaparina 40 mg subcutánea, llama al anestesiólogo, asiste la respiración de la paciente con oxígeno y AMBU y la paciente mejora saturación de oxígeno de 80 a 89%.

El 28 noviembre 2010 a las 11:01, aparece una "Nota de enfermería" firmada por " ENF ALEJANDRO CHIAPPE DUARTE CC 80413619 Especialidad Enfermería" Hace referencia a hechos acaecidos el **27 noviembre 2010 a las 13:30**. Relata textualmente "Por solicitud expresa de la paciente, según su adecuada evolución, desea salida para la casa. Por esta razón se deja en observación post operatoria pendiente de definir alta por parte de anestesiología".

El 28 noviembre 2010 a las 11:04, aparece una "Nota de enfermería" firmada por " ENF ALEJANDRO CHIAPPE DUARTE CC 80413619 Especialidad Enfermería" Hace referencia a hechos acaecidos el **27 noviembre 2010 a las 20:30**. Menciona que el día **27** el esposo de la paciente llama al Dr. Chiappe a informarle que la paciente presenta ansiedad y dificultad para respirar. El Dr. Ordena telefónicamente al familiar traslado inmediato de la paciente a la Clínica La Carolina para valoración y solicita al Dr. Mauricio Rodríguez Médico de turno valoración y manejo inicial para la paciente. El Dr. Mauricio Rodríguez le informa al Dr. Chiappe que la paciente llega con disnea (dificultad para respirar) y cianosis peribucal y distal (coloración morada de boca, manos y pies) con una saturación del 50% y por esta razón se inició oxígeno por máscara y remisión a una institución de alta complejidad en ambulancia medicalizada. Dice el Dr. Chiappe que ingresa a la Clínica la Carolina a las **20:30** encontrando la paciente ansiosa, con cianosis peribucal y distal y dificultad respiratoria severa. Ordena canalización venosa para la aplicación de bolo de Heparina de 5000 unidades de inmediato, pero no hay disponibilidad del medicamento en la Clínica, por lo que ordenan 40 miligramos subcutáneos de enoxaparina y llamado al anestesiólogo disponible para asegurar la vía aérea de la paciente mientras se espera remisión. Inicia ventilación con Bolsa

Autoinflable (AMBU) con mejoría de saturación de 70 a 89% y de estado de ansiedad de la paciente.

El 28 noviembre 2010 a las 11:22, aparece una “Nota de enfermería” firmada por “ ENF ALEJANDRO CHIAPPE DUARTE CC 80413619 Especialidad Enfermería” Hace referencia a hechos acaecidos el **27 noviembre 2010 a las 21:25** . Llega la ambulancia y se entrega al personal médico paciente estable con saturación de oxígeno del (no legible) % con frecuencia cardiaca de 140 por minuto, con acceso venoso, máscara de oxígeno a 10 litros minuto. Se confirma por parte de funcionarios de PanamericanLife (Póliza de complicaciones adquirida por la paciente) su remisión a Clínica Palermo.

DESCRIPCION DE LAS PATOLOGIAS Y CONDICIONES MÉDICAS DESCRITAS EN LA HISTORIA CLINICA

Definiciones

Coagulo sanguíneo: Masa o grumo de la sangre al pasar de un estado líquido a un estado sólido.

Trombo: Coagulo que se origina y se mantiene físicamente sin su sitio o vaso de origen.

Embolo: Coagulo que se desprende de su sitio o vaso de origen y viaja por el torrente circulatorio hasta taponar el flujo sanguíneo de un órgano a distancia (pulmón, cerebro, corazón piernas, intestino, etc.)

Tromboembolismo: Fenómeno patológico en que un trombo y/o un émbolo ocluyen la circulación sanguínea de un territorio o un órgano.

Endotelio: Capa lisa y delgada de células que recubren el interior o la luz de los vasos sanguíneos.

Hipercoagulabilidad. Fenómeno patológico en el que diversas sustancias existentes en la sangre o en los vasos sanguíneo generan un aumento en la producción de coágulos.

TVP Trombosis venosa profunda. Aparición de trombos en las venas profundas de los miembros inferiores

TEP Trombo Embolismo Pulmonar. Aparición de trombos o émbolos en las arterias o capilares pulmonares

Oclusión vascular. Fenómeno patológico en el que los trombos o embolos tapan los vasos (arterias o venas) deteniendo el flujo sanguíneo de los mismo

Contexto general

La enfermedad tromboembólica es la tercera causa de morbilidad cardiovascular después de la cardiopatía isquémica y la enfermedad cerebrovascular. Su prevalencia en la población hospitalizada alcanza el 1% (1).

La sangre se mantiene líquida dentro de los vasos sanguíneos debido a: 1 La presencia un nivel adecuado de agua en el torrente sanguíneo y un flujo constante del torrente circulatorio, 2: La existencia de un balance entre componentes naturales anticoagulantes y pro coagulantes de la sangre y 3 La integridad de las paredes de los vasos sanguíneos (endotelio)

La evolución natural de la enfermedad tromboembólica empieza en con la clásica tríada que el médico alemán Rudolph Virchow, padre de la patología moderna describió en el siglo XIX : 1 Estasis venosa (enlentecimiento del flujo sanguíneo venoso), 2 Hipercoagulabilidad sanguínea y 3 Lesiones en las paredes vasculares. Estos eventos de la triada están presentes en los factores de riesgo que se resumen en la **Tabla 1.** (1).

TABLA 1

FACTORES DE RIESGO PARA ENFERMEDAD TROMBOEMBOLICA

- Cirugías con anestesia general o regional (en especial mayor a 2 horas de duración)
- Prótesis o fractura de cadera o rodilla
- Artroscopia de rodilla
- Liposucción con volúmenes mayores a tres litros o combinada con otros procedimientos
- Politraumatismo
- Lesiones de la medula espina
- Inmovilización con férula de yeso de los miembros inferiores
- Eventos cerebrales con parálisis de extremidades inferiores
- Embarazo y puerperio
- Fibrilación auricular
- Falla cardíaca o respiratoria crónica
- TEP o TVP previa
- Fármacos hormonales estrogénicos
- Fármacos antipsicóticos
- Quimioterapia
- Cáncer
- Trombofilia (Enfermedades hematológicas con hipercoagulabilidad)
- Poliglobulia (Aumento de la concentración de glóbulos rojos)
- Enfermedad inflamatoria intestinal
- Enfermedades del colágeno
- Catéteres o dispositivos venosos centrales
- Edad mayor de 40 años
- Sobrepeso y obesidad
- Varices de miembros inferiores
- Viajes prolongados de más de 6 horas

Una vez que los elementos de la triada de Virchow se han hecho manifiestos, empezarán a aparecer coágulos trombos en diversos sitios del cuerpo pero en especial en los miembros inferiores. Esos coágulos inicialmente son microscópicos y pueden ser disueltos por el sistema fibrinolítico del cuerpo, pero ante la persistencia de la triada de Virchow los coágulos van a aumentar en tamaño hasta hacerse macroscópicos, momento en el cual por su naturaleza sólida van a ocluir los diferentes lechos sanguíneos venosos o arteriales. Si el trombo se originó en las venas de los miembros inferiores o en una víscera intraabdominal este puede desprenderse y con el flujo normal de la sangre venosa irse hacia el corazón en forma de émbolos que van a llegar a la aurícula derecha del corazón y luego al ventrículo derecho para luego ser eyectados hacia las arterias pulmonares. Las arterias pulmonares son vasos grandes que van a ramificarse en vasos cada vez más pequeños hasta formar los capilares pulmonares, vasos microscópicos encargados de hacer el recambio de oxígeno necesario para la oxigenación sanguínea. Según su tamaño los émbolos van a ocluir las arterias y en últimas van a tapar los capilares pulmonares produciéndose una disminución en la oxigenación sanguínea que se manifiesta clínicamente con la disnea o dificultad respiratoria del paciente, la cianosis (color morado de las mucosa de la boca o de la piel ya que la sangre oxigenada es roja brillante y la sangre desoxigenada es de color morado oscuro), la elevación de la frecuencia cardíaca, de la frecuencia respiratoria y de la tensión arterial, así como la aparición de un estado de excitación y ansiedad importantes debido a la sensación de ahogo o muerte inminente. Si el evento no es corregido de forma oportuna, la falta de oxígeno en los tejidos principalmente el cerebro y el corazón van a ocasionar en pocos minutos una isquemia cerebral o cardíaca que se manifiesta con la pérdida del estado de conciencia, la disminución de la frecuencia cardíaca y respiratoria, la baja de la presión arterial para finalmente culminar en un paro cardio respiratorio, el coma y la muerte.

Todos los procedimientos quirúrgicos producen cambios fisiopatológicos que van a ocasionar en mayor o menor grado la aparición de los elementos componentes de la triada de Virchow.

Estasis venosa. En primer lugar en el paciente quirúrgico el flujo sanguíneo de algunos territorios va a disminuir, tal es el caso de las extremidades que en un acto quirúrgico con anestesia general o regional permanecen inmóviles; la bomba muscular que se activa con la contracción de los diferentes grupos musculares, aumenta el movimiento de la sangre para regresar al corazón, y al estar paralizados se favorece un estado de estasis venoso. Los anestésicos en mayor o menor grado producen un estado de depresión del sistema cardiovascular que ocasiona cambios en el flujo sanguíneo por parte del organismo lo que va a disminuir el flujo de sangre arterial hacia los músculos, la piel y las vísceras intraabdominales para así redirigir la sangre al cerebro corazón y pulmón. Los niveles de agua corporal disminuyen por el ayuno pre quirúrgico, las pérdidas sanguíneas intra operatorias, la exposición de los tejidos con la consiguiente evaporación de agua, la presencia de edema tisular, lo que ocasiona una hemoconcentración (espesamiento de la sangre) lo que favorece la formación de coágulos.

Hipercoagulabilidad. Todo acto quirúrgico conlleva una incisión y un traumatismo tisular inherente al procedimiento los cuales van a activar de forma inmediata la cascada de la

coagulación induciéndose así la formación de coágulos necesaria para el control de la hemorragia. Algunas enfermedades o condiciones aumentan este efecto pro coagulante.

Lesión de la pared vascular. De igual forma los vasos sanguíneos son cortados o traumatizados en el acto operatorio, se colocan catéteres venosos y se infunden medicamentos dentro de las venas, lo que va a lesionar el propio endotelio, a exponer el colágeno subyacente y otras sustancias del intersticio celular que activan la agregación de plaquetas a las paredes de los vasos lesionados ocluyéndolos e iniciando la fase plaquetaria de la coagulación.

El grado de estasis venoso, de lesión de la pared vascular así como la activación de la cascada de la coagulación es directamente proporcional a la extensión y duración del trauma quirúrgico. Es así como una pequeña cirugía de hernia umbilical o corrección de párpados que son procedimientos relativamente cortos (duración entre 20 a 60 minutos) tienen mucho menor riesgo tromboembólico que una gastrectomía o una liposucción, procedimientos quirúrgicos que duran varias horas y que van a ocasionar un trauma tisular muy importante, aumentando así el riesgo de patologías tromboembólicas. Para este caso en la liposucción el cirujano utilizando una cánula cilíndrica de succión la cual es introducida en la grasa del tejido celular subcutáneo realizando innumerables cortes cilíndricos en la grasa, con su simultánea extracción mediante un dispositivo de succión, en el troco, glúteo o diferentes regiones corporales. Luego en la minilipéctomía abdominal, la lipoinyección en glúteos y la pexia mamaria bilateral el cirujano realiza diversos cortes y manipulaciones en diversas regiones del cuerpo, procedimientos que generan un importante trauma quirúrgico inherente a la operación. En la paciente este procedimiento tuvo una duración de 5 horas, tiempo que se puede catalogar como prolongado y suficiente para dar un riesgo importante de patologías tromboembólicas. El paciente acostado en una mesa de operaciones, inmóvil por 5 horas en un acto quirúrgico va a desarrollar trombos en un gran porcentaje de casos en diversas partes del organismo y en especial en los miembros inferiores y para disminuir la probabilidad del tromboembolismo el equipo de profesionales debe establecer grado de riesgo y según el mismo, tomar medidas tendientes a disminuir el porcentaje de casos que desarrollen la enfermedad (TVP, TEP).

En 1975, Dalen y colaboradores, (2) resumieron la historia natural para la enfermedad tromboembólica. La mayoría de los decesos se producen en las primeras horas (Figura 1). En este grupo de temprana mortalidad solamente la profilaxis la disminuirá en forma significativa. De los que sobreviven y pueden acceder a un tratamiento adecuado, la mortalidad es del 6-10%, pero puede alcanzar el 25-30% en los casos no diagnosticados y no tratados. Las estadísticas actuales (a la fecha de publicación del artículo (1) son similares a las publicadas en 1975 (2), lo que demuestra lo poco que se ha avanzado en el diagnóstico temprano de esta patología (1). Se estima que hasta el 70% de los casos no son diagnosticados. Esta situación refuerza la necesidad de, por una parte, mejorar la prevención y, por otra, intensificar las estrategias de diagnóstico precoz, comenzando por un cambio en la actitud médica, ya que es la sospecha clínica el primer eslabón ineludible de esta cadena (3) y el reconocimiento de los factores de riesgo la piedra angular de su prevención.

La frecuencia de TVP en pacientes sometidos a una simple cirugía de hernia puede ser de hasta el 5%, en cirugías mayores abdominales del 15% al 30%, en la de cadera es del 50-70% y en lesiones medulares graves es del 50% al 100%. (1).

Debemos tener en cuenta que el 25% de las embolias posoperatorias pueden producirse luego de alta hospitalaria. (1)

Registros realizados en distintos países demuestran que cerca de la mitad de los pacientes que necesitan prevención no la reciben en absoluto o reciben profilaxis inadecuada a su riesgo (6).

La incidencia de Tromboembolismo pulmonar durante las liposucciones y abdominoplastias combinadas con otros procedimientos oscilan entre un 0 a 23% (6).

Es importante mencionar que el Tromboembolismo pulmonar es la principal causa de muertes después de las liposucciones (4)

En los EE UU la agencia National Quality Forum ha considerado que las muertes en pacientes ASA I – la mayoría de los casos en cirugía plástica – son eventos que nunca deben pasar. (8)

En la American Society of Aesthetic Surgery en 2001 una encuesta reveló una mortalidad de 1 en 47.415 liposucciones, 1 en 7.314 si se combinaba la liposucción con otros procedimientos y de 1 en 3.281 cuando se había combinado la liposucción con abdominoplastia (9). Cabe analizar esta cifra dentro del contexto actual revelado por La Sociedad Internacional de Cirugía Plástica Estética que en 2009 reveló que en el mundo se realizaron 17 millones de procedimientos estéticos. Es interesante saber que Colombia que se ubica en el cuarto lugar del mundo entre los países que más procedimientos estéticos realiza detrás de EE UU, Brasil y México.

La prevención de la enfermedad tromboembólica es un tema que requiere todavía mucho trabajo y difusión ya que aun no se ha creado una conciencia colectiva de su reconocimiento y prevención. El consenso de las Asociaciones Colombianas de Anestesia y Cirugía plástica en noviembre de 2009 mencionó que en EEUU solo un 60% de los cirujanos plásticos conocía y aplicaba las recomendaciones en este sentido. (7).

EVALUACION Y PREVENCION DEL RIESGO DE TROMBOEMBOLISMO

Existen en la literatura diversas clasificaciones y algoritmos para determinar el tipo de riesgo de los pacientes para desarrollar eventos tromboembólicos. Si bien no han consenso mundial sobre la escogencia de una en particular todas coinciden en que los pacientes se dividen en términos generales en tres grupos: Bajo riesgo, Mediano riesgo y Alto riesgo.

El Grupo de Bajo riesgo son pacientes que no tienen ninguno de los factores de riesgo para tromboembolismo en listados en la tabla 1

El Grupo de Mediano riesgo tiene uno o dos factores de riesgo,

El Grupo de Alto riesgo tiene tres o más factores de riesgo.

Una de las escalas frecuentemente usadas en el mundo y recomendadas por las Asociaciones Colombianas de Anestesia y Cirugía Plástica en el 2009 es la escala de Caprini descrita en el año 2005 (5) (10). (Cuadro 1 Escala de Caprini).

Escala de Caprini	
2 Puntos	3 Puntos
Edad 60-74 años	Edad >75 años
Artroscopia	Antecedente de trombosis venosa
Cáncer (actual o previo)	Historia familiar de trombosis
Cirugía mayor (>45 minutos)	Factor V Leiden positivo
Laparoscopia (>45 minutos)	Mutación 20210A de Protrombina
Paciente confinado a cama (>72 horas)	Hiperhomocisteinemia
Inmovilización con yeso (<1 mes)	Anticoagulante lúpico positivo
Catéter venoso central	Anticuerpos anticardiolipinas positivos
	Trombocitopenia inducida por Heparina
	Otras trombofilias

CAPRINI JOSEPH A., Thrombosis Risk Assessment as a Guide to Quality Patient Care to Quality Patient Care. Dis Mon 2005; 51: 70-68.

PREVENCIÓN DE LOS EVENTOS TROMBOEMBÓLICOS

Las conductoras recomendadas para la prevención de eventos tromboembólicos son:

- Posición confortable en la mesa quirúrgica, flexión de la rodilla.
- Cambios de posición frecuentes del paciente en el intraoperatorio en la mesa de cirugía
- Uso de Dispositivo de Compresión neumática intermitente CNI
- Uso de Medias de compresión graduada
- Deambulación temprana
- Aplicación de heparina o heparinas de bajo peso molecular en el pre o post quirúrgico

Las recomendaciones dadas en 2009 en el Consenso de Anestesia y Cirugía Plástica que están en acuerdo con la escala de Caprini son.

Primero se asigna o estadifica el grado de riesgo de acuerdo al puntaje obtenido por cada paciente y según el mismo se deben realizar las acciones preventivas así:

- Grupo de pacientes de Bajo riesgo: Deambulación temprana - Compresión neumática intermitente CNI
- Grupo de pacientes de Mediano riesgo: Deambulación temprana - Compresión neumática intermitente CNI –Medias de compresión –Considerar unos de heparinas
- Grupo de paciente de Alto riesgo: Deambulación temprana - Compresión neumática intermitente CNI –Medias de compresión –Considerar unos de heparinas por 5 días.
- Grupode paciente de Muy Alto riesgo Deambulación temprana - Compresión neumática intermitente CNI –Medias de compresión –Considerar unos de heparinas por 10-14 días.

También algunos grupos han considerado la aplicación de heparina no fraccionada o de heparinas de bajo peso molecular pre quirúrgico (6). Si bien existe evidencia fuerte de que el uso de estos medicamentos disminuye en forma significativa la aparición de complicacionestrombo embolicas, no hay consenso sobre su exacta aplicación en los diferentes pacientes. No obstante es claro en hecho de que se debe tener en consideración su uso en la prevención en paciente de mediano y alto riesgo. Existen protocolos que mencionan la aplicación de heparinas en el pre operatorio pero no hay un nivel adecuado de evidencia que respalde o desapruebe la aplicación preoperatoria.

Existen evidencias respecto a que su aplicación se debe realizar despídos de las 6 horas post operatorias para disminuir el riesgo de sangrado (11)

Vale la pena anotar que si bien no se mencionan en los estudios citados es importante recordar que el paciente debe mantener un adecuado nivel de hidratación ya que la deshidratación conlleva a una hemoconcentración y consiguienteaumento de la viscosidad de la sangre que también es factor de riesgo para la aparición de trombos.

DIAGNOSTICO Y TRATAMIENTO DE LA ENFERMEDAD TROMBO EMBOLICA

La clave del diagnóstico y tratamiento de los eventos tromboembólicosen el paciente quirúrgico es la alta sospecha clínica y una actuación médica oportuna. La presencia de factores de riesgo debe poner en alerta al médico. Los síntomas son la aparición de taquicardia o taquipnea no explicadas, la desaturación de oxígeno, dificultad para respirar, cianosis o dolor del tórax. Ante la sospecha se debe realizar la aplicación inmediata de anticoagulantes parenterales tipo heparina o enoxaparina en dosis adecuadas. Para la enoxaparina la dosis es de 1 miligramo por kilo de peso repetida cada 12 horas. Se deba aumentar el aporte de oxígeno y tomar exámenes paraclínicos que confirmen el diagnóstico tales como un electrocardiograma, pruebas de coagulación, gases arteriales, ecografía Doppler y la tomografía de Torax con Angio TAC. Menos útiles y prácticos son la gammagrafía de ventilación perfusión o la angiografía. Una vez se haya sospechado el diagnóstico de TVP o TEP el paciente debe ser monitorizado y trasladado de inmediato a un unidad de cuidadointermedio o intensivo dependiendo de la gravedad del caso. En caso de insuficiencia ventilatoria grave el

paciente debe ser llevado a una intubación orotraqueal de urgencia para ventilación mecánica. Una demora en la decisión de intubar un paciente con una insuficiencia ventilatoria puede llevar a un paro cardiorespiratorio, secuelas neurológicas por hipoxia o la muerte.

ANALISIS DE LA ATENCION MEDICA Y PARAMEDICA EN EL CASO

Según la información registrada en la historia clínica en la valoración pre quirúrgica del 25 noviembre 2010 se anotan todos los antecedentes de la paciente y hallazgos del examen físico. Se concluye que la paciente tenía los siguientes factores de riesgo para enfermedad tromboembólica:

Edad de más de 40 años (se anota edad de 47 años)

Sobrepeso leve (talla 150 cm peso 62 kg) con IMC índice de masa corporal de 27.6 (normal de 18 a 24,9)

Procedimiento quirúrgico múltiple y prolongado (5 horas de duración).

Estos hallazgos tanto en escala anotada en el artículo de la Revista Colombiana de Cirugía Plástica, como en el índice de Caprini y en las publicadas en el Consenso de la Sociedad Colombiana de Anestesia y Cirugía Plástica de 2009 dan un grado de riesgo moderado.

Evaluando la paciente con el índice de Caprini 2005 (escala que para evaluar el riesgo tromboembólico de la paciente) este arroja un score de 4 puntos (Edad, tipo y duración de la cirugía, índice de masa corporal) compatible con un riesgo moderado y que por ende recomienda el uso de Dispositivos de compresión neumática, el uso de medias de compresión graduada y si el paciente no representa un riesgo de complicaciones por sangrado mayor el uso de heparinas a dosis bajas para disminuir las complicaciones tromboembólicas (5)

CIRUGIA PLASTICA

Revisando los registros de anotados por el Cirujano en el pre trans y post operatorios, se evidencia que:

En el consentimiento informado se anota el riesgo de Tromboembolismo pulmonar.

En la historia clínica de ingreso no se describen ni evalúan objetivamente los factores de riesgo para enfermedad tromboembólica de la paciente (peso, talla, índice de masa corporal IMC antecedentes generales) en la historia clínica prequirúrgica como tampoco se hace mención a ninguna escala ni clasificación de riesgo tromboembólico.

No se anotan cambios de posición de la paciente en el intraoperatorio, posición de las rodillas ni uso de dispositivos de compresión neumática.

No se evidencia colocación ni formulación de medias anti embolicas por parte del cirujano.

No se evidencia aplicación pre ni post quirúrgica, de heparina ni heparinas de bajo peso molecular

No se dan indicaciones sobre hidratación oral adecuada.

No se dan signos de alarma sobre disnea, tos, dificultad para respirar, sensación de taquicardia o taquipnea que alertaran a la paciente sobre la aparición de un posible tromboembolismo pulmonar

Sí se anota recomendación sobre deambulaci3n con acompa1ante

Sí se da recomendaci3n sobre uso permanente de faja.

Sí se dan formulas de tres analgésicos para un adecuado control del dolor.

La Fundaci3n Espa1ola del Coraz3n (FEC) ha informado que usar fajas muy ajustada favorece el desarrollo de problemas cardiocirculatorios al dificultar la circulaci3n sanguínea venosa dificultando el retorno de la sangre al coraz3n y favoreciendo la aparici3n de edemas, en las extremidades y propiciando la aparici3n de la trombosis, especialmente en las piernas. No obstante las fajas sobre el abdomen favorecen la disminuci3n de hematomas en el tejido celular subcutáneo de las cirugías realizadas sobre el tejido graso del abdomen y su uso es habitual en este tipo de procedimientos.

Los factores de riesgo de la enfermedad tromboemb3lica son acumulativos y la presencia de uno o m1s factores van sumando al porcentaje de probabilidades de desarrollar trombosis venosas profundas o trombo embolismos pulmonares.

Analizando los registros realizados por el cirujano **y el equipo medico**, en la historia de la Clínica La Carolina puedo concluir que:

No se realiz3 un juicioso an1lisis sobre los antecedentes y factores de riesgo de la paciente que como se describi3 arriba tenía un riesgo moderado de eventos tromboemb3licos dada la presencia de sobrepeso edad de m1s de 40 a1os y la realizaci3n de una cirugía múltiple prolongada de de 5 horas.

No se dej3 registro en la historia clínica de la mayoría de maniobras acciones o uso de fármacos tendientes a disminuir el riesgo de la aparici3n de trombos.

No se evidenci3 registro de notas de evoluci3n de la paciente en el post operatorio por parte del especialista en Cirugía plástica

No se hizo énfasis en los signos de alarma de un posible evento trombo embolico en el post operatorio.

Existen tres notas en la historia clínica elaboradas de forma extemporánea y fechadas el día 28 noviembre 2010 es decir el día posterior a la cirugía y al fallecimiento de la paciente. Dichas notas

describen hechos acaecidos el día 27 noviembre 2010 en las horas de la tarde y la noche. Si bien estas notas son coherentes con la temporalidad de los hechos, no tienen una secuencialidad dentro del documento ya que fueron elaboradas más de 19 horas después de los sucesos. Es de anotar que algunas notas de enfermería también se registran de esta misma forma es decir se escriben los sucesos varias horas después de ocurridos, aspecto que no es optimo ni adecuado en el diligenciamiento de una historia clínica¹.

Es importante resaltar el hecho de que la literatura menciona que siendo el Tromboembolismo pulmonar la primera causa de muerte en paciente sometidos a liposucciones, y que la principal manifestación clínica de esta grave enfermedad es la dificultad respiratoria, el hecho que el medico Chiappe le haya dado indicaciones, una vez instaurada la dificultad para respirar, a la paciente de asistir de nuevo a la Clínica La Carolina, siendo esta una institución de segundo nivel que no cuenta con el personal ni con los equipos necesarios para el diagnóstico ni el tratamiento de una condición potencialmente mortal, se constituye en una falla, que resto tiempo vital para el manejo de la paciente.

El Tromboembolismo pulmonar es una urgencia de prioridad o Triage 1 y su atención debe ser dada y su tratamiento inicial prestado de forma inmediata ya que la condición del paciente puede evolucionar y deteriorarse con rapidez. En el caso de la paciente el Cirujano fue informado del síntoma a las 19:30 y la paciente finalmente se le practica una reanimación cardiopulmonar avanzada a las 21:34 en la Fundación Santa Fe, es decir 2 horas y 4 minutos después de la notificación de los síntomas al cirujano. Este tiempo es demasiado largo para la atención de una patología con Triage 1 que debió ser sospechada desde su inicio.

Una vez sospechado en Tromboembolismo pulmonar se indicó la administración de una dosis del anticoagulante enoxaparina de 40 miligramos. Esta dosis es la usada en la profilaxis de la enfermedad tromboembólica pero las dosis para una anticoagulación plena en un TEP debe ser de 1 miligramo por kilo es decir 60 miligramos para el caso de la paciente que pesaba 62 kilos.

El Dr. Chiappe en conjunto con el médico general hospitalario valoraron e identificaron la condición de dificultad respiratoria de la paciente e iniciaron reposición de oxígeno y apoyo con AMBU, la saturación en los registro de enfermería hablan de haber llegado a 80% con AMBU, dispositivo que en teoría aporta una concentración de oxígeno cercana al 100%. Este dato junto con la presencia de Una frecuencia cardíaca de 140 una frecuencia respiratoria de 30 y un estado de agitación psicomotora hace sospechar que la paciente está ante una insuficiencia ventilatoria con el consecuente riesgo de paro cardiorespiratorio que la paciente desarrolló al parecer en el mismo ascensor de la Clínica La Carolina según lo reportó el Dr. Cohen emergenciólogo de la FSFB

¹La Resolución número 1995 de 1999 Por la cual se establecen normas para el manejo de la Historia Clínica, señala en su ARTÍCULO 3.- CARACTERÍSTICAS DE LA HISTORIA CLÍNICA, respecto de la oportunidad del registro lo siguiente: Es el diligenciamiento de los registros de atención de la historia clínica, simultánea o inmediatamente después de que ocurre la prestación del servicio.

por información del personal de la ambulancia y que después llevó al fallecimiento de la paciente. La valoración adecuada y el juicio clínico correcto en una paciente con dificultad respiratoria tienen como objetivo garantizar el aseguramiento de la vía aérea y una adecuada oxigenación una vez se instaure la insuficiencia ventilatoria. Debe sospecharse insuficiencia ventilatoria en pacientes con dificultad respiratoria, fatiga respiratoria visible o cianosis, o cambios en el sensorio y en aquellos con afecciones que producen debilidad neuromuscular. La taquipnea también es un problema; una frecuencia respiratoria > 28 a $30/\text{min}$ no puede sostenerse durante mucho tiempo (12). La paciente presentaba para ese momento cianosis, alteración del estado de la conciencia y una frecuencia respiratoria de 30 por minuto. La ventilación no invasiva con presión positiva puede ser la primera opción pero ante la presencia de un paro cardiorespiratorio la mejor opción es la intubación orotraqueal y ventilación con presión positiva. Su síndrome de dificultad respiratoria encuadra en una inminencia de falla ventilatoria que por normativa Colombiana, el personal médico está en competencias de identificar y manejar dichas circunstancias. En definitiva a la salida de la Clínica La Carolina la paciente no tenía una vía aérea asegurada hecho agravado por la circunstancia que la ambulancia que realizaba el traslado era básica y no contaba con personal médico entrenado en el procedimiento de intubación orotraqueal y ventilación con presión positiva.

Analizando los registros realizados por el cirujano en la historia Clínica La Carolina puedo concluir que:

No se realizó un juicioso análisis sobre los antecedentes y factores de riesgo de la paciente que como se describió arriba tenía un riesgo moderado de eventos tromboembólicos dada la presencia de sobrepeso con un ICM de 27.7, edad de más de 40 años y la realización de una cirugía múltiple y de 5 horas de duración. No se dejó registro en la historia clínica de la mayoría de maniobras acciones o uso de fármacos tendientes a disminuir el riesgo de la aparición de un evento tromboembólico.

No se hizo énfasis en los signos de alarma de un posible evento tromboembólico en el post operatorio.

No se administró la dosis adecuada de anticoagulante ante la sospecha clínica de un TEP.

En general el personal médico de la clínica no logró asegurar la vía aérea de una paciente con una inminencia de falla ventilatoria

ANESTESIA

Para este concepto se contó con la colaboración (análisis y concepto) del Dr. Rodrigo Chaparro Anestesiólogo además de mi experiencia de más de 10 años como jefe y coordinador de urgencias de diversas Clínicas de Bogotá.

Revisando los registros de anotados por parte de anestesia en el pre trans y post operatorios, se evidencia que:

En la consulta preanestésica sí se describen los factores de riesgo para enfermedad tromboembólica de la paciente (peso, talla, antecedentes generales).

No se hace una evaluación específica del riesgo tromboembólico de la paciente es decir, no anota ninguna escala de riesgo ni se evalúa el grado (bajo, mediano o alto de riesgo tromboembólico). No se hace el cálculo del índice de masa corporal importante para el diagnóstico del sobrepeso y la obesidad.

Sí se describen los signos vitales y la monitoria en el trans operatorio los cuales muestran que la paciente permaneció estable y sin complicaciones en la inducción, el transoperatorio y la finalización del acto quirúrgico - anestésico.

No se anotan si se realizaron cambios de posición de la paciente en el intraoperatorio, posición de las rodillas ni uso de dispositivos de compresión neumática.

No se evidencia la colocación de medias antiembólicas en pre trans o post operatorio.

No se evidencia aplicación pre ni post qx de heparina ni heparinas de bajo peso molecular

No se evidencia registro en el sistema (historia clínica electrónica de la Clínica) de la evolución post operatoria por parte del especialista en Anestesia excepto por la evidencia en la hoja de formato de Anestesia un registro a mano en los últimos tres de cinco medios renglones, sobre la condición y la salida de la paciente, esta nota se encuentra ubicada en el documento en un campo no diseñado para tal fin, la nota es incompleta en su información, corta en su redacción e imprecisa en sus indicaciones y hora de elaboración de las 17:15, dato que es contradictorio con la nota de la Enfermera Hayda Yazmin Aguirre en la que a las "14:30 se entregan fórmulas, se entrega boleta de salida, se retira vía venosa se baja al sótano en silla de ruedas en compañía de familiar y se da egreso de la Clínica La Carolina". La información anotada a mano por anestesia no es entonces coherente con la lógica cronología del caso y carece de secuencialidad dentro de la historia clínica aportada de la Clínica La Carolina. Dicha nota no aporta información sobre datos claves en la evolución post anestésica y post operatoria de una paciente como son: tensión arterial, frecuencia cardíaca, saturación de oxígeno, nivel de conciencia, nivel de dolor. Da unas recomendaciones generales sobre medidas antiembólicas pero no da la información exacta sobre las medias presoras (Ni talla, ni grado de compresión, ni largo de la media) ni sobre las heparinas de bajo peso molecular, no existe evidencia de entregar ninguna fórmula a la paciente como tampoco se anotan las normas básicas de toda prescripción medicamentosa como lo son presentación, dosis, vía de aplicación, frecuencia de aplicaciones y precauciones.

Esta irregular anotación a mano que no quedó registrada en el sistema desestima la calidad, integridad, idoneidad y temporalidad de la nota. Por ende no existió en la historia clínica un registro ni manual ni en el sistema de una valoración completa, idónea ni oportuna registrada por

un profesional con firma, nombre legible y número de registro médico (como lo exigen los estándares) que avalara una salida segura de la paciente.

Una vez la paciente regresa con la dificultad respiratoria a la Clínica La Carolina el anestesiólogo es requerido para atender a la paciente pero no hay registro de su llegada. Ante esto desconozco las condiciones de contratación del personal de anestesia en la Clínica de segundo nivel como lo es la Clínica La Carolina

AMBULANCIA

Sobre los hechos ocurridos con la remisión en ambulancia mi concepto es el siguiente.

La solicitud de traslado referida en las notas del Dr. Chiappe dice que se solicitó en ambulancia medicalizada. Esta solicitud es coherente con el estado de la paciente que tenía un grave estado de salud (ingresó saturando 50% con cianosis, frecuencia respiratoria de 30 y frecuencia cardíaca de 140 por minuto). El personal que se registra en la planilla de AMBULANCIAS MEDICAS PROFESIONALES SA (Factura de venta 6260 y record No. 6260) del 27 noviembre 2020 es de TAB (Transporte en Ambulancia Básica) consta que el personal que realiza el servicio es de un paramédico y un conductor. La paciente es recogida en la Clínica la Carolina inicialmente con destino a la Clínica Palermo pero durante el traslado la paciente presenta paro cardiorespiratorio y es derivada a la Fundación Santa Fe de Bogotá, centro que queda más cerca a la clínica la Carolina. Las notas de la ambulancia se describen aquí:

21:15 Contacto con el paciente

21:19 Monitoria Básica. No hay monitoria avanzada

21:25 Llegada al destino

A su ingreso encuentran paciente excitada, incoherente, en mal estado general con dificultad respiratoria. Sin oxígeno suplementario se sube a la camilla, se moviliza en dirección al trayecto del ascenso, paciente con cianosis generalizada. 21+17 paciente se embarca en ambulancia. Se coloca máscara laríngea sc 21+19(TA registrada 180/90 frecuencia cardíaca 180) Luego a las 21:25 anotan TA 160/90 FC. 54 .

Durante el traslado “Verifica no respiración y no pulso, se inicia reanimación básica, se decide ingresar a FSFB por estado crítico del paciente. 21+28 ingresa paciente a sala de reanimación. Se comenta al médico. Médico retira máscara laríngea. Inician maniobras. Paciente se entrega en urgencias de FSFpte se “recniema” Realizando maniobras de reanimación.

El médico urgenciólogo Eliecer Cohen hace la observación que por información del personal de la ambulancia la paciente presentó paro cardio respiratorio en el ascensor de la Institución remitente y que llevaba unos 10 a 15 minutos en paro, llega la ambulancia sin sirena, ingresando a la sala de reanimación, en mal estado general sin signos vitales y en coma profundo, con máscara laríngea

desinflada y llama la atención sobre “ausencia de compresiones torácicas y actitud de reanimación del caso”.

Análisis. No hay coherencia de la información de los registros de la Ambulancia: Anotan TA 160/90 y FC 54 a las 21:25, misma hora de llegada al destino, pero en la anotación del traslado mencionan: Verifica no respiración y no pulso, se inicia reanimación básica, se decide ingresar a FSFB por estado crítico del paciente” es decir que en el mismo minuto (21:25) anotan varios eventos simultáneos (tensión arterial detectable 160/90 y pulso de 54, ausencia de pulso, inicio de reanimación básica, decisión de traslado a la FSFB y llegada a la FSFB) lo cual no es coherente con una secuencia lógica de los hechos. Por estos registros es muy probable que las cifras de tensión arterial y frecuencia cardíaca anotadas hayan sido escritas de forma errada haciendo muy probable que la información del médico urgenciólogo Dr. Cohen que anota un paro de 10 a 15 minutos y que ocurre en el ascensor de la clínica La Carolina. También es preocupante el hecho de que una paciente en pleno paro cardio respiratorio llegue a la central de urgencias con “ausencia de compresiones torácicas y sin actitud de reanimación del caso” es decir, que el personal de la ambulancia no dio continuidad a la supuesta reanimación básica a que hacen referencia en las notas. La no continuidad de las maniobras de reanimación (compresiones torácicas y ventilación asistida) puede dar como resultado el fracaso de la reanimación con la muerte del paciente o con secuelas neurológicas graves sin el paciente sale vivo.

ANALISIS DEL INFORME DE NECROPSIA

El informe de la necropsia realizada a la señora María Inés López el 28 noviembre 2010 por la médico Forense Lyda Hernández Rojas en el Instituto colombiano de Medicina Legal revela como datos positivos un cadáver de sexo femenino con heridas e hilo de sutura en una abdominoplastia clásica y en glándulas mamarias. La incisión de la herida de abdominoplastia mide 27 cm de longitud y en las glándulas mamarias unas heridas circulares de 5 x 5 cm y una herida vertical en los cuadrantes inferiores de mamas. Los pulmones colapsados bilateralmente disminuidos de tamaño, aumentados en consistencia, de color gris café. Al corte histológico septos engrosados con congestión vascular marcada, a nivel de los alveolos hay líquido de edema y sangre. Los vasos de pequeño tamaño muestran trombos recientes. Antracosis moderada.

El hígado alterado por la presencia de hemangioma cavernoso (no describen su tamaño) con infiltrado inflamatorio, con vasos de diverso tamaño algunos de ellos con trombos adheridos a la pared.

Venas de los miembros inferiores e iliacas no hay ninguna descripción.

Los hallazgos de la necropsia orientan a una muerte asociada a Trombo Embolismo Pulmonar (TEP) secundario a trombosis de hemangioma cavernoso del hígado en periodo post operatorio. Manera de muerte: Natural.

Analizando el informe de la necropsia se encuentra que la causa de muerte en efecto fue un Trombo Embolismo Pulmonar (TEP) evidenciado por el examen pulmonar que revela “vasos de pequeño tamaño muestran trombos recientes” Según la autopsia el origen de estos trombos fue un Hemangioma Cavernoso del Hígado que desafortunadamente no tiene mediciones de su tamaño o volumen. Los hemangiomas cavernosos son lesiones benignas que pueden aparecer en el Hígado de forma relativamente frecuente ya que como dice el informe se han reportado entre el 1% y el 20% de las autopsias. En vida los hemangiomas hepáticos suelen ser lesiones asintomáticas y de curso benigno y es extraordinariamente raro que produzcan complicaciones graves o mortales. y en su mayoría son descubiertos de forma incidental durante la toma de una ecografía abdominal indicadas por diversas molestias abdominales.. En los casos típicos es apropiado un enfoque conservador (nivel de evidencia II-2, grado de la recomendación 1). Los hemangiomas sintomáticos de crecimiento progresivo pueden requerir resección quirúrgica seleccionando muy bien los casos ya que en muchas ocasiones los síntomas abdominales obedecen a otras patologías. Son externamente raros los reportes de la literatura mundial sobre complicaciones de trombo embolismo pulmonar en pacientes con hemangiomas hepáticos².

Por otro lado la presencia de Trombosis Venosa Profunda TEP de los miembros inferiores (venas soleas, gastronecmias, poplíteas, femorales e iliacas), explica la inmensa mayoría de los Trombo Embolismos Pulmonares (TEP). Infortunadamente el informe de la necropsia no describe en lo absoluto información sobre el estado de las venas soleas, gastronecmias, poplíteas, femorales ni iliacas) omitiéndose una valiosa información que podría ofrecer elementos para determinar de manera más exacta la causa de muerte de la paciente.

CONCLUSIONES GENERALES

CAUSA DE MUERTE DE LA PACIENTE

La señora MARIA INES LOPEZ SANABRIA (QEPD) falleció a causa de una sucesión de eventos que inician con presencia de tres factores de riesgo como son una edad de más de 40 años, un índice de masa corporal mayor de 25 y el sometimiento a una cirugía múltiple bajo anestesia general de liposucción extensa más miniliplectomia abdominal, más lipoinyección glútea bilateral más pexia mamaria bilateral la cual que fue prolongada con una duración de 5 horas. La conjunción de estos factores le daban a la paciente un riesgo importante (índice tromboembólico de Caprini 2005 de 4 puntos o riesgo moderado) para la aparición de complicaciones tromboembólicas. Este grado de riesgo requeriría de medidas profilácticas antiembólicas que no fueron implementadas en su totalidad. Debido a estos factores de riesgo para trombosis aunado a la presencia no advertida de un hemangioma hepático que hasta ese momento era no advertido y asintomático, la paciente desarrolla trombos. La necropsia realizada tiene la falencia de no haber informado además de los

²SEÑALAR SU EXPERIENCIA EN ESTE TEMA

trombos a nivel del hemangioma hepático, si existían o no trombos a nivel de las venas de los miembros inferiores ya que para el caso había una alta probabilidad de que el origen de los trombos también ocurrieran en el territorio venoso profundo de los miembros inferiores (TVP). De cualquier manera los trombos originados en el hígado y/o en los miembros inferiores migran en el post operatorio hacia el pulmón produciéndose un Trombo embolismo pulmonar, que ocasiona una disnea importante se sospecha un TEP y se le aplica una dosis insuficiente del anticoagulante enoxaparina. Posteriormente la paciente progresa a una dificultad respiratoria severa y una grave desoxigenación de la sangre que finalmente lleva a la paciente a una insuficiencia ventilatoria aguda y a un paro cardiorespiratorio que no fueron oportunamente manejados y que al momento de su arribo a la FSFB habían ocasionado en la paciente irreversibles cambios post paro con hallazgos clínicos compatibles con muerte cerebral. Las maniobras realizadas en urgencias de la FSFB resultan infructuosas y la paciente fallece 9 horas y 50 minutos después de terminada la cirugía.

De acuerdo a la descripción de los hechos consignados en los registros clínicos y de la autopsia en mi calidad de perito expongo a continuación las conclusiones finales del presente dictamen:

Se evidenciaron varios errores y falencias en la atención de la paciente MARIA INES LOPEZ SANABRIA, a saber:

No se reconocieron manera explícita en las valoraciones pre quirúrgicas los factores de riesgo que tenía la paciente para desarrollar una tromboembolia (Edad mayor de 40 años, sobrepeso, Procedimiento quirúrgico de más de 2 horas que incluía liposucción extensa de 3 litros mas tres procedimientos adicionales: minilipectomía abdominal, lipoinyección glútea bilateral y péxica mamaria bilateral)

No se registraron en la historia clínica escalas de riesgo ni graduación riesgo de la paciente con miras a prevenir un evento tromboembólico. Tampoco se calculó el índice de masa corporal IMC.

Excepto la deambulación temprana, no se tomaron en el pre, tras ni post operatorio las medidas de prevención de Tromboembolismo recomendadas en la literatura y en la lex artis y específico no se hizo uso de medias de compresión graduada (OJO LA SUPUESTA NOTA DE LA ANESTESIOLOGA), dispositivos de compresión neumática intermitente CNI, ni se usaron heparinas en pre ni post operatorio.

Las indicaciones dadas por escrito a la salida de la paciente no advirtieron los signos de alarma sobre aparición de síntomas de TEP.

No se entregaron a la paciente o a la familia formulación de fármacos anticoagulantes para prevenir complicaciones tromboembólicas pese a ser una paciente de mediano riesgo, como tampoco se expidieron las formulas de medias de compresión graduada para pre ni el post operatorio.

Muchas de las notas de la historia clínica de la Clínica La Carolina están elaboradas a destiempo, no son cronológicamente secuenciales o son incompletas en especial la nota de anestesia de las

17:15 en la que se da de alta de la clínica por parte de anestesia y las notas realizadas el siguientedía (28 de noviembre) del especialista en cirugía Plástica.

No existieron valoraciones médicas completas, idóneas ni cronológicamente adecuadas para definir el alta de la paciente de la Clínica la Carolina

Los síntomas de TEP presentados por la paciente fueron subvalorados por el cirujano plástico tratante debido a que el médico al saber de la dificultad respiratoria de la paciente la direcciona hacia la Clínica la Carolina, institución de segundo nivel no apta para el manejo de esta grave patología.

La aplicación de la enoxaparina no se hizo en las dosis recomendadas de 1 miligramo por kilo de peso, siendo la dosis de 40 mg muy baja para el peso de la paciente (62 kilos)

La insuficienciaventilatoriapresentada por la pacienteno fue oportunamente manejada por el médicogeneral de la Clínica la Carolina, ni por el cirujano plástico, ni por el personal de la ambulancia y prueba de ello es que la paciente se intuba tardíamente en urgencias de la FSFB cuando llevaba más de 10 minutos en paro y presentabaya claros signos de muerte cerebral. El profesional de anestesia no se hizo presenteen la Clínica la Carolina (O AL MENOS NO HAY REGISTRO DE ELLO) para al valoración ni manejo de la vía aérea de la paciente.

Las notas del cirujano plástico son muy posteriores a su ocurrencia

El traslado de una paciente gravementeenferma no fue realizado en una ambulancia medicalizada, no se realizó de manera oportuna y no se aseguró de manera adecuada la vía aérea durante el traslado.

En ningún momento se contempló la necesidad de traslado a una Unidad de Cuidados intensivos UCI que la paciente sin duda necesitaba.

Existe incoherencia en los tiempos de paro y reanimaciónrelatados por el personal de la ambulancia.

Las maniobras dereanimación Cardio Pulmonar no se realizaron de acuerdo a los protocolos establecidos siendo ésta suspendidas de manera inexplicada y reasumidas solo en la sala de reanimación de la FSFB.

Doy fe de que este cuestionario se ha respondido dentro de mi conocimiento como Médico especialista en Cirugía General, con 31 años de experiencia profesional , dentro de la *lex artis* y según la revisión documental de los folios del expediente que el Dr. Carlos Alberto Camargo me aportó

HERNAN SEPULVEDA MARTINEZ

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American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients

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Background: Venous thromboembolism (VTE) is a common source of perioperative morbidity and mortality.

Objective: These evidence-based guidelines from the American Society of Hematology (ASH) intend to support decision making about preventing VTE in patients undergoing surgery.

Methods: ASH formed a multidisciplinary guideline panel balanced to minimize bias from conflicts of interest. The McMaster University GRADE Centre supported the guideline-development process, including performing systematic reviews. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess evidence and make recommendations, which were subject to public comment.

Results: The panel agreed on 30 recommendations, including for major surgery in general ($n = 8$), orthopedic surgery ($n = 7$), major general surgery ($n = 3$), major neurosurgical procedures ($n = 2$), urological surgery ($n = 4$), cardiac surgery and major vascular surgery ($n = 2$), major trauma ($n = 2$), and major gynecological surgery ($n = 2$).

Conclusions: For patients undergoing major surgery in general, the panel made conditional recommendations for mechanical prophylaxis over no prophylaxis, for pneumatic compression prophylaxis over graduated compression stockings, and against inferior vena cava filters. In patients undergoing total hip or total knee arthroplasty, conditional recommendations included using either aspirin or anticoagulants, as well as for a direct oral anticoagulant over low-molecular-weight heparin (LMWH). For major general surgery, the panel suggested pharmacological prophylaxis over no prophylaxis, using LMWH or unfractionated heparin. For major neurosurgery, transurethral resection of the prostate, or radical prostatectomy, the panel suggested against pharmacological prophylaxis. For major trauma surgery or major gynecological surgery, the panel suggested pharmacological prophylaxis over no prophylaxis.

Summary of recommendations

These American Society of Hematology (ASH) guidelines are based on updated and original systematic reviews of evidence conducted by researchers and developed under the direction of the McMaster

University GRADE Centre with international collaborators. The panel followed best practice for guideline development recommended by the Institute of Medicine (now the National Academy of Medicine) and the Guidelines International Network.¹⁻⁴ The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach^{5,6} to assess the certainty in the evidence and formulate recommendations.

The population of postoperative patients is heterogeneous with regard to the degree of risk of venous thromboembolism (VTE), depending on intrinsic patient factors and those factors that are related to the type of surgery, mobilization, anatomic location of the procedures, and risk of bleeding. Surgeons have a long history of accepting prophylactic measures against VTE, be they mechanical or pharmacological.

Interpretation of strong and conditional recommendations

The strength of a recommendation is expressed as strong ("the guideline panel recommends...") or conditional ("the guideline panel suggests...") and has the following interpretation:

Strong recommendation

- For patients: most individuals in this situation would want the recommended course of action, and only a small proportion would not.
- For clinicians: most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.
- For policy makers: the recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.
- For researchers: the recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendation.

Conditional recommendation

- For patients: the majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.
- For clinicians: different choices will be appropriate for individual patients, and clinicians must help each patient to arrive at a management decision consistent with the patient's values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences.
- For policy makers: policy-making will require substantial debate and involvement of various stakeholders. Performance measures about the suggested course of action should focus on whether an appropriate decision-making process is duly documented.

- For researchers: this recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help to identify possible research gaps.

Recommendations

Mechanical vs pharmacological prophylaxis for patients undergoing major surgery

RECOMMENDATIONS 1 TO 5. For patients undergoing major surgery, the ASH guideline panel *suggests* the following:

1. Using pharmacological prophylaxis or mechanical prophylaxis (conditional recommendation based on low certainty in the evidence of effects ⊕⊕○○)
2. For patients who do not receive pharmacologic prophylaxis, using mechanical prophylaxis over no mechanical prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).
3. For patients who receive mechanical prophylaxis, using intermittent compression devices over graduated compression stockings (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).
4. For patients who receive pharmacologic prophylaxis, using combined prophylaxis with mechanical and pharmacological methods over prophylaxis with pharmacological agents alone (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).
5. Depending on the risk of VTE and bleeding based on the individual patient and the type of surgical procedure, using combined prophylaxis or mechanical prophylaxis alone (conditional recommendation based on low certainty in the evidence of effects ⊕⊕○○).

Remarks: For patients considered at high risk of bleeding, the balance of effects may favor mechanical methods over pharmacological prophylaxis. For patients considered at high risk for VTE, combined prophylaxis is particularly favored over mechanical or pharmacological prophylaxis alone.

Prophylactic insertion of an inferior vena cava filter

RECOMMENDATION 6. For patients undergoing major surgery, the ASH guideline panel *suggests against* using inferior vena cava (IVC) filters for prophylaxis of VTE (conditional recommendation based on very low certainty in the evidence of effects, ⊕○○○).

Timing of antithrombotic prophylaxis

RECOMMENDATIONS 7 AND 8. For patients undergoing major surgery, the ASH guideline panel *suggests* using extended antithrombotic prophylaxis over short-term antithrombotic prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○). The ASH guideline panel further *suggests* using early or delayed antithrombotic prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○). **Remarks:** Extended prophylaxis was generally considered as beyond 3 weeks (range, 19-42 days) compared with short-term prophylaxis, which was considered as up to 2 weeks (range, 4-14 days). Twelve hours following surgery was arbitrarily

selected to be the cutoff point between early and late postoperative antithrombotic administration.

Orthopedic surgery

RECOMMENDATIONS 9 TO 13. For patients undergoing total hip arthroplasty or total knee arthroplasty, the ASH guideline panel *suggests* using aspirin (ASA) or anticoagulants (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○). When anticoagulants are used, the panel *suggests* using direct oral anticoagulants (DOACs) over low-molecular-weight heparin (LMWH) (conditional recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕○); the panel *suggests* using any of the DOACs approved for use (conditional recommendation based on low certainty in the evidence of effects ⊕⊕○○). If a DOAC is not used, the panel *suggests* using LMWH rather than warfarin (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○) and *recommends* LMWH rather than unfractionated heparin (UFH) (strong recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕○).

RECOMMENDATIONS 14 AND 15. For patients undergoing hip fracture repair, the ASH guideline panel *suggests* using pharmacological prophylaxis over no pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○) and *suggests* using LMWH or UFH (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Major general surgery

RECOMMENDATIONS 16 AND 17. For patients undergoing major general surgery, the ASH guideline panel *suggests* using pharmacological prophylaxis over no pharmacological prophylaxis (conditional recommendation based on low certainty in the evidence of effects ⊕⊕○○) and *suggests* using LMWH or UFH (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Laparoscopic cholecystectomy

RECOMMENDATION 18. For patients undergoing laparoscopic cholecystectomy, the ASH guideline panel *suggests against* using pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○). **Remark:** Patients with other risk factors for VTE (such as history of VTE, thrombophilia, or malignancy) may benefit from pharmacological prophylaxis.

Major neurosurgical procedures

RECOMMENDATIONS 19 AND 20. For patients undergoing major neurosurgical procedures, the ASH guideline panel *suggests against* using pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○). For the subset of patients undergoing major neurosurgical procedures for whom pharmacological prophylaxis is used, the ASH guideline panel *suggests* using LMWH over UFH (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○). **Remarks:** Patients undergoing major neurosurgical procedures are expected to receive prophylaxis with mechanical methods. Pharmacological prophylaxis may be warranted in a higher-risk subgroup of patients, such as those experiencing prolonged

immobility following surgery. In addition, pharmacological prophylaxis could be considered for patients undergoing major neurosurgical procedures that carried a lower risk for major bleeding and in those patients with persistent mobility restrictions after the bleeding risk declines following surgery.

Urological procedures

RECOMMENDATIONS 21 AND 22. For patients undergoing transurethral resection of the prostate (TURP), the ASH guideline panel *suggests against* using pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○). For the subset of patients undergoing TURP for whom pharmacological prophylaxis is used, the ASH guideline panel *suggests* using LMWH or UFH (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○). **Remark:** Patients with other risk factors for VTE (such as history of VTE, thrombophilia, or malignancy) may benefit from pharmacological prophylaxis.

RECOMMENDATIONS 23 AND 24. For patients undergoing radical prostatectomy, the ASH guideline panel *suggests against* using pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○). For patients undergoing radical prostatectomy in whom pharmacological prophylaxis is used, the ASH guideline panel *suggests* using LMWH or UFH (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○). **Remark:** Patients undergoing an extended node dissection and/or open radical prostatectomy may have a higher VTE risk and may potentially benefit from pharmacological prophylaxis.

Cardiac or major vascular surgery

RECOMMENDATIONS 25 AND 26. For patients undergoing cardiac or major vascular surgery, the ASH guideline panel *suggests* using pharmacological prophylaxis or no pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○). When pharmacological prophylaxis is used, the panel *suggests* using LMWH or UFH (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Major trauma

RECOMMENDATION 27A. For patients experiencing major trauma and who are at low to moderate risk for bleeding, the ASH guideline panel *suggests* using pharmacological prophylaxis over no pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

RECOMMENDATION 27B. For patients experiencing major trauma and who are at high risk for bleeding, the ASH guideline panel *suggests against* pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

RECOMMENDATION 28. For patients experiencing major trauma in whom pharmacological prophylaxis is used, the ASH guideline panel *suggests* using LMWH or UFH (conditional recommendation based on low certainty in the evidence of effects ⊕⊕○○).

Major gynecological surgery

RECOMMENDATIONS 29 AND 30. For patients undergoing major gynecological surgery, the ASH guideline panel *suggests* using pharmacological prophylaxis over no pharmacological prophylaxis

(conditional recommendation based on very low certainty in the evidence of effects ⊕○○○) and *suggests* using LMWH or UFH

(conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Introduction

Aim of these guidelines and specific objectives

The purpose of these guidelines is to provide evidence-based recommendations about the prevention of VTE for patients undergoing major surgical procedures. The target audience includes patients, surgeons, intensivists, internists, hematologists, general practitioners, hospitalists, other clinicians, pharmacists, and decision makers. Policy makers interested in these guidelines include those involved in developing local, national, or international programs aiming to safely reduce the incidence of VTE and/or to evaluate direct and indirect harms and costs related to VTE and its prevention. This document may also serve as the basis for adaptation by local, regional, or national guideline panels.

Description of the health problem

Deep vein thrombosis (DVT) and pulmonary embolism (PE) (collectively, VTE) are well-recognized, clinically important, and potentially devastating complications that may occur following major surgical procedures, defined as any surgical intervention that carries greater than minimal risk, is performed in the operating room, and requires specialized training. Before the era of the routine use of effective prophylaxis, VTE was a common cause of morbidity and mortality following major surgery. It has been estimated to cause >50 000 deaths per annum in the United States alone.⁷ The importance of preventative measures to minimize the risk of VTE following major surgery has been recognized for decades; however, even with the use of prophylaxis, surgery accounts for ~25% of VTEs observed in communities.⁸

Although most surgical procedures carry some risk for VTE, this risk varies considerably across surgical procedures and among individual patients undergoing surgery. Surgical procedures carrying the highest risk of developing postoperative VTE include hip and knee arthroplasty, invasive neurosurgical procedures, and major vascular procedures.⁹

Patient factors that carry greater risks for thrombosis include histories of VTE, particularly if unprovoked or associated with cancer, or cancer, even in the absence of previous VTE. Scoring systems that calculate the risk of postoperative VTE for individual patients, such as the Caprini score, have been developed and validated following some surgical procedures.¹⁰

Although postoperative VTE has historically been a complication primarily occurring in the hospital, with shortened hospital stays, postoperative VTE often occurs in the days to weeks following discharge from the hospital.¹¹

Description of the target populations

The primary target population of this guideline is patients hospitalized for major surgical procedures that carry a risk for postoperative VTE. This guideline also addresses patients hospitalized following major trauma; most, but not all, subsequently required major surgical procedures. The panel recognized that there are 2 major modalities applied for the prevention of VTE in the postoperative period: pharmacological antithrombotic prophylaxis and mechanical

prophylaxis. For evaluation of the pharmacological methods for the prevention of VTE, the panel weighed the benefits and risks of the various options for individual surgical procedures or domains, such as hip or knee arthroplasty, general surgery, or urological or neurosurgical procedures.

For mechanical interventions, such as graduated or mechanical compression devices or IVC filters, the effectiveness of these interventions was assessed across all surgical domains. Likewise, other questions, such as the duration of pharmacological prophylaxis and timing of the initiation of pharmacological prophylaxis, were also assessed across all surgical domains.

The target populations included patients who underwent surgery for cancer or noncancer-related procedures. Patients hospitalized for major trauma were included whether they underwent surgery or not.

Methods

The guideline panel developed and graded the recommendations and assessed the certainty in the supporting evidence following the GRADE approach.^{5,6,12-16} The overall guideline-development process, including funding of the work, panel formation, management of conflicts of interest, internal and external review, and organizational approval, was guided by ASH policies and procedures derived from the Guidelines International Network–McMaster Guideline Development Checklist (<http://cebgrade.mcmaster.ca/guidecheck.html>) and was intended to meet recommendations for trustworthy guidelines by the Institute of Medicine and the Guidelines International Network.¹⁻⁴

Organization, panel composition, planning, and coordination

The work of this panel was coordinated with 9 other guideline panels (addressing other aspects of VTE management) by ASH and the McMaster GRADE Centre (funded by ASH under a paid agreement). Project oversight was provided initially by a coordination panel, which reported to the ASH Committee on Quality, and then by the coordination panel chair (Adam Cuker) and vice chair (H.J.S.). ASH vetted and appointed individuals to the guideline panel. The McMaster GRADE Centre vetted and retained researchers to conduct systematic reviews of evidence and coordinate the guideline-development process, including the use of the GRADE approach. The membership of the panels and the GRADE Centre team is described in Supplement 1.

The panel included surgeons with subspecialty representation, hematologists, internists, and a pharmacist, all of whom had clinical and research expertise on the guideline topic. The panel also included methodologists with expertise in evidence appraisal and guideline development and 2 patient representatives. Both patient representatives participated in question prioritization, and 1 participated in all remaining steps of the development process. The panel chair was a content expert. The vice chair was a urological surgeon with specialized expertise in guideline development.

In addition to synthesizing evidence systematically, the McMaster GRADE Centre supported the guideline-development process, including determining methods, preparing agendas and meeting materials, and facilitating panel discussions. The panel's work was done using Web-based tools (www.surveymonkey.com and www.gradeapro.org) and face-to-face and online meetings.

Guideline funding and management of conflicts of interest

Development of these guidelines was wholly funded by ASH, a nonprofit medical specialty society that represents hematologists. Some members of the guideline panel were members of ASH. ASH staff supported panel appointments and coordinated meetings but had no role in choosing the guideline questions or determining the recommendations.

Members of the guideline panel received travel reimbursement for attendance at in-person meetings. The patient representative (C.B.) received an honorarium of \$200. The panelists received no other payments. Some researchers who contributed to the systematic evidence reviews received salary or grant support through the McMaster GRADE Centre. Other researchers participated to fulfill requirements of an academic degree or program.

Conflicts of interest of all participants were managed according to ASH policies based on recommendations of the Institute of Medicine¹⁷ and the Guidelines International Network.⁴ At the time of appointment, a majority of the guideline panel, including the chair and the vice chair, had no conflicts of interest as defined and judged by ASH (ie, no current material interest in any commercial entity with a product that could be affected by the guidelines). Some panelists disclosed new interests or relationships during the development process, but the majority continued to have no conflicts of interest with commercial entities, as judged by ASH.

Before appointment to the panel, individuals disclosed financial and nonfinancial interests. Members of the VTE Guideline Coordination Panel reviewed the disclosures and judged which interests were conflicts and should be managed. Supplement 2 provides the complete "Disclosure of Interests" forms of all panel members. In Part A of the forms, individuals disclosed material interests for 2 years prior to appointment. In Part B, they disclosed other interests that were not mainly financial. Part C summarizes ASH decisions about which interests were judged to be conflicts. Part D describes new interests disclosed by individuals after appointment.

Recusal was used to manage conflicts of interest. During deliberations, panel members with a current direct financial interest in a commercial entity with any product that could be affected by the guidelines participated in discussions about the evidence and clinical context but were recused from making judgments or voting about individual domains (eg, magnitude of desirable consequences) and the direction and strength of relevant recommendations.^{4,18-20} The Evidence-to-Decision (EtD) framework for each recommendation describes which individuals were recused from making judgments about each recommendation.

None of the McMaster-affiliated researchers who contributed to the systematic evidence reviews or who supported the guideline-development process had any current material interest in a commercial entity with any product that could be affected by the

guidelines. Supplement 3 provides the complete "Disclosure of Interest" forms of researchers who contributed to these guidelines.

Formulating specific clinical questions and determining outcomes of interest

The panel used the GRADEpro Guideline Development Tool (www.gradeapro.org) and SurveyMonkey (www.surveymonkey.com) to brainstorm and then prioritize the questions described in Table 1.

The panel selected outcomes of interest for each question a priori, following an approach described in detail elsewhere.²¹ The panel rated the following outcomes as critical for clinical decision making across all questions: mortality, symptomatic PEs, symptomatic proximal DVTs, symptomatic severe distal DVTs, major bleeding, and reoperation. The panel used an explicit process to rate the clinical severity of DVTs and PEs. The panel determined that all symptomatic proximal DVTs and PEs confirmed by objective diagnostic imaging were considered of moderate severity and were clinically important.²² For several outcomes, the studies reported outcomes that were different or were in addition to the outcomes that the panel determined to be important for decision making. Typically, included studies reported outcomes as any PE, any DVT, or any proximal or distal DVT. Some studies did not distinguish asymptomatic thromboembolic events that were detected by the routine performance of sensitive screening studies for VTEs from symptomatic thromboembolic events where patients developed overt symptoms that were subsequently confirmed by objective testing to be associated with VTEs. Reporting of symptomatic thromboembolic events was inconsistent across studies.

Where available, questions were addressed with studies that reported symptomatic outcome events. In the absence of reports of symptomatic VTE in a clinical question, modeling was performed using estimates of the proportion of asymptomatic DVTs that would become clinically important symptomatic events (Supplement 4). Only "severe" distal DVTs were rated as clinically important distal DVTs, and it was estimated that only ~25% of symptomatic postoperative distal DVTs would be considered severe.

Major bleeding definitions varied across clinical studies. For the purposes of this analysis, outcome events that met the definition of major bleeding for individual studies were applied. The exception was that the need for a blood transfusion itself was not considered major bleeding unless other criteria for major bleeding were met. The definition of reoperation was not specific for reoperation caused by or related to major bleeding.

Studies evaluated included patients with cancer and without cancer. We tested potential differences in the effects on studies with >50% and <50% of participants with cancer. Subgroup analyses did not demonstrate a difference in the relative effectiveness of interventions whether cancer patients were included or not. As a result, recommendations do not distinguish between cancer and noncancer patients.

For the use of pharmacological and mechanical methods of prophylaxis, the panel advises to follow manufacturer's recommendations regarding patient-specific restrictions in the use of individual products (such as levels of renal function for patients receiving LMWHs or DOACs). The panel also advises periodic monitoring of the platelet count for patients receiving LMWH and, in particular, UFH, as postoperative prophylaxis in consideration of the risk of heparin-induced thrombocytopenia.

Table 1. Prioritized clinical questions

Perioperative VTE prophylaxis in major surgery in general
1. Pharmacological prophylaxis vs mechanical prophylaxis
2. Mechanical prophylaxis vs no prophylaxis
3. Pneumatic compression devices vs graduated compression stockings
4. Pharmacological prophylaxis combined with mechanical prophylaxis vs pharmacological prophylaxis alone
5. Mechanical prophylaxis combined with pharmacological prophylaxis vs mechanical prophylaxis alone
6. Insertion of an IVC filter vs no IVC filter
7. Extended antithrombotic prophylaxis vs short-term antithrombotic prophylaxis
8. Early vs delayed antithrombotic prophylaxis
Orthopedic surgery: total hip and knee arthroplasty
9. ASA prophylaxis vs anticoagulants
10. DOAC prophylaxis vs LMWH prophylaxis
11. DOAC prophylaxis vs prophylaxis with another DOAC
12. LMWH prophylaxis vs warfarin prophylaxis
13. LMWH prophylaxis vs UFH prophylaxis
Orthopedic surgery: hip fracture repair
14. Pharmacological prophylaxis vs no pharmacological prophylaxis
15. LMWH prophylaxis vs UFH prophylaxis
Major general surgery
16. Pharmacological prophylaxis vs no pharmacological prophylaxis
17. LMWH prophylaxis vs UFH prophylaxis
Laparoscopic cholecystectomy
18. Pharmacological prophylaxis vs no pharmacological prophylaxis
Major neurosurgical procedures
19. Pharmacological prophylaxis vs no pharmacological prophylaxis
20. LMWH prophylaxis vs UFH prophylaxis
TURP
21. Pharmacological prophylaxis vs no pharmacological prophylaxis
22. LMWH prophylaxis vs UFH prophylaxis
Radical prostatectomy
23. Pharmacological prophylaxis vs no pharmacological prophylaxis
24. LMWH prophylaxis vs UFH prophylaxis
Cardiac or major vascular surgery
25. Pharmacological prophylaxis vs no pharmacological prophylaxis
26. LMWH prophylaxis vs UFH prophylaxis
Major trauma
27. Pharmacological prophylaxis vs no pharmacological prophylaxis
28. LMWH prophylaxis vs UFH prophylaxis
Major gynecological surgery
29. Pharmacological prophylaxis vs no pharmacological prophylaxis
30. LMWH prophylaxis vs UFH prophylaxis

Evidence review and development of recommendations

For each guideline question, the McMaster GRADE Centre prepared a GRADE EtD framework, using the GRADEpro Guideline Development Tool (www.gradepr.org).^{12,13,16} The EtD table summarized the results of systematic reviews of the literature that were updated or performed

for this guideline. The EtD table addressed effects of interventions, resource utilization (cost-effectiveness), values and preferences (relative importance of outcomes), equity, acceptability, and feasibility. The guideline panel reviewed draft EtD tables before, during, or after the guideline panel meeting and made suggestions for corrections and identified missing evidence. To ensure that recent studies were not missed, searches (Supplement 5) were updated during October and November 2016, and panel members were asked to suggest any studies that may have been considered missed and fulfilled the inclusion criteria for the individual questions. Monthly search alerts were created and monitored to capture relevant new studies up to 1 July 2019, prior to submission of the manuscript for publication.

Under the direction of the McMaster GRADE Centre, researchers followed the general methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions (handbook.cochrane.org) for conducting updated or new systematic reviews of intervention effects. When existing reviews were used, judgments of the original authors about risk of bias were randomly checked for accuracy and accepted or conducted de novo if they were not available or not reproducible. For new reviews, risk of bias was assessed at the health outcome level using the Cochrane Collaboration's risk of bias tool for randomized trials or nonrandomized studies. In addition to conducting systematic reviews of intervention effects, the researchers searched for evidence related to baseline risks, values, preferences, and costs and summarized findings within the EtD frameworks.^{12,13,16} Subsequently, the certainty in the body of evidence (also known as quality of the evidence or confidence in the estimated effects) was assessed for each effect estimate of the outcomes of interest following the GRADE approach based on the following domains: risk of bias, precision, consistency and magnitude of the estimates of effects, directness of the evidence, risk of publication bias, presence of large effects, dose-response relationship, and an assessment of the effect of residual, opposing confounding. The certainty was categorized into 4 levels ranging from very low to high.^{5,6,14}

During a 2-day in-person meeting, followed by online communication and conference calls, the panel developed clinical recommendations based on the evidence summarized in the EtD tables. For each recommendation, the panel took a population perspective and came to consensus on the following: the certainty in the evidence, the balance of benefits and harms of the compared management options, and the assumptions about the values and preferences associated with the decision. The guideline panel also explicitly took into account the extent of resource use associated with alternative management options. The panel agreed on the recommendations (including direction and strength), remarks, and qualifications by consensus or, in rare instances, by voting (an 80% majority was required for a strong recommendation), based on the balance of all desirable and undesirable consequences. In the event that consensus was not reached based on discussion, the recommendation was made based on a vote of the panel, with the results of such votes listed in the text following the recommendation. The final guidelines, including recommendations, were reviewed and approved by all members of the panel.

Interpretation of strong and conditional recommendations

The recommendations are labeled as "strong" or "conditional" according to the GRADE approach. The words "the guideline panel recommends" are used for strong recommendations, and "the guideline panel suggests" is used for conditional recommendations.

Table 2. Interpretation of strong and conditional recommendations

Implications for:	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.
Clinicians	Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients; clinicians must help each patient arrive at a management decision consistent with the patient's values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences.
Policy makers	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Policy making will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision making is appropriate.
Researchers	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendations.	The recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help to identify possible research gaps.

Table 2 provides the suggested interpretation of strong and conditional recommendations by patients, clinicians, and health care policy makers.

Document review

Draft recommendations were reviewed by all members of the panel, revised, and then made available online on 22 June 2018 for external review by stakeholders, including allied organizations, other medical professionals, patients, and the public. Sixteen individuals or organizations submitted comments. The document was revised to address pertinent comments, but no changes were made to the recommendations. The guidelines were reviewed by the ASH Guideline Oversight Subcommittee on 28 August 2019, approved by the Committee on Quality on 6 September 2019 and by the ASH officers on 13 September 2019, and then subjected to peer review.

How to use these guidelines

ASH guidelines are primarily intended to help clinicians make decisions about diagnostic and treatment alternatives. Other purposes are to inform policy, education, and advocacy and to state future research needs. They may also be used by patients. These guidelines are not intended to serve or be construed as a standard of care. Clinicians must make decisions on the basis of the clinical presentation of each individual patient, ideally through a shared process that considers the patient's values and preferences with respect to the anticipated outcomes of the chosen option. Decisions may be constrained by the realities of a specific clinical setting and local resources, including, but not limited to, institutional policies, time limitations, and availability of treatments. These guidelines may not include all appropriate methods of care for the clinical scenarios described. As science advances and new evidence becomes available, recommendations may become outdated. Following these guidelines cannot guarantee successful outcomes. ASH does not warrant or guarantee any products described in these guidelines.

Statements about the underlying values and preferences, as well as qualifying remarks accompanying each recommendation, are its integral parts and serve to facilitate more accurate interpretation. They should never be omitted when recommendations from these guidelines are quoted or translated. Implementation of the guidelines

will be facilitated by the related interactive forthcoming decision aids. The use of these guidelines is also facilitated by the links to the EtD frameworks and interactive summary-of-findings tables in each section.

Recommendations

Mechanical vs pharmacological prophylaxis for patients undergoing major surgery

Question: Should pharmacological prophylaxis vs mechanical prophylaxis be used for patients undergoing major surgery?

Recommendation 1

For patients undergoing major surgery, the ASH guideline panel suggests using pharmacological prophylaxis or mechanical prophylaxis (conditional recommendation based on low certainty in the evidence of effects ⊕⊕○○). **Remark:** For patients considered at high risk for bleeding, the balance of effects may favor mechanical methods over pharmacological prophylaxis.

Summary of the evidence. We identified 11 systematic reviews addressing, in part, this question.²³⁻³³ We identified 38 studies in this review that fulfilled our inclusion criteria and measured outcomes relevant to this context.³⁴⁻⁷² Our systematic search of randomized controlled trials (RCTs) identified 2 additional studies not included in previous systematic reviews and that fulfilled the inclusion criteria.^{70,72}

Fifteen studies reported the effect of the pharmacological prophylaxis compared with mechanical prophylaxis alone on risk of mortality.^{35,36,40,42,51,54,57,59-61,63-65,68,72} Thirteen studies reported the effect on the development of symptomatic PEs,^{35,37,39,43,45,62,64,67-72} and 17 studies reported the effect on the development on any PE.^{34,36,38,40,42,46,47,50,51,53,58,60,61,63,67,71,72} Six studies reported data on symptomatic DVTs,^{35,67,69-72} and 17 studies reported data on any proximal DVT.^{34,35,37,39,41,45,52,53,57,58,64,65,67,69-72} Four studies reported data on symptomatic distal DVTs,^{35,70-72} and 16 studies reported data on any distal DVT.^{34,35,37,39,40,45,52,53,57,58,63,64,66,67,71,72}

Eighteen studies reported the effect of pharmacological prophylaxis compared with mechanical prophylaxis alone on the risk of major bleeding,^{35-37,41,42,43,48,51,54,59-61,63-66,68,72} and 6 studies reported the effect on the risk of reoperation.^{37,42,46,48,54,72}

The EtD framework is available at <https://guidelines.gradeapro.org/profile/B57A59FE-FCA9-8C9A-8C8D-55089B4E8FB1>.

Benefits. The systematic review found that there may be no difference in mortality between pharmacological and mechanical prophylaxis (relative risk [RR], 0.92; 95% confidence interval [CI], 0.46-1.84; low certainty in the evidence of effects); this corresponds to 1 fewer (5 fewer to 7 more) death per 1000 patients. Similarly, irrespective of the baseline risk chosen, which was derived from a cohort study of 172 320 patients,⁷³ there may be no difference for symptomatic PEs (RR, 1.04; 95% CI, 0.36-2.96; low certainty in the evidence of effects), corresponding to 0 fewer events (2 fewer to 7 more). There is also likely little to no difference in symptomatic proximal DVTs (RR, 0.75; 95% CI, 0.11-5.32; moderate certainty in the evidence of effects); depending on the baseline risk of 1.6% or 2.6%,⁷³ this corresponds to anywhere from 4 fewer (15 fewer to 71 more) to 7 fewer (23 fewer to 113 more) events, respectively. For symptomatic distal DVTs, pharmacological prophylaxis likely results in a reduction in risk (RR, 0.16; 95% CI, 0.05-0.58; moderate certainty in the evidence of effects); however, this corresponds to a possibly small, and likely unimportant, reduction in symptomatic distal DVTs in absolute terms of 2 fewer (1-2 fewer) per 1000 patients, based on a baseline risk of 1.2% from observational data.⁷³

Harms and burden. Pharmacological prophylaxis likely leads to more major bleeding (RR, 2.87; 95% CI, 1.68-4.92; moderate certainty in the evidence of effects). This corresponds to a small absolute increase of 12 more (4-25 more) major bleeds per 1000 patients. Pharmacological prophylaxis probably results in no difference in reoperations (RR, 2.01; 95% CI, 0.29-14.05; low certainty in the evidence of effects), corresponding to 1 more (1 fewer to 19 more) per 1000 patients.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as low based on the lowest certainty in the evidence for the critical outcomes, downgrading twice for very serious imprecision.

Other EtD criteria and considerations. The panel determined that, on balance, neither approach was favored over the other for patients undergoing major surgery at low or moderate risk for major bleeding because of the low certainty in the evidence, as well as concerns about compliance with mechanical prophylaxis. For patients at high baseline risk for major bleeding, mechanical prophylaxis would more clearly be favored because of the incremental risk of bleeding with pharmacological prophylaxis. There was possibly important uncertainty or variability in how much affected individuals valued the main outcomes. The panel further judged the costs associated with pharmacological prophylaxis to be moderate based on very low certainty in the evidence about resource requirements. Cost-effectiveness probably favors mechanical prophylaxis. The panel did not account for potential risks of mechanical prophylaxis, including fall risk, risk of skin damage, and limitation in mobility. There would probably be no impact on health equity, and pharmacological and mechanical prophylaxis would be acceptable to stakeholders and probably feasible to implement.

The panel recognized that most of the evidence informing this recommendation came from the orthopedic literature (elective knee and hip arthroplasty).

Conclusions and research needs for this recommendation.

The guideline panel suggests using pharmacological prophylaxis or mechanical prophylaxis for patients undergoing major surgery, based on low certainty in the evidence of effects. For patients deemed at high risk for major bleeding (because of the nature of the surgical procedure), there is likely a net benefit in favor of mechanical prophylaxis.

The panel determined that it would be valuable to have further high-quality studies comparing these interventions outside of the orthopedic setting to confirm the generalizability of the results across surgical domains. The panel would also welcome high-quality studies to determine the effectiveness of mechanical prophylaxis administered outside the hospital setting. The panel identified the need for more and better studies on how patients value the various outcomes in the perioperative setting and to what degrees these values vary by patients as a future research priority.

Question: Should mechanical prophylaxis vs no prophylaxis be used for patients undergoing major surgery?

Recommendation 2

For patients undergoing major surgery who do not receive pharmacologic prophylaxis, the ASH guideline panel *suggests* using mechanical prophylaxis over no mechanical prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Summary of the evidence. We identified 5 systematic reviews addressing, in part, this question.^{24,25,27,28,30} We identified 25 studies in these reviews that fulfilled our inclusion criteria and measured outcomes relevant to this context.^{37,49,53,66,74-94} Our systematic search of RCTs did not identify any additional study that fulfilled the inclusion criteria.

Ten studies reported the effect of mechanical prophylaxis compared with no prophylaxis on risk of mortality.^{49,77,78,81,83-85,88,90,94} Nine studies reported the effect on the development of symptomatic PEs,^{37,76,78,81,83,84,86,88,92} and 5 studies reported the effect on any PE.^{53,77,85,86,93} No study reported data on symptomatic proximal or distal DVT, but 8 studies reported on any proximal DVT,^{37,78,79,82,84,85,92,93} and 7 studies reported on any distal DVT.^{37,77,79,82,85,92,93}

The EtD framework is available online at <https://guidelines.gradeapro.org/profile/61E7ADC1-4C91-8D58-9E3A-56BFEE3EAC20>.

Benefits. There may be no difference in mortality between mechanical prophylaxis and no prophylaxis (RR, 1.33; 95% CI, 0.71-2.51; low certainty in the evidence of effects); this corresponds to 6 more (5 fewer to 28 more) deaths per 1000 patients. There may be a small difference in symptomatic PEs (RR, 0.61; 95% CI, 0.27-1.40; low certainty in the evidence of effects) corresponding to 3 fewer (6 fewer to 3 more) symptomatic PEs per 1000 patients based on a baseline risk of 0.8% and 4 fewer (8 fewer to 4 more) per 1000 patients based on a baseline risk of 1.1% from observational data.⁷³ There may be no difference in symptomatic proximal DVTs (RR, 0.75; 95% CI, 0.35-1.61; very low certainty in the evidence of effects), but we are uncertain of this. The risk of symptomatic distal DVTs may be

reduced (RR, 0.66; 95% CI, 0.50-0.86; very low certainty in the evidence of effects), but we are uncertain of this.

Harms and burden. There were no relevant adverse events deemed critical for this comparison. The panel was unable to assess the relative effect of mechanical prophylaxis on potential hazards, such as falls or skin complications.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations, imprecision, and inconsistency.

Other EtD criteria and considerations. The panel determined that there was possibly important uncertainty or variability in how much affected individuals valued the main outcomes. They further judged that the balance between desirable and undesirable effects probably favors mechanical prophylaxis over no prophylaxis for patients at moderate or high risk for VTE but not patients at low risk for VTE. The panel judged the costs associated with mechanical prophylaxis to be moderate based on very low certainty in the evidence about resource requirements, with no available studies explicitly addressing this question. Cost-effectiveness probably favors mechanical prophylaxis. There would probably be no impact on health equity; mechanical prophylaxis would probably be acceptable to stakeholders and probably feasible to implement. The panel recognized that many patients considered at moderate to high risk for VTE would receive pharmacological prophylaxis in addition to mechanical methods. The guideline panel determined that there was very low certainty evidence for a net health benefit/harm for mechanical prophylaxis. Most of the evidence comes from orthopedics (elective hip and knee arthroplasty). In settings where intermittent pneumatic compression is not available, the use of stockings as mechanical prophylaxis is an acceptable and feasible option (see Recommendation 3).

Conclusions and research needs for this recommendation.

For patients undergoing major surgery and at risk for VTE, the ASH guideline panel suggests using mechanical prophylaxis over no mechanical prophylaxis, recognizing that the certainty in the evidence is very low for this recommendation.

The panel recognizes that there is a need for high-quality clinical trials using clinically relevant end points to improve the certainty of the evidence supporting this recommendation, particularly outside the orthopedic setting. However, this is likely a lower priority for research than studies evaluating mechanical prophylaxis in combination with pharmacological prophylaxis.

Question: Should pneumatic compression devices vs graduated compression stockings be used for patients undergoing major surgery?

Recommendation 3

For patients undergoing major surgery who receive mechanical prophylaxis, the ASH guideline panel *suggests* using intermittent compression devices over graduated compression stockings (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Summary of the evidence. We identified 6 systematic reviews addressing this question.^{25-28,31,32} We identified 11 studies in these reviews that fulfilled our inclusion criteria and measured outcomes relevant to this context.^{37,94-103} Our systematic search of RCTs did not identify any additional study that fulfilled the inclusion criteria.

Five studies reported the effect of pneumatic compression prophylaxis compared with graduated compression stockings prophylaxis on risk of mortality.^{94,96,97,101,102} Eight studies reported the effect on the development of symptomatic PEs,^{37,95-99,102,103} and 4 studies reported the effect on any PE.^{94,100,101,103} One study reported data on symptomatic proximal and symptomatic distal DVTs,⁹⁸ whereas 6 studies reported on any proximal DVT,^{37,94,96,98-100} and 5 studies reported on any distal DVT.^{37,94,96,98,100}

The EtD framework is available online at <https://guidelines.grade-pro.org/profile/1584FD2F-9CC6-9C59-8DF5-48F0045F1BE5>.

Benefits. There is no difference in mortality between pneumatic compression and graduated compression stockings prophylaxis (RR, 1.04; 95% CI, 0.16-6.63; low certainty in the evidence of effects); this corresponds to 2 more (41 fewer to 274 more) per 1000 patients. There may also be no difference in symptomatic PEs (RR, 0.56; 95% CI, 0.17-1.86; low certainty in the evidence of effects). The risk of symptomatic proximal DVTs may be reduced (RR, 0.48; 95% CI, 0.25-0.93, very low certainty in the evidence of effects), but we are uncertain of this finding. This benefit likely corresponds to 9 fewer (1-12 fewer) symptomatic proximal DVTs in 1000 patients with a baseline risk of 1.6% and 14 fewer (2-20 fewer) symptomatic proximal DVTs per 1000 patients based on a baseline risk of 2.6% from observational data.⁷³ The risk of distal DVT (RR, 0.55; 95% CI, 0.25-1.22, very low certainty in the evidence of effects) appears to be similar, but we are uncertain of this finding.

Harms and burden. There were no relevant adverse events deemed critical for this comparison. Potential harms included reduced mobility, and pneumatic compression prophylaxis may be uncomfortable. There is also a small risk for inappropriate use of pneumatic compression prophylaxis for some patients (eg, those with lower extremity fractures).

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations, imprecision, and inconsistency.

Other EtD criteria and considerations. The panel determined that there was possibly important uncertainty or variability in how much affected individuals valued the main outcomes. They further judged that the balance between desirable and undesirable effects probably favors pneumatic compression prophylaxis over graduated compression stockings prophylaxis. The panel was unable to assess the relative effect of pneumatic compression compared with that of graduated compression stockings on the risk of other hazards, such as falls or skin complications. These might be considered "unmeasured harms" of mechanical prophylaxis. The panel judged the costs associated with pneumatic compression prophylaxis to be moderate based on very low certainty in the evidence about resource requirements, with no available studies explicitly addressing this question. Cost-effectiveness probably favors pneumatic compression prophylaxis. There would probably be no impact on health equity; pneumatic compression prophylaxis would probably

be acceptable to stakeholders and probably feasible to implement. Lack of information regarding out-of-hospital use of pneumatic compression was a limitation of this technique. The panel recognizes that most of the evidence about the effectiveness comes from orthopedics (elective hip and knee arthroplasty).

Conclusions and research needs for this recommendation.

The panel suggests using pneumatic compression devices over graduated compression stockings for patients undergoing major surgery, recognizing that there was very low certainty evidence for a net health benefit/harm. The recommendation applies to patients undergoing major surgery who are considered at risk for VTE.

In settings where pneumatic compression devices are not available, the use of graduated compression stockings is reasonable, because mechanical prophylaxis is an acceptable and feasible option. Further well-designed studies using clinically relevant end points are required to improve the quality of evidence related to this question. Studies outside the field of orthopedics would be particularly useful.

Question: Should combined pharmacological and mechanical prophylaxis vs pharmacological prophylaxis alone be used for patients undergoing major surgery?

Recommendation 4

For patients undergoing major surgery who receive pharmacologic prophylaxis, the ASH guideline panel *suggests* using combined prophylaxis with mechanical and pharmacological methods over prophylaxis with pharmacological agents alone (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○). **Remark:** For patients considered at high risk for VTE, combined prophylaxis is particularly favored over mechanical or pharmacological prophylaxis alone.

Summary of the evidence. We identified 7 systematic reviews addressing this question.^{23-26,28,29,31-33} We identified 19 studies in these reviews that fulfilled our inclusion criteria and measured outcomes relevant to this context.^{36,60,62,68,70,104-117} Our systematic search of RCTs did not identify any additional study that fulfilled the inclusion criteria.

Seven studies reported the effect of the combination of pharmacological and mechanical prophylaxis compared with pharmacological prophylaxis alone on the risk of mortality.^{36,60,62,68,104,105,107} Ten studies reported the effect on the development of symptomatic PEs,^{60,62,68,70,105,107,109-111,117} and 6 studies reported the effect on any PE.^{36,104,108,112,116,117} Three studies reported data on symptomatic proximal DVTs,^{62,70,112} and 8 studies reported data on any proximal DVT.^{62,70,104,108,112-114} Three studies reported data on symptomatic distal DVTs,^{70,105,112} and 7 studies reported on any distal DVT.^{68,105,108,109,112-114} Six studies reported the effect of combination pharmacological and mechanical prophylaxis compared with pharmacological prophylaxis alone on the risk of major bleeding,^{60,62,68,104,109,112} and 2 studies reported the effect on the risk of reoperation.^{107,117}

The EtD framework is available online at <https://guidelines.gradepro.org/profile/9AC669C6-30BB-C8DF-8430-3EDA0D4842C8>.

Benefits. There may be no difference in mortality between pharmacological prophylaxis combined with mechanical prophylaxis and pharmacological prophylaxis alone (RR, 0.29; 95% CI,

0.06-1.38; low certainty in the evidence of effects); this corresponds to 5 fewer (7 fewer to 3 more) deaths per 1000 patients. There may be a reduction in symptomatic PEs (RR, 0.40; 95% CI, 0.25-0.65; low certainty in the evidence of effects) favoring combined prophylaxis. Depending on the baseline risk, this benefit likely corresponds to 5 fewer (3-6 fewer) per 1000 patients with a baseline risk of 0.8% to up to 7 fewer (4-8 fewer) per 1000 patients based on a baseline risk of 1.2% from observational data.⁷³ We are very uncertain whether the risks of symptomatic proximal DVTs (RR, 0.14; 95% CI, 0.01-2.63; very low certainty in the evidence of effects) and symptomatic distal DVTs (RR, 1.99; 95% CI, 0.35-11.33; very low certainty in the evidence of effects) differ between the 2 groups.

Harms and burden. Rates of major bleeding may be similar (RR, 1.05; 95% CI, 0.32-3.40; low certainty in the evidence of effects), corresponding to 0 fewer (5 fewer to 17 more) events per 1000 patients. We were unable to estimate the RR of major reoperation given that there were no events in either group in the 2 included trials.^{107,117}

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations and imprecision.

Other EtD criteria and considerations. The panel determined that there was possibly important uncertainty or variability in how much affected individuals valued the main outcomes. They further judged that the balance between desirable and undesirable effects probably favors combined pharmacological and mechanical prophylaxis over pharmacological prophylaxis alone. The panel was unable to assess the impact of adding mechanical prophylaxis on the risk of other outcomes, such as falls or skin complications. These might be considered “unmeasured harms” of mechanical prophylaxis. The panel judged the costs associated with combined prophylaxis to be moderate based on very low certainty in the evidence about resource requirements. Cost-effectiveness probably favors combined pharmacological and mechanical prophylaxis. There would probably be no impact on health equity; combined pharmacological and mechanical prophylaxis would probably be acceptable to stakeholders and probably feasible to implement. The panel determined that there was very low certainty evidence for a net health benefit/harm for combined pharmacological and mechanical prophylaxis over pharmacological prophylaxis alone. Most of the evidence evaluating this question comes from the orthopedic (joint arthroplasty) setting.

Conclusions and research needs for this recommendation.

The guideline panel suggests using combined pharmacological and mechanical prophylaxis over pharmacological prophylaxis alone for patients undergoing major surgery, based on very low certainty in the evidence of effects. The panel judged that combined pharmacological and mechanical prophylaxis would be most beneficial for patients considered at very high risk for VTE following major surgery.

Further high-quality research studies using clinically important outcomes comparing combination pharmacological and mechanical methods with pharmacological methods alone are required to provide greater certainty about this recommendation. Studies addressing this question outside the orthopedic setting are most needed.

Question: Should mechanical prophylaxis combined with pharmacological prophylaxis vs mechanical prophylaxis alone be used for patients undergoing major surgery?

Recommendation 5

For patients undergoing major surgery, the ASH guideline panel *suggests* using combined mechanical and pharmacological prophylaxis or mechanical prophylaxis alone, depending on the risk of VTE and bleeding based on the individual patient and the type of surgical procedure (conditional recommendation based on low certainty in the evidence of effects ⊕⊕○○).

Remark: For patients considered at high risk for VTE, combined prophylaxis is particularly favored over mechanical or pharmacological prophylaxis alone.

Summary of the evidence. We identified 7 systematic reviews addressing, in part, this question.^{23-26,29,32,33} We identified 19 studies in these reviews that fulfilled our inclusion criteria and measured outcomes relevant to this context.^{36,60,62,68,118-132} Our systematic search of RCTs identified 5 additional studies that fulfilled the inclusion criteria.^{70,72,133-136}

Fourteen studies reported the effect of combined mechanical and pharmacological prophylaxis compared with mechanical prophylaxis alone on the risk of mortality.^{36,60,62,68,120,121,124,125,127,128,130,133,134,136}

Sixteen studies reported the effect on the development of symptomatic PEs,^{60,62,70,120-131,134} and 11 studies reported on the effect on any PEs.^{36,118,120,121,126,128,130,131,133,135,136} Six studies reported data on symptomatic DVTs,^{62,70,120,127,128,131} and 10 studies reported data on any proximal DVT.^{62,70,120-122,124,125,127,128,130}

Five studies reported data on symptomatic distal DVTs,^{70,120,127,128,131} and 14 studies reported on any distal DVT.^{118,120-122,124,125,127,128,130}

Fifteen studies reported the effect of combined mechanical and pharmacological prophylaxis on the risk of major bleeding,^{60,62,68,118,119,121,123-125,127,128,130,134-136} and 4 studies reported the effect on the risk of reoperation.^{118,125,134,135}

The EtD framework is available online at <https://guidelines.gradeapro.org/profile/75138F44-7AFE-A008-A8BD-10DD1DFD5377>.

Benefits. There is likely no difference in mortality between combined prophylaxis and mechanical prophylaxis alone (RR, 1.24; 95% CI, 0.67-2.30; moderate certainty in the evidence of effects), corresponding to 3 more (4 fewer to 17 more) deaths per 1000 patients. There is likely a reduction in symptomatic PEs (RR, 0.34; 95% CI, 0.13-0.90; moderate certainty in the evidence of effects) favoring combined prophylaxis. Depending on the baseline risk, assumed to be 0.8% or 1.1% based on a large observational study,⁷³ this benefit likely corresponds to 5 fewer (1-7 fewer) per 1000 patients in a lower-risk population to 7 fewer (1-10 fewer) per 1000 patients in a higher-risk population. The risk of symptomatic proximal DVT (RR, 0.71; 95% CI, 0.07-6.75; low certainty in the evidence of effects) and symptomatic distal DVT (RR, 0.38; 95% CI, 0.06-2.42; low certainty in the evidence of effects) may be similar between the 2 interventions, irrespective of the baseline risk group.

Harms and burden. Combined prophylaxis likely results in a small increased risk for major bleeding (RR, 2.23; 95% CI, 1.09-4.57; moderate certainty in the evidence of effects). This likely corresponds to 14 more (1-42 more) per 1000 patients. Rates of

major reoperation may be similar (RR, 2.96; 95% CI, 0.73-12.05; low certainty in the evidence of effects) between the 2 interventions, corresponding to 4 more (1 fewer to 21 more) per 1000 patients.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations and imprecision.

Other EtD criteria and considerations. The panel judged that the balance between desirable and undesirable effects does not favor combined pharmacological and mechanical prophylaxis vs mechanical prophylaxis alone. Instead, the balance between desirable and undesirable effects will depend upon the risk of VTE and bleeding based on the individual patient and the type of surgical procedure. The panel judged the costs associated with combined prophylaxis to be moderate based on very low certainty in the evidence about resource requirements. The panel determined that there was possibly important uncertainty or variability in how much affected individuals valued the main outcomes. Cost-effectiveness varies based on the underlying VTE and bleeding risk categories. There would probably be no impact on health equity, and combined prophylaxis and mechanical prophylaxis alone would be acceptable to stakeholders and probably feasible to implement.

Conclusions and research needs for this recommendation.

The guideline panel suggests using combined mechanical and pharmacological prophylaxis or mechanical prophylaxis alone for patients undergoing major surgery (based on low certainty in the evidence of effects). The balance of effects was considered dependent upon the risk of VTE and bleeding. Therefore, it is important to establish the baseline risk for VTE and major bleeding in surgical patients. For patients considered at high thrombosis risk and low bleeding risk, combined mechanical and pharmacological prophylaxis should be considered. For patients at high bleeding risk, mechanical prophylaxis methods alone may be preferred.

Further high-quality research studies using clinically important outcomes to identify patients with high baseline risk for VTE in whom combined pharmacological and mechanical prophylaxis would be of value, particularly outside the orthopedic setting, are needed.

Prophylactic insertion of an IVC filter. *Question: Should insertion of an IVC filter vs no IVC filter be used for VTE prophylaxis for patients undergoing major surgery?*

Recommendation 6

For patients undergoing major surgery, the ASH guideline panel *suggests against* using IVC filters for prophylaxis of VTE (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Summary of the evidence. We identified 2 systematic reviews of RCTs and observational studies^{137,138} that addressed this research question in bariatric surgery and trauma patients. We identified 14 studies¹³⁹⁻¹⁵² in these reviews that fulfilled our inclusion criteria and measured outcomes relevant to this context. Our search for RCTs and observational studies identified 1 additional study that fulfilled the inclusion criteria.¹⁵³ Additionally, we identified 1 systematic review of RCTs and

observational studies that was published after our initial literature search, which did not include any new study not already included in our meta-analysis.¹⁵⁴ We also identified 1 RCT published in July 2019, evaluating the use of IVC filters for patients experiencing trauma.¹⁵⁵ Although we did not update the meta-analysis, the trial results were assessed by the panel as consistent with the recommendation.

Of the 15 studies included in the meta-analysis, 1 was an RCT.¹⁵⁰ Twelve of the studies reported the effect of IVC filters on the risk of mortality.^{139,143-147,149-153} Five studies assessed the development of symptomatic PEs,^{142,149,150,152,153} and 10 studies assessed the development of any PE.^{139-141,143-148,151} Ten studies assessed the development of DVTs,^{139,141,143,144,146-148,150,151,153} with 1 study assessing the development of symptomatic DVTs specifically¹⁴¹ and 1 study assessing the development of proximal DVTs specifically.¹⁵³

The EtD framework is available online at <https://guidelines.grade-pro.org/profile/4885EDB9-B445-5554-BD62-CFE2EED6D08E>.

Benefits. IVC filter use may increase mortality slightly (RR, 1.38; 95% CI, 0.81-2.37; very low certainty in the evidence of effects), although the confidence interval was wide and included the possibility of no increase. Overall, we are very uncertain of this finding. Based on the control group event rate of 1.1% in this meta-analysis, this would correspond to 4 more deaths (2 fewer to 15 more) per 1000 patients receiving an IVC filter following major surgery or trauma. IVC filters may reduce the risk of symptomatic PE following major surgery and trauma (RR, 0.29; 95% CI, 0.11-0.80; very low in the evidence of effects), but we are very uncertain about this finding. Based on a baseline risk of 0.8% from observational data,⁷³ this corresponds to 6 fewer (2-7 fewer) symptomatic PEs. Based on a higher baseline risk of 1.1%,⁷³ this could result in 8 fewer PEs (2-10 fewer) per 1000 patients receiving an IVC filter; however, this is very uncertain. Rates of symptomatic proximal DVT may be increased with use of IVC filters (RR, 2.19; 95% CI, 1.07-4.50; very low certainty in the evidence of effects), but we are once again very uncertain of this finding. This corresponds to 20 more (1-58 more) or 31 more (2-92 more) per 1000 patients, based on baseline risks of 1.6% and 2.6%, respectively, from observational data.⁷³ We are also uncertain whether rates of symptomatic distal DVT are increased (RR, 2.72; 95% CI, 1.41-5.21; very low certainty in the evidence of effects), corresponding to 2 more (1-6 more) to 4 more (1-9 more) per 1000 patients, based on baseline risks of 0.1% and 0.2%, respectively, from observational data.⁷³

Harms and burden. The panel did not consider potential harms of IVC filters beyond VTE. These potential harms would include potentially severe complications, such as IVC perforation and IVC filter embolization.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations, inconsistency, and indirectness.

Other EtD criteria and considerations. The panel determined that there was possibly important uncertainty or variability in how much affected individuals might value the main outcomes. They judged that the balance between desirable and undesirable effects favored not using IVC filters in the setting of major surgery or trauma. The panel judged from our analysis of data, largely from

observational studies, that the high rates of DVT and the trend for higher mortality associated with the use of IVC filters outweighed the potential reduction in PEs. Furthermore, a recently published high-quality RCT of IVC filters, following major trauma for patients in whom pharmacological prophylaxis was considered contraindicated, did not find that IVC filters reduced symptomatic PE or death.¹⁵⁵ Given there are serious nonthrombotic risks associated with IVC filters (eg, IVC perforation and IVC filter embolization) that were not considered in our analysis, this would further strengthen our recommendation against IVC filter use.¹⁵⁶

The panel also recognized that the cost of IVC filters and resources associated with their insertion were large. The panel concluded that routine use of IVC filters following major surgery or trauma was probably not cost-effective and favored not placing a filter. Because of the increased resources required, high costs, and limited availability of interventional radiology units, health equity would probably be reduced by use of IVC filters. Routine use of IVC filters might also not be acceptable or feasible to implement for some stakeholders.

Conclusions and research needs for this recommendation.

The panel suggests against using IVC filters for prophylaxis of VTE for patients undergoing major surgery or trauma patients based upon very low certainty in the evidence. The very low quality evidence underlying this recommendation supports the need for well-designed RCTs evaluating clinically important outcomes to better define the role of IVC filters for patients who cannot safely or feasibly receive pharmacological or mechanical prophylaxis following major surgery or trauma. Further studies quantifying the nonthrombotic risks of IVC filters would also be of value.

Timing of antithrombotic prophylaxis

Question: Should extended antithrombotic prophylaxis vs short-term antithrombotic prophylaxis be used for patients undergoing major surgery?

Recommendation 7

For patients undergoing major surgery, the ASH guideline panel *suggests* using extended antithrombotic prophylaxis over short-term antithrombotic prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○). **Remark:** Extended prophylaxis was generally considered as beyond 3 weeks (range: 19-42 days), and short-term prophylaxis was considered as up to 2 weeks (range: 4-14 days).

Summary of the evidence. We identified 9 systematic reviews addressing this research question.¹⁵⁷⁻¹⁶⁵ We identified 14 studies¹⁶⁶⁻¹⁷⁹ in these reviews that fulfilled our inclusion criteria and measured outcomes relevant to this context. Our systematic search of RCTs identified 6 additional studies¹⁸⁰⁻¹⁸⁵ not included in previous systematic reviews that fulfilled the inclusion criteria.

Seventeen studies reported the effect of extended vs short-term duration of pharmacological thromboprophylaxis on the development of mortality,^{166,167,170-173,175-185} 17 studies reported the effect on the development of PEs,^{166,167,170-184} 18 studies reported the effect on the development of proximal DVTs,^{166-173,175-184}

14 studies reported the effect on the development of distal DVTs,^{166,169,171-173,175,177-184} 16 studies reported the effect on the risk of major bleeding,^{167-173,177-185} and 6 studies reported the effect on the risk of reoperation.^{166,173,174,179,184,185} In general, these studies compared shorter courses of pharmacological prophylaxis (4-14 days) with extended courses of pharmacological prophylaxis (19-42 days) and then followed patients for a common period (3-9 months) for VTE and bleeding complications.

The EtD framework is available online at <https://guidelines.gradeapro.org/profile/79bce70d-c689-4fbf-b0e4-c2ec3142bb2c>.

Benefits. There is likely no difference in mortality between extended- and standard-course antithrombotic prophylaxis (RR, 0.94; 95% CI, 0.64-1.39; moderate certainty in the evidence of effects); this corresponds to 1 fewer death (6 fewer to 6 more) per 1000 patients. There is likely a small reduction in symptomatic PEs (RR, 0.44; 95% CI, 0.22-0.85; moderate certainty in the evidence of effects). Depending on baseline risk,⁷³ this corresponds to 4 fewer (1-6 fewer) deaths per 1000 patients with a baseline risk of 0.8% and 6 fewer (2-9 fewer) deaths per 1000 patients with a baseline risk of 1.1% receiving extended pharmacological prophylaxis. Symptomatic proximal DVTs are also likely reduced (RR, 0.30; 95% CI, 0.21-0.42; moderate certainty in the evidence of effects). Depending upon the baseline risk,⁷³ this corresponds to 12 fewer (10-13 fewer) symptomatic proximal DVTs per 1000 patients in a lower-risk group of patients with a 1.6% baseline risk or 18 fewer (15-21 fewer) per 1000 patients in a higher-risk group with a 2.6% baseline risk. Extended pharmacological prophylaxis likely reduces distal DVTs (RR, 0.57; 95% CI, 0.37-0.87; moderate certainty in the evidence of effects), which corresponds to 1 fewer (0-1 fewer) symptomatic distal DVT per 1000 patients based on a 0.1% baseline risk from observational data.⁷³

Harms and burden. Rates of major bleeding may be similar (RR, 1.00; 95% CI, 0.59-1.70; low certainty in the evidence of effects), corresponding to 0 fewer (3 fewer to 6 more) per 1000 patients. Rates of reoperation may also be similar (RR, 0.82; 95% CI, 0.34-1.99; very low certainty in the evidence of effects), but we are very uncertain about this finding.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations and very serious imprecision.

Other EtD criteria and considerations. The panel determined that there was possibly important uncertainty or variability in how much affected individuals valued the main outcomes. They further judged that the balance between desirable and undesirable effects probably favors extended-duration vs standard-duration prophylaxis. The panel judged the costs associated with extended-duration prophylaxis to be moderate based on very low certainty in the evidence. Cost-effectiveness probably favors extended-duration prophylaxis. Health equity is possibly reduced with extended-duration prophylaxis, with economically disadvantaged patients potentially being unable to afford the required medications or medication copayments. Extended-duration prophylaxis would probably be acceptable to stakeholders and probably feasible to implement. The panel recognized that most of the trials compared a prolonged prophylaxis (up to 42 days, or ~6 weeks following surgery) with a

short duration of anticoagulant prophylaxis designed to approximate the length of a postoperative hospital stay (~4-14 days) in the eras in which the studies were performed. Furthermore, the panel recognized that these studies were largely limited to 2 high-risk surgical scenarios (total hip or knee arthroplasty and major cancer general surgical procedures).

Conclusions and research needs for this recommendation.

The guideline panel determined that the net benefit favored using extended-course antithrombotic prophylaxis over short-term antithrombotic prophylaxis for patients undergoing major surgery based on very low certainty evidence. Given the very low certainty in the evidence of effects this is based upon, there is a critical need for higher-quality studies comparing extended vs short-term prophylaxis using clinically important outcomes in contemporary surgical practices, which are marked by early patient mobilization and shorter hospital stays. There is particularly a need for studies outside the general hip and knee arthroplasty and cancer general surgical settings to confirm the benefits of extended prophylaxis in other settings. There also appears to be a need for further research to determine the optimal duration of extended prophylaxis.

Question: Should early vs delayed antithrombotic prophylaxis be used for patients undergoing major surgery?

Recommendation 8

For patients undergoing major surgery, the ASH guideline panel suggests using early or delayed antithrombotic prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○). **Remark:** Twelve hours following surgery was arbitrarily selected to be the cutoff point between early and late postoperative antithrombotic administration.

Summary of the evidence. We did not find any systematic reviews that addressed this question. In our systematic search of the literature we found 6 studies that fulfilled our inclusion criteria and measured outcomes relevant to this context.¹⁸⁶⁻¹⁹¹ We cross-referenced the studies found in our search with the references from a recent narrative review¹⁹² but did not identify any additional studies that fulfilled our inclusion criteria. All studies included surgical patients. Twelve hours was selected to be the cutoff point between early and late postsurgical antithrombotic administration. Six studies¹⁸⁶⁻¹⁹¹ reported the effect of early vs late postsurgical antithrombotic administration on the risk of mortality and on the risk of development of any PEs. Five studies^{186,188-191} reported the effect on the risk of any proximal and any distal DVTs, and 1 reported the effect on the risk of any DVT.¹⁸⁷ Only the 5 studies that specified the location of the DVT were included in the evidence profile. Six studies¹⁸⁶⁻¹⁹¹ reported the effect of early vs late postsurgical antithrombotic administration on the risk of major bleeding and on the risk of reoperation.

The EtD framework is available online at <https://guidelines.gradeapro.org/profile/E664E38D-FA7C-DBC9-8E77-373D0582050E>.

Benefits. Early prophylaxis may result in no difference in mortality (RR, 1.57; 95% CI, 0.77-3.19; very low certainty in the evidence of effects), but we are very uncertain about this finding. This corresponds to 1 more (1 fewer to 6 more) per 1000 patients. We are uncertain about the effect of early prophylaxis on

symptomatic PEs (RR, 0.63; 95% CI, 0.23-1.72; very low certainty in the evidence of effects); depending on the baseline risk from observational data,⁷³ this corresponds to 3 fewer (6 fewer to 6 more) to 4 fewer (8 fewer to 8 more) per 1000 patients with baseline risks of 0.8% and 1.1%, respectively. We are also uncertain of the effect of early prophylaxis on symptomatic proximal DVTs (RR, 0.88; 95% CI, 0.40-1.96; very low certainty in the evidence of effects), corresponding to 2 fewer (10 fewer to 16 more) to 3 fewer (16 fewer to 25 more) per 1000 patients when applying baseline risks of 1.6% and 2.6%, respectively.⁷³ Early prophylaxis has an uncertain effect on distal DVTs (RR, 0.68; 95% CI, 0.41-1.12; very low certainty in the evidence of effects), with an absolute risk reduction from 0 fewer (0-1 fewer; baseline risk, 0.1%⁷³) to 1 fewer (0-1 fewer; baseline risk, 0.2%⁷³) symptomatic distal DVT per 1000 patients.

Harms and burden. The risk of major bleeding may be similar (RR, 1.63; 95% CI, 0.81-3.29; very low certainty in the evidence of effects), corresponding to 5 fewer (1 fewer to 17 more), although we are very uncertain of this finding. Also, the need for reoperation may be increased (RR, 1.84; 95% CI, 0.89-3.80; very low certainty in the evidence of effects) corresponding to 2 more reoperations (0 fewer to 6 more) per 1000 patients. Once again, we are very uncertain about this finding.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes and downgrading for study limitations, indirectness, and imprecision.

Other EtD criteria and considerations. Based on very low certainty in the evidence of effects, the panel judged that the balance of effects did not favor early or delayed institution of pharmacological antithrombotic prophylaxis in major surgical patients. Costs and saving would likely be negligible, and the panel saw no particular issues related to equity, acceptability, or feasibility.

Conclusions and research needs for this recommendation.

The guideline panel suggests early administration (postoperative, within 12 hours) or late administration (postoperative, after 12 hours) of antithrombotic prophylaxis in major surgical patients, based on very low certainty in the evidence of effects. In light of the very low certainty in the evidence of effects, further high-quality studies using clinically important outcomes are important to provide greater certainty about the benefits and risks of early pharmacological prophylaxis. The panel was particularly interested in seeing future high-quality studies of early vs late pharmacological prophylaxis studies in high-risk bleeding patients, examining the benefits and risks of later intervention (days following surgery) once the bleeding risk had greatly subsided.

Orthopedic surgery

Question: Should ASA vs anticoagulants be used for patients undergoing total hip or knee arthroplasty?

Recommendation 9

For patients undergoing total hip arthroplasty or total knee arthroplasty, the ASH guideline panel suggests using ASA or anticoagulants (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Summary of the evidence. We found 7 RCTs that compared the use of ASA vs anticoagulants for patients undergoing total hip arthroplasty or total knee arthroplasty.¹⁹³⁻¹⁹⁹ Additionally, we identified 2 trials comparing ASA with LMWH in total hip arthroplasty patients²⁰⁰ and ASA with DOAC in total hip arthroplasty or total knee arthroplasty patients,²⁰¹ in which all participants received a 10-day period of LMWH or a 5-day period of DOACs, respectively, prior to randomization. The trials were reviewed by the panel but were not included in the main meta-analysis because of differences in the comparator groups. Of the 7 studies included in the analysis, 2 studies compared ASA with UFH,^{193,195} 4 studies compared ASA with LMWH,^{194,196,198,199} and 2 studies compared ASA with oral anticoagulants.^{197,199} All 7 studies reported the outcomes of mortality and PE,¹⁹³⁻¹⁹⁹ 6 studies reported on proximal and distal DVTs,¹⁹⁵⁻¹⁹⁹ and 5 studies reported on major bleeding.^{194-196,198,199} We found no studies addressing the outcome of reoperation.

The EtD framework is available online at <https://guidelines.gradepro.org/profile/3532ED1D-6A40-A982-BC3F-6DA318B3B611>.

Benefits. There may be no difference in mortality between ASA and anticoagulants (RR, 2.32; 95% CI, 0.15-36.90; low certainty in the evidence of effects). There also may be no difference in the risk of symptomatic PEs between ASA and anticoagulants (RR, 1.49; 95% CI, 0.37-6.09; very low certainty in the evidence of effects), corresponding to 3 more (4 fewer to 29 more) symptomatic PEs per 1000 patients based on a baseline risks of 0.6%^{202,203} from observational data; however, we are very uncertain of this finding. There also may be no difference in the risk of proximal DVTs (RR, 1.49; 95% CI, 0.51-4.34; very low certainty in the evidence of effects), corresponding to 3 more symptomatic (3 fewer to 30 more) proximal DVTs per 1000 patients based on a baseline risk of 0.6%,^{202,203} or in the risk of distal DVTs (RR, 1.45; 95% CI, 0.86-2.46; very low certainty in the evidence of effects), corresponding to 0 fewer symptomatic distal DVTs (0 fewer to 1 more) per 1000 patients based on a baseline risk of 0.05%,^{202,203} although we were very uncertain about both findings.

Harms and burden. ASA may lead to a small increased risk for major bleeding (RR, 2.63; 95% CI, 0.64-10.79; low certainty in the evidence of effects). These findings correspond to 6 more (1 fewer to 35 more) major bleeding events per 1000 patients. We found no evidence to inform the comparative risk of reoperation.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations, indirectness, and imprecision.

Other EtD criteria and considerations. The panel determined that there was probably important uncertainty or variability in how much affected individuals value the main outcomes. It further judged that use of ASA saved costs and resources; however, the results of cost-effectiveness studies varied, with some favoring ASA and others favoring anticoagulant prophylaxis. Health equity would probably be increased as a consequence of the use of ASA. Acceptability was thought to also vary depending on the type of stakeholder (patient vs health care provider). There were no concerns about the feasibility of implementation. A recent large RCT supports our recommendation that ASA or anticoagulants be used for VTE prophylaxis following total hip or knee arthroplasty. However, this study was not included in our analysis

because all patients received a 5-day course of a DOAC before being randomized to ASA or to stay on a DOAC for extended prophylaxis.²⁰¹

Conclusions and research needs for this recommendation.

The guideline panel suggests using ASA or anticoagulants for patients undergoing total hip arthroplasty or total knee arthroplasty (conditional recommendation based on very low certainty in the evidence of effects). They determined that there was very low certainty evidence for any net health benefit/harm from using ASA vs anticoagulants. Of 8 panel members who voted on this recommendation, 5 voted for recommending either intervention, and 3 voted for a conditional recommendation in favor of anticoagulants.

The panel identified that there is a need for large well-designed clinical trials using clinically important end points comparing ASA with other pharmacological methods following total hip and knee arthroplasty. The panel noted that such studies are underway.

Question: Should DOACs vs LMWH be used for patients undergoing total hip or knee arthroplasty?

Recommendation 10

For patients undergoing total hip arthroplasty or total knee arthroplasty in which anticoagulants are used, the ASH guideline panel *suggests* using DOACs over LMWH (conditional recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕○).

Summary of the evidence. We identified 1 systematic review²⁰⁴ that addressed this question. Twenty-two studies in this review fulfilled our inclusion criteria. Our update of the systematic review identified 16 additional studies. All studies included patients undergoing elective hip or knee replacement.

Five studies assessed the effects of dabigatran,^{191,205-208} 15 studies assessed the effects of rivaroxaban,^{180,185,189,190,199,209-218} 4 studies assessed the effects of apixaban,²¹⁹⁻²²² 5 studies assessed the effects of darexaban²²³⁻²²⁶ and edoxaban,²²⁷⁻²³¹ and 4 studies assessed the effects of other DOACs.²³²⁻²³⁵

Thirty-four studies reported mortality,^{180,185,189-191,199,205-215,218-222,224-231,233-235} whereas 33 studies reported nonfatal PEs.^{180,185,189-191,199,205-212,214-216,219-222,224-231,233-235} We estimated proximal and distal DVTs using the pooled estimate from symptomatic DVTs, which was reported in 30 studies.^{185,189-191,199,205-212,214-216,219-222,224-230,234,235} Thirty-two studies reported major bleeding,^{180,185,189-191,205-212,214,215,219-222,224-235} whereas only 15 studies reported bleeding leading to reoperation.^{180,185,189-191,205-207,209-212,215,220,221}

We tested potential differences in the effects with specific drugs and between classes (anti-factor IIa vs anti-factor Xa). We found no interaction for any of the outcomes. Additionally, we conducted a sensitivity analysis excluding dose-finding studies. The results did not change appreciably.

The EtD framework is available online at <https://guidelines.gradepr.org/profile/9160FAA2-4F98-A3AA-9816-64DF796ABBC7>.

Benefits. DOACs probably do not reduce mortality compared with that associated with LMWH (RR, 0.94; 95% CI, 0.53-1.66;

moderate certainty in the evidence of effects); this corresponds to 0 fewer deaths (1 fewer to 1 more) per 1000 patients. DOACs probably slightly reduce the rate of symptomatic PEs (RR, 0.74; 95% CI, 0.50-1.10; moderate certainty in the evidence of effects); based on a baseline risk of 0.6% from observational data,^{202,203} this corresponds to 1 fewer (3 fewer to 1 more) symptomatic PE per 1000 patients. The use of DOACs reduces symptomatic proximal DVTs slightly (RR, 0.56; 95% CI, 0.39-0.79; high certainty in the evidence of effects), which corresponds to 3 fewer (1-4 fewer) symptomatic proximal DVTs per 1000 patients, based on a baseline risk of 0.6% from observational data.^{202,203} This effect on symptomatic distal DVTs is probably not clinically relevant (RR, 0.56; 95% CI, 0.39-0.79; high certainty in the evidence of effects), which corresponds to 0 fewer symptomatic distal DVTs per 1000 patients based on a baseline risk of 0.049%, from observational data.^{202,203}

Harms and burden. DOACs probably do not increase major bleeding compared with LMWH (RR, 1.03; 95% CI, 0.79-1.35; moderate certainty in the evidence of effects), which corresponds to 0 fewer major bleeding events (2 fewer to 4 more) per 1000 patients. Similarly, rates of reoperation may not be meaningfully increased (RR, 1.43; 95% CI, 0.75-2.71; moderate certainty in the evidence of effects) given the low event rates; this corresponds to 0 fewer reoperations (0 fewer to 2 more) per 1000 patients.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as moderate based on the lowest certainty in the evidence for the critical outcomes, downgrading for imprecision.

Other EtD criteria and considerations. The panel judged the desirable and undesirable effects as being small and trivial, respectively, in magnitude. Cost-effectiveness was judged to probably favor the use of DOACs. Similarly, equity, acceptability, and feasibility each favored the use of DOACs and contributed to the recommendation in their favor. Use of out-of-hospital prophylaxis, which is routine following total hip or knee arthroplasty, particularly favored DOACs over LMWH, given the need for parenteral administration of the latter agent.

Conclusions and research needs for this recommendation.

The guideline panel suggests using DOACs rather than LMWH for patients undergoing total hip or knee arthroplasty. Based on an overall moderate certainty in the evidence of effects, the panel judged the balance of effects to probably favor the use of DOACs over LMWH. The ultimate judgment of a conditional recommendation for DOACs was based on anonymous voting by panel members without direct financial conflicts, with a majority of 5 voting for this recommendation (vs 4 in favor of a recommendation for using either). The panel recommended a need for large clinical trials using clinically relevant end points comparing different DOACs. Further studies regarding the optimal timing of the initiation of postoperative dosing of DOACs are warranted.

Question: Should 1 DOAC vs another DOAC be used for patients undergoing total hip or knee arthroplasty?

Recommendation 11

For patients undergoing surgery, the ASH guideline panel *suggests* using any of the DOACs approved for use (conditional recommendation based on low certainty in the evidence of effects ⊕⊕○○).

Summary of the evidence. We found no study that compared different classes of DOACs or individual DOACs of the same class head to head. Therefore, we used the body of evidence comparing DOAC prophylaxis vs LMWH (see recommendation 10) as the basis for an indirect assessment of their relative effectiveness.

The EtD framework is available online at <https://guidelines.gradepro.org/profile/16A3927F-FB2D-C278-9FE5-D4535020FE27>.

Benefits. In the absence of comparative trials of different classes of DOACs (anti-factor IIa vs anti-factor Xa) or individual DOACs of the same class, we tested potential differences by analyzing potential subgroup effects. Based on the tests for interaction, we did not demonstrate any evidence for a clinically relevant subgroup effect for any of the potentially desirable outcomes. Based on this finding, the panel assumed that the beneficial effects were likely similar for different DOACs.

Harms and burden. Similarly, based on tests for interaction, we did not find any evidence for a clinically relevant subgroup effect for any of the potentially undesirable outcomes. Based on this finding, the panel assumed that the undesirable effects were likely similar for different DOACs.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as low based on the lowest certainty in the evidence for the critical outcomes, downgrading for indirectness and imprecision.

Other EtD criteria and considerations. Based on these findings, the panel judged that the balance of effects did not favor any particular DOAC over another. The panel also judged that issues surrounding cost-effectiveness, equity, acceptability, and feasibility also did not weigh in sufficiently to favor 1 DOAC over another.

Conclusions and research needs for this recommendation. Based on overall low certainty in the evidence of effects, the panel judged that there were no net benefits in favor of any DOAC vs another. Given the lack of direct comparative evidence, the panel identified an important need for high-quality head-to-head studies comparing different DOACs for the prevention of VTEs following total hip or knee arthroplasty.

Question: Should LMWH vs warfarin be used for patients undergoing total hip or knee arthroplasty?

Recommendation 12

For patients undergoing total hip arthroplasty or total knee arthroplasty, if a DOAC is not used, the ASH guideline panel suggests using LMWH rather than warfarin (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Summary of the evidence. We identified 1 systematic review that addressed this question.²³⁶ We identified 7 trials in this review that fulfilled our inclusion criteria and measured outcomes relevant to this context.^{39,219,237-241} Our systematic search of RCTs did not identify any additional study that fulfilled the inclusion criteria. Three studies were conducted with patients undergoing total hip arthroplasty,^{39,239,241} 3 studies were conducted with patients undergoing total knee arthroplasty,^{219,237,240} and 1 study addressed

both populations.²³⁸ Five studies^{219,237-240} reported the effect of LMWH compared with warfarin on mortality, 5 studies reported the effect on the development of symptomatic PEs,^{39,219,237,238,240} 6 studies reported on any proximal DVT,^{219,237-241} and 2 studies reported on any distal DVT.^{237,241} All 7 studies reported the effect on the risk of major bleeding,^{39,219,237-241} and 2 studies reported on the risk of reoperation.^{237,241}

The EtD framework is available online at <https://guidelines.gradepro.org/profile/BC1783C1-D62B-AECB-B9F7-87A9D474A834>.

Benefits. LMWH may result in little or no difference in mortality compared with warfarin (RR, 0.51; 95% CI, 0.14-1.88; low certainty in the evidence of effects). LMWH likely does not reduce symptomatic PEs (RR, 0.83; 0.27-2.54; moderate certainty in the evidence of effects). LMWH may reduce symptomatic proximal DVTs (RR, 0.61; 95% CI, 0.36-1.02; very low certainty in the evidence of effects) and symptomatic distal DVTs (RR, 0.61; 95% CI, 0.42-0.88; low certainty in the evidence of effects). This corresponds to 2 fewer (0-4 fewer) symptomatic proximal DVTs and 0 fewer symptomatic distal DVTs with the use of LMWH than with warfarin for 1000 patients treated, based on baseline risks of 0.6% and 0.049%, respectively, from observational data.^{202,203}

Harms and burden. LMWH use likely results in increased major bleeding compared with the use of warfarin (RR, 1.81; 95% CI, 1.31-2.50; moderate certainty in the evidence of effects). This corresponded to 16 more (5-22 more) major bleeds per 1000 patients. There was no difference with regard to reoperation rates between those receiving LMWH or warfarin (RR, 3.09; 95% CI, 0.13-75.48; moderate certainty in the evidence of effects), which corresponded to 0 more events per 1000 patients.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations and very serious imprecision.

Other EtD criteria and considerations. The panel judged that there was possibly important uncertainty or variability in how much people value the main outcomes. The balance between desirable and undesirable effects probably favored LMWH. Resources requirements of warfarin were deemed moderate, particularly with regard to the need for, and the complexity of, anticoagulant monitoring, but cost-effectiveness data probably did not favor warfarin or LMWH. There probably would be no impact on health equity; both agents appear acceptable to stakeholders and are feasible to implement.

Conclusions and research needs for this recommendation.

The guideline panel suggests using LMWH rather than warfarin for patients undergoing total hip arthroplasty or total knee arthroplasty. The guideline panel determined that there was very low certainty evidence for a net health benefit/harm from using LMWH rather than warfarin. Based on the body of available evidence, it is likely that warfarin reduces the risk of major bleeding based on evidence of moderate certainty. However, it may also increase the risk of proximal DVTs, based on very low quality evidence.

Further high-quality studies using clinically important outcomes would be of value to improve the certainty in the recommendation. However, given the availability of DOACs as oral agents that do not require anticoagulant monitoring or dose adjustment, further

clinical trials using warfarin are not regarded as a high priority at this time.

Question: Should LMWH vs UFH be used for patients undergoing total hip or knee arthroplasty?

Recommendation 13

For patients undergoing total hip arthroplasty or total knee arthroplasty, if a DOAC is not used, the ASH guideline panel *suggests* using LMWH rather than UFH (strong recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕○).

Summary of the evidence. We identified 1 systematic review that addressed this question.²³⁶ We identified 12 trials in this review that fulfilled our inclusion criteria and measured outcomes relevant to this context.²⁴²⁻²⁵³ Our systematic search of RCTs did not identify any additional study that fulfilled the inclusion criteria. Ten trials were performed on patients undergoing total hip arthroplasty,^{242-244,246,247,249-253} and 2 trials were conducted on patients undergoing total knee arthroplasty.^{245,248} Five trials reported the effect of LMWH compared with UFH on mortality,^{244,247,249,251,252} 10 studies reported the effect on the development of symptomatic PEs,^{242-245,247-249,251-253} 8 studies reported the effect on any proximal DVT,^{242,244-249,251} and 6 studies reported the effect on any distal DVT.^{242,244-249,251} Six studies reported the effect on the risk of major bleeding,^{244,245,249-251,253} and 2 studies reported the effect on the risk of reoperation.^{247,248}

The EtD framework is available online at <https://guidelines.gradepr.org/profile/06FDBFB0-4D4E-E0D0-AEAD-C8B371DFA939>.

Benefits. LMWH results in little or no difference in mortality compared with UFH (RR, 0.26; 95% CI, 0.03-2.36; high certainty in the evidence of effects), which corresponded to 3 fewer (4 fewer to 5 more) deaths per 1000 patients. LMWH probably reduces the risk of symptomatic PEs slightly (RR, 0.37; 95% CI, 0.19-0.71; moderate certainty in the evidence of effects). This corresponds to 4 fewer (2-5 fewer) symptomatic PEs per 1000 patients, based on a baseline risk of 0.6% from observational data.^{202,203} LMWH also likely reduces the risk of symptomatic proximal DVTs (RR, 0.48; 95% CI, 0.34-0.69; moderate certainty in the evidence of effects), corresponding to 3 fewer (2-4 fewer) per 1000 patients, based on a baseline risk of 0.6% from observational data.^{202,203} LMWH appears to result in little or no difference in symptomatic distal DVTs (RR, 1.18; 95% CI, 0.81-1.72; low certainty in the evidence of effects), with very small corresponding absolute effect size estimates based on a baseline risk of 0.049% from observational data.^{202,203}

Harms and burden. LMWH likely results in a small decrease in the risk of major bleeding (RR, 0.55; 95% CI, 0.27-1.13; moderate certainty in the evidence of effects); this corresponds to 19 fewer (30 fewer to 5 more) major bleeds per 1000 patients. We were unable to estimate an effect on the risk of reoperation given that the included studies reported no events for this outcome.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as moderate based on the lowest certainty in the evidence for the critical outcomes, downgrading for imprecision.

Other EtD criteria and considerations. The panel determined that there was probably important uncertainty or variability in how much affected individuals value the main outcomes. Cost-effectiveness likely differs by country but probably favors LMWH. The panel assessed that this recommendation probably would have no impact on health equity and would be acceptable to stakeholders. LMWH is already widely used, and the panel had no concern about the feasibility of implementation.

Conclusions and research needs for this recommendation.

The guideline panel recommends LMWH rather than UFH for patients undergoing total hip arthroplasty or total knee arthroplasty.

The guideline panel determined that there is moderate certainty evidence for a net health benefit/harm from using LMWH over UFH. Future large studies using clinically relevant end points would help to better inform this recommendation, although this research question would not be regarded as high priority.

Question: Should pharmacological prophylaxis vs no pharmacological prophylaxis be used for patients undergoing hip fracture repair?

Recommendation 14

For patients undergoing hip fracture repair, the ASH guideline panel *suggests* using pharmacological prophylaxis over no pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Summary of the evidence. We identified 1 systematic review²⁵⁴ that addressed, in part, this question. We identified 5 studies in this review that fulfilled our inclusion criteria and measured outcomes relevant to this context.²⁵⁵⁻²⁵⁹ Our systematic search of RCTs identified 7 additional studies that fulfilled the inclusion criteria.²⁶⁰⁻²⁶⁶ Nine studies reported the effect of pharmacological prophylaxis compared with no intervention on risk of mortality.^{255,256,258,259,261-265} Nine studies reported the effect on development of any PEs,^{255-259,261,264-266} and 5 studies reported the effect of any proximal DVT and any distal DVT.^{257,260,261,263,265} Eleven studies reported the effect of pharmacological prophylaxis compared with no intervention on risk of major bleeding,^{255,256,258-266} and 3 studies reported the effect on risk of reoperation.^{258,261,266}

We tested potential differences in the effects with ASA and anti-coagulant prophylaxis and performed a subgroup analysis. The analysis indicated no subgroup effect with regard to desirable and undesirable effects comparing ASA with anticoagulant prophylaxis. As a result, in this analysis, studies with ASA are pooled with those of anticoagulant prophylaxis compared with no pharmacological prophylaxis.

The EtD framework is available online at <https://guidelines.gradepr.org/profile/A10CDC06-B411-D572-959A-A8405E1373A1>.

Benefits. Pharmacological prophylaxis appears to result in little or no difference in mortality (RR, 0.95; 95% CI, 0.84-1.07; very low certainty in the evidence of effects), although we are very uncertain about this finding. This would correspond to 4 fewer deaths (11 fewer to 5 more) per 1000 patients based on a baseline risk of 7.1% from the control group event rate in the meta-analysis.

Pharmacological prophylaxis may reduce symptomatic PEs (RR, 0.49; 95% CI, 0.33-0.72; very low certainty in the evidence of effects), but we are very uncertain of this finding. This corresponds to 6 fewer (3-7 fewer) events per 1000 patients based on a baseline risk of 1.1% from the control group event rate in the meta-analysis. Based on lower baseline risk of 0.3% from observational data,²⁶⁷ this would correspond to 2 fewer (1-2 fewer) symptomatic PEs per 1000 patients. Pharmacological prophylaxis may reduce symptomatic proximal DVTs (RR, 0.51; 95% CI, 0.38-0.69; very low certainty in the evidence of effects), but we are very uncertain of this finding. In a moderate-risk population with a baseline risk of 2.5%,²⁶⁷ this corresponds to 12 fewer (8-16 fewer) per 1000 patients. Pharmacological prophylaxis likely has little or no effect on symptomatic distal DVTs (RR, 0.85; 95% CI, 0.56-1.29; very low certainty in the evidence of effects), but once again we are very uncertain of this finding.

Harms and burden. Pharmacological prophylaxis may increase major bleeding (RR, 1.24; 95% CI, 1.12-1.37; low certainty in the evidence of effects). Depending on baseline risk, this corresponds to 1 more (1-2 more) major bleed per 1000 patients in a lower-risk population (baseline risk of 0.5% from observational data)²⁶⁷ or as many as 20 more (10-31 more) per 1000 patients in a higher-risk population (baseline risk of 8% from the control group event rate in the meta-analysis). Pharmacological prophylaxis appears to have little or no effect on the need for reoperation (RR, 1.05; 95% CI, 0.82-1.35; very low certainty in the evidence of effects); however, we are very uncertain of this finding.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations, indirectness, and very serious imprecision.

Other EtD criteria and considerations. The panel judged the magnitude of the desirable effects as moderate in size and the undesirable effects as small in size. There was possibly important uncertainty or variability about how patients may value these outcomes. There would probably be no impact on equity, and the panel foresaw no issues with regard to acceptability and feasibility of using pharmacological prophylaxis in this patient population.

Conclusions and research needs for this recommendation. Although the overall certainty in the evidence of effects was very low, the panel judged that the balance of effects probably favored the use of pharmacological prophylaxis for VTE prophylaxis following hip fracture repair. Given the overall very low certainty in the evidence, the panel indicated that there remains an important need for large high-quality RCTs using clinically important end points to determine the optimal role of ASA or anticoagulant pharmacological prophylaxis in this patient population. However, higher priority would be comparative studies of different antithrombotic regimens for the prevention of VTEs in these patients requiring repair of hip fracture.

Question: Should LMWH prophylaxis vs UFH prophylaxis be used for patients undergoing hip fracture repair?

Recommendation 15

For patients undergoing hip fracture repair, the ASH guideline panel *suggests* using LMWH or UFH (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Summary of the evidence. We identified 1 systematic review²⁵⁴ that addressed this question. We identified 3 studies in this review that fulfilled our inclusion criteria and measured outcomes relevant to this context.²⁶⁸⁻²⁷⁰ Our update of the systematic review did not identify any additional study that fulfilled the inclusion criteria. Two studies reported the effect of LMWH prophylaxis compared with UFH prophylaxis on risk of mortality, as well as any proximal and distal DVTs,^{268,269} and 3 studies reported the effect on any PEs and major bleeding.²⁶⁸⁻²⁷⁰ No information on reoperation rates was available in any of the included studies.

The EtD framework is available online at <https://guidelines.gradepro.org/profile/80C377E5-E3C0-36CD-B646-C2532AB4D4B9>.

Benefits. LMWH appears to result in little or no difference in mortality compared with UFH prophylaxis following hip fracture repair (RR, 0.47; 95% CI, 0.10-2.12; very low certainty in the evidence of effects), although we are very uncertain about the effect. Assuming a baseline risk of 7.4% for UFH-treated patients, this would correspond to 39 fewer (66 fewer to 88 more) deaths per 1000 patients. We are very uncertain about the effect of LMWH on symptomatic PEs (RR, 2.13; 95% CI, 0.06-81.3; very low certainty in the evidence of effect). LMWH may result in a small, possibly unimportant, increase in symptomatic proximal DVTs (RR, 2.24; 95% CI, 0.92-5.43; low certainty in the evidence of effect) corresponding to 31 more (2 fewer to 111 more) per 1000 patients based on a baseline risk of 2.5% from observational data.²⁶⁷ LMWH appears to result in little or no difference in symptomatic distal DVTs (RR, 0.66; 95% CI, 0.21-2.17; very low certainty in the evidence of effects).

Harms and burden. LMWH appears to result in little or no difference in major bleeding compared with UFH after hip fracture surgery (RR, 0.85; 95% CI, 0.19-3.79; very low certainty in the evidence of effects). This corresponds to 9 fewer (50 fewer to 173 more) major bleeds per 1000 moderate-risk patients with a baseline risk of 6.2% based on a lower baseline risk of 0.5% from observational data²⁶⁷; the corresponding absolute risk reduction would be 1 fewer (4 fewer to 14 more) per 1000 patients. No comparative information is available regarding the risks of reoperation following hip fracture with the use of LMWH or UFH.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations, indirectness, and very serious imprecision.

Other EtD criteria and considerations. The panel determined that there was possibly important uncertainty or variability in how much affected individuals valued the main outcomes. They further judged that the balance between desirable and undesirable effects did not favor LMWH or UFH following hip fracture repair. The panel recognized the very low certainty in comparative evidence, which was based on three small RCTs that did not report symptomatic DVT outcomes. The panel recognized that the comparative resources associated with LMWH and UFH prophylaxis were probably negligible. Cost-effectiveness was considered to favor LMWH based upon results of a single study.²⁷¹ Using LMWH or UFH would probably not impact health equity, and either drug was deemed to be probably acceptable to stakeholders and feasible to implement.

Conclusions and research needs for this recommendation. Taking into consideration the very low certainty in the evidence, the panel judged that LMWH or UFH prophylaxis could be

recommended following hip fracture repair. Large RCTs using clinically important outcomes are needed to better define the relative benefits and risks of LMWH compared with UFH following hip fracture surgery.

Major general surgery

Question: Should pharmacological prophylaxis vs no pharmacological prophylaxis be used for patients undergoing major general surgery?

Recommendation 16

For patients undergoing major general surgery, the ASH guideline panel *suggests* using pharmacological prophylaxis over no pharmacological prophylaxis (conditional recommendation based on low certainty in the evidence of effects ⊕⊕○○).

Summary of the evidence. We identified a systematic review of RCTs²⁷² addressing this research question. We identified 3 studies²⁷³⁻²⁷⁵ in this review that fulfilled our inclusion criteria and measured outcomes relevant to this context. Our systematic search for RCTs identified 32^{49,122,125,131,274,276-302} additional studies that fulfilled the inclusion criteria, including patients undergoing major general surgery. Sixteen studies^{122,125,274-278,284,285,291,293,296,297,299,300,302} reported the effect of pharmacological prophylaxis vs no pharmacological prophylaxis on the risk of mortality, and 11 studies^{125,273,276-279,285,286,289,293,295} reported the effect on the development of symptomatic PEs. Six studies^{49,125,278,285,287,290} reported the effect on development of screening-detected proximal DVTs, and 6 studies^{124,277,283,284,286,289} reported the effect on development of screening-detected distal DVTs.

Twelve studies^{125,273-276,282,285,287,293,295,297,298} reported the effect of pharmacological prophylaxis vs no pharmacological prophylaxis on risk of major bleeding, and 3 studies^{275,282,295} reported the effect on risk of reoperation.

The EtD framework is available online at <https://guidelines.gradepr.org/profile/3B5A5678-B1D9-4D60-8E1F-F3AD700132F8>.

Benefits. Pharmacological prophylaxis compared with no pharmacological prophylaxis probably reduces mortality (RR, 0.76; 95% CI, 0.61-0.93; moderate certainty in the evidence of effects). This finding corresponds to 4 fewer deaths (1-7 fewer) per 1000 patients undergoing major general surgery. Pharmacological prophylaxis probably also reduces symptomatic PEs (RR, 0.45; 95% CI, 0.23-0.88; moderate certainty in the evidence of effects). This corresponds to 4 fewer (1-6 fewer) pulmonary embolic events per 1000 patients undergoing major general surgery. Pharmacological prophylaxis may also reduce symptomatic proximal DVTs (RR, 0.38; 95% CI, 0.14-1.00; very low certainty in the evidence of effects), but we are very uncertain of this finding. This corresponds to 10 fewer (0-14 fewer) symptomatic proximal DVTs per 1000 patients based on a baseline risk of 1.6% from observational data.⁷³ It may reduce symptomatic distal DVTs (RR, 0.57; 95% CI, 0.36-0.90; low certainty in the evidence of effects), which corresponds to 1 fewer (0-1 fewer) symptomatic distal DVT per 1000 patients undergoing major general surgery based on a baseline risk of 1.6% from observational data.⁷³

Harms and burden. Pharmacological prophylaxis probably increases major bleeding (RR, 1.37; 95% CI, 0.89-2.13; moderate certainty in the evidence of effects). This corresponds to 10 more (3 fewer to 29 more) major bleeding events per 1000 patients undergoing major general surgery. Pharmacological prophylaxis results in little or no difference in reoperation (RR, 0.75; 95% CI, 0.21-2.77; low certainty in the evidence of effects).

Certainty in the evidence of effects. The overall certainty of the estimates of effects was based on the low certainty outcomes and was not based on the lowest certainty of evidence for the critical outcomes. In this case, the recommendation was sufficiently supported by the favorable impact on desirable effects for which there was higher quality evidence.

Other EtD criteria and considerations. The panel judged the desirable effects to be of moderate magnitude and the undesirable effects to be of small magnitude. They assumed that there was possibly important uncertainty or variability in patients' values. Pharmacological prophylaxis probably would incur moderate additional costs but was judged to be probably cost-effective. Pharmacological prophylaxis would probably have no impact on equity, was probably acceptable, and was likely feasible.

Conclusions and research needs for this recommendation.

The panel judged that the overall balance of effects favored pharmacological prophylaxis over no pharmacological prophylaxis for patients undergoing major general surgery based on low certainty in the evidence of effects. Further high-quality comparative studies, using appropriate clinical outcomes, would be of value to add more certainty to these recommendations. However, such studies would not be considered as high priority by the panel.

Question: Should LMWH prophylaxis vs UFH prophylaxis be used for patients undergoing major general surgery?

Recommendation 17

For patients undergoing major general surgery, the ASH guideline panel *suggests* using LMWH or UFH (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Summary of the evidence. We identified 2 systematic reviews of RCTs^{272,303} addressing this research question. We identified 40 studies³⁰⁴⁻³⁴³ in these reviews that fulfilled our inclusion criteria and measured outcomes relevant to this context. Our systematic search for RCTs identified 6 additional studies^{295,344-348} that fulfilled the inclusion criteria. Thirty studies reported the effect of LMWH vs UFH on risk of mortality.^{305,307,308,310-312,314,317-319,321,322,325-327,329-339,341,342,346,347} Thirty-one studies reported the effect of LMWH vs UFH on development of symptomatic PEs.^{295,305-306,310-312,314-319,321,322,324,326-335,337,339,344-346} 5 studies reported the effect on symptomatic proximal DVTs,^{306,316,326,334,336} and 7 reported the effect on symptomatic distal DVTs.^{306,316,326,329,334,336,341} Thirty-four studies reported the effect of LMWH vs UFH on risk of major bleeding,^{295,305-307,311,313,315-319,321-339,341,344-346} and 16 studies reported the effect on risk of reoperation.^{305,307,309,317,319,322,323,326,329,330,333-337,341}

The EtD framework is available online at <https://guidelines.gradepr.org/profile/EF7ADEAO-49F1-7E89-A0DB-DE7A9E854A2B>.

Benefits. Prophylaxis with LMWH vs UFH probably does not reduce mortality following major general surgery (RR, 1.03; 95% CI, 0.89-1.18; moderate certainty in the evidence of effects). We are very uncertain about the effect of LMWH on symptomatic PEs compared with that of UFH (RR, 0.83; 95% CI, 0.58-1.19; very low certainty in the evidence of effects), which corresponds to 1 fewer (3 fewer to 2 more) symptomatic PE per 1000 patients undergoing major general surgery based on a baseline risk of 0.8% from observational data.⁷³ It also appears to result in little or no difference in symptomatic proximal DVTs (RR, 1.01; 95% CI, 0.20-5.00; very low certainty in the evidence of effects) or a reduction in symptomatic distal DVTs (RR, 1.01; 95% CI, 0.30-3.44; very low certainty in the evidence of effects). We are very uncertain about the last 2 findings.

Harms and burden. Prophylaxis with LMWH vs UFH probably does not affect major bleeding (RR, 0.97; 95% CI, 0.78-1.20; moderate certainty in the evidence of effects). This corresponds to 0 fewer (3 fewer to 3 more) major bleeding events per 1000 patients undergoing major general surgery. LMWH probably results in little or no difference in reoperations (RR, 0.79; 95% CI, 0.57-1.08; moderate certainty in the evidence of effects), which corresponds to 3 fewer (6 fewer to 1 more) reoperations per 1000 patients undergoing major general surgery.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations and very serious inconsistency.

Other EtD criteria and considerations. There was possibly important uncertainty or variability in how patients valued the outcomes. Potential costs and savings were deemed of negligible relevance, assuming only in-hospital short-term prophylaxis. There was probably no impact on equity, because both LMWH and UFH were thought to be acceptable and feasible to implement. If extended prophylaxis beyond hospital discharge is planned, LMWH may be preferable given its once-daily dosing. The panel thought that both treatment options are already widely used and there should be few issues with implementation.

Conclusions and research needs for this recommendation. The guideline panel judged that the net benefit did not favor LMWH or UFH prophylaxis for patients undergoing major general surgery. Based on a very low overall certainty in the evidence, the panel determined that the balance of effects did not favor LMWH or UFH. In light of the very low certainty in the evidence, further high-quality comparative studies, using appropriate clinical outcomes, would be of value to add more certainty to this recommendation. However, such comparative studies are not regarded as high priority at this time.

Question: Should pharmacological prophylaxis vs no pharmacological prophylaxis be used for patients undergoing laparoscopic cholecystectomy?

Recommendation 18

For patients undergoing laparoscopic cholecystectomy, the ASH guideline panel *suggests against* using pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○). **Remark:** Patients with other risk factors for VTEs (eg, history of VTE, thrombophilia, or malignancy) may benefit from pharmacological prophylaxis.

Summary of the evidence. We identified 1 systematic review of RCTs addressing this research question.³⁰ We identified 2 studies^{118,349} in that review that fulfilled our inclusion criteria and measured outcomes relevant to this context. Because of the relative paucity of studies on patients undergoing laparoscopic cholecystectomy, data across major general, major gynecological, and major urological procedures were pooled, and laparoscopic cholecystectomy-specific baseline risk estimates were applied.³⁵⁰ Five studies^{66,294,301,351,352} were conducted on patients undergoing major gynecological surgery. Thirty-one^{49,122,125,131,275-279,281-293,295-300,302} studies were conducted on patients undergoing major general surgery. Two studies^{118,349} were conducted on patients undergoing laparoscopic cholecystectomy. Six studies^{38,280,353-356} were conducted on patients undergoing urological surgery. Eighteen studies^{122,125,274-278,284,285,291,293,296,297,299,300,302,353,354} reported the effect of pharmacological prophylaxis vs no pharmacological prophylaxis on risk of mortality, 16 studies^{38,118,125,273,276-279,285,286,289,293,295,354-356} reported the effect on risk of symptomatic PEs, 6 studies^{49,125,278,285,287,290} reported the effect on risk of screening-detected proximal DVTs, and 7 studies^{66,125,278,284,285,287,290} reported the effect on risk of screening-detected distal DVTs. Fifteen studies^{118,125,273-275,277,282,285,287,293,295,297,298,349,354} reported the effect of pharmacological prophylaxis vs no pharmacological prophylaxis on risk of major bleeding, and 6 studies^{38,118,275,282,295,354} reported the effect on risk of reoperation.

The EtD framework is available online at <https://guidelines.grade-pro.org/profile/E753AE97-D04A-D35F-ABE1-F9CAB9461DD1>.

Benefits. Pharmacological prophylaxis probably results in a small unimportant reduction in overall mortality (RR, 0.75; 95% CI, 0.61-0.93; low certainty in the evidence of effects). This corresponds to 2 fewer (0-2 fewer) deaths per 1000 patients based on a baseline risk of 0.6% from observational data.³⁵⁷ It may not reduce symptomatic PEs following laparoscopic cholecystectomy (RR, 0.48; 95% CI, 0.26-0.88; very low in the evidence of effects), but we are very uncertain of this finding. Given the very low baseline risk of VTE events in this specific patient population,³⁵⁰ this would be expected to result in 0 fewer (0 fewer to 0 more) symptomatic PEs per 1000 patients. Similarly, pharmacological prophylaxis may not reduce symptomatic proximal DVTs (RR, 0.38; 95% CI, 0.14-1.00; very low certainty in the evidence of effects) or symptomatic distal DVTs (RR, 0.52; 95% CI, 0.31-0.87; very low certainty in the evidence of effects). Again, given the very low baseline risks, this would correspond to 0 fewer (0 fewer to 0 more) events per 1000 patients for both outcomes. We are very uncertain about the effects on symptomatic proximal DVTs and symptomatic distal DVTs.

Harms and burden. Pharmacological prophylaxis may result in a small increase in major bleeding (RR, 1.24; 95% CI, 0.87-1.77; low certainty in the evidence of effects). This would be expected to result in 6 more (3 fewer to 20 more) major bleeds per 1000 patients. We are very uncertain whether pharmacological prophylaxis results in little or no difference in reoperation (RR, 0.93; 95% CI, 0.35-2.50; very low certainty in the evidence of effects); this corresponds to 1 fewer (8 fewer to 18 more) reoperation per 1000 patients.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest

certainty in the evidence for the critical outcomes, downgrading for study limitations, indirectness, and imprecision.

Other EtD criteria and considerations. The panel based this recommendation on the trivial incremental benefits and the small increased risk of major bleeding associated with pharmacological prophylaxis. The panel judged that the potential benefits of pharmacological prophylaxis were outweighed by the small increased risk of major bleeding in average-risk patients undergoing laparoscopic cholecystectomy. This relates to the very low baseline risk of VTE for patients undergoing laparoscopic cholecystectomy. The panel discounted the mortality difference observed in this analysis as unlikely to relate to pharmacological prophylaxis, given the very low baseline risk of VTE. Patients with other risk factors for VTE (eg, history of VTE, thrombophilia, or malignancy) may benefit from pharmacological prophylaxis.

Conclusions and research needs for this recommendation.

The guideline panel determined that potential undesirable effects of pharmacological prophylaxis, in particular major bleeding, outweighed its potential benefit for patients undergoing laparoscopic cholecystectomy. The panel acknowledges that the overall certainty in the evidence was low, in particular as a result of indirectness, with most of the trial data included in the analysis involving patients undergoing major surgical procedures. Further research into pharmacological prophylaxis following laparoscopic cholecystectomy was not regarded as high priority given the low baseline incidence of VTE complications in this patient population.

Major neurosurgical procedures

Question: Should pharmacological prophylaxis vs no pharmacological prophylaxis be used for patients undergoing major neurosurgical procedures?

Recommendation 19

For patients undergoing major neurosurgical procedures, the ASH guideline panel *suggests against* using pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○). **Remarks:** Patients undergoing major neurosurgical procedures are expected to receive prophylaxis with mechanical methods. Pharmacological prophylaxis may be warranted in a higher-risk subgroup of patients, such as those experiencing prolonged immobility following surgery. In addition, pharmacological prophylaxis could be considered for patients undergoing major neurosurgical procedures that carried a lower risk for major bleeding and in those patients with persistent mobility restrictions after the bleeding risk declines following surgery.

Summary of the evidence. We identified 1 systematic review³⁵⁸ that addressed this question. We identified 6 studies in this review that fulfilled our inclusion criteria and measured outcomes relevant to this context.^{68,123,128,359-361} Our update of the systematic review identified 1 additional study that fulfilled the inclusion criteria.¹³⁵ We additionally searched for and identified 3 nonrandomized studies that informed this question.³⁶²⁻³⁶⁴ All studies included patients undergoing neurosurgical procedures. Five studies assessed the effect of LMWH,^{68,128,130,135,362} 4 studies assessed the effect of UFH,^{359,361-363} 1 study assessed

the effect of warfarin,¹²⁴ and 1 study assessed the effect of heparin-dihydroergotamine.³⁶⁰ Additionally, across the 10 studies, mechanical prophylaxis was used as a cointervention in 6 of the randomized studies^{68,123,128,130,135,359} and in all 3 of the nonrandomized studies.³⁶¹⁻³⁶³ Supplement 6 presents the characteristics of all included studies.

Five RCTs^{68,104,128,130,359,362} and 2 nonrandomized studies^{361,363} reported the effect of any pharmacological thromboprophylaxis vs no pharmacological intervention on mortality, 3 RCTs^{123,128,360} and 2 nonrandomized studies reported on development of PEs,^{361,363} 2 RCTs reported on screening-detected proximal DVTs,^{128,130} and 1 study reported on development of screening-detected distal DVTs.¹²⁸ Seven RCTs^{68,123,128,130,135,359,360} and 3 nonrandomized studies³⁶¹⁻³⁶³ reported risk of major bleeding, and 2 RCTs reported on risk of reoperation.^{135,359}

The EtD framework is available online at <https://guidelines.grade-pro.org/profile/C5A1B92D-0E70-50BA-847C-0497617938F5>.

Benefits. Pharmacological prophylaxis does not appear to reduce mortality (RR, 1.27; 95% CI, 0.57-2.69; low certainty in the evidence of effects) when considering the body of evidence from RCTs, in which we have more confidence than the nonrandomized data. This corresponds to 9 more deaths (15 fewer to 65 more) per 1000 patients. Based on RCT evidence, pharmacological prophylaxis may result in little or no difference in symptomatic PEs (RR, 0.84; 95% CI, 0.03-27.42; very low certainty in the evidence of effects), but we are very uncertain of this finding. This corresponds to 0 fewer events (2 fewer to 53 more) per 1000 patients based on a baseline risk of 0.2% from observational data.³⁶⁴ The absolute effect size is similarly small when considering the body of evidence from nonrandomized trials. Pharmacological prophylaxis may result in a small, possibly unimportant, effect on symptomatic proximal DVTs (RR, 0.50; 95% CI, 0.30 to 0.84; low certainty in the evidence of effects) and symptomatic distal DVTs (RR, 0.60; 95% CI, 0.33-1.08; very low certainty in the evidence of effects). This would correspond to 6 fewer (2-8 fewer) symptomatic proximal DVTs and 0 fewer (0-1 fewer) symptomatic distal DVTs per 1000 patients undergoing major neurosurgical procedures, based on baseline risks from observational data of 1.2% and 0.1%, respectively.³⁶⁴

Harms and burden. From RCTs, pharmacological prophylaxis may increase major bleeding (RR, 1.57; 95% CI, 0.70-3.50; low certainty in the evidence of effects), corresponding to 10 more (5 fewer to 43 more) events per 1000 patients undergoing major neurosurgical procedures. We are very uncertain of the effect of pharmacological prophylaxis on reoperation (RR, 0.43; 95% CI, 0.06-2.84; very low certainty in the evidence of effects), which would correspond to 18 fewer (29 fewer to 57 more) reoperations per 1000 patients.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations and very serious imprecision.

Other EtD criteria and considerations. The panel noted that observed RR ratios from observational studies tended to view pharmacological prophylaxis more favorably than RCTs. The panel based its recommendation on RR ratios from meta-analysis of RCTs rather than observational studies, given the greater risk of bias with the latter studies. The panel noted that the small benefit of

pharmacological prophylaxis for the prevention of DVT was based upon randomized controlled studies using screening venography to detect rates of asymptomatic DVTs. The panel rated the harms of major bleeding associated with pharmacological prophylaxis as moderate because of the potential for greater morbidity associated with surgical site bleeding following these procedures. The panel recognized that patients undergoing major neurosurgical procedures would routinely receive prophylaxis with mechanical methods. The panel acknowledged that pharmacological prophylaxis might still be warranted in a higher-risk subgroup of patients, such as those experiencing prolonged immobility following surgery. In addition, the panel acknowledged that pharmacological prophylaxis could be considered for patients undergoing neurosurgical procedures that carried a lower risk for major bleeding. It may also be considered for patients with persistent mobility restrictions after the bleeding risk subsides following surgery.

Conclusions and research needs for this recommendation.

The panel judged, based on the available very low certainty evidence, that the expected net benefit favored no prophylaxis following major neurosurgical procedures, because the potential small benefit of reducing VTE events was outweighed by the potential moderate increased risk of major bleeding. The panel also recognized that mechanical methods of thromboprophylaxis are commonly used in this patient population. There is a great need for the performance of large RCTs evaluating pharmacological prophylaxis following major neurosurgical procedures, and using clinically important end points, to add certainty to this recommendation. The panel acknowledges that the current recommendation may not reflect standard practice in some centers.

Question: If pharmacological prophylaxis is indicated, should LMWH vs UFH be used for patients undergoing major neurosurgical procedures?

Recommendation 20

For the subset of patients undergoing major neurosurgical procedures for whom pharmacological prophylaxis is used, the ASH guideline panel *suggests* using LMWH over UFH (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Summary of the evidence. We identified 1 systematic review³⁵⁸ that addressed this question. We identified 4 studies in this review that fulfilled our inclusion criteria and measured outcomes relevant to this context.^{348,365-367} Our update of the systematic review identified 1 additional study that fulfilled the inclusion criteria.³⁶⁸ All studies included patients undergoing neurosurgical procedures. Five studies reported the effect of LMWH compared with that of UFH on development of mortality,^{348,365-368} 2 studies reported on the development of PEs,^{365,366} 1 study reported on the development of screening-detected proximal DVTs,³⁴⁸ and 1 study reported on screening-detected distal DVTs.³⁶⁶ Four studies reported risk of major bleeding^{348,365-367} and 1 study reported on risk of reoperation.³⁶⁶

All participants wore compression stockings, with the exception of 1 study in which their use was not reported.³⁶⁸

The EtD framework is available online at <https://guidelines.grade-pro.org/profile/E9D1EF22-EEC9-560E-A0CC-9FD435188BBE>.

Benefits. Pharmacological prophylaxis with LMWH may result in little to no difference in mortality compared with UFH (RR, 0.34; 95% CI, 0.04-3.21; low certainty in the evidence of effects) following major neurosurgical procedures; this corresponds to 3 fewer (5 fewer to 11 more) deaths per 1000 patients. LMWH may result in little or no difference in symptomatic PEs (RR, 0.20; 95% CI, 0.01-4.03; low certainty in the evidence of effects) compared with UFH following major neurosurgical procedures. Based on a baseline risk of 0.2% from observational data,³⁶⁴ this corresponds to 2 fewer (2 fewer to 6 more) symptomatic PEs in a cohort of 1000 patients following major neurosurgical procedures. We are uncertain whether LMWH affects proximal DVTs (RR, 1.00; 95% CI, 0.14-6.91; very low certainty in the evidence of effects). Similarly, the impact of LMWH on symptomatic distal DVTs is very uncertain (RR, 0.33; 95% CI, 0.01-7.93; very low certainty in the evidence of effects). In absolute terms, this corresponds to 1 fewer (1 fewer to 7 more) symptomatic distal DVT per 1000 patients, based on a baseline risk of 0.2% from observational data.³⁶⁴

Harms and burden. LMWH may result in little or no difference in major bleeding (RR, 0.76; 95% CI, 0.20-2.95; low certainty in the evidence of effects) compared with UFH, which corresponds to 5 fewer (18 fewer to 43 more) major bleeding events per 1000 patients. We were unable to assess the effect on reoperations.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations and very serious imprecision.

Other EtD criteria and considerations. In formulating this recommendation, the panel formally acknowledges its prior conditional recommendation against pharmacological prophylaxis (Recommendation 19) for patients undergoing neurosurgical procedures. Nevertheless, if pharmacological prophylaxis is considered, the panel judged the desirable effects of LMWH over UFH as small and the undesirable effects as trivial. Considering the very low certainty in the evidence, and possibly important uncertainty about or variability in how much people value the main outcomes, the balance of effects favored LMWH. Equity, acceptability, and feasibility were not considered major factors.

Conclusions and research needs for this recommendation.

In the subset of high-risk patients following major neurosurgical procedures for whom pharmacological prophylaxis is being considered, the ASH guideline panel judged the net benefit to favor LMWH over UFH. The panel recognizes this as being based upon very low certainty in the evidence.

The research priorities following major neurosurgical procedures are to better establish the benefits and risks of any pharmacological prophylaxis compared with no pharmacological prophylaxis. For patients considered at very high risk of postoperative VTE and at low bleeding risk, high-quality comparative studies of LMWH vs UFH using clinically important outcome measures would be of value.

Urological procedures. *Question: Should pharmacological prophylaxis vs no pharmacological prophylaxis be used for patients undergoing TURP?*

Recommendation 21

For patients undergoing TURP, the ASH guideline panel *suggests against* using pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○). **Remark:** Patients with other risk factors for VTE (eg, history of VTE, thrombophilia, or malignancy) may benefit from pharmacological prophylaxis.

Summary of the evidence. We did not identify any systematic reviews of RCTs addressing this research question. Because of the paucity of studies related to TURP, data across all major general, urological, and gynecological surgical procedures were pooled, and TURP-specific baseline risk estimates were applied, where available. The evidence base to inform the relative effectiveness of pharmacological prophylaxis vs no pharmacological prophylaxis was comparable to that used to inform this question for patients undergoing laparoscopic cholecystectomy (see Recommendation 18). To determine the desirable and undesirable effects of prophylaxis in absolute terms, the baseline risks specific for TURP outcomes were drawn from a systematic review by Tikkinen et al³⁶⁹ and from observational studies.³⁷⁰⁻³⁷²

The EtD framework is available online at <https://guidelines.gradepro.org/profile/05201A35-BCDA-9EFA-98CB-892C0AB72944>.

Benefits. Pharmacological prophylaxis may not reduce overall mortality compared with no pharmacological prophylaxis (RR, 0.75; 95% CI, 0.61 to 0.93; low certainty in the evidence of effects). This corresponds to 1 fewer (0-1 fewer) death per 1000 patients undergoing TURP. Pharmacological prophylaxis may not reduce symptomatic PEs (RR, 0.48; 95% CI, 0.26 to 0.88; low certainty in the evidence of effects), which corresponds to 0 fewer events in lower-risk patients and 0 fewer (0-1 fewer) events in higher-risk patients undergoing TURP. We are very uncertain of its effect on symptomatic proximal DVTs (RR, 0.38; 95% CI, 0.14-1.00; very low certainty in the evidence of effects), which would correspond to 1 fewer (0-1 fewer) symptomatic event in 1000 lower-risk patients or 3 fewer (0-5 fewer) events per 1000 higher-risk patients. We are very uncertain about its effect on symptomatic distal DVTs (RR, 0.52; 95% CI, 0.31-0.87; very low certainty in the evidence of effects). Based upon the very low baseline risk for patients undergoing TURP, this would correspond to 0 fewer symptomatic events per 1000 higher-risk patients.

Harms and burden. The risk of major bleeding is probably slightly increased (RR, 1.24; 95% CI, 0.87-1.77; moderate certainty in the evidence of effects) with the use of pharmacological prophylaxis. This corresponds to 6 more (3 fewer to 20 more) major bleeding events per 1000 patients. We are very uncertain about reoperations (RR, 0.93; 95% CI, 0.35-2.50; very low certainty in the evidence of effects) related to pharmacological prophylaxis.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations, indirectness, and imprecision.

Other EtD criteria and considerations. The panel judged the desirable effects of pharmacological prophylaxis for patients

undergoing TURP as trivial and the undesirable effects as small in magnitude. It further judged that there was possibly important uncertainty or variability in how much people value the main outcomes. Based primarily on the very low baseline risk of VTE following TURP, the panel judged that the balance of effects ultimately favored not using pharmacological prophylaxis. Pharmacological prophylaxis would also incur moderate costs and not be cost-effective.

Conclusions and research needs for this recommendation.

The guideline panel suggests against pharmacological prophylaxis for patients undergoing TURP. Based on overall very low certainty in the evidence, the panel judged that the desirable effects of pharmacological prophylaxis were outweighed by the undesirable effects, specifically the increased risk of bleeding in this setting. Given the very low baseline risks of VTE following this procedure and the increasing use of alternative modalities to treat lower urinary tract symptoms attributed to benign prostatic hyperplasia,³⁷³ further RCTs conducted on patients undergoing TURP do not appear to be a major priority.

Question: If pharmacological prophylaxis is indicated, should LMWH vs UFH be used for patients undergoing TURP?

Recommendation 22

For the subset of patients undergoing TURP for whom pharmacological prophylaxis is used, the ASH guideline panel *suggests using LMWH or UFH* (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Summary of the evidence. We did not identify any systematic reviews of RCTs addressing this research question. Because of the paucity of studies related to TURP, data across all major general, urological, and gynecological surgical procedures were pooled. Thirty-one studies reported the effect of LMWH vs UFH on risk of mortality,^{305,307,308,310-312,314,317-319,321,322,325-327,329-339,341,342,346,347,374} and 36 studies reported on development of symptomatic PEs.^{295,305-307,310-312,314-319,321,322,324,326-335,337,339,344-346,374-378} Six studies reported the effect of LMWH vs UFH on development of symptomatic proximal DVTs,^{306,316,326,334,336,375} 8 studies reported the effect on development of symptomatic distal DVTs,^{306,316,326,329,334,336,341,375} 31 studies reported on risk of major bleeding,^{295,305-307,311,313,315-319,321-339,341,344-346,374-377,379} and 19 studies reported on risk of reoperation.^{305,307,309,317,319,322,323,326,329,330,333-337,341,375-377} To determine the desirable and undesirable effects of prophylaxis in absolute terms, the baseline risks specific for TURP outcomes obtained from a systematic review by Tikkinen et al³⁶⁹ were applied to the corresponding pooled RRs.

The EtD framework is available online at <https://guidelines.gradepro.org/profile/59BDE78B-362E-9573-980D-41A280D79D9E>.

Benefits. The risks of mortality may be similar for patients treated with LMWH and UFH (RR, 1.03; 95% CI, 0.89-1.18; very low certainty in the evidence of effects), but we are very uncertain of this finding. Given an assumed baseline risk of 0.2%,³⁷⁰⁻³⁷² this corresponds to 0 fewer (0 fewer to 0 more) deaths per 1000 patients. Similarly, there may be little difference for other outcomes,

such as symptomatic PEs (RR, 0.84; 95% CI, 0.59-1.20; very low certainty in the evidence of effects), corresponding to 0 fewer (0 fewer to 0 more) events per 1000 patients. We are equally uncertain about the risk of symptomatic proximal DVTs (RR, 1.01; 95% CI, 0.20-5.0; very low certainty in the evidence of effects) and symptomatic severe distal DVTs (RR, 1.01; 95% CI, 0.30-3.44; very low certainty in the evidence of effects). Corresponding absolute effect size estimates are very small.

Harms and burden. The risks of bleeding may be similar with LMWH and UFH (RR, 0.97; 95% CI, 0.78-1.20; low certainty in the evidence of effects), corresponding to 0 fewer (4 fewer to 3 more) major bleeding events per 1000 patients undergoing TURP. The use of LMWH does not appear to decrease the risk of reoperation (RR, 0.79; 95% CI, 0.57-1.08; low certainty in the evidence of effects) for patients undergoing TURP. When applying a TURP-specific baseline risk of 0.2%, this corresponded to 0 fewer (0-1 fewer) reoperations per 1000 patients undergoing TURP.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations, indirectness, and very serious imprecision.

Other EtD criteria and considerations. The panel rated the magnitude of the desirable effects and undesirable effects of using LMWH or UFH as trivial. They further determined that there was possibly important uncertainty and/or variability in how much patients value the main outcomes. Overall, the balance of effects did not favor LMWH or UFH, nor did cost-effectiveness or issues surrounding equity, acceptability, and feasibility, at least for inpatient prophylaxis. The panel recognized that this particular comparison applied only to patients undergoing TURP considered at very high risk for VTE (eg, patients with a history of VTE) in whom pharmacological prophylaxis might be considered.

Conclusions and research needs for this recommendation.

Based on very low certainty in the evidence for effects, the guideline panel did not find a net benefit for using LMWH or UFH for patients undergoing TURP in whom pharmacological prophylaxis is indicated and suggests that either can be used. For most patients undergoing TURP, the panel recommended against the use of pharmacological prophylaxis (see Recommendation 21). No high-priority research needs were identified.

Question: Should pharmacological prophylaxis vs no pharmacological prophylaxis be used for patients undergoing radical prostatectomy?

Recommendation 23

For patients undergoing radical prostatectomy, the ASH guideline panel *suggests against* using pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○). **Remark:** Patients undergoing an extended node dissection and/or open radical prostatectomy may have a higher VTE risk and may potentially benefit from pharmacological prophylaxis.

Summary of the evidence. Because of the paucity of RCTs specific to this setting, the evidence base to inform the relative effectiveness of pharmacological prophylaxis vs no pharmacological

prophylaxis was comparable to that used to inform this question for patients undergoing TURP (see Recommendation 21); we pooled data across all surgical procedures and applied surgery-specific baseline risk estimates for radical prostatectomy drawn from a systematic review by Tikkinen et al.³⁸⁰

The EtD framework is available online at <https://guidelines.gradepro.org/profile/F99386B2-4C08-3F36-8029-61B51278B574>.

Benefits. Pharmacological prophylaxis vs no prophylaxis may not reduce mortality (RR, 0.75; 95% CI, 0.61 to 0.93; low certainty in the evidence of effects), corresponding to 0 fewer deaths per 1000 patients. Pharmacological prophylaxis probably does not reduce symptomatic PEs (RR, 0.48; 95% CI, 0.26-0.88; moderate certainty in the evidence of effects). Depending on patient risk, this corresponds to 0 fewer symptomatic PEs in lower-risk patients to 0 fewer (0-1 fewer) symptomatic PEs per 1000 higher-risk patients undergoing radical prostatectomy. We are very uncertain about the effect on symptomatic proximal DVTs (RR, 0.38; 95% CI, 0.14-1.00; very low certainty in the evidence of effects). This corresponds to 1 fewer (0-1 fewer) symptomatic proximal DVT per 1000 lower-risk patients to 4 fewer (0-5 fewer) per 1000 higher-risk patients. Distal DVTs may be reduced (RR, 0.52; 95% CI, 0.31-0.87; low certainty in the evidence of effects), but this also corresponds to a negligible effect of 0 fewer symptomatic distal DVT events, irrespective of baseline risk category.

Harms and burden. Pharmacological prophylaxis compared with no prophylaxis may increase major bleeding (RR, 1.24; 95% CI, 0.87-1.77; low certainty in the evidence of effects). This corresponds to 6 more (3 fewer to 20 more) major bleeding events per 1000 patients undergoing radical prostatectomy. We are uncertain about the effect of pharmacological prophylaxis compared with no prophylaxis on reoperations (RR, 0.93; 95% CI, 0.35-2.50; very low certainty in the evidence of effects); this corresponds to 0 fewer (3 fewer to 6 more) reoperations per 1000 men based on a baseline risk of 0.4%.³⁸⁰

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations, indirectness, and imprecision.

Other EtD criteria and considerations. The panel recognized during its deliberations that the practice of radical prostatectomy varies greatly, ranging from robotically assisted laparoscopic radical prostatectomy with no or a limited pelvic lymph node dissection to open radical prostatectomy with extended pelvic lymph node dissection. Based on a systematic review by Tikkinen et al,³⁸⁰ this results in substantially different baseline risks for VTEs, which are important considerations for these recommendations. The majority of radical prostatectomies performed by urologists in the United States are performed robotically, typically with no or only a limited lymph node dissection. In this group, the panel judged the desirable effects of pharmacological prophylaxis as trivial and undesirable effects as small. Patients undergoing open radical prostatectomy with lymph node dissection were considered at higher risk for VTEs and bleeding. Cost-effectiveness probably favored no pharmacological prophylaxis, whereas issues of equity, acceptability, and feasibility were not deemed important in this setting.

Conclusions and research needs for this recommendation.

The guideline panel judged that the net benefit favors no pharmacological prophylaxis for patients undergoing radical prostatectomy, based on very low certainty in the evidence of effects. The panel perceived it as important to emphasize that this recommendation was based on the panel's assessment of average patients undergoing radical prostatectomy in the form of robotically assisted laparoscopic prostatectomy with no or limited lymph node dissection. Patients undergoing an extended node dissection and/or open radical prostatectomy may have a higher VTE risk and may potentially benefit from pharmacological prophylaxis. Further high-quality comparative studies, using appropriate clinical outcomes, would be of value to add more certainty to these recommendations. Further studies on patient values regarding prevention of VTEs and bleeding would allow for optimal shared decision making regarding thromboprophylaxis for radical prostatectomy.

Question: If pharmacological prophylaxis is indicated, should LMWH vs UFH be used for patients undergoing radical prostatectomy?

Recommendation 24

For patients undergoing radical prostatectomy in whom pharmacological prophylaxis is used, the ASH guideline panel *suggests* using either LMWH or UFH (conditional recommendation based on very low certainty in the evidence of effects, ⊕○○○).

Summary of the evidence. In the absence of RCTs specific to this setting, the evidence base to inform the relative effectiveness of LMWH prophylaxis vs UFH prophylaxis was comparable to that used to inform this question for patients undergoing TURP (see Recommendation 22); we pooled data across all surgical procedures and applied surgery-specific baseline risk estimates for radical prostatectomy drawn from a systematic review by Tikkinen et al.³⁸⁰

The EtD framework is available online at <https://guidelines.gradepr.org/profile/AEF71CF4-AB9F-1DDF-A08B-1F5E2484EA5F>.

Benefits. The risks of mortality may be similar for patients treated with LMWH and UFH (RR, 1.03; 95% CI, 0.89-1.18; low certainty in the evidence of effects); this corresponds to 0 fewer deaths per 1000 men. Similarly, there may be little difference for the other outcomes of symptomatic PEs (RR, 0.84; 95% CI, 0.59-1.20; very low certainty in the evidence of effects), symptomatic proximal DVTs (RR, 1.01; 95% CI, 0.20-5.0; very low certainty in the evidence of effects), and symptomatic distal DVTs (RR, 1.01; 95% CI, 0.30-3.44; very low certainty in the evidence of effects), with all 95% CIs crossing the line of no effect and very small absolute effect sizes.

Harms and burden. The risks of bleeding may be similar with LMWH and UFH (RR, 0.97; 95% CI, 0.78-1.20; low certainty in the evidence of effects), corresponding to 0 fewer (4 fewer to 3 more) major bleeding events per 1000 patients undergoing radical prostatectomy. The risks of reoperation may be similar with LMWH and UFH (RR, 0.79; 95% CI, 0.57-1.08; low certainty in the

evidence of effects), corresponding to 1 fewer (0-2 fewer) event based on a baseline risk of 0.4%.³⁸⁰

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations, indirectness, and very serious imprecision.

Other EtD criteria and considerations. The panel rated the magnitude of the desirable and undesirable effects of using LMWH over UFH as trivial. They further determined that there was possibly important uncertainty and/or variability in how much people value the main outcomes. Overall, the balance of effects did not favor LMWH or UFH, nor did cost-effectiveness or issues surrounding equity, acceptability, and feasibility, at least for inpatient prophylaxis. The panel recognized that this particular comparison applied only to select patients undergoing radical prostatectomy considered at high risk for VTEs (eg, patients with prior VTEs). For most patients undergoing radical prostatectomy, the panel recommended against the use of pharmacological prophylaxis (see Recommendation 23).

Conclusions and research needs for this recommendation.

The guideline panel judged that, for patients undergoing radical prostatectomy requiring pharmacological prophylaxis, based upon very low certainty in the evidence, LMWH or UFH can be used. There is a need for high-quality randomized trials specific to patients undergoing radical prostatectomy, particularly those treated with robotically assisted laparoscopic prostatectomy, the most widely used surgical approach for clinically localized prostate cancer.

Cardiac or major vascular surgery

Question: Should pharmacological prophylaxis vs no pharmacological prophylaxis be used for patients undergoing cardiac or major vascular surgery?

Recommendation 25

For patients undergoing cardiac or major vascular surgery, the ASH guideline panel *suggests* using pharmacological prophylaxis or no pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Summary of the evidence. Our systematic search for RCTs identified 3 studies^{70,381,382} that fulfilled our inclusion criteria and measured outcomes relevant to this context. Because of the paucity of RCTs, we also systematically searched for observational studies and identified 1 additional study that fulfilled our inclusion criteria.³⁸³

One trial reported the effect of pharmacological prophylaxis vs no intervention on risk of mortality.³⁸¹ Two trials reported the effect on the risk of symptomatic PEs and on the risk of any proximal and distal DVTs.^{70,381,382} The effect on the risk of major bleeding was reported from an RCT³⁸¹ and a nonrandomized controlled study.³⁸³ Surgery-specific baseline risk estimates were obtained from a systematic review and meta-analysis of risk of VTE after cardiac surgery.³⁸⁴

The EtD framework is available online at <https://guidelines.gradepr.org/profile/D5319730-F947-FFB7-B1F7-D4E9E4697079>.

Benefits. We were unable to assess the effect of pharmacological prophylaxis on mortality (RR, not estimable because no deaths were observed, low certainty in the evidence of effects). Pharmacological prophylaxis appears to result in little or no difference in symptomatic PEs (RR, 2.40; 95% CI, 0.10-55.7; low certainty in the evidence of effects); this corresponds to 5 more (3 fewer to 198 more) PEs per 1000 patients receiving pharmacological prophylaxis based on a baseline risk of 0.4%.³⁸⁴ We are very uncertain whether pharmacological prophylaxis results in little or no difference in proximal DVTs (RR, 2.85; 95% CI, 0.12-67.83; low certainty in the evidence of effects). This finding corresponds to 45 more (21 fewer to 1631 more) symptomatic proximal DVTs per 1000 patients, based on a baseline risk of 2.4%.³⁸⁴ We are also very uncertain about the effect of pharmacological prophylaxis on distal DVTs (RR, 0.32; 95% CI, 0.01-7.54; very low certainty in the evidence of effects). This corresponds to 1 fewer (2 fewer to 13 more) symptomatic distal DVT per 1000 high-risk patients, based on a baseline risk of 0.2%.³⁸⁴

Harms and burdens. Based on 1 large observational study³⁸³ and supported by a single relevant RCT,³⁸¹ the rates of major bleeding may be increased with pharmacological prophylaxis (RR, 1.26; 95% CI, 1.07-1.47; low certainty in the evidence of effects). This corresponds to 4 more (1-6 more) major bleeds per 1000 patients.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes informed by observational studies.

Other EtD criteria and considerations. The panel recognized that very high doses of UFH are routinely administered to most patients undergoing cardiac and major vascular surgery. Thus, for this recommendation, the benefits and harms of postoperative pharmacological prophylaxis are being considered in an incremental context. The panel recognized there was a paucity of high-quality evidence addressing this particular question, and this recommendation was made in the face of very uncertain evidence. Based upon available evidence, the panel judged that the incremental desirable and undesirable effects of pharmacological prophylaxis were trivial and, therefore, balanced.

The panel recognized that cardiac surgery itself is associated with a risk for the development of heparin-induced thrombocytopenia (HIT). The panel reviewed the available literature and found that the risk of HIT among heparin preparations was higher with the use of UFH than with LMWH. Available evidence from RCTs did not allow the panel to quantitate whether there was an incremental risk for HIT associated with the use of pharmacological heparin prophylaxis beyond that of UFH administered during the procedure itself. However, the panel acknowledged that concerns about HIT would lead some panelists to be less likely to routinely use postoperative pharmacological prophylaxis with a heparin preparation, particularly UFH. The panel did not believe that there were important implementation considerations with the use of postoperative pharmacological prophylaxis in this patient population. Should LMWH or UFH be given, the panel recommended periodic monitoring of platelet counts because of the concern for postoperative HIT.

Conclusions and research needs for this recommendation.

The panel found that the overall net benefit did not favor pharmacological prophylaxis or no pharmacological prophylaxis for patients undergoing cardiac and major vascular surgery; this was based on

very low certainty in the evidence. For subgroup considerations, the panel judged that, for patients at higher baseline risk for VTE (eg, those with a history of VTE), pharmacological prophylaxis might be considered over no prophylaxis.

The panel supported that further research, in the form of well-designed RCTs using clinically important end points, is needed to determine the role of pharmacological prophylaxis in the prevention of VTEs following cardiac and major vascular surgery. Further research on the incremental impact of postoperative UFH and LMWH exposure on the development of HIT in this patient population is also warranted.

Question: Should LMWH prophylaxis vs UFH prophylaxis be used for patients undergoing cardiac or major vascular surgery?

Recommendation 26

When pharmacological prophylaxis is used for patients undergoing cardiac or major vascular surgery, the ASH guideline panel suggests using LMWH or UFH (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Summary of the evidence. We identified 1 systematic review³⁸⁵ of RCTs and observational studies that addressed this research question. We identified 3 studies³⁸⁶⁻³⁸⁸ in these reviews that fulfilled our inclusion criteria and measured outcomes relevant to this context. Our update of the systematic review did not identify any additional studies that fulfilled the inclusion criteria. One study reported the effect of LMWH vs UFH on the risk of mortality, PE, and major bleeding.³⁸⁷ Three studies reported the effect of LMWH vs UFH on the risk of any DVT, including 1 study reporting data for proximal and distal DVTs separately.³⁸⁶⁻³⁹⁸

Surgery-specific baseline risk estimates were obtained from a systematic review and meta-analysis of risk of VTEs after cardiac surgery.³⁸⁴

The EtD framework is available online at <https://guidelines.grade.pro.org/profile/D32EF371-AE1E-1ACF-82CD-E11528E7B8E0>.

Benefits. We are very uncertain whether LMWH vs UFH affects mortality following cardiac or major vascular surgery (RR, 4.55; 95% CI, 0.22-93.81; low certainty in the evidence of effects). This corresponds to 0 fewer deaths per 1000 patients. We were unable to estimate an effect on symptomatic PEs (RR, not estimable). We are also very uncertain about the effect of LMWH on symptomatic proximal DVTs (RR, 1.33; 95% CI, 0.30-6.01; very low certainty in the evidence of effects) and symptomatic distal DVTs (RR, 1.20; 95% CI, 0.45-3.22; very low certainty in the evidence of effects). This would correspond to 8 more (17 fewer to 122 more) symptomatic proximal DVTs per 1000 patients and 0 more (1 fewer to 4 more) symptomatic distal DVTs per 1000 patients based on baseline risks of 2.4% and 0.2%, respectively.

Harms and burden. LMWH vs UFH appears to result in little or no difference in major bleeding (RR, 0.91; 95% CI, 0.19-4.42; low certainty in the evidence of effects). We found no data on reoperation.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for indirectness and very serious imprecision.

Other EtD criteria and considerations. The panel recognizes that they have judged that evidence was insufficient and of

very low quality to recommend for or against pharmacological prophylaxis following cardiac surgery. Nevertheless, particularly for patients considered at high risk for VTE (eg, those with history of VTEs), postoperative pharmacological prophylaxis would be considered for use in the cardiac and major vascular surgery settings by some panelists. This recommendation is relevant for patients considered at high risk for VTEs.

As discussed in the previous recommendation, HIT is a recognized complication in the cardiac and vascular surgery settings. Furthermore, it is recognized that the risk of HIT in other settings has been shown to be higher with the use of UFH vs LMWH. Available evidence from RCTs did not allow the panel to quantitate whether there was an incremental risk for HIT associated with the use of pharmacological UFH or LMWH prophylaxis beyond that of heparin administered during the procedure itself or whether there was a relatively greater incremental risk for HIT in the cardiac surgery setting with postoperative UFH prophylaxis than with LMWH. Nevertheless, given the above factors, if pharmacological prophylaxis is chosen for use, panelists concurred that an anticoagulant with a lower risk for HIT (eg, LMWH over UFH) should be considered.

The panel did not believe that there were important implementation considerations with use of postoperative LMWH or UFH pharmacological prophylaxis in this patient population. Should either agent be given, the panel recommended the periodic monitoring of platelet counts.

Conclusions and research needs for this recommendation.

The panel judged that, based upon available evidence, LMWH or UFH could be selected for VTE prophylaxis following cardiac surgery based on very low quality evidence. The panel judged that this question was only of relevance for patients considered at very high risk for postoperative VTEs following cardiac or major vascular surgery in whom pharmacological prophylaxis would be considered over no prophylaxis.

The panel supported that the more important research question for this patient population is the role of pharmacological prophylaxis vs no pharmacological prophylaxis for the prevention of VTEs following cardiac and major vascular surgery. Further research on the incremental impact of postoperative UFH and LMWH exposure on the development of HIT in this patient population would also be of value.

Major trauma

Question: Should pharmacological prophylaxis vs no pharmacological prophylaxis be used for patients experiencing major trauma?

Recommendation 27a

For patients experiencing major trauma at low to moderate risk for bleeding, the ASH guideline panel *suggests* using pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Recommendation 27b

For patients experiencing major trauma at high risk for bleeding, the ASH guideline panel *suggests against* pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Summary of the evidence. We identified 1 systematic review that addressed this question.³⁸⁹ We identified 2 studies^{47,390} in this review that fulfilled our inclusion criteria and measured outcomes relevant to this context. Our update of the systematic review did not identify any additional studies that fulfilled the inclusion criteria. Two small studies reported the effect of pharmacological prophylaxis compared with no intervention on risk of mortality, on development of symptomatic PEs, and on any DVT.^{47,390} No study reported the effect of pharmacological prophylaxis compared with no intervention on risk of major bleeding or on risk of reoperation. The small amount of direct evidence, with a lack of information on undesirable outcomes, together with the very low certainty on the treatment effect, led the panel to consider the indirect data from hip fracture repair studies for treatment RR estimates²⁵⁵⁻²⁶⁶ and applying baseline VTE and bleeding risks from studies on trauma patients.^{391,392}

The EtD framework is available online at <https://guidelines.grade-pro.org/profile/434A9C2D-3417-F3ED-B7C1-4A0BA3EC6699>.

Benefits. We are uncertain about the effect of pharmacological prophylaxis on mortality following major trauma (RR, 0.95; 95% CI, 0.84-1.07; very low certainty in the evidence of effects). Pharmacological prophylaxis may reduce symptomatic PEs, but we are very uncertain of this finding (RR, 0.49; 95% CI, 0.33-0.72; very low certainty in the evidence of effects). Depending upon baseline risk, this benefit corresponds to 3 fewer (2-5 fewer) patients with symptomatic PEs per 1000 moderate-risk patients and 2 fewer (1-2 fewer) patients per 1000 low-risk patients.

Pharmacological prophylaxis may also reduce the risk of proximal DVTs (RR, 0.51; 95% CI, 0.38-0.69; very low certainty in the evidence of effects), which corresponds to 7 fewer (4-9 fewer) in 1000 higher-risk patients and 3 fewer (2-4 fewer) in 1000 lower-risk patients. We are uncertain of the effect of pharmacological prophylaxis on distal DVTs (RR, 0.85; 95% CI, 0.5-1.29, very low certainty in the evidence of effects). This would correspond to 1 fewer (3 fewer to 2 more) symptomatic distal DVT in 1000 higher-risk patients and 0 fewer in 1000 lower-risk patients.

Harms and burden. Pharmacological prophylaxis may result in more major bleeding than no prophylaxis (RR, 1.24; 95% CI, 1.12-1.37; very low certainty in the evidence of effects), but this finding is uncertain. Depending upon baseline risk, the risk of major bleeding corresponds to 3 more (2-5 more) major bleeds per 1000 lower-bleeding-risk patients and to 14 more (7-21 more) major bleeds per 1000 patients with higher bleeding risk.

We are very uncertain about the effect of pharmacological prophylaxis on the need for reoperation (RR, 1.05; 95% CI, 0.82-1.35; very low certainty in the evidence of effects).

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations, indirectness, and imprecision.

Other EtD criteria and considerations. The overall certainty in the evidence was rated as very low for this question, given the absence of RCTs comparing pharmacological prophylaxis vs no prophylaxis for patients experiencing major trauma. The benefits and harm/burden data were extrapolated from the closest surgical indication for which we had adequate comparative evidence (ie, hip fracture repair). It is recognized that these hip

fracture studies are dated and that rates of patient-important DVT events were derived from modeling of asymptomatic events detected by routine screening studies. The panel presumed that, in the absence of specific contraindications (eg, lower limb injuries), patients experiencing major trauma would receive mechanical prophylaxis. The panel emphasized the need to periodically reevaluate bleeding risk as patients recover from major trauma. Once bleeding is stabilized and the patient is no longer considered at high risk for major bleeding, the use of pharmacological prophylaxis should be reconsidered.

Conclusions and research needs for this recommendation.

Based upon the totality of the evidence, the panel judged that the moderate overall benefits of pharmacological prophylaxis outweighed the increased risk of major bleeding for patients at low or moderate risk for bleeding. In contrast, for patients at high risk for major bleeding, the large undesirable consequences of major bleeding led to a balance that favors no pharmacological prophylaxis. The very low certainty in the evidence justifies conditional recommendations for both scenarios.

Well-designed trials using clinically important VTE end points are required for patients at low to moderate risk for bleeding following trauma to determine the incremental benefits of pharmacological prophylaxis beyond mechanical methods alone. Well-designed studies are also needed to determine the benefits and risks of introducing delayed pharmacological prophylaxis for patients experiencing major bleeding, including intracranial hemorrhage as a consequence of major trauma, as the bleeding risk subsides.

Question: Should LMWH vs UFH be used for patients experiencing major trauma?

Recommendation 28

For patients experiencing major trauma in whom pharmacological prophylaxis is used, the ASH guideline panel *suggests* using LMWH or UFH (conditional recommendation based on low certainty in the evidence of effects ⊕⊕○○).

Summary of the evidence. We identified 1 systematic review that addressed this question.³⁸⁹ Our update of the systematic review identified 1 additional study that fulfilled the inclusion criteria,³⁹⁴ and our systematic search of RCTs identified 2 studies that fulfilled the inclusion criteria^{394,395} and were not included in the review. Three studies reported the effect of LMWH prophylaxis vs UFH prophylaxis on risk of mortality, on development of any PEs, and on major bleeding,³⁹³⁻³⁹⁵ whereas 2 studies informed on the risk of development of proximal and distal DVTs.^{393,394}

The EtD framework is available online at <https://guidelines.gradepro.org/profile/96D5A309-8606-4469-B732-E1844465CC75>.

Benefits. LMWH vs UFH appears to result in little or no difference in mortality for patients experiencing major trauma (RR, 1.32; 95% CI, 0.14-12.39; low certainty in the evidence of effects). This corresponds to 2 more (4 fewer to 54 more) deaths per 1000 trauma patients receiving LMWH vs UFH. Similarly, LMWH may result in little or no difference in symptomatic PEs (RR, 1.04; 95% CI, 0.11-9.92; low certainty in the evidence of effects). This corresponds to 0 fewer (6 fewer to 61 more) symptomatic PEs per 1000 patients based on a baseline risk of 0.7% from observational

data.³⁹¹ LMWH vs UFH likely results in no important effect on proximal DVTs (RR, 0.57; 95% CI, 0.25-1.31; moderate certainty in the evidence of effects). This corresponds to 3 fewer (5 fewer to 2 more) symptomatic proximal DVTs per 1000 patients based on a baseline risk of 0.7% from observational data.³⁹¹

LMWH probably also results in little or no difference in symptomatic distal DVTs (RR, 0.74; 95% CI, 0.46-1.20; moderate certainty in the evidence of effects). This corresponds to 0 fewer symptomatic distal DVTs per 1000 patients based on a baseline risk of 0.1% from observational data.³⁹¹

Harms and burden. LMWH may result in a small increase in major bleeding (RR, 2.4; 95% CI, 0.53-10.78; low certainty in the evidence of effects). This corresponds to 20 more (7 fewer to 138 more) major bleeding events per 1000 patients receiving LMWH vs UFH. There were no comparative data about rates of reoperation of LMWH vs UFH following major trauma.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as low based on the lowest certainty in the evidence for the critical outcomes, downgrading for very serious imprecision.

Other EtD criteria and considerations. The panel judged that the minor differences in the effects of the interventions on benefits and undesirable outcomes led to an overall balance that did not favor either intervention. The benefits observed with LMWH were limited to a minor reduction in the rates of symptomatic proximal DVTs, which was negated by the small observed increased risk of major bleeding. It was recognized that patients at high risk for major bleeding were excluded from the studies that formed the basis of this recommendation.

Because LMWH and UFH are in widespread use for this indication, the panel did not judge there to be major implementation considerations with either intervention. The panel presumed that, in the absence of specific contraindications (eg, lower limb injuries), patients experiencing major trauma would receive mechanical prophylaxis.

Conclusions and research needs for this recommendation.

The panel suggested that, for patients experiencing major trauma who are judged to be at low to moderate risk for bleeding, LMWH or UFH may be used for pharmacological VTE prophylaxis based on low certainty in the evidence.

The panel judged that the research priorities in major trauma related to establishing the effectiveness and the timing of intervention with pharmacological prophylaxis for patients receiving mechanical prophylaxis following major trauma, rather than comparative studies of LMWH vs UFH.

Major gynecological surgery

Question: Should pharmacological prophylaxis vs no pharmacological prophylaxis be used for patients undergoing major gynecological surgery?

Recommendation 29

For patients undergoing major gynecological surgery, the ASH guideline panel *suggests* using pharmacological prophylaxis over no pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Summary of the evidence. We identified 1 systematic review of RCTs addressing this research question.²⁹ We identified only 5 studies^{118,273-275,349} in this review that fulfilled our inclusion criteria and measured outcomes relevant to this context. Because of the paucity of studies on patients undergoing major gynecological procedures, data across major general, laparoscopic cholecystectomy, and major gynecological and urological procedures were pooled. The evidence base to inform the relative effectiveness of pharmacological prophylaxis vs no pharmacological prophylaxis was comparable to that used to inform this question for patients undergoing laparoscopic cholecystectomy (see Recommendation 18). Baseline risk estimates specific to gynecological procedures^{396,397} were applied to determine the desirable and undesirable effects of prophylaxis in absolute terms.

The EtD framework is available online at <https://guidelines.gradeapro.org/profile/B2FD665A-5A79-4E46-875E-9BB7F3FAFF9F>.

Benefits. Pharmacological prophylaxis probably reduces mortality slightly following major gynecological surgery (RR, 0.75; 95% CI, 0.61-0.93; low certainty in the evidence of effects). This corresponds to a benefit of 4 fewer (1-7 fewer) deaths per 1000 patients. Pharmacological prophylaxis probably reduces the risk of symptomatic PEs (RR, 0.48; 95% CI, 0.26-0.88; low certainty in the evidence of effects), corresponding to a benefit of 2 fewer (0-3 fewer) symptomatic PEs per 1000 higher-risk patients and 0 fewer (0-1 fewer) per 1000 lower-risk patients, based on baseline risks from observation data of 0.1% and 0.4%, respectively.^{396,397}

We are uncertain whether pharmacological prophylaxis reduces the rates of proximal DVTs (RR, 0.38; 95% CI, 0.14-1.00; very low certainty in the evidence of effects), corresponding to reduction of 4 fewer (0-6 fewer) symptomatic proximal DVTs per 1000 lower-risk patients and 17 fewer (0-23 fewer) per 1000 higher-risk patients based on baseline risks from observation data of 0.7% and 2.7%, respectively.^{396,397} We are uncertain about the effect of pharmacological prophylaxis on distal DVTs (RR, 0.52; 95% CI, 0.31-0.87; low certainty in the evidence of effects), corresponding to no reduction per 1000 patients treated based on a lower baseline risk of 0.1%.

Harms and burden. Pharmacological prophylaxis may slightly increase the risk of major bleeding (RR, 1.24; 95% CI, 0.87-1.77; low certainty in the evidence of effects). This corresponds to 6 more (3 fewer to 20 more) major bleeding events per 1000 patients receiving pharmacological prophylaxis. Pharmacological prophylaxis does not appear to increase the risk of reoperation (RR, 0.93; 95% CI, 0.35-2.50; very low certainty in the evidence of effects) following major gynecological procedures.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations, indirectness, and imprecision.

Other EtD criteria and considerations. The panel based its recommendation on the judgment that the desirable benefits of pharmacological prophylaxis outweighed the likely small increased risk of major bleeding following major gynecological procedures. The panel acknowledges that the overall certainty in the evidence was very low given the issue of indirectness, with most of the available trial data not being specific to gynecological

procedures. The panel considered that patients at increased risk for VTE would receive mechanical prophylaxis in addition to pharmacological prophylaxis. There were no major implementation considerations.

Conclusions and research needs for this recommendation.

The panel judged that pharmacological prophylaxis should be administered to patients undergoing major gynecological surgery, and this recommendation was conditional given the very low certainty in the evidence. There is a need for large high-quality clinical trials using clinically relevant end points to determine the benefit of pharmacological prophylaxis following gynecological procedures. These studies should include detailed clinical characteristics of the patient populations.

Question: Should LMWH vs UFH prophylaxis be used for patients undergoing major gynecological surgery?

Recommendation 30

For patients undergoing major gynecological surgery, the ASH guideline panel *suggests* using LMWH or UFH (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Summary of the evidence. We identified 1 systematic review of RCTs addressing this research question.³⁰ We identified only 4 studies^{374,376,377,379} overall that were conducted with patients undergoing major gynecological surgery. Because of the paucity of studies on patients undergoing major gynecological procedures, data across major general, laparoscopic cholecystectomy, and major gynecological and urological procedures were pooled. The evidence base to inform the relative effectiveness of LMWH prophylaxis vs UFH prophylaxis was comparable to that used to inform this question for patients undergoing TURP (see Recommendation 22).

Baseline risk estimates specific to gynecological procedures^{396,397} were applied to determine the desirable and undesirable effects of prophylaxis in absolute terms.

The EtD framework is available online at <https://guidelines.gradeapro.org/profile/F213C6D1-F2D9-221A-B8EE-92B6F94F5BB3>.

Benefits. LMWH prophylaxis appears to result in little or no difference in mortality compared with UFH prophylaxis (RR, 1.03; 95% CI, 0.89-1.18; low certainty in the evidence of effects), corresponding to 1 more (2 fewer to 3 more) deaths per 1000 patients. Likewise, use of LMWH prophylaxis vs UFH prophylaxis appears to result in little or no difference in symptomatic PEs (RR, 0.91; 95% CI, 0.63-1.3; low certainty in the evidence of effects). For a higher baseline risk of 0.4% from observational data,³⁹⁶ this corresponds to 1 fewer (2 fewer to 1 more) symptomatic PE per 1000 participants. For symptomatic proximal DVTs (RR, 1.01; 95% CI, 0.20-5.00; low certainty in the evidence of effects), the absolute risk reduction is 0 per 1000 patients, with the 95% CI varying by baseline risk from 5 fewer to 27 more³⁹⁷ to 22 fewer to 108 more (baseline risks of 0.7% and 2.7%, respectively).³⁹⁶ We are very uncertain about the effect on symptomatic distal DVTs (RR, 1.01; 95% CI, 0.30-3.44; very low certainty in the evidence of effects) following major gynecological surgical procedures.

Harms and burden. LMWH appears to confer little or no difference in major bleeding compared with UFH prophylaxis following major gynecological procedures (RR, 0.97; 95% CI, 0.78-1.20; low certainty in the evidence of effects); this corresponds to 0 fewer (4 fewer to 3 more) major bleeds per 1000 patients. LMWH prophylaxis may result in a small, possibly unimportant, reduction in reoperations compared with UFH (RR, 0.79; 95% CI, 0.57-1.08; low certainty in the evidence of effects). This corresponds to 4 fewer (8 fewer to 1 more) reoperation procedures per 1000 patients receiving LMWH prophylaxis.

Certainty in the evidence of effects. We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations and indirectness.

Other EtD considerations. The panel based its recommendation on the judgment that the desirable benefits and the risk of complications were balanced between use of LMWH and UFH pharmacological prophylaxis. The panel acknowledges that the overall certainty in the evidence was very low, given the issue of indirectness, with most of the available trial data not being specific to gynecological procedures. There was not deemed to be any major implementation consideration.

Conclusions and research needs for this recommendation. The panel suggests using LMWH or UFH for patients undergoing major gynecological surgery procedures based upon very low certainty in the evidence of effects. There is a need for large high-quality clinical trials using clinically relevant end points to determine the relative benefits of LMWH vs UFH pharmacological prophylaxis following gynecological procedures. These studies should include detailed clinical characteristics of the patient populations.

Limitations of these guidelines

The panel recognized that many studies of pharmacological and mechanical prophylaxis for VTE prevention following major surgery date back decades, thereby raising questions about the applicability of this evidence. This includes largely outdated means (eg, venography) to assess for VTEs postoperatively. Surgical practice has changed considerably over the decades, aimed at improving the patient experience. In most circumstances, these innovations would be expected to reduce the overall risk of postoperative VTEs. Examples of such innovations include use of minimally invasive surgical procedures, early and increased postoperative patient mobilization, and use of regional anesthesia; however, it is uncertain whether such changes in surgical practice impact the relative effectiveness of various thromboembolic interventions. Therefore, for the purpose of this guideline, this type of evidence informing the relative effectiveness of these interventions was included when obtained in the setting of RCTs. For determining baseline risk of VTEs and major bleeding, we used data, where available, from contemporary large cohort studies that were deemed representative of contemporary patients.

Although the panel rated symptomatic VTE end points as those upon which recommendations should be based, the panel recognized that most studies of VTE prophylaxis following surgery used asymptomatic DVTs detected by the routine performance of sensitive screening tests (eg, venography) as the primary study outcome. Reporting of symptomatic DVTs in some studies could have been influenced by diagnostic suspicion bias. The panel

also acknowledges that modeling was required to determine rates of symptomatic DVTs when only asymptomatic DVT events were reported, based on the best available estimates drawn from the literature.

The panel recognized that most of the evidence on mechanical methods of VTE prophylaxis comes from the orthopedic literature. Studies of the benefits of mechanical prophylaxis for other surgical settings are needed. Finally, the panel acknowledges that, for some questions, limited direct data were available (eg, VTE prophylaxis following urological and gynecological procedures and for major trauma). In these settings, estimates of the benefits of prophylaxis were based upon related surgical settings, such as general surgical procedures and hip fracture surgery, respectively.

What are others saying and what is new in these ASH guidelines?

These ASH guidelines stand out by their scope, which includes general issues relevant to any surgical procedure and those related to surgical subspecialties. They make consistent use of high-quality systematic reviews and provide a formal EtD framework for every recommendation, thereby enhancing transparency about the judgments that were made.

A widely used high-quality guideline is the 2012 Guideline of the American College of Chest Physicians (ACCP), which places a strong emphasis on patients' VTE risk scores.³⁹⁸ In the guideline recommendations for VTE prevention in nonorthopedic surgical patients, patient-oriented VTE risk calculators, such as the Caprini score¹⁰ and Rogers score,³⁹⁹ were adopted. When the risk for VTE is very low, it was recommended not to use pharmacological or mechanical prophylaxis. For patients at low risk for VTE, mechanical prophylaxis was suggested over no prophylaxis, preferably with intermittent pneumatic compression. For patients at moderate risk for VTE who are not at high risk for major bleeding complications, it was suggested to use LMWH, low-dose UFH, or mechanical prophylaxis with intermittent pneumatic compression over no prophylaxis. For patients at high risk for VTE who are not at high risk for major bleeding complications, it was recommended to use pharmacological prophylaxis with LMWH or low-dose UFH over no prophylaxis, and it was suggested to add mechanical prophylaxis with graduated compression stockings or intermittent pneumatic compression to pharmacological prophylaxis. Guidelines by the Scottish Intercollegiate Guidelines Network (SIGN)⁴⁰⁰ and the National Institute for Clinical Excellence (NICE)⁴⁰¹ also emphasize the importance of risk stratification.^{400,401}

Mechanical methods of perioperative VTE prophylaxis have been addressed by a number of guidelines.^{398,400-404} The 2012 ACCP guidelines did not provide a detailed comparison of the effectiveness of graduated compression stockings and pneumatic compression stockings, but they generally favor pneumatic compression stockings on the basis of indirect evidence, from the Clots in Legs or Stockings after Stroke trial for patients with stroke, that elastic stockings increased the risk of skin complications without reducing the risk of VTEs.⁴⁰⁵ Other guidelines presented by SIGN,⁴⁰⁰ NICE,⁴⁰¹ the American Academy of Orthopedic Surgeons (AAOS),⁴⁰² the Neurocritical Society,⁴⁰⁴ and the International Union of Angiology⁴⁰³ discuss the use of pneumatic compression and graduated compression stockings in various surgical settings but generally consider these modalities together as "mechanical devices" and do not offer a

direct comparison of their effectiveness or safety other than noting that graduated compression stockings cannot be used for patients with certain lower extremity pathologies.

Guidelines addressing the prophylactic placement of IVC filters include the 2012 ACCP guidelines,³⁹⁸ the 2011 AAOS guideline for orthopedic patients,⁴⁰² the 2013 European Venous Forum,⁴⁰³ the 2013 guidelines by the Neurocritical Care Society,⁴⁰⁴ the 2013 British Committee for Standards in Hematology guidelines, and the “appropriateness criteria” by the American College of Radiology.⁴⁰⁶ The recommendation made by these ASH guidelines corresponds with many of these existing recommendations that are mostly critical of prophylactic IVC filter placement for patients requiring major surgery or who have experienced trauma.

Several recent guidelines comment on VTE prophylaxis after total hip or knee arthroplasty. The 2012 ACCP guideline for orthopedic surgery patients⁴⁰⁷ recommended LMWH, fondaparinux, apixaban, dabigatran, rivaroxaban, low-dose UFH, adjusted-dose vitamin K antagonists (VKAs), ASA, and/or intermittent pneumatic compression, with the proviso that they are portable, out of concerns regarding compliance. They further indicate a preference for LMWH over the other listed agents, with the exception of ASA. The 2011 AAOS guideline⁴⁰² recommends some form of chemoprophylaxis (including ASA) along with intermittent pneumatic compression after total hip or knee arthroplasty. The 2012 Asian Venous Thromboembolism Guideline⁴⁰⁸ recommends LMWH, fondaparinux, rivaroxaban, apixaban, edoxaban, dabigatran, warfarin, or ASA with intermittent pneumatic compression, referencing and effectively accepting the 2012 ACCP and 2011 AAOS guidelines. The 2013 International Angiology guideline favors LMWH, fondaparinux, VKAs, rivaroxaban, apixaban, or dabigatran, along with use of intermittent pneumatic compression after total hip arthroplasty.⁴⁰³ The most current NICE guideline recommends LMWH or rivaroxaban after total hip arthroplasty and the same after total knee arthroplasty, with the additional option of ASA.⁴⁰¹

For VTE prophylaxis after surgery for hip fractures, the 2012 ACCP guideline recommends LMWH for VTE prophylaxis vs fondaparinux and low-dose UFH over adjusted-dose VKAs or ASA.⁴⁰⁷ Concurrent use of an intermittent pneumatic compression device was also recommended. The 2011 AAOS guideline does not specifically address hip fractures; however, in the face of hip arthroplasty as a treatment for hip fracture, their recommendations of some form of chemoprophylaxis (including ASA), along with intermittent pneumatic compression for total hip arthroplasty, would be applicable.⁴⁰² The 2012 Asian Venous Thromboembolism Guideline recommended LMWH, fondaparinux, rivaroxaban, apixaban, edoxaban, dabigatran, warfarin, or ASA with intermittent pneumatic compression.⁴⁰⁸ The Agency for Healthcare Research and Quality 2017 guideline favors chemoprophylaxis but is neutral on specific agents because of a lack of evidence.²³⁶ The 2013 International Angiology Guideline favors LMWH, fondaparinux, VKAs, or low-dose UFH.⁴⁰³ The most current NICE guideline recommends LMWH or fondaparinux.⁴⁰¹

For general and abdominal surgery, which includes gastrointestinal, urological, gynecological, bariatric, vascular, plastic, or reconstructive surgery in its scope, the 2012 ACCP guidelines are once again the best known. In the very low risk setting, no specific pharmacological or mechanical prophylaxis is recommended other

than early ambulation. At low risk, mechanical prophylaxis (preferably with intermittent pneumatic compression) is suggested over no prophylaxis. For moderate-risk patients, assuming there is no high risk for major bleeding, LMWH, low-dose UFH, and mechanical prophylaxis, preferably with intermittent pneumatic compression devices, are all options. If patients are at high risk for major bleeding complications or if consequences of bleeding are thought to be particularly severe, mechanical prophylaxis (preferably with intermittent pneumatic compression devices) is suggested over no prophylaxis.³⁹⁸

For patients undergoing neurosurgical procedures, there are a total of 6 guidelines that offer somewhat conflicting recommendations on pharmacological VTE prophylaxis. These guidelines include the 2012 ACCP guideline, the 2014 Korean Society of Thrombosis and Hemostasis Evidence-Based Clinical Practice Guidelines, the 2018 NICE guideline, the 2010 SIGN guideline, the 2017 European Society of Anesthesiology guideline, and the 2016 Neurocritical Care Society guidelines.^{398,400,401,404,409,410} The recommendations provided by these current ASH guidelines are similar to the 2010 SIGN guidelines, the 2019 Congress of Neurological Surgeons Guidelines for Spine Trauma, and the 2012 ACCP guidelines. Overall, mechanical prophylaxis is recommended for most neurosurgical patients. The benefit of pharmacological prophylaxis should be considered for patients at high risk or very high risk for VTE, but the overall risk/benefit profile is questionable, given an increase in bleeding events, particularly because neurosurgical bleeding events can be more serious. Similar to the 2010 SIGN recommendations, our ASH guidelines suggest that, for patients who do receive pharmacological prophylaxis, LMWH be used over UFH, whereas the 2012 ACCP guidelines do not give preference to any specific drug.

Urology is covered within the scope of guidelines by the ACCP, the Australian National Health and Medical Research Council, and the National Institute for Health and Care Excellence, among others.⁴¹¹ Urology-specific guidelines are available from the American Urological Association, the German Association of Scientific Medical Societies, and, most recently, the European Association of Urology.⁴¹²⁻⁴¹⁴ In the absence of direct evidence for urology, the European Association of Urology guideline makes the assumption of a 50% risk reduction for “any serious VTE event” as well as a 50% increase in the risk of major bleeding requiring reoperation. When assessing the net benefit in making the recommendation, the major bleeding was given twice the weight of the outcome of VTE prevention. The resulting recommendations were supported by a systematic review of the procedure-specific VTE risk and the bleeding risk.^{369,380} For patients undergoing TURP, this resulted in a conditional recommendation against pharmacological prophylaxis across risk groups. For radical prostatectomy, the guideline provides a more nuanced set of recommendations that differ by surgical approach (open, laparoscopic, or robotically assisted laparoscopic) and extent of the node dissection (without, standard, or extended). For patients undergoing robotically assisted laparoscopic prostatectomy with a standard lymph node dissection, which was considered the index case for these ASH guidelines, there is a conditional recommendation against pharmacological prophylaxis.

For cardiac surgery patients with an uncomplicated postoperative course, the 2012 ACCP guideline suggested the use of

mechanical prophylaxis, preferably with optimally applied intermittent pneumatic compression, over no prophylaxis or pharmacological prophylaxis.³⁹⁸ For cardiac surgery patients whose hospital course is prolonged by ≥ 1 nonhemorrhagic surgical complication, the guideline suggested adding pharmacological prophylaxis with UFH or LMWH to mechanical prophylaxis. They considered that the risk of VTE following cardiac surgery is uncertain but judged that most patients were at moderate risk for VTEs and at high risk for anticoagulant prophylaxis-related bleeding. Based on these considerations, it was concluded that, in cardiac patients at usual risk for VTE, the harms of anticoagulant prophylaxis outweighed the benefits, whereas anticoagulation may be of net benefit for patients with high-risk characteristics. The ACCP guidelines did not provide recommendations specific to major vascular surgery. The International Consensus Statement on Prevention and Treatment of Venous Thromboembolism published by the European Venous Forum, in cooperation with several other organizations, offers guidelines for general, vascular, bariatric, and plastic surgical patients.⁴⁰³ Major vascular surgery was considered with other “major surgery,” and patients were judged to generally be at moderate risk in the absence of specific high-risk characteristics, such as age older than 60 years or prior VTE. Pharmacological prophylaxis was recommended in the absence of unusual bleeding risks. Recommendations specific to cardiac surgery patients were not presented. An update of NICE guidelines published in 2018 offers guidelines regarding VTE prophylaxis for patients undergoing cardiac or major vascular surgery.⁴⁰¹ This guideline recommends considering mechanical VTE prophylaxis on admission for patients who are undergoing cardiac surgery and are at increased risk for VTE and continuing this until the patient no longer has significantly reduced mobility relative to their normal or anticipated mobility. They recommend considering pharmacological VTE prophylaxis for a minimum of 7 days for patients who are undergoing open vascular surgery or major endovascular procedures, including endovascular aneurysm repair, and whose risk of VTE outweighs their risk of bleeding. Further, they recommend considering mechanical prophylaxis on admission for people who are undergoing open vascular surgery or major endovascular procedures, including endovascular aneurysm repair, if pharmacological prophylaxis is contraindicated. SIGN published a relevant updated guideline in 2014.⁴⁰⁰ The guideline notes that cardiac surgery patients often receive anticoagulants and antiplatelet agents for reasons independent of VTE and that this may impact their VTE risk. Despite this, these guidelines recommend that patients undergoing coronary artery bypass grafting surgery should be offered mechanical thromboprophylaxis where feasible and that patients undergoing coronary artery bypass grafting surgery who are not at high risk for bleeding can also be offered pharmacological thromboprophylaxis.

The most relevant guideline on the perioperative management of trauma patients is that by the ACCP in 2012.³⁹⁸ For major trauma, including traumatic brain injury, acute spinal injury, and traumatic spine injury, VTE prophylaxis is suggested (over no prophylaxis) with LMWH, low-dose UFH, or mechanical prophylaxis, preferably with intermittent pneumatic compression. For patients at high risk for VTE, addition of mechanical prophylaxis to pharmacological prophylaxis is suggested when not contraindicated by lower extremity injury. It further suggests against placement of an IVC filter for primary VTE prevention, as well as against periodic surveillance with venous compression ultrasound.

A guidance document from the American College of Gynecology dates back to 2007⁴¹⁵; as a result, the 2012 ACCP guidelines provide the timeliest guidance for gynecological surgery. One set of recommendations is made across gastrointestinal, urological, gynecological, bariatric, vascular, plastic, and reconstructive surgery (see above).

Revision or adaptation of the guidelines

Plans for updating these guidelines

After publication of these guidelines, ASH will maintain them through surveillance for new evidence, ongoing review by experts, and regular revisions.

Updating or adapting recommendations locally

Adaptation of these guidelines will be necessary in many circumstances. These adaptations should be based on the associated EtD framework.⁴¹⁶ The Agency for Healthcare Research and Quality in the United States provides a guide for implementing effective quality improvement in this patient population.⁴¹⁷

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Authorship

Contribution: D.R.A. and P.D. wrote the first draft of the manuscript and revised the manuscript based on the authors' suggestions; C.B., F.D., C.W.F., D.A.G., S.R.K., M.R., A.R., F.B.R., M.A.S., K.A.O.T., and A.J.Y. critically reviewed the manuscript and provided suggestions for improvement; members of the knowledge synthesis team (G.P.M., T.B., S.B., J.L.B., I.E.-I., H.J., I.N., W.W., J.J.Y.-N., and H.J.S.) contributed evidence summaries to the guidelines; D.R.A. and P.D. were the chair and vice chair of the panel and led the panel meeting; and all authors approved the content.

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Validation of the Caprini Risk Assessment Model in Plastic and Reconstructive Surgery Patients

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- BACKGROUND:** The Venous Thromboembolism Prevention Study (VTEPS) Network is a consortium of 5 tertiary referral centers established to examine venous thromboembolism (VTE) in plastic surgery patients. We report our midterm analyses of the study's control group to evaluate the incidence of VTE in patients who receive no chemoprophylaxis, and validate the Caprini Risk Assessment Model (RAM) in plastic surgery patients.
- STUDY DESIGN:** Medical record review was performed at VTEPS centers for all eligible plastic surgery patients between March 2006 and June 2009. Inclusion criteria were Caprini score ≥ 3 , surgery under general anesthesia, and postoperative hospital admission. Patients who received chemoprophylaxis were excluded. Dependent variables included symptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE) within the first 60 postoperative days and time to DVT or PE.
- RESULTS:** We identified 1,126 historic control patients. The overall VTE incidence was 1.69%. Approximately 1 in 9 (11.3%) patients with Caprini score >8 had a VTE event. Patients with Caprini score >8 were significantly more likely to develop VTE when compared with patients with Caprini score of 3 to 4 (odds ratio [OR] 20.9, $p < 0.001$), 5 to 6 (OR 9.9, $p < 0.001$), or 7 to 8 (OR 4.6, $p = 0.015$). Among patients with Caprini score 7 to 8 or Caprini score >8 , VTE risk was not limited to the immediate postoperative period (postoperative days 1-14). In these high-risk patients, more than 50% of VTE events were diagnosed in the late (days 15-60) postoperative period.
- CONCLUSIONS:** The Caprini RAM effectively risk-stratifies plastic and reconstructive surgery patients for VTE risk. Among patients with Caprini score >8 , 11.3% have a postoperative VTE when chemoprophylaxis is not provided. In higher risk patients, there was no evidence that VTE risk is limited to the immediate postoperative period. (J Am Coll Surg 2011;212:105-112. © 2011 by the American College of Surgeons)
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Venous thromboembolism (VTE) is a disorder with short-term mortality and long-term morbidity. VTE has been deemed a major threat to patient safety by policymakers and payers, including the US Surgeon General,¹ the Centers for Medicare and Medicaid Services,² and the National Quality Forum.³ To fully identify VTE risk in surgical patients, recent publications advocate individualized patient risk assessment.⁴⁻⁷ The Caprini Risk Assessment Model (RAM) was derived more than a decade ago, based on a combination of clinical experience and published data.⁸⁻¹⁰ Recently, the Caprini RAM has been validated for 30-day VTE events in a large series of general, urology, and vascular surgery patients.⁵ Revised versions of the model have also been validated in postbariatric body contouring patients⁷ and medical inpatients.^{11,12}

Plastic and reconstructive surgery patients are known to be at high risk for venous thromboembolism after surgery.

Abbreviations and Acronyms

DVT	= deep venous thrombosis
HR	= hazard ratio
LMWH	= low molecular weight heparin
OR	= odds ratio
PE	= pulmonary embolism
RAM	= risk assessment model
VTE	= venous thromboembolism
VTEPS	= Venous Thromboembolism Prevention Study

Symptomatic VTE occurs with high frequency after post-bariatric body contouring surgery, including circumferential abdominoplasty (7.7%), abdominoplasty (5.0%), and breast or upper body contouring (2.9%) procedures.⁷ Using the modified Davison-Caprini RAM,¹³ Seruya and colleagues¹⁴ showed a 7.5% VTE incidence in patients stratified to the “highest risk” group. Symptomatic, postoperative VTE occurs in 2.2% of women having flap-based breast reconstruction after mastectomy.¹⁵ However, asymptomatic VTE rates in the flap-based breast reconstruction population may be much higher. A recent study screened asymptomatic women before discharge using duplex ultrasonography and demonstrated that 4% had occult deep venous thrombosis (DVT).¹⁶ In addition, a small case series demonstrated that 16.7% of women may have occult pulmonary embolism (PE) within 3 days of surgery.¹⁷

The Venous Thromboembolism Prevention Study (VTEPS) was funded by the Plastic Surgery Educational Foundation in 2008. The study’s primary objective is to examine the effectiveness of postoperative, prophylactic dose enoxaparin (Lovenox [Sanofi Aventis]) for prevention of symptomatic VTE events in a diverse population of adult plastic and reconstructive surgery patients. The study’s control group is comprised of historic control patients who had plastic and reconstructive surgery but did not receive postoperative heparin, low molecular weight heparin (LMWH), anti-factor Xa medications, or warfarin (collectively referred to as “chemoprophylaxis”).

In this initial analysis of the VTEPS data, we sought to examine VTE incidence and when VTE events occur after plastic surgery. In addition, we examined the ability of the Caprini RAM to risk-stratify plastic and reconstructive surgery patients. Analyses were limited to VTEPS control patients, none of whom received chemoprophylaxis.

METHODS**Study design**

VTEPS is being conducted at 5 tertiary care facilities in the United States. VTEPS sites include Regions Hospital (St.

Paul, MN), University of Michigan (Ann Arbor, MI), University of Pittsburgh (Pittsburgh, PA), University of Texas-Southwestern (Dallas, TX), and University of Washington (Seattle, WA). The analyses described here were limited to data from the VTEPS historic control group. Historic control patients were identified using medical record review for all plastic and reconstructive surgery procedures performed at each of the 5 VTEPS sites between March 2006 and June 2009. During this time period, the standard of care for VTE prophylaxis at all VTEPS sites did not include routine chemoprophylaxis. Postoperative chemoprophylaxis was provided to less than 10% of patients based on attending surgeon discretion. Historic control eligibility criteria included moderate to high risk for VTE (Caprini score ≥ 3), operation under general anesthesia, and overnight hospital stay. Control patients did not receive heparin, LMWH, factor Xa inhibitors, warfarin, or other means of prophylactic or therapeutic anticoagulation for 60 days after surgery. This included the patient’s inpatient stay and postdischarge course. Perioperative sequential compression devices were used.

Independent variables

At each study site, medical record review was performed by physician-led teams. Before chart review, each team participated in a standardized training session administered by the VTEPS study coordinators. Retrospective chart review was carried out to identify VTE risk factors per the Caprini RAM (Fig. 1). The factors were used to calculate a risk score based on risk factors present before (eg, medical comorbidities or known thrombophilia) and during (eg, surgery length or central venous line insertion) hospitalization. Additional independent variables included the year the procedure was performed, VTEPS site, patient sex, total number of operations, description of surgical procedure, receipt of chemoprophylaxis, administration of aspirin or clopidogrel, and length of hospitalization.

Dependent variables

Dependent variables of interest were identified using medical record review, including documentation from the operating room, inpatient stay, and outpatient visits. Records were reviewed for 60 days after surgery. Patients who lacked 60-day followup were excluded. Chart review identified symptomatic DVT (including upper and lower extremity DVT), symptomatic PE, or hematoma requiring a second operation. All VTE events required confirmation using objective imaging (lower extremity venous duplex ultrasound, ventilation-perfusion scan, or PE protocol CT scan). Autopsy-proved DVT or PE were considered positive outcomes when they were believed to be the proximate cause of death. Among patients with an outcome of interest, time to VTE and time to



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Thrombosis Risk Factor Assessment

Patient's Name: _____ Age: ____ Sex: ____ Wgt: ____ lbs

Choose All That Apply

Each Risk Factor Represents 1 Point	Each Risk Factor Represents 2 Points
☐ Age 41-60 years ☐ Minor surgery planned ☐ History of prior major surgery (< 1 month) ☐ Varicose veins ☐ History of inflammatory bowel disease ☐ Swollen legs (current) ☐ Obesity (BMI > 25) ☐ Acute myocardial infarction ☐ Congestive heart failure (< 1 month) ☐ Sepsis (< 1 month) ☐ Serious lung disease incl. pneumonia (< 1 month) ☐ Abnormal pulmonary function (COPD) ☐ Medical patient currently at bed rest ☐ Other risk factors _____	☐ Age 60-74 years ☐ Arthroscopic surgery ☐ Malignancy (present or previous) ☐ Major surgery (> 45 minutes) ☐ Laparoscopic surgery (> 45 minutes) ☐ Patient confined to bed (> 72 hours) ☐ Immobilizing plaster cast (< 1 month) ☐ Central venous access
Each Risk Factor Represents 3 Points	Each Risk Factor Represents 5 Points
☐ Age over 75 years ☐ History of DVT/PE ☐ Family history of thrombosis* ☐ Positive Factor V Leiden ☐ Positive Prothrombin 20210A ☐ Elevated serum homocysteine ☐ Positive lupus anticoagulant ☐ Elevated anticardiolipin antibodies ☐ Heparin-induced thrombocytopenia (HIT) ☐ Other congenital or acquired thrombophilia If yes: Type _____ *most frequently missed risk factor	☐ Elective major lower extremity arthroplasty ☐ Hip, pelvis or leg fracture (< 1 month) ☐ Stroke (< 1 month) ☐ Multiple trauma (< 1 month) ☐ Acute spinal cord injury (paralysis)(< 1 month)
	For Women Only (Each Represents 1 Point)
	☐ Oral contraceptives or hormone replacement therapy ☐ Pregnancy or postpartum (<1 month) ☐ History of unexplained stillborn infant, recurrent spontaneous abortion (≥ 3), premature birth with toxemia or growth-restricted infant

Total Risk Factor Score

Figure 1. The Caprini Risk Assessment Model. (Adapted from: Caprini JA. Thrombosis risk assessment as a guide to quality patient care. *Dis Mon* 2005;51:70-78, with permission.)

reoperative hematoma in days were identified as additional dependent variables.

Data storage and analysis

A secure, password-protected Website was created through a modification of the American Society of Plastic Surgeons' Tracking Operations and Outcomes for Plastic Surgeons (TOPS) platform (<http://tops.plasticsurgery.org>). The Website was developed and maintained by Outcomes, Inc. Deidentified patient-level data for risk factors and outcomes were uploaded and stored on Outcomes, Inc's secure data server. For analysis purposes, deidentified data were extracted by the American Society of Plastic Surgeons and provided to study personnel in Microsoft Excel spreadsheets.

Data analysis was performed using Stata 11 (Stata-Corp LP). A VTE variable, including patients with either DVT or PE, was created. Descriptive statistics that examined DVT, PE, and VTE incidence were generated. For VTE risk analysis, patients were stratified by Caprini score at accepted and published levels (Caprini scores of 3 to 4, 5 to 6, 7 to 8, and >8).^{5,18} Descriptive statistics on VTE rate by stratified Caprini score were generated. Group differences were examined using logistic regression. A value of $p < 0.05$ was considered significant. Kaplan-Meier analysis using stratified Caprini score was performed to examine the number of VTE events over time. Hazard ratios (HRs) were generated. The institutional review board at each VTEPS site approved this study.

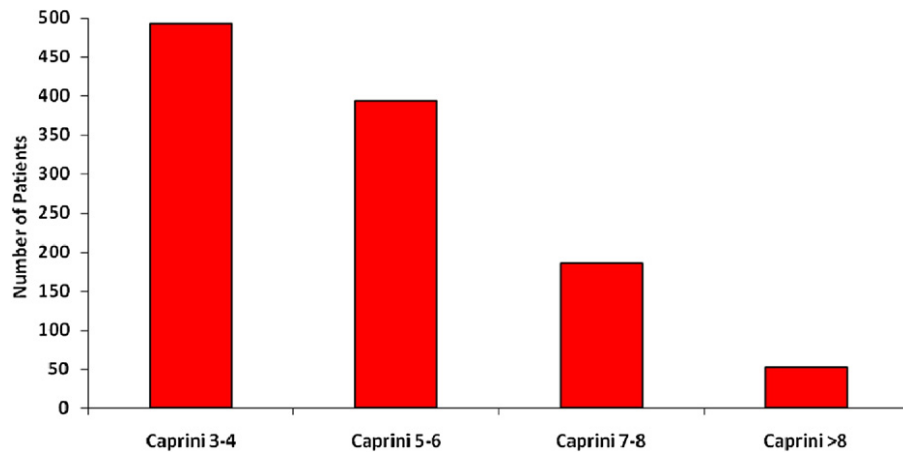


Figure 2. Histogram of Caprini score in plastic and reconstructive surgery patients (n = 1,126).

RESULTS

A total of 1,126 historic control patients were identified from 5 VTEPS network sites. No patient in this series received pre- or postoperative chemoprophylaxis. Most patients (79%) were in the Caprini 3 to 4 or Caprini 5 to 6 groups (Fig. 2).

At 60 days after surgery, the overall VTE incidence was 1.69%. Overall DVT incidence was 1.26% and overall PE incidence was 0.89%. Patients with both DVT and PE comprised 0.44% of the total number of patients. A stratified analysis of VTE by procedure type is shown in Table 1. A univariate analysis examining individual risk factors in patients with and without VTE is presented in Table 2.

VTE incidence increased dramatically with increased Caprini score (Fig. 3). In patients with Caprini score >8, 11.3% had a symptomatic VTE event between postoperative days 0 and 60. Patients with Caprini score >8 were

significantly more likely to develop VTE when compared with patients with Caprini score of 3 to 4 (odds ratio [OR] 20.9, $p < 0.001$), 5 to 6 (OR 9.9, $p < 0.001$), or 7 to 8 (OR 4.6, $p = 0.015$). Additionally, patients with Caprini score 7 to 8 were significantly more likely to develop VTE when compared with patients with Caprini score 3 to 4 (OR 4.5, $p = 0.04$) (Table 3).

Two of 5 sites systematically omitted data on time to VTE. These 2 sites did not provide the postoperative day on which VTE occurred for any patient with VTE at their institution. As required by our Institutional Review Board, data were initially uploaded to our secure, web-based server in a de-identified fashion. Thus, we were unable to re-query the primary data source to obtain time to VTE data for these two sites. All data from these 2 sites were dropped before time series analysis. Kaplan-Meier analysis was per-

Table 1. Venous Thromboembolism Stratified By Procedure Type

Procedure type	Patients, n	Patients with VTE, n (%)
Upper extremity reconstruction	153	0
Breast reconstruction	307	4 (1.3)
Breast reduction	99	1 (1.0)
Cosmetic breast surgery	12	0
Post-bariatric body contouring	26	0
Other body contouring	27	0
Lower extremity reconstruction	47	0
Head and neck reconstruction	198	4 (2.0)
Trunk reconstruction	82	6 (7.3)
Burn reconstruction	16	1 (6.3)
Surgery for decubitus ulcers	96	3 (3.1)
Genitourinary reconstruction	28	0
Facial cosmetic surgery	35	0

VTE, venous thromboembolism.

Table 2. Univariate Analysis Examining Individual Risk Factors in Patients With and Without Venous Thromboembolism

Risk factor	Without VTE	With VTE	p Value
Patients, n	1,107	19	
Age (y), mean	48.2	54.2	0.083
Female, %	64.8	63.2	0.864
BMI > 25, %	66.5	79.0	0.252
BMI > 40, %	8.3	10.5	0.727
Prior surgery within 1 mo, %	11.9	47.4	<0.001
OR time, mean	3.5	3.8	0.621
History of VTE	2.5	0	0.481
Family history of VTE, %	0.53	5.26	0.008
Cancer (present or previous), %	37.6	36.8	0.946
Central venous access, %	11.3	47.4	<0.001
Women, n	734	12	
Oral contraceptive use, %	9.1	16.7	0.371

VTE, venous thromboembolism; BMI, body mass index.

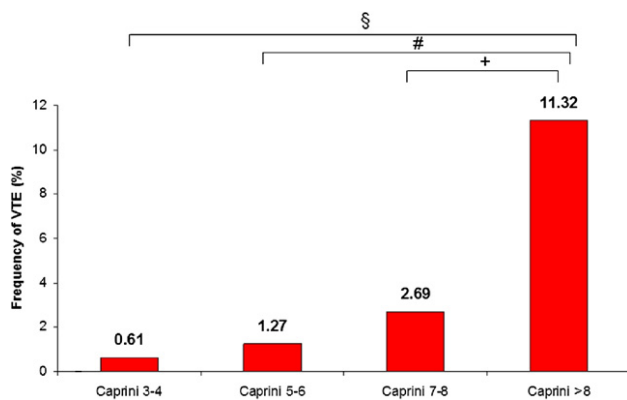


Figure 3. Rates of venous thromboembolism (VTE) in the first 60 postoperative days by stratified Caprini score ($n = 1,126$). OR, odds ratio; § Compares Caprini >8 to Caprini 3-4, OR 20.85, $p < 0.001$; # compares Caprini >8 to Caprini 5-6, OR 9.93, $p < 0.001$; + compares Caprini >8 to Caprini 7-8, OR 4.62, $p = 0.015$.

formed on 1,087 patients from the remaining 3 sites. Patients with Caprini score >8 had significantly increased hazard for VTE when compared with patients with Caprini score 3 to 4 (HR 48.6, $p < 0.001$), 5 to 6 (HR 9.3, $p = 0.001$), or 7 to 8 (HR 3.6, $p = 0.041$) (Table 4). In patients with Caprini score 7 to 8 and >8, VTE events occurred across the 60-day follow-up period (Fig. 4).

DISCUSSION

Our data demonstrate that the Caprini RAM is a useful and effective tool to stratify plastic and reconstructive surgery patients for VTE risk. For patients with higher Caprini scores, a significantly greater likelihood of VTE events was observed. Approximately 1 in 9 patients (11.3%) with Caprini score >8 had a VTE event within 60 days after surgery. Particularly among patients with Caprini score 7 to 8 or >8, there was no evidence that VTE risk is limited to the immediate postoperative period.

Venous thromboembolism in plastic surgery patients

Venous thromboembolic events carry the risk of both morbidity and mortality. Patients presenting with symptomatic

Table 4. Sixty-Day Hazard for Venous Thromboembolism Stratified by Caprini Score

Score	Caprini 5-6	Caprini 7-8	Caprini >8
Caprini 3-4	5.2 (0.6-46.7) $p = 0.139$	13.3 (1.6-114.1) $p = 0.018$	48.6 (5.7-416.0) $p < 0.001$
Caprini 5-6	—	2.6 (0.7-9.5) $p = 0.162$	9.3 (2.5-34.7) $p = 0.001$
Caprini 7-8	—	—	3.6 (1.1-12.6) $p = 0.041$

Data are presented as hazard ratio (95% CI).

Table 3. Sixty-Day Odds for Venous Thromboembolism Stratified by Caprini Score

Score	Caprini 5-6	Caprini 7-8	Caprini >8
Caprini 3-4	2.1 (0.5-8.8) $p = 0.312$	4.5 (1.1-19.1) $p = 0.040$	20.9 (5.1-86.1) $p < 0.001$
Caprini 5-6	—	2.2 (0.6-7.5) $p = 0.231$	9.9 (2.9-33.8) $p < 0.001$
Caprini 7-8	—	—	4.6 (1.4-15.8) $p = 0.015$

Data are presented as odds ratio (95% CI).

PE have a 10% death rate within 1 hour. Of patients who survive, 50% demonstrate evidence of right ventricular dysfunction. An additional 5% will eventually develop chronic pulmonary hypertension.¹⁹ Between 4% and 7% of plastic surgeons report a patient death from postoperative PE.^{20,21} DVT can damage venous valves, which can result in venous reflux and the post-thrombotic syndrome. Severe PTS occurs in approximately 10% of patients with symptomatic DVT¹⁹ and manifest as a chronically swollen, tender, and ulcerated extremity. Post-thrombotic syndrome is a major predictor of poor quality of life after DVT.²²

Plastic surgeons underuse chemoprophylaxis in high-risk patients and may fail to recognize risk factors when present.²⁰⁻²⁴ Others may recognize risk factors but fail to actively modify them before surgery.²⁵ Plastic surgeons commonly cite risk of re-operative hematoma and lack of evidence in the plastic surgery literature as reasons for not providing chemoprophylaxis.²¹ Recently, plastic surgeons have been inundated with information on postoperative thromboembolic complications. Multiple recent publications have defined VTE incidence and risk factors in plastic surgery patients.^{7,14,15,17,26-33} Barriers to surgeons providing chemoprophylaxis and methods to minimize VTE risk have been discussed in several letters to the editor.³⁴⁻³⁶ A modified version of

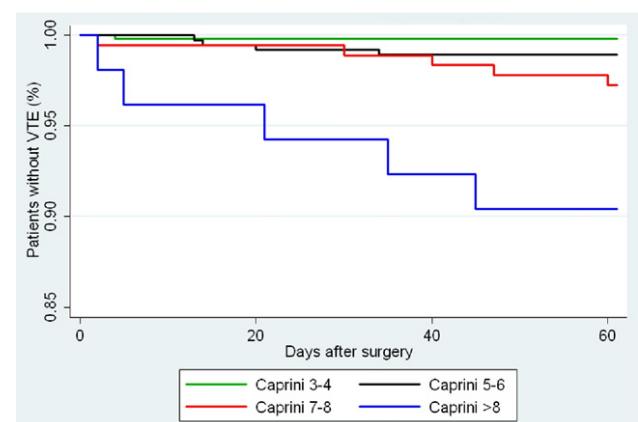


Figure 4. Survival analysis examining time to venous thromboembolism (VTE) by stratified Caprini score ($n = 1,087$).

the Caprini RAM has been validated in postbariatric body contouring patients.⁷ However, no RAM had previously been validated in a broad range of adult plastic and reconstructive surgery patients.

Validation of the Caprini Risk Assessment Model

Earlier versions of the Caprini RAM⁹ placed all patients with a score ≥ 5 into the same “highest risk” group. This designation was challenged by a recent publication by Bahl and colleagues⁵ from the University of Michigan. In a series of more than 8,000 general, urology, and vascular surgery patients, widely variable VTE rates were seen among patients previously lumped into the same “highest risk” category. Observed differences in VTE incidence among patients with Caprini score of 5 to 6 (1.3%), 7 to 8 (2.6%), and >8 (6.5%) were statistically significant. As a result, recent modifications of the Caprini RAM recognize patients with Caprini score >8 as a separate, “super high risk” group. Extended-duration chemoprophylaxis for 30 days after surgery is recommended for this “super high risk” patient subgroup.^{18,37}

Superficially, the study design for VTEPS and Bahl and colleagues⁵ analyses appear similar. Both used the Caprini RAM to retrospectively risk-stratify surgical patients, and they then examined VTE incidence by stratified Caprini score. However, the observed VTE incidence by stratified Caprini score was notably different between the VTEPS and Bahl patient populations. VTE incidence among “super high risk” patients included in VTEPS approached twice the incidence seen in Bahl’s patient population (11.3% vs 6.5%).

Plastic surgery patients are not necessarily at increased risk for VTE events when compared with general, urology, and vascular surgery patients. The differences in observed VTE incidence between the 2 studies may be explained by differences in study methodology. First, the VTEPS dataset contains 60-day patient follow-up, compared with 30-day outcomes in the Bahl study. Second, VTEPS methodology used manual chart review to identify VTE events; this method may be more robust than using hospital billing data. Finally, 32% of Bahl’s Caprini >8 group received LMWH prophylaxis. In contrast, this analysis of the VTEPS database specifically excluded patients who received chemoprophylaxis.

Late venous thromboembolism risk

For patients with Caprini score 7 to 8 and >8 , VTE risk was not limited to the immediate postoperative period. Our results echo recently published data from the UK’s Million Women Study.³⁸ The Million Women Study demonstrated that in middle-aged women, VTE risk may remain substantially elevated for at least 90 days after surgery. Published

guidelines for total hip or knee replacement and hip fracture surgery support postdischarge chemoprophylaxis for up to 5 weeks after surgery.³⁹ Similar recommendations for extended duration chemoprophylaxis have been made in selected groups of medical patients⁴⁰ and general surgery patients.^{18,41-43} The Enoxaparin and Cancer (ENOXACAN II) study was a randomized control trial examining 7 versus 28 days of LMWH for VTE prevention after surgery for intra-abdominal or pelvic malignancy. Extended-duration prophylaxis significantly reduced VTE events at 30 and 90 days after surgery.⁴³ Interestingly, plastic surgery patients have demonstrated excellent compliance with outpatient LMWH injections for VTE prophylaxis. A small case series of postdischarge subcutaneous LMWH prophylaxis has shown $>90\%$ medication compliance.¹⁴

Limitations

Our analysis is limited by several factors. The VTEPS data were identified and uploaded in a retrospective manner. Risk factors were identified using physician review of the medical record. So, inadvertent omissions from the dictated medical record may have resulted in underestimation of a patient’s Caprini risk score.

Multiple physicians and physician-led teams at 5 separate VTEPS sites identified and uploaded data to the study’s central Website. Sites contributed variable numbers of patients to the 2 study cohorts (historic control and clinical protocol). Intersite variability in data collection may have been present. Before undertaking VTEPS, we attempted to control for this confounder. Each individual involved in data collection was provided with explicit, written study protocols. All individuals who collected VTEPS data participated in a standardized training session, administered by study personnel. Data were retrospectively checked by VTEPS core investigators for completeness. Ongoing feedback was provided to each VTEPS site. Incomplete data were dropped from the analysis.

Medical record review was conducted at each VTEPS site. Patients who had a VTE event diagnosed and/or treated at another hospital may not be represented in the VTEPS database. Literature published after our study protocol was designed and implemented supports elevated VTE risk for at least 90 days after surgery.³⁸ However, patients whose VTE event occurred after postoperative day 60 are not included in our database. Clinical diagnoses of DVT and PE are known to be unreliable. Clinical examination alone is known to underestimate true incidence of VTE.⁴⁴⁻⁴⁸ We did not screen patients for asymptomatic VTE, as has been done in other high risk surgical groups.^{16,17,49,50} As a result of these factors, the VTEPS database likely under-represents the true incidence of VTE after plastic surgery.

In conclusion, the Caprini RAM effectively risk-stratifies plastic and reconstructive surgery patients for perioperative VTE risk. Among patients with Caprini score >8 , 11.3% have a postoperative VTE when chemoprophylaxis is not provided. In patients with Caprini score 7 to 8 or Caprini score >8 , there was no evidence that VTE risk is limited to the immediate postoperative period. Future goals of the VTEPS study will include examination of both VTE and re-operative hematoma rates between patients who receive and do not receive post-operative, prophylactic dose enoxaparin.

Author Contributions

Study conception and design: Pannucci, Hamill, Hume, Hoxworth, Fisher, Rubin, Pusic, Wilkins

Acquisition of data: Pannucci, Bailey, Fisher, Dreszer, Zumsteg, Jaber

Analysis and interpretation of data: Pannucci, Pusic, Wilkins

Drafting of manuscript: Pannucci, Wilkins

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CONSENSO

Consenso de la Sociedad Colombiana de Anestesiología y Reanimación, SCARE, y de la Sociedad Colombiana de Cirugía Plástica sobre las recomendaciones para el manejo de pacientes electivos de bajo riesgo¹

Colombian Society of Anesthesiology and Resuscitation and Colombian Plastic Surgery Society Consensus ¹

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SUMMARY

This document defines some particular aspects involved in practising anaesthesia in plastic surgery which are intended to improve patient safety. It presents strategies for reducing the most common serious preventable complications, such as thrombotic, embolic and infectious events. It should be stressed that these goals have been established and must be achieved with surgeons and anaesthesiologists' participation. These recommendations provide detailed are additions to the Minimum Standards which SCARE has developed.

Key words: consensus, surgery, plastic, outpatients, safety. (Source: MeSH, NLM)

RESUMEN

Este documento define algunos aspectos particulares al ejercicio de la anestesia en cirugía plástica que pretenden mejorar la seguridad de los pacientes. Se hace énfasis en la presentación de estrategias para reducir las complicaciones graves prevenibles más comunes, como los eventos de trombosis, embolias e infecciones. Se establece que estas metas se logran con la participación de los cirujanos y de los anestesiólogos. Estas recomendaciones son adiciones puntuales a las normas mínimas que ha desarrollado la SCARE.

Palabras claves: conferencia de consenso, cirugía plástica, procedimientos quirúrgicos electivos, seguridad. (Fuente: DeCS, BIREME)

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OBJECTIVES

This consensus' objective is to provide recommendations promoting high safety standards for patients undergoing elective plastic and aesthetic procedures.

CONSENSUS METHOD

Serious complications in patients undergoing plastic surgery have been common during the last few years and have led to many press stories. (1-3) The situation has reached such magnitude that some authorities have sought to introduce strategies for reducing them (4). Dr. Carlos Castro (the Colombian minister of health) prompted the Colombian Plastic Surgery Society (*Sociedad Colombiana de Cirugía Plástica* - SCCP) and the Colombian Anaesthesiology Society (*Sociedad Colombiana de Anestesiología y Reanimación* - SCARE) to hold a forum in May 2002 to discuss this problem and provide proposals. SCCP and SCARE represented by the Safety Committee and other anaesthesiologists having expertise in this area participated in this forum held on June 22nd 2002 in Bogotá (5). However, following a day of multiple presentations, no agreement was reached and alarms regarding safety in this area have persisted, being the motive for headlines in the mass media (6,7) and even alarms suggesting that this a public health problem (8).

SCARE (via its Safety Committee) thus proposed holding the First Consensus for Safety in Anaesthesia for Plastic Surgery in November 2008 during the 28th National Anaesthesiology Congress 2009.

Firstly, a group of three expert anaesthesiologists was formed, designated by the Colombian Anaesthesiology Congress' Organising Committee for presenting some topics orientated towards presenting experience and safety schemes used in different institutions; two more anaesthesiologists having a lot of experience in the field were then added who were to be exclusively involved in anaesthesia for plastic surgery and an ad hoc Anaesthesia for Plastic Surgery Safety Committee was formed.

OBJETIVO

El objetivo de este consenso es aportar recomendaciones que promuevan una seguridad alta para los pacientes que se someten a procedimientos electivos plásticos y estéticos.

MÉTODO DE CONSENSO

En los últimos años las complicaciones serias de pacientes sometidos a cirugía plástica han sido comunes, y han motivado numerosos titulares de prensa (1-3). La situación ha llegado a tal magnitud que algunas autoridades han buscado poder introducir estrategias para reducirlas (4). En mayo del 2002, el ministro de Salud encargado, Dr. Carlos Castro instó a las Sociedad Colombiana de Cirugía Plástica (SCCP) y a la Sociedad Colombiana de Anestesiología y Reanimación (SCARE) a desarrollar un foro para discutir esta problemática y generar propuestas. La SCCP y la SCARE representada por el Comité de Seguridad y otros anestesiólogos con experiencia en esta área, participaron de este foro realizado en Bogotá el 22 de junio de 2002. (5). Sin embargo, luego de un día de múltiples presentaciones, no se produjo ningún acuerdo y han persistido las alarmas respecto a la seguridad en esta área, siendo noticia en los medios masivos (6,7), e incluso con alarmas como problema de salud pública (8).

Instados, por ello, la SCARE a través de su Comité de Seguridad, propuso en noviembre del 2008, la realización del Primer Foro de Consenso para la Seguridad en Anestesia para Cirugía Plástica durante el XXVIII Congreso Nacional de Anestesiología de 2009.

En primer lugar, se conformó un grupo de tres expertos anestesiólogos, designados por el Comité Organizador del Congreso Colombiano de Anestesiología para que presentaran algunos temas para exponer la experiencia y los esquemas de seguridad usados en diferentes instituciones, y posteriormente, se vincularon dos anestesiólogos adicionales dedicados exclusivamente a la anestesia de cirugía plástica con una larga trayectoria y se conformó un comité *ad hoc* de Seguridad en Anestesia para Cirugía Plástica.

The SCCP which was very interested in the project was contacted in January 2009 to ensure an interdisciplinary nature. The above group of anaesthesiologists defined some topics which were presented to the SCCP for it to give its opinion. The Committee's coordinator (in turn being SCARE's Safety Committee coordinator) drew up an initial document with the pertinent references which was modified by using the Delphi method (9,10). Five more sessions were held electronically with the group of experts to elicit their opinion. The resulting proposal was sent by e-mail to more than 400 anaesthesiologists throughout Colombia and SCCP prior to being presented during a forum held during the Colombian Anaesthesiology Congress. More than 300 anaesthesiologists took part in the Consensus Forum and a dozen plastic surgeons including a member of SCCP's board of directors. Some comments were made by e-mail (6) and dozens of comments during the Forum. Such comments were recorded and discussed by members of the ad hoc Committee and considered in the final document which will be reviewed later on.

Due to the topic's enormous interest and relevance, SCARE's board of directors held a meeting with delegates from all regional branches on June 8th 2009. One delegate from the Valle del Cauca branch made many additional observations prior to this meeting; these were discussed with the active participation of the Special Fund for Integral Help regarding Lawsuits (*Fondo Especial para el Auxilio Solidario de Demandas* – FEPASDE). Small modifications were made to the text (mostly regarding its form) and the definitive text was defined, leading to this final document with the approval of all SCARE and FEPASDE branches.

This document has been sent to SCCP and has been presented at Colombian forums held in Bogotá, Bucaramanga, Cartagena and Cúcuta.

Para lograr un carácter interdisciplinario, en enero de 2009 se contactó a la SCCP, que se mostró muy interesada en el proyecto. En este grupo de anestesiólogos se definieron unos tópicos que se presentaron a la SCCP para su opinión. El coordinador del comité –a su vez, coordinador del Comité de Seguridad de la SCARE– redactó un documento inicial con sus referencias y se modificó usando el método Delphi (9,10). Se llevaron a cabo cinco secuencias de opiniones con el grupo de expertos de manera electrónica, y la propuesta resultante se divulgó por correo electrónico a más de 400 anestesiólogos en todo el país y a la SCCP, antes de su presentación en el foro, en el marco del Congreso Colombiano de Anestesiología. En este foro de consenso participaron más de 300 anestesiólogos, y una docena de cirujanos plásticos, que incluyó un miembro de la Junta Directiva de la SCCP. Hubo pocos comentarios por vía electrónica (seis) y decenas de comentarios de los asistentes al foro. La retroalimentación fue registrada y discutida entre los miembros del comité ad hoc y considerada en el documento final que fue revisado más adelante.

Debido al enorme interés y relevancia del tema, la junta directiva de SCARE convocó una reunión con delegados de todas las regiones seccionales el 8 de junio de 2009. Un delegado del Valle del Cauca hizo múltiples observaciones adicionales previas a esta reunión, las cuales se discutieron con la presencia y participación activa del Fondo Especial para el Auxilio Solidario de Demandas, FEPASDE. Hubo ajustes de forma al texto, y se definió el texto definitivo que arrojó este documento, con el aval de todas las seccionales de la SCARE y FEPASDE.

Finalmente, el documento ha sido enviado a la Sociedad Colombiana de Cirugía Plástica, y se ha presentado en cinco foros en Bogotá, Bucaramanga, Cartagena, Cúcuta y Medellín.

INTRODUCTION

The National Quality Forum agency in the USA has considered that deaths in ASA I patients (most being plastic surgery cases) are events which “should never have happened” and must be reported (11).

An editorial by Davison established that procedures and complications which have been traditionally attributed to the “patient” and not to surgery, such as deep venous thrombosis and other medical complications should be included in morbidity (12).

Some publications in the USA have suggested that procedures involving sedation, without anaesthesiological care, are safer than those involving anaesthesiological management. A review of world literature has shown that such reported procedures become less, the more often they are performed in ASA I patients, surgery lasting less than 2 hours and less than 3 litre liposuction volume. Differences between events become understood when these corrections are performed (13-16) Likewise, there is great support showing the safety of procedures under general / regional anaesthesia when safety standards similar to those ruling non-plastic procedures are followed (14,17).

It is apparent that part of this literature regarding morbidity is permeated by a conflict between dermatologists and plastic/anaesthetic surgeons where each side has an interest in demonstrating its greater safety, which is why they should be interpreted with care (18).

Many publications indicate that the adverse event rate in consulting-rooms (office-based anaesthesia: Colombian equivalent - basic medical centres or consulting-rooms) is significantly greater than that for established outpatient surgery centres (19-21).

The surgical group working as a team must be made aware that mortality should be the closest possible to zero and morbidity occurring in spite of all efforts made should result in the least possible handicap.

INTRODUCCIÓN

En los Estados Unidos, la agencia *National Quality Forum* ha considerado que las muertes en pacientes clasificados ASA I –la mayoría de los casos en cirugía plástica– son eventos que “nunca deben pasar” y son de notificación obligatoria (11).

Además, un editorial de Davison estableció que debía incluirse dentro de la morbilidad del procedimiento las complicaciones que tradicionalmente se atribuyen “al paciente” y no a la cirugía, como la trombosis venosa profunda y otras complicaciones médicas (12).

Algunas publicaciones de los Estados Unidos sugieren que los procedimientos con sedación, sin cuidados de anestesia, son más seguros que con manejo anestésico. Una revisión de la literatura mundial muestra que estos procedimientos reportados son menores, toda vez que son realizados, en su mayoría, en pacientes ASA I, con duración de cirugía menor de 2 horas y volúmenes de liposucción menores de 3 litros. Cuando se hacen estos ajustes, se entienden las diferencias de eventos en los unos y los otros (13-16). Asimismo, hay casuísticas grandes que demuestran la seguridad de los procedimientos bajo anestesia general o regional, siempre y cuando se ciñan a estándares de seguridad similares a los de los procedimientos no plásticos (14,17).

Es aparente que parte de esta literatura de morbilidad está permeada por un conflicto entre los dermatólogos y los cirujanos plásticos y estéticos, en los que cada uno tiene el interés de demostrar mayor seguridad, razón por la cual debe interpretarse con cuidado (18).

Debe entenderse que existen múltiples publicaciones que indican que la tasa de eventos adversos en consultorios con *office-based anesthesia* (cuyo equivalente colombiano son los centros médicos básicos o los consultorios) es significativamente mayor a la de centros establecidos de cirugía ambulatoria (19-21).

El trabajo en equipo del grupo quirúrgico debe propender porque la mortalidad sea lo más cer-

Mortality reported via ASPS (American Society of Plastic Surgeons) surveys in the USA was 1:4,926 in 1997 and 1:5,224 in 2000 (Grazer), even though some reports have listed more deaths in lesser liposuction (0:15,336) (16, 22, 23, 24). An ASAPS (American Society of Aesthetic Plastic Surgeons) 2001 survey revealed mortality of 1 per 47,415 liposuctions, 1 per 7,314 combined liposuction with other procedures and 1 per 3,281 when liposuction was combined with abdominoplasty (25). This was fourteen times higher than for just liposuction. Even though there have been some reports like that of Grant,²⁶ where there was no increased risk, such experience was particular considering that average times were 2.2 hours and transfusion and hospitalisation incidence was 0% in 406 cases. Likewise, there have been reports in which prolonged procedures did not lead to morbidity; this was reported from an academic centre (Yale) where all standards for non-plastic surgical procedures were followed. A crude report from Medellín (lacking detailed analysis of clinical histories) detected 6 deaths from an estimated 30,896 surgeries, giving a mortality rate of 1:5,149 surgeries, this being very close to that found in the literature. However, it is worth noting that these cases were detected by the doctors involved; the possibility of data under-recording is thus significant (27).

Safety recommendations

As the first safety standard, SCARE recognises that minimum standards regarding safety in anaesthesiology must be strictly adhered to in all procedures involving an anaesthesiologist. Such standards are also backed by the Latin-American Confederation of Anaesthesiology Societies (*Confederación Latinoamericana de sociedades en Anestesiología* – CLASA).

Current Minimum Standards are available on SCARE's website: www.scare.org.co

The commonest causes of morbidity and mortality described in the literature and arising from local experience are: (28-37).

a. Venous thrombosis-related events (31).

cana posible a cero y que la morbilidad que se presente, a pesar de los esfuerzos realizados, sea la que resulte en la menor discapacidad posible.

La mortalidad reportada a través de encuestas en la *American Society of Plastic Surgeons* (ASPS) en 1997 fue de 1 en 4.926 intervenciones; en el 2000, 1 en 5.224, según Grazer, aunque hay algunos reportes con cifras inferiores de 0 en 15.336 en liposucciones menores (16,22,23,24). En la *American Society for Aesthetic Plastic Surgery* (ASAPS) en el 2001, una encuesta reveló una mortalidad de 1 por 47.415 liposucciones; de 1 por 7.314 si se combinaba la liposucción con otros procedimientos, y de 1 por 3.281 cuando se había combinado la liposucción con abdominoplastia (25), 14 veces mayor que con liposucción exclusivamente. Aunque hay reportes como el de Grant (26), en el cual no tienen aumento del riesgo, su experiencia es particular si se considera que sus tiempos promedio son de 2,2 horas y su incidencia de transfusión y hospitalización fue de 0% en 406 casos. También, hay reportes en los que procedimientos prolongados no tuvieron morbilidad asociada; esta casuística se informó en un centro académico (Yale University School of Medicine) con los estándares para procedimientos quirúrgicos no plásticos. En un reporte crudo (sin análisis detallado de las historias clínicas) de Medellín, se detectaron 6 muertes de un total estimado de 30.896 cirugías, para una tasa de mortalidad es de 1 por 5.149 cirugías, muy similar a la encontrada en la literatura. Sin embargo, vale la pena anotar que son casos detectados a través de los médicos involucrados, luego, la posibilidad de subregistro es significativa (27).

Recomendaciones de seguridad

Como primera norma de seguridad, la sociedad Colombiana de Anestesiología y Reanimación, SCARE, reconoce las normas mínimas de seguridad en Anestesiología como de obligatorio cumplimiento en todo procedimiento en el cual intervenga un anestesiólogo. Dichas normas son, a demás, avaladas por la Confederación Latinoamericana de sociedades en Anestesiología, CLASA.

Las Normas Mínimas vigentes están en el sitio Web de las SCARE. www.scare.org.co

Las causas de morbilidad y mortalidad más comunes descritas en la literatura y por la experiencia local son (28-37):

Incidence ranges from 0.35% in rithydooplasty to 30% in combined procedures; (37,38).

b. Infections: these could be related to perforated viscera, infected fluid collections such as hematomas or serosas, or by contamination (39).

c. Fat embolism;

d. Pulmonary oedema;

e. Vascular lesions;

f. Other causes.

Based on this knowledge, the first topic to be dealt with should be preventing deep venous thrombosis (DVT) and pulmonary thromboembolism (PTE), given their frequency, morbimortality and that they can be prevented by preparing guidelines which are reasonable, acceptable and which can be applied by the professionals involved in managing these patients. Only 60% of the plastic surgeons in the USA know and apply such recommendations. (32,38) The objective in our setting is to ensure that the main cause of complications and deaths during plastic surgery becomes reduced and ensure that this indicator reaches the lowest possible levels.

Davison (31) has made an extensive review of prophylaxis in venous thrombosis during plastic surgery and this has been adopted in the Caprini model; (40) this scheme/algorithm is the most popular in the plastic surgery area.

It is proposed that this simple algorithm be adopted as this consensus' recommendation. Each patient's score must be noted on the anaesthetic record, thereby establishing a risk leading to designing recommendations regarding prophylaxis. These recommendations must be implemented according to the surgical team's practice. Publications such as that by Hafez (34) have demonstrated the benefits of implementing these strategies even in high-risk and very high-risk patients, thereby demonstrating that DVT/PTE incidence can be lowered by up to 80%.

a. Eventos relacionados con la trombosis venosa: 31. La incidencia va desde 0.35% en ritidoplastia hasta 30% en procedimientos combinados. (37, 38).

b. Infecciones: pueden relacionarse con perforación de víscera, infección de las colecciones como hematomas o serosas, o por contaminación (39).

c. Embolismo graso

d. Edema pulmonar

e. Lesiones vasculares

f. Otras

Con base en este conocimiento, el primer tema que se debe intervenir es la prevención de la trombosis venosa profunda y del tromboembolismo pulmonar, dada su frecuencia, morbimortalidad y posibilidad de prevención, mediante la elaboración de guías que sean razonables, aceptables y aplicables por los profesionales involucrados en el manejo de estos pacientes. En los Estados Unidos sólo el 60% de los cirujanos plásticos conoce y aplica las recomendaciones en este sentido (32,38). El objetivo en nuestro medio es poder disminuir la principal causa de complicaciones y muertes en cirugía plástica y llevar este indicador a los niveles más bajos posibles.

Una revisión muy difundida sobre la profilaxis en trombosis venosa en cirugía plástica es la de Davison (31) quien adoptó el esquema de Caprini (40). Este esquema/algorithm es el más popular en el área de cirugía plástica.

Se propone adoptar este algoritmo sencillo como la recomendación de este consenso. El puntaje de cada paciente debe anotarse en el hoja de anestesia, y con él se establece un riesgo que permite diseñar las recomendaciones de profilaxis. La implementación de estas recomendaciones se debe hacer según la práctica del equipo quirúrgico. Hay publicaciones, como la de Hafez (34), que demuestran las bondades de la implementación de estas estrategias aun en pacientes de riesgo alto y muy alto demostrando bajar la incidencia de trombosis venosa profunda y tromboembolismo pulmonar hasta en el 80%.

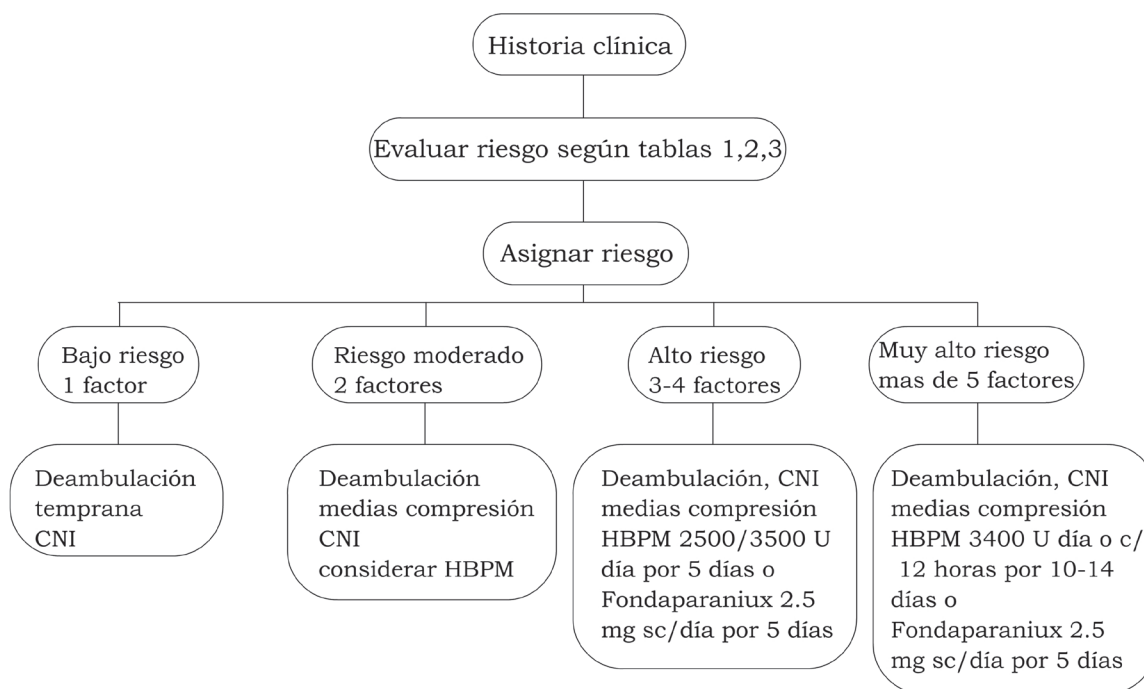


Figura 1. Modelo de evaluaci3n de riesgo de la SCARE y la Sociedad Colombiana de Cirug3a Pl3stica

Tabla 1. Puntuaci3n de los factores de riesgo

Puntos	Condiciones
1	Cirug3a menor Procedimiento $\geq$ 2 horas
2	Cirug3a mayor Procedimiento $\leq$ 2 horas Yeso inmovilizaci3n Permanencia en cama $\geq$ 72 horas
3-4	Cirug3a combinada con abdominoplastia Infarto de miocardio previo Colgajo libre
5	Fractura de cadera, pelvis, f3mur

Fuente: modificado Davison / Caprini

Tabla 2. Factores de riesgo predisponentes

Escenario cl3nico	Cong3nito	Adquirido
Edad 40 a 60 (1 Punto)	Cualquier alteraci3n de hipercoagulabilidad (3 Puntos)	Anticoagulante l3pico (3 Puntos)
Edad 40 a 60 (1 Punto)		Anticuerpos antifosfolipido (3 Puntos)
Edad > 60 (2 Puntos)		Enfermedades mieloproliferativas (3 puntos)
Embarazo o < 1 mes postparto (2 Puntos)		Trombocitopenia inducida por heparina (3 Puntos)
Enfermedad maligna (2 Puntos)		Hiperviscosidad (3 Puntos)
Obesidad > 30 IMC (1 Punto)		Homocistinemia (3 Puntos)
Obesidad > 35 IMC (2 Punto)		
Obesidad > 35 IMC (2 Punto)		

Tabla 3. Sumatoria de asignaci3n de riesgo (tablas 1 + 2)

Puntos	Condiciones
1	Bajo riesgo
2	Riesgo moderado
3-4	Alto riesgo
> 4	Altisimo riesgo

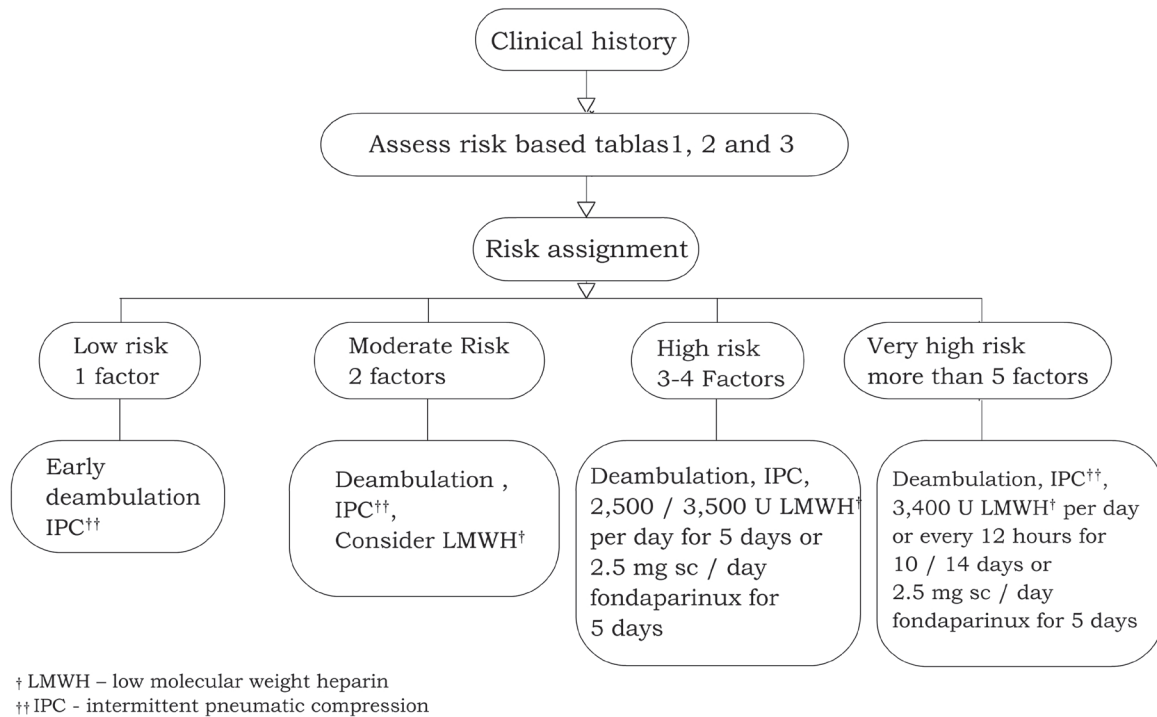


Figure 1. Risk model SCARE- Colombian Plastic Surgery Society

Table 1. Risk factors (point-score)

Points	Terms
1	Minor surgery (procedures lasting less than 2 hours)
2	Mayor surgery (surgery lasting more than 2 hours) Plaster immobilisation Staying in bed for more than 72 hrs
3-4	Surgery combined with abdominoplasty Prior myocardial infarction Free flap
5	Fracture of the hip, pelvis, femur

Source: Modified Davison / Caprini

Table 3. Additioning table 1 + 2

Points	Terms
1	Low risk
2	Moderate risk
3-4	High risk
> 4	Very high risk

Table 2. Predisposing risk factors

Clinical scenario	Congenital	Acquired
Age 40 - 60 (1 point)	Any alteration in hypercoagulability (3 points)	Lupus anticoagulant (3 points)
Age > 60 (2 points)		Antiphospholipid antibodies (3 points)
Background of DVT/PTE (3 points)		Myeloproliferative diseases (3 points)
Pregnancy or < 1 month postpartum (2 points)		Heparin-induced thrombocytopenia (3 points)
Malign disease Enfermage (2 Points)		Hyperviscosity (3 points)
Obesity > 30 IMC (1Point)		Homocystinaemia (3 Points)
Obesity > 35 IMC (2 Point)		
Oral contraceptive / hormone replacement therapy (1point)		

Algorithm for preventing deep-vein thrombosis (DVT): good position refers to a comfortable position, having partial flexing of the knees; intermittent pneumatic compression (IPC) until being discharged; elastic compression stockings (ECS) from preoperative period until to deambulation at home becomes standard; low-molecular-weight heparin (LMWH): in very high risk LMWH consider giving c/ 12hrs, in both cases until deambulation becomes standard (usually one week). Modified from Davison 2004 (31).

A group of increased risk patients was defined as follows:

- a. Patients having 5 or more risk factors for venous thrombosis;
- b. Patients undergoing procedures with sedation must be excluded from this scheme; CNI with or without ECS is only indicated in such patients, according to additional surgery points;
- c. Patients undergoing procedures lasting more than five hours (even though there are reports of safety regarding them, the literature is consistent in confirming that duration is a risk factor); (41)
- d. Patients undergoing large volume liposuction (defined as >5,000 mls) (42).
- e. Patients undergoing combined procedures including abdominoplasty;
- f. Patients arriving in cities located at high altitude (>2,000 mts) two or less than 2 days before surgery;
- g. Patients expecting to travel for 4 or more hours one week POP (appendix 1: SCCP and Aeronáutica Civil recommendations); and
- h. Patients receiving gluteal lipoinjections ¹.

It is proposed that this group of patients at increased risk be supervised by the surgeon treating the case at least 18 hrs POP (43). This implies that institutions carrying out these procedures must be able to carry out POP observation or

Algoritmo para la prevención de la trombosis venosa profunda: la “buena posición” se refiere a una posición cómoda, con las piernas en flexión parcial de rodillas, y de extremidades; CNI: compresión neumática intermitente durante la intervención quirúrgica hasta ser dado de alta; MEC: medias elásticas de compresión, desde el periodo preoperatorio hasta que la deambulación en casa sea normal; HBPM (heparina de bajo peso molecular): se debe considerar la posibilidad en pacientes de muy alto riesgo, administrándola cada 12 horas, en ambos casos hasta que la deambulación sea normal, generalmente una semana (modificado de Davison) (31).

Se define un grupo de pacientes con riesgo aumentado; estos pacientes son:

- a. Los pacientes con cinco factores o más de riesgo de trombosis venosa;
- b. De este listado se deben excluir los pacientes que se someten a procedimientos con sedación, en éstos solo se indica la compresión neumática intermitente con medias, elásticas de compresión o sin ellas según puntos adicionales a la cirugía.
- c. Los pacientes que se someten a procedimientos de más de cinco horas (aunque hay reportes de la seguridad de estos, la literatura es consistente en confirmar la duración como factor de riesgo) (41).
- d. Los pacientes que se someten a liposucciones de gran volumen (definidas como >5000 mls) (42).
- e. Los pacientes que se someten a procedimientos combinados que incluyan la abdominoplastia.
- f. Los pacientes que llegan a ciudades de gran altitud (>2000 metros sobre el nivel del mar), dos o menos días antes de la cirugía.
- g. Los pacientes que aspiren a viajar con una duración de 4 o más horas antes de una semana POP (anexo 1: recomendaciones de la SCCP y de la Aeronáutica Civil).
- h. Los pacientes que se someten a lipoinyecciones glúteas¹

1 Se sugirió en el foro de filiales, que se discuta con los cirujanos plásticos en cada sitio, la técnica utilizada en estos procedimientos, pues la percepción es que el riesgo de estos es muy alto, y que las técnicas quirúrgicas así como los elementos usados con muy variables. Se entiende que aún la SCCP no ha tomado posiciones oficiales al respecto. Existe muy escasa literatura al respecto.

domiciliary surveillance ². This seeks to identify signs of venous thrombosis, bleeding, fluid collections and early signs of other complications, such as infections (39).

- a. Haematocrite must be controlled prior to being discharged in increased risk procedures, except for e, f and g (44).
- b. Patients expecting to travel before one week POP must be made aware of express recommendations regarding the high risk of morbidity caused by venous thrombosis when adding perioperative risk regarding travelling and the surgeon's express authorisation.

All patients being cared for by an anaesthesiologist must have an explicit preanaesthetic evaluation, appended to the clinical history.

- a. Similar to recommendations in non-aesthetic surgeries, no routine preanaesthetic exam is recommended, beyond clinical indication or history.
- b. It is recommended that medicaments / substances having no clear pharmacology / interaction with anaesthetic medications (homeopathic or naturist drugs, ginkgo biloba etc.) should be suspended at least one week prior to operation (45-47).
- c. The anaesthetic technique must be that which the surgical team considers to be most appropriate according to its expertise and the patient's consent. There is a wealth of very good experience with regional (48) or general anaesthesia (27) or sedation techniques (49).
- d. It is recommended making the patient clearly aware in writing of the high risk of the interaction of substances such as cocaine, amphetamines, extasis and other recreational drugs and anaesthetic and vasoactive medicaments;
- e. It is recommended that such clarification be appended to the clinical history so that the patient signs it along with the informed consent form;
- f. It may be considered that a preoperative sample of urine/blood should be taken

Se propone que este grupo de pacientes de riesgo aumentado, sean supervisados por el cirujano tratante, al menos, durante 18 horas después de la cirugía (43). Esto implica que las instituciones que realicen estos procedimientos deben poseer estas disponibilidades de observación posoperatoria o vigilancia domiciliaria². Se busca identificación de los signos de trombosis venosa, sangrado, colecciones y signos precoces de otras complicaciones, como las infecciones (39).

En todos estos procedimientos de riesgo aumentado debe haber control del valor del hematocrito antes de darlos de alta, excepto los numerales e, f y g (44). Los pacientes que aspiren a viajar antes de una semana después de la cirugía deben tener recomendaciones expresas del alto riesgo de morbilidad por la trombosis venosa al sumar el riesgo perioperatorio al del viaje, y debe contar con la autorización expresa del cirujano.

Todo paciente que tenga cuidado por anestesiología, DEBE tener una evaluación preanestésica explícita, anexa a la historia. Similar a las recomendaciones en las cirugías no estéticas, no se recomienda ningún examen preanestésico rutinario, a no ser por indicación clínica o por historia. Se recomienda la suspensión, al menos, durante una semana antes de la intervención, de todo medicamento o sustancia que no tenga clara la farmacología e interacción con las medicaciones anestésicas (productos homeopáticos o naturistas, ginkgo biloba, etc.) (45-47).

La técnica anestésica debe ser la que el equipo quirúrgico considere más apropiada, de acuerdo con su experiencia y el consentimiento del paciente. Hay experiencias nacionales muy buenas con técnicas de anestesia regional (48), general (27) y sedación (49).

Se recomienda aclararle por escrito al paciente, el alto riesgo de la interacción de sustancias como la cocaína, las anfetaminas, el éxtasis y demás drogas de recreo y los medicamentos anestésicos y vasoactivos.

2 Se sugirió en el Foro de filiales que se defina la supervisión domiciliaria, para efecto de garantizar una vigilancia que sea suficiente para detectar los problemas que indican esta supervisión extendida de estos procedimientos de riesgo aumentado.

for toxicology analysis in case of adverse events, following the patient's consent. (50). If such consent is not forthcoming, then this must be recorded on the clinical history. If it is taken, then it should be clearly labelled and preserved until the patient is discharged; and

- g. An outpatient should be discharged by the doctor responsible for verifying the patient's state. This should never be delegated to non-medical personnel.

Other aspects which should be considered (42).

- a. All patients should receive antibiotic prophylaxis one hour before the incision. This may be administered during anaesthetic induction;
- b. Using Klein's solution (50 mg/kg maximum tolerable limit (51) and up to 35 mg/kg (52). if there are comorbidities considered to a risk for higher doses) (53).
- c. If a patient receives Anaesthesia, it is recommended reducing lidocaine dose in infiltration solution during liposuction;
- d. Using bupivacaine and/or other local anaesthetics different to lidocaine in tumescent solution is NOT recommended (42).
- e. It is recommended that lipid parenteral feed solutions (such as lipofundin) are available as an essential medicament for controlling toxicity events caused by local anaesthetics; (54 <http://lipidrescue.squarespace.com/laminates-instructions-and-lab/lipidrescue%20spa.pdf>)
- f. The effect of dermoclisis must be considered in liposuction for minimising the additional administration of fluids and avoiding hydric overload, a relatively frequent complication in liposuction (55).
- g. It is highly desirable that the surgeon in charge evaluates liposuction patients one day after the procedure has been performed (39).
- h. Any non-conventional substances which have been administered must be explicitly noted on patients' records, ensuring that all those used have a current INVIMA licence/record;

Se recomienda que se anexe esta aclaración para que el paciente la firme con el consentimiento informado.

Se puede considerar tomar una muestra de orina o de sangre preoperatoria para el análisis de toxicología en caso de eventos adversos, previo consentimiento del paciente (50). Si no da su consentimiento, debe quedar registrado en la historia clínica. Si se toman, deben ser claramente rotuladas y preservarse hasta dar de alta al paciente.

El alta del paciente ambulatorio debe ser hecha por un MÉDICO responsable de verificar el estado del paciente. Nunca puede ser delegada a personal no médico.

Otros aspectos por considerar (42).

- a. Todo paciente debe recibir profilaxis antibiótica en la hora anterior a la incisión. Puede administrarse durante la inducción anestésica
- b. Uso de solución de Klein con límites máximo tolerable de 50 mg/kg (51), y hasta 35 mg/kg 52 si hay enfermedades concomitantes que se consideren de riesgo para dosis más altas (53).
- c. Si el paciente recibe anestesia se recomienda disminuir las dosis de la lidocaína en la solución de infiltración en la liposucción.
- d. No se recomienda el uso de bupivacaína, u otros anestésicos locales diferentes a la lidocaína en la solución tumescente (42).
- e. Se recomienda disponer de soluciones de alimentación parenteral lipidos (tipo Lipofundin®) como medicamento esencial para controlar eventos de toxicidad por anestésico local. (54 <http://lipidrescue.squarespace.com/laminates-instructions-and-lab/lipidrescue%20spa.pdf>).
- f. El efecto de dermoclisis debe considerarse en la liposucción para minimizar la administración adicional de fluidos y evitar la sobrecarga hídrica, complicación relativamente frecuente en las liposucciones (55).
- g. Es altamente deseable que el cirujano evalúe los pacientes de liposucción un día después del procedimiento (39).
- h. Se debe anotar explícitamente en los registros del paciente las sustancias no con-

- i. Blood transfusion must be considered an undesirable event and strategies must be used for avoiding it due to its inherent risk;
 - j. Combining aesthetic/plastic procedures with non-plastic ones (e.g. gynaecological procedures such as hysterectomy, colporectomy) must be avoided due to the high risk of morbidity (infections, increased risk of DVT, etc.); and
 - k. Patients undergoing plastic surgery must be encouraged to take out an insurance policy against hospitalisation / complications.
- vencionales que se administren, procurando que todas las que se usen tenga registro vigente del INVIMA.
 - i. La transfusión sanguínea debe considerarse un evento indeseable, por lo tanto deben usarse estrategias para evitarla, por el riesgo inherente que poseen.
 - j. La combinación de procedimientos estéticos o plásticos con no plásticos (por ejemplo: procedimientos ginecológicos, como histerectomía, colporrafia) deben evitarse por el alto riesgo de morbilidad (infecciones, aumento del riesgo de trombosis venosa profunda, etc.)
 - k. Se debe incentivar la toma de pólizas de seguros de hospitalización o complicaciones por los pacientes de cirugía plástica

Conflicto de intereses: ninguno declarado.

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Consenso de enfermedad tromboembólica

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1. GRADOS DE RECOMENDACIÓN

Clase I: Existe evidencia y/o consenso general de que el procedimiento es útil y efectivo.

Clase II: La evidencia es contradictoria o hay conflicto en la opinión sobre la utilidad y/o eficacia del procedimiento.

Clase IIa: El peso de la evidencia o la opinión de expertos se inclina a favor de su utilidad y su eficacia.

Clase IIb: La utilidad o la eficacia está menos establecida por la evidencia o por la opinión de expertos.

2. NIVELES DE EVIDENCIA

Nivel de evidencia A: Evidencia sólida, proveniente de estudios aleatorizados o metaanálisis.

Nivel de evidencia B: Evidencia derivada de un solo estudio clínico aleatorizado.

Nivel de evidencia C: Consenso de expertos, estudios retrospectivos o registros.

3. INTRODUCCIÓN

La tromboembolia pulmonar es una de las causas más frecuentes de muerte en los pacientes internados e incluye un solo proceso patológico con dos componentes esenciales: la trombosis venosa profunda (TVP) y la embolia pulmonar (TEP), constituyendo ambas la denominada enfermedad tromboembólica. (1) Pasada la etapa aguda, todavía se ciernen amenazas sobre ellos: el síndrome posttrombótico, la hipertensión pulmonar y la recurrencia.

La enfermedad tromboembólica es la tercera causa de morbilidad cardiovascular después de la cardiopatía isquémica y la enfermedad cerebrovascular. Su incidencia anual está próxima a 100 casos/100.000 habitantes y su prevalencia en la población hospitalizada alcanza el 1%. En 1975, Dalen y colaboradores,

(1) sobre la base de diversos factores epidemiológicos y hallazgos patológicos, resumieron una historia natural para la enfermedad tromboembólica. La mayoría de los decesos se producen en las primeras horas (Figura 1). En este grupo de temprana mortalidad solamente la profilaxis la disminuirá en forma significativa. De los que sobreviven y pueden acceder a un tratamiento adecuado, la mortalidad es del 6-10%, pero puede alcanzar el 25-30% en los casos no diagnosticados y no tratados. Las estadísticas actuales son similares a las publicadas en 1975, lo que demuestra lo poco que se ha avanzado en el diagnóstico temprano de esta patología. Se estima que aún hoy el 70% de los casos no son diagnosticados. Esta situación refuerza la necesidad de, por una parte, mejorar la prevención y, por otra, intensificar las estrategias de diagnóstico precoz, comenzando por un cambio en la actitud médica, ya que es la sospecha clínica el primer eslabón ineludible de esta cadena. (2)

4. CONSIDERACIONES FISIOPATOLÓGICAS

La gravedad del daño producido por estas embolias es en gran medida proporcional a su tamaño; es por ello que la mayor parte de las que generan manifestaciones clínicas provienen de los miembros inferiores, especialmente de las venas ilíacas y femorales. Otras localizaciones, como las venas de los miembros superiores, la pelvis, la vena cava inferior y también las cavidades derechas del corazón son fuentes alternativas menos frecuentes.

El compromiso hemodinámico será tanto más grave cuanto más proximal sea la localización y cuanto mayor sea el grado de obstrucción e inversamente proporcional a la reserva cardiopulmonar del paciente. En ocasiones, los trombos son los suficientemente friables como para que el flujo pulsátil los fragmente y los desplace hacia la periferia de la circulación

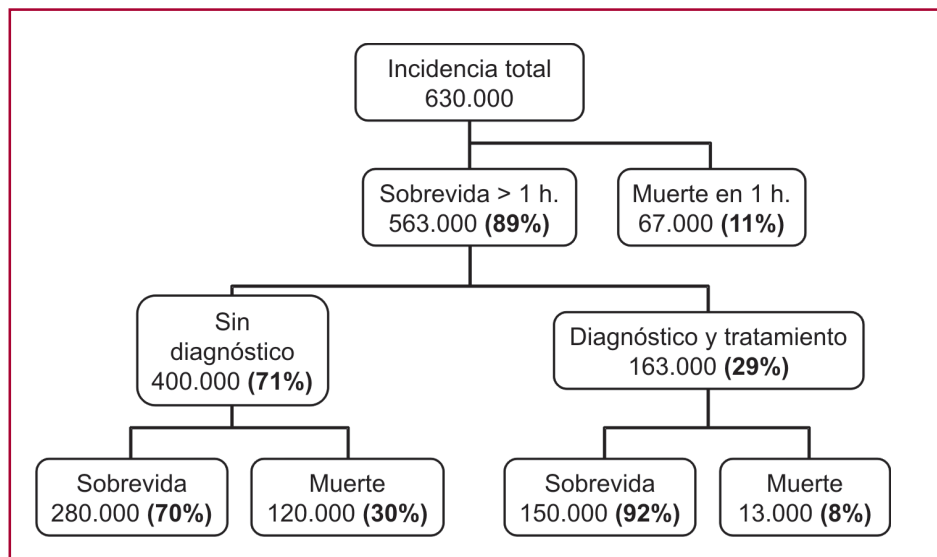


Fig. 1. Incidencia de embolia pulmonar por año en los Estados Unidos.

pulmonar, en donde el área de sección es mayor y, en consecuencia, el daño a la hemodinamia disminuye. Más del 50% de los émbolos son múltiples y en la mayoría de los casos están comprometidos los lóbulos inferiores, unilateral o bilateralmente. (3)

Los trombos más pequeños se alojan directamente en la periferia, con la producción de un impacto hemodinámico menor y a menudo son responsables de un proceso inflamatorio próximo a la pleura que produce dolor pleurítico, que no necesariamente implica infarto pulmonar.

Los trombos de mayor volumen pueden quedar atrapados transitoriamente en la aurícula derecha o entre las cuerdas tendinosas de la válvula tricúspide y los músculos papilares del ventrículo derecho (trombos en tránsito) y ser detectables mediante ecocardiografía. (4)

La asociación de trombos en tránsito con la presencia de un foramen oval permeable es especialmente grave, porque los trombos se cruzan con facilidad de la aurícula derecha hacia la aurícula izquierda y provocan embolias en el circuito arterial periférico. Su desplazamiento en este sentido se ve facilitado por el aumento en la presión auricular derecha, a consecuencia de la hipertensión pulmonar producida por embolias pulmonares previas.

5. FACTORES DE RIESGO

Los factores de riesgo primarios y secundarios conocidos están en relación con la clásica tríada que Virchow describió en el siglo XIX (estasis venosa, hipercoagulabilidad sanguínea y lesiones en las paredes vasculares); los más importantes se resumen en la Tabla 1.

La predisposición congénita a la trombosis se considera relativamente frecuente, pero su verdadera pre-

valencia en nuestro medio no se conoce. Debe pensarse en pacientes con TVP inexplicada, en personas menores de 40 años o con TEP o TVP recurrente y/o historia familiar positiva. (6)

La incidencia de fenómenos trombóticos aumenta con la edad hasta la octava década. Con respecto al sexo, es ligeramente más frecuente en hombres que en mujeres.

La recidiva de los fenómenos tromboembólicos se presenta con mucha más frecuencia en el sexo masculino.

La enfermedad tromboembólica se ha comunicado en el 30-60% de los pacientes con accidentes cerebrovasculares, en el 5-35% de los pacientes con infarto agudo de miocardio y en el 12% de los pacientes con insuficiencia cardíaca congestiva cuando no reciben profilaxis.

La inmovilización aun por lapsos cortos (mayores de 3 días) predispone a TVP. La frecuencia de TVP en pacientes sometidos a una simple cirugía de hernia puede ser de hasta el 5%, en cirugías mayores abdominales es del 15% al 30%, en la de cadera es del 50-70% y en lesiones medulares graves es del 50% al 100%.

Debemos tener en cuenta que el 25% de las embolias posoperatorias pueden producirse luego del alta hospitalaria.

El 70-90% de los trombos están en el área de la vena cava inferior, generalmente a nivel de venas femorales o ilíacas. Algunos estudios recientes mostraron un incremento de la incidencia de compromiso de venas pelvianas: periprostáticas o periuterinas.

En el 10-20% de los casos, los trombos se originan en el territorio de la vena cava superior y su frecuencia se ha incrementado en relación con los procedimientos invasivos diagnósticos y terapéuticos que se realizan en la actualidad (catéteres, marcapasos, quimioterapia, etc.).

6. PREVENCIÓN DE LA TVP (7-10)

Registros realizados en distintos países demuestran que cerca de la mitad de los pacientes que necesitan prevención no la reciben en absoluto o reciben profilaxis inadecuada a su riesgo.

6.1 Métodos de profilaxis de la TVP (Tabla 2)

La profilaxis incluye métodos mecánicos y farmacológicos. Estos últimos son los que se han estudiado más extensamente y son la primera indicación. Los métodos mecánicos se emplean cuando los farmacológicos están contraindicados o como complemento de ellos en casos de mayor riesgo.

a. Métodos mecánicos

Se emplean muy poco en nuestro medio, a pesar de que su utilidad está relativamente comprobada. Se encuentran en marcha varios estudios para evaluarlos. No son tan eficaces como los farmacológicos, por lo que en cuanto la contraindicación que impidió su empleo esté superada, debe volverse a ellos.

Tabla 1. Factores de riesgo (5)

Factores primarios	Factores secundarios
Deficiencia de antitrombina III	Traumatismos
Síndrome antifosfolipídico	Reposo en cama (> 3 días)
Factor V de Leyden	Cirugía
Mutación de la protrombina 20210	Accidente cerebrovascular
Deficiencia de proteína C	Edad avanzada
Deficiencia de proteína S	Insuficiencia cardíaca
Deficiencia de factor XII	Enfermedad pulmonar crónica
Disfibrinogenemia	Neoplasias
Deficiencia de plasminógeno	Síndrome nefrótico
Hiperhomocisteinemia	Enfermedad de Crohn
	Viajes prolongados
	Embarazo/puerperio/anticonceptivos

- Compresión mecánica intermitente

El modo de acción de la compresión mecánica intermitente (CMI) no está totalmente aclarado. Algunos piensan que actuarían incrementando el flujo sanguíneo en las venas de los miembros inferiores. Otros atribuyen su acción a las sustancias fibrinolíticas liberadas por la compresión de las paredes venosas.

- Medias de compresión graduada

La medias de compresión graduada (MCG), al comprimir de manera decreciente desde la pantorrilla hacia la raíz del muslo, actúan incrementando el flujo sanguíneo. Son efectivas en pacientes con un riesgo quirúrgico moderado y se pueden combinar con métodos farmacológicos en pacientes de alto riesgo.

Las limitaciones son: a) no está demostrado fehacientemente que las MCG reduzcan el riesgo de TEP mortal, b) hay poca experiencia sobre su uso en pacientes no quirúrgicos, c) algunos pacientes no toleran su colocación y d) deben utilizarse con especial cuidado en los pacientes que padecen isquemia de los miembros inferiores.

Son muy útiles en la prevención de la recidiva y del proceso posflebítico. Todo paciente que ha padecido una enfermedad tromboembólica debería utilizar medias de compresión graduada desde que comienza la deambulación y por un lapso de dos años.

b. Métodos farmacológicos

- Heparina no fraccionada (HNF) subcutánea

Es el método usado con más frecuencia en la profilaxis de la TVP.

Hay un incremento del riesgo de hematomas posquirúrgicos, pero no de sangrado mayor o mortal. Las contraindicaciones de la heparina incluyen: trastornos hemorrágicos previos, sangrado activo, lesiones potencialmente sangrantes (úlceras activas, várices esofágicas, hipertensión grave, endocarditis) y también las primeras horas de la anestesia epidural. Puede ocurrir trombocitopenia en el 0,3% de los pacientes que reciben heparina profiláctica.

La dosis recomendada es de 5.000 U cada 12 horas para los enfermos de menor riesgo y de 5.000 U cada 8 horas para los de riesgo intermedio.

Sigue siendo la primera indicación para los pacientes con insuficiencia renal y los ancianos mayores de 75 años.

Todos los enfermos que reciben heparina (de cualquier tipo, HNF, HBPM, etc.) deben tener un hemograma con recuento de plaquetas al inicio de la terapéutica. Para los pacientes que recibieron heparina en los últimos 100 días se sugiere un recuento plaquetario antes y otro 24 horas después. Se recomienda un nuevo control al cuarto día y si se requiere continuar con el tratamiento, reiterar los controles cada 2 a 4 días.

- Heparinas de bajo peso molecular (HBPM)

Tienen algunas ventajas importantes: 1) la posibilidad de su administración en una sola dosis diaria, 2)

la menor incidencia de sangrado y 3) la menor incidencia de trombocitopenia.

Algunos estudios indican superioridad frente a la HNF, especialmente en los enfermos de mayor riesgo.

Su inconveniente más importante es su costo más elevado.

Las dosis de las drogas más utilizadas en nuestro medio se encuentran detalladas en la Tabla 2.

- Pentasacáridos

Los pentasacáridos son inhibidores selectivos del factor X activado. Recientemente se ha incorporado en nuestro medio el fondaparinux (Tabla 2).

Según los estudios, una inyección subcutánea diaria de estas drogas produce una reducción de la flebotrombosis profunda superior a las heparinas de bajo peso molecular, especialmente en los pacientes de cirugía ortopédica. Tiene las siguientes ventajas: 1) al ser un anti X puro, no interactúa con las plaquetas y, por lo tanto, no produce trombocitopenia, 2) en cirugía ortopédica, la primera dosis de profilaxis se aplica 6 a 24 horas después de finalizada la cirugía, lo que permite evaluar previamente el sangrado perioperatorio y 3) tiene una vida media más prolongada (17 horas).

No tiene un antagonista específico. Se sugiere no utilizarlo en pacientes con depuración de creatinina inferior a 30 ml/min.

- Anticoagulantes orales

Se han utilizado los dicumarínicos y se ha demostrado que son efectivos en pacientes con riesgo mediano y alto de TVP. La warfarina es el agente que más se ha estudiado. Se ha empleado en dosis bajas o en dosis escalonadas.

Su uso se reservaría para las profilaxis por tiempos prolongados, manteniendo una RIN de entre 2 y 3.

Nuevos anticoagulantes orales: se encuentran en estudio tres nuevas drogas. Un antitrombótico directo, el dabigatrán, que está ya disponible en nuestro medio, y dos anti X, apixabán y rivaroxabán, que están en un estado avanzado de desarrollo.

La dosis de dabigatrán en profilaxis de TVP es de 220 mg/día. En los operados se recomienda comenzar con 110 mg dentro de las 4 horas del posoperatorio y al día siguiente continuar con la dosis de 220 mg.

Tabla 2. Dosis de las drogas más utilizadas en nuestro medio

Heparina de bajo peso molecular	Dosis usual para profilaxis
Enoxaparina	40 mg por vía s.c./día
Nandroparina	3.400 UAXa por vía s.c./día
Dalteparina	5.000 U por vía s.c./día
Pentasacárido	
Fondaparinux	2,5 mg por vía s.c./día

Se aconseja no emplearlo con depuración de creatinina menor de 30 ml/min.

No tiene antagonista específico.

- Agentes antiplaquetarios

Drogas como el ácido acetilsalicílico (AAS), el dipiridamol y la ticlopidina no se han mostrado eficaces y no están indicadas en la prevención de la TVP.

La prevención de la TVP en pacientes quirúrgicos se esquematiza sobre la base de los distintos factores de riesgo, como se muestra en la Tabla 3.

6.2 Recomendaciones generales para la prevención de TVP (10)

Clase I

Los pacientes de bajo riesgo menores de 40 años con cirugías menores que van a permanecer en reposo por menos de 3 días no necesitan métodos de profilaxis. Lo mismo se recomienda para pacientes clínicos de bajo riesgo menores de 40 años internados por lapsos cortos (< 3 días).

Solamente se recomienda la movilización precoz frecuente (A).

Los pacientes sometidos a cirugía laparoscópica y que no presentan riesgo adicional no requieren profilaxis (A). (11, 12)

Clase I

- Heparinas de bajo peso molecular (A).
- Fondaparinux (A).
- Heparina sódica 5.000 U c/12 horas para los pacientes de riesgo bajo (A).

- Heparina sódica 5.000 U c/8 horas para los pacientes de mayor riesgo (A).
- Para enfermos con múltiples factores de riesgo clínico o quirúrgico, a los que se considera de muy alto riesgo, se recomienda HNF 5.000 UI, 3 veces al día, o HBPM o fondaparinux, asociado con un método mecánico (MCG o CMI) (C).

Es muy importante tomar en cuenta la función renal cuando se emplean estas drogas, especialmente las que se eliminan por esta vía (HBPM, fondaparinux). En pacientes con depuración de creatinina menor de 30 ml/min, o creatinina plasmática superior a 2,5 mg/dl, sugerimos el empleo de HNF.

Clase I

- Manguitos de compresión neumática (B).
- Medias elásticas de compresión graduada (B). Estos métodos se recomiendan para los pacientes que no pueden recibir drogas antitrombóticas y para los de muy alto riesgo asociado con ellas.

Se desaconseja el empleo de aspirina como prevención de enfermedad tromboembólica en todos los casos (A).

6.3 Consideraciones sobre profilaxis en situaciones especiales

a. Unidad coronaria (13) y cirugía cardiovascular (14)

Para los pacientes con infarto de miocardio, insuficiencia cardíaca descompensada, edema pulmonar y en general pacientes cardiológicos que no van a deam-

Tabla 3. Niveles de riesgo de TEP en pacientes quirúrgicos sin profilaxis (9)

Riesgo	Distal	Proximal	Clínica	Mortal	Estrategia
Bajo Cirugía menor en paciente < 40 años sin otro factor de riesgo	2%	0,4%	0,2%	< 0,01%	Movilización precoz
Moderado Cirugía menor en paciente con un factor de riesgo Cirugía en pacientes de 40-60 años sin factores de riesgo	10-20%	2-4%	1-2%	0,1-0,4%	HNF c/12 h HBPM/día MCG CMI
Alto Cirugía en pacientes mayores de 60 años, o de entre 40 y 60 años con un factor de riesgo (TVP previa, hipercoagulación, cáncer)	20-40%	4-8%	0,4-1%	0,4-1%	HNF c/8 h HBPM/día Fondaparinux CMI
Muy alto Cirugía en pacientes con múltiples factores de riesgo (edad > 40 años, cáncer, TVP previa) Cirugía o fractura de cadera o rodilla Politrauma, lesión medular	40-80%	10-20%	4-10%	0,2-5	HBPM/día Fondaparinux, HNF/HBPM + CMI/MCG

HNF: Heparina sódica no fraccionada. HBPM: Heparina bajo peso molecular. CMI: Compresión mecánica intermitente. MCG: Medias de compresión graduada.

Geerts, et al. Chest 2004;126:3385-4005.

bular por un lapso superior a tres días y que no están bajo tratamiento anticoagulante, se sugiere efectuar profilaxis con antitrombóticos.

Clase I

- HNF, HBPM (B), fondaparinux (C).

El fondaparinux tiene más incidencia de trombosis en catéter que la enoxaparina. Si el paciente va a ser cateterizado, debe recibir una dosis de HNF, que se estima en 5.000 UI.

Para los pacientes en recuperación de cirugía vascular sin factor de riesgo se recomienda solamente deambulación frecuente y precoz.

Para los pacientes con factores de riesgo se recomienda profilaxis con antitrombóticos.

Clase I

- HNF, HBPM (B), fondaparinux (C).

Para enfermos sometidos a cirugía cardíaca (puentes aortocoronarios) se recomienda efectuar profilaxis.

La misma recomendación es válida para la cirugía torácica.

Clase I

- HBPM, HNF (C).
- CMI o MCG para los enfermos que no pueden recibir antitrombóticos (C).

b. Terapia intensiva (15)

Los enfermos críticos tienen múltiples factores de riesgo para TVP; algunos de ellos son: cirugía mayor reciente, politrauma, sepsis, ACV, edad avanzada, insuficiencia cardíaca o respiratoria, TVP previa o quemaduras extensas. Otros factores de riesgo se van adquiriendo durante la internación, como inmovilización prolongada, sedación o parálisis, vías centrales, asistencia respiratoria, diálisis, etc. La incidencia comunicada varía entre el 10% y el 90%, lo que refleja la gran variabilidad de los enfermos críticos.

Clase I

- HNF (A), HBPM (A), fondaparinux (A).
- Métodos mecánicos para los que no pueden recibir antitrombóticos (A).

c. Quemados (16)

Los pacientes con quemaduras extensas presentan un estado de hipercoagulabilidad sistémica importante, al que se le suman el efecto del reposo prolongado, las cirugías repetidas, los catéteres y los episodios sépticos repetidos.

Clase I

- HNF (A), HBPM (A).

Clase I

- Para los pacientes con riesgo de sangrado se recomienda tromboprofilaxis mecánica con MCG o CMI (A).

d. Lesión medular (17)

Más del 50% de los pacientes con lesiones medulares traumáticas presentan TVP cuando son controlados sistemáticamente. A pesar de conocerse el alto riesgo, la TEP sigue siendo la tercera causa de muerte en estos pacientes y su incidencia no ha disminuido en los años recientes.

La profilaxis con heparina no fraccionada, la compresión mecánica y/o las medias de compresión graduada solas no parecen ser efectivas. Su asociación o la utilización de heparina de bajo peso molecular está recomendada.

Clase I

- HBPM una vez que se obtiene una hemostasia adecuada (A).
- HNF con un método mecánico (B).
- En los pacientes con riesgo de sangrado o con un hematoma en el canal medular se recomiendan los métodos mecánicos (C).

e. Politraumatizados (18)

Los pacientes politraumatizados tienen un riesgo alto de desarrollo de TVP; sin profilaxis, estos pacientes la padecen en el 50% de los casos y la TEP es la tercera causa de muerte en los que sobreviven al primer día de internación.

Sobre la base de numerosos estudios, los factores que se asociaron con un incremento del riesgo incluyen lesión medular espinal, fractura de pelvis o extremidades inferiores, necesidad de cirugía, catéter venoso femoral e inmovilidad prolongada.

Clase I

- HBPM una vez que se obtiene una hemostasia adecuada (A).
- En los pacientes con riesgo de sangrado usar métodos mecánicos hasta que se pueda emplear HBPM (C).
- En los pacientes de más riesgo se sugiere asociar HBPM con un método mecánico (B).

f. Neurocirugía (19)

Los pacientes neuroquirúrgicos presentan un riesgo posoperatorio moderado de TVP, por lo que la profilaxis debe ser obligatoria. Los factores de riesgo más frecuentemente asociados con la TVP son la cirugía intracraneal (más que la medular), la presencia de cáncer activo, la duración de la cirugía, la debilidad prolongada y la edad avanzada. Los pacientes con tumores cerebrales malignos tienen un particular riesgo muy aumentado de TVP.

Clase I

- CMI hasta que se pueda usar HBPM o HNF (B).
- HBPM o HNF en el posoperatorio 12 a 24 horas después de la cirugía.
- Continuar con CMI + HBPM en los pacientes de alto riesgo.

g. Cirugía de cadera (11)

Los pacientes sometidos a cirugía de reemplazo de cadera tienen un riesgo alto de TVP y los estudios realizados por flebografía han mostrado una incidencia del 50%. La incidencia de TEP mortal está comunicada en un rango del 1,4% al 7,5% dentro de los 3 meses de la cirugía.

Las heparinas de bajo peso molecular y especialmente los pentasacáridos tienen mayor efectividad en la prevención a expensas de un incremento en el costo. (20)

Está altamente recomendado que estos pacientes reciban una extensión de la profilaxis hasta los 28 a 35 días posteriores a la cirugía. Las opciones aceptadas son el fondaparinux, la heparina de bajo peso molecular o los anticoagulantes orales.

Clase I

- Fondaparinux 2,5 mg, comenzando en el posoperatorio, 6 a 24 horas luego de la cirugía (A).
- HBPM. Se puede comenzar en el prequirúrgico, 12 horas antes, o en el posoperatorio, 12 a 24 horas después de la cirugía (A).
- Si el riesgo de sangrado es elevado, se puede comenzar la profilaxis con métodos mecánicos hasta que disminuya (A) y luego rotar a antitrombóticos o asociarlos si el riesgo es alto (C).

h. Cáncer (11, 12)

El cáncer es un estado hipercoagulable que incrementa el riesgo de la enfermedad tromboembólica venosa.

Los mecanismos patogénicos de la trombosis en pacientes neoplásicos se debe a una compleja interacción entre las células tumorales con el sistema hemostático, que genera una activación en el sistema de la coagulación, inhibición de los factores anticoagulantes y del sistema fibrinolítico, junto con un daño endotelial importante, que desembocan en un estado hipercoagulable. Además, cabe destacar que los factores extrínsecos también desempeñan un papel fundamental en la fisiopatogenia, como son la cirugía, la quimioterapia y la colocación de catéteres endovenosos.

El paciente con cáncer presenta un incremento seis veces mayor del riesgo de enfermedad tromboembólica en comparación con el individuo sin esa patología. Cuando el cáncer se halla en actividad, produce casi el 20% de la totalidad de los nuevos episodios de enfermedad tromboembólica que ocurren en la población general. Cuando el paciente con cáncer es sometido a cirugía, en el posoperatorio presenta, como mínimo, el doble de riesgo de TVP y el triple de riesgo de TEP mortal que los pacientes sin cáncer sometidos a un procedimiento quirúrgico similar.

Por otra parte, el cáncer también es un predictor de respuesta disminuida a la profilaxis.

i. Viajes de larga distancia (21)

En viajes prolongados, en vuelos o en ómnibus, en los que se permanece sentado por más de 8 horas se reco-

mienda vestir ropas sueltas, evitar la compresión de los miembros inferiores, mantener una buena hidratación y efectuar ejercicios con los miembros inferiores, procurando la contracción de los músculos de las pantorrillas (Clase I -C-). En los pacientes de riesgo aumentado se recomienda el uso de medias de compresión graduada (Clase II -C-) o una dosis única de HBPM previo a la partida (Clase II -C-).

j. Profilaxis prolongada

Algunos enfermos requieren profilaxis extendida más allá de su internación:

- Pacientes clínicos o quirúrgicos que deben permanecer en reposo en cama luego del egreso hospitalario, mientras dure el reposo (Clase I -A-).
- Pacientes con cirugía ortopédica compleja: reemplazo total de cadera, reemplazo total de rodilla (Clase I -A-).
- Paciente con cirugía abdominopelviana por cáncer (Clase I -B-).

La duración de la profilaxis se extiende por un período de 2 a 4 semanas y puede realizarse con alguno de los antitrombóticos ya mencionados.

k. Profilaxis y analgesia neuroaxial

El empleo posoperatorio de anestesia neuroaxial prolongada es cada vez más frecuente. Cuando concluye, se debe retirar su catéter con el mínimo efecto antitrombótico, es decir, en el horario de la siguiente dosis de profilaxis, dosis que se debe diferir por 2 horas.

7. DIAGNÓSTICO DE TVP (22)

El diagnóstico de TVP basado exclusivamente en la clínica es poco confiable. Más del 70% son asintomáticas y el 50% de los diagnósticos clínicos de TVP son erróneos. Los hallazgos más comunes, edema y dolor, son inespecíficos y el signo clínico más específico, que es el edema unilateral, sólo se presenta en el 10% de los pacientes; por lo tanto, casi siempre se requiere un estudio confirmatorio. Por otra parte, el edema unilateral puede aparecer, por ejemplo, en un miembro inferior pléjico en ausencia de trombosis.

La venografía se ha descripto como el método patrón para el diagnóstico de TVP de los miembros inferiores, pero es invasivo y no siempre accesible en todos los hospitales. En la Tabla 4 se comparan los distintos métodos, sus ventajas, desventajas, sensibilidad y especificidad en el diagnóstico de TVP.

Los nuevos tomógrafos *multislice* de alta velocidad pueden tomar las imágenes arteriales pulmonares y las de todo el sistema venoso con la misma inyección de contraste. Lo que no se puede evitar es el incremento de la radiación que asocia con la toma de una cantidad mayor de imágenes. En este sentido se han levantado voces de alarma, especialmente cuando se estudian pacientes jóvenes.

8. DIAGNÓSTICO DE TEP

8.1 Manifestaciones clínicas

Los síntomas y los signos de embolia pulmonar son de baja sensibilidad e inespecíficos (Tabla 5). Sin embargo, el estudio diagnóstico de embolia pulmonar se basa fuertemente en la probabilidad clínica de que ésta exista, que puede ser alta, mediana o baja según el grado de riesgo y la suma de síntomas y signos que la sugieren.

Aun considerando su bajo poder predictivo, conviene tener presente que los síntomas y los signos encontrados con más frecuencia son disnea, dolor pleurítico, taquipnea y taquicardia. La presencia de un cuarto ruido o un reforzamiento del componente pulmonar del segundo ruido son, en cambio, infrecuentes pero de mayor especificidad. Cuanto mayor sea el número de estos síntomas y signos, mayor será la probabilidad clínica de que el paciente efectivamente haya sufrido una embolia. Los exámenes auxiliares corrientes no modifican el valor predictivo del cuadro clínico. (23)

Lógicamente, es importante relacionar el cuadro clínico del paciente con los factores de riesgo.

La embolia pulmonar debe considerarse altamente probable frente a tres síndromes clínicos, que pueden presentarse en forma aislada o en conjunto:

Disnea aguda de causa desconocida. Estos pacientes presentan un cuadro de disnea súbita, taquipnea y taquicardia. El electrocardiograma y la radiografía de tórax pueden ser normales. Esta disnea puede manifestarse en forma intermitente, de tal forma que cuando el paciente es asistido el episodio ha concluido.

Hemoptisis y/o dolor pleurítico. Los enfermos con esta condición presentan al menos tres de las cuatro manifestaciones siguientes: dolor pleurítico, disnea, hemoptisis y un infiltrado radiográfico. Puede haber también fiebre, frotos pleurales y leucocitosis, que obligan al diagnóstico diferencial con neumonía.

Shock cardiogénico. Es la manifestación crítica de la embolia masiva. Los pacientes generalmente presentan algún grado de compromiso del estado de conciencia, angustia, disnea pronunciada, en ocasiones dolor torácico opresivo que hace sospechar un infarto del miocardio, acentuación del segundo ruido pulmonar y signos de shock.

8.2 Laboratorio de rutina (24)

No es de utilidad diagnóstica. Pueden existir cambios inespecíficos, como aumento de la eritrosedimentación y leucocitosis.

8.3 Radiografía de tórax

En los pacientes con patología previa, la radiografía de tórax tiene escaso valor. Sus manifestaciones dependerán en buena medida de éstas.

En el estudio PIOPED I en pacientes con TEP y sin patología cardiovascular previa, los hallazgos más frecuentes son los que se describen en la Tabla 6.

8.4 Electrocardiograma

Sus hallazgos dependen del nivel de hipertensión pulmonar y de la presencia de enfermedad cardiopulmonar preexistente.

En 117 pacientes sin patología cardiopulmonar incluidos en el estudio PIOPED, el 30% de los ECG fueron normales y el 70% restante presentó alteraciones inespecíficas; la anomalía más frecuente fue la taquicardia sinusal.

Los patrones $S_1 Q_3 T_3$ y $S_1 S_2 S_3$ se describieron en menos del 12% de los pacientes. La presencia de alteraciones del segmento ST y de la onda T se observa en las dos terceras partes de los casos. La inversión de la onda T en las derivaciones precordiales, así como la presencia de BCRD agudo, se relacionaron con la magnitud de la TEP, el aumento de la presión pulmonar y la gravedad de la disfunción del ventrículo derecho. Ocasionalmente, la elevación del segmento ST en las derivaciones V1, V2 y V3 tienen una magnitud y una morfología tales que pueden confundir con el diagnóstico de infarto agudo de cara anterior, aunque en realidad estos cambios son representativos de la lesión y la isquemia del ventrículo derecho.

La presencia de alteraciones agudas del ECG, ya sean arritmias, bloqueo de rama derecha, patente $S1Q3$ o alteraciones del segmento ST se asocia con una mortalidad mayor a los 30 días (29% versus 11%).

8.5 Gases en sangre y gradiente alveoloarterial de O_2

En la mayoría de los casos, el patrón gasométrico muestra hipoxemia, hipocapnia, alcalosis respirato-

Método	Sensibilidad	Especificidad	Costo	Desventajas
Flebografía	100%	100%	Bajo	Invasiva Contraste Rx
Doppler	66-90%	85-95%	Muy bajo	Dependiente del operador
TACHMI	95-100%	95-100%	Moderado	Contraste Rx Se realiza con TAC de Tx
RMN	90-97%	100%	Alto	Poco accesible

TACHMI: Tomografía computarizada helicoidal de miembros inferiores. RMN: Resonancia magnética nuclear.

Tabla 4. Métodos diagnósticos de TVP

Tabla 5. Valor diagnóstico de síntomas y signos aislados en la embolia pulmonar*

Signo o síntoma	Sensibilidad (%)	Especificidad (%)	VPP (%)	VPN (%)
Disnea	73	28	32	31
Dolor pleurítico	66	41	34	66
Estertores crepitantes	51	60	38	28
Cuarto ruido	24	86	45	29
Segundo ruido	23	87	45	30

Modificada de Stein, et al. Chest 1991;100:598-603.* Pacientes sin enfermedad cardiopulmonar previa.VPP: Valor predictivo positivo. VPN: Valor predictivo negativo.

Tabla 6. Anormalidades más frecuentes halladas en la radiografía de tórax en la TEP

Anormalidades (n = 2.315)	%
Cardiomegalia	27
Derrame pleural	23
Elevación diafragmática	20
Agrandamiento de la arteria pulmonar	19
Atelectasia	18
Infiltrado intersticial	17
Congestión pulmonar	14
Oligohemia	8
Infarto de pulmón	5
Hiperinsuflación	5

ria y aumento del gradiente alveoloarterial de O_2 . Esta combinación, en ausencia de otro diagnóstico alternativo, debería despertar la sospecha de embolia pulmonar.

La presencia de una PaO_2 normal no excluye el diagnóstico de TEP.

En la TEP masiva con shock e insuficiencia respiratoria puede haber hipercapnia con acidosis respiratoria simple, que puede ser mixta cuando el aumento del ácido láctico aporta el componente metabólico secundario a insuficiencia cardíaca grave.

8.6 Dímero D (25)

Es un producto de degradación de la fibrina que se forma cuando ésta es lisada por la plasmina. Detecta la presencia de trombos sometidos a un proceso de fibrinólisis.

En la mayoría de los pacientes con TEP se hallan niveles elevados de dímero D (> 500 unidades/ml). Estos niveles también pueden detectarse en otras circunstancias (pacientes añosos, hospitalizados, con enfermedad maligna, cirugía reciente, entre otras), lo que convierte a este marcador sensible en muy poco específico ($< 40\%$) para el diagnóstico de enfermedad

tromboembólica (TVP - TEP). Por esta razón, su utilidad disminuye en pacientes internados, ya que un alto porcentaje de ellos tendrá una prueba positiva aun en su ausencia.

A pesar de su baja especificidad, varios trabajos han demostrado una sensibilidad elevada y especialmente un valor predictivo negativo alto para TVP - TEP.

Las pruebas utilizadas para la determinación de dímero D pueden dividirse en dos grandes grupos con diferencias importantes entre sí:

1. Métodos de muy alta sensibilidad: alcanzan una sensibilidad $\geq 98\%$ y un valor predictivo negativo muy elevado.
2. Métodos de sensibilidad moderada a alta: poseen una sensibilidad de entre el 85% y el 98%. Su valor predictivo negativo no es tan alto como para descartar por sí solo el diagnóstico de TEP y, por lo tanto, un resultado negativo requiere otro método para confirmarlo.

El método del látex convencional, muy utilizado en nuestro medio, tiene una sensibilidad baja (alrededor del 70%) y por supuesto también escasa especificidad.

En conclusión, se recomienda la utilización de los métodos de mediana y alta sensibilidad asociados con la clínica, para descartar tromboembolia con mayor exactitud. Los métodos de muy alta sensibilidad tienen un valor predictivo negativo tan alto que pueden emplearse en forma aislada.

Recientemente se han publicado estudios que muestran que la magnitud del incremento tiene valor pronóstico y que la persistencia de valores elevados aumenta las chances de recidiva. (26) Se ha propuesto continuar con el tratamiento anticoagulante mientras el DD permanezca elevado.

8.7 Troponinas (27)

Si bien los niveles séricos de troponina T y de troponina I no son de utilidad en el diagnóstico de TEP por su escasa especificidad, adquieren un valor creciente como marcadores de riesgo.

Se encuentran elevados en el 30-50% de los pacientes con TEP moderado o masivo.

Los pacientes con niveles altos de troponinas tienen cinco veces más riesgo de complicaciones que aquellos con aumentos moderados. Hay una incidencia mayor de shock cardiogénico y de mortalidad hospitalaria.

8.8 Ecocardiograma transtorácico

En el momento actual es un estudio indispensable en la evaluación de un paciente en el que se sospecha esta patología. Un alto porcentaje de los pacientes que padecen una TEP tienen anormalidades en las cavidades cardíacas derechas detectables mediante el ecocardiograma transtorácico.

El signo de Mc Connell es el hallazgo más específico; consiste en la hipocinesia franca de la pared late-

ral del VD, con preservación de la motilidad de la punta. Pero la presencia de insuficiencia tricuspídea, con hipertensión pulmonar sistólica (no mayor de 40 a 50 mm Hg en un corazón previamente sano) que no tiene otra causa aparente, o simplemente la dilatación del ventrículo derecho, con dilatación e inmovilidad de la vena cava inferior, son elementos indirectos que pueden orientar el diagnóstico. (28)

Por otra parte, frente a un paciente en shock, un ecocardiograma transtorácico normal aleja la posibilidad de que la TEP sea la causa del deterioro hemodinámico.

Una vez confirmado el diagnóstico de TEP, el ecocardiograma transtorácico sigue siendo útil por su valor pronóstico. El compromiso del VD derecho es un fuerte predictor independiente de mortalidad.

Otro indicador de mala evolución, que se encuentra en el 4% de los ecocardiogramas, es la presencia de trombos en tránsito. En este caso, la asociación con foramen oval permeable aumenta el riesgo.

8.9 Ecocardiografía transesofágica (29)

Se utiliza cada vez con mayor frecuencia por la posibilidad de efectuarla al lado de la cama del enfermo. Su rendimiento mejora sustancialmente cuando se emplean transductores multiplanares. Tiene otra gran ventaja adicional: permite descartar otras patologías cardiovasculares graves como, por ejemplo, la disección aórtica.

8.10 Centellograma de ventilación/perfusión (V/Q)

Para que tenga valor diagnóstico, el centellograma debe estar adecuadamente realizado. Se deben tomar las imágenes en las seis posiciones que establece el estudio PIOPED (anterior, posterior y cuatro oblicuas).

Un centellograma normal excluye la TEP, pero ello ocurre en pocos pacientes. Por otra parte, sólo el 10% de las TEP tienen un estudio de alta probabilidad y la gran mayoría (65-78%) tiene una intermedia, por lo que es necesario otro estudio para arribar al diagnóstico. Además, la mayoría de los pacientes con enfermedad cardiopulmonar previa entran dentro de esta categoría. Es un método diagnóstico que, en buena medida, ha sido desplazado por la tomografía axial computarizada helicoidal (TACH). Sin embargo, cuando este último método no está disponible o no se considera conveniente, el centellograma V/Q sigue siendo una herramienta útil, especialmente en los individuos sin enfermedad cardiopulmonar previa. (30) Una radiografía de tórax normal aumenta significativamente la especificidad del método.

8.11 Tomografía computarizada helicoidal (31)

Si bien este método se ha utilizado en el diagnóstico en los últimos años, sólo recientemente se ha aceptado dentro del algoritmo diagnóstico, aunque con algunas consideraciones:

1. Los defectos intraluminales en arterias lobulares o el tronco de las pulmonares tienen un valor predictivo positivo del 85% y ello es equivalente a un centellograma de alta probabilidad.
2. Los defectos subsegmentarios son más difíciles de diagnosticar con este método.
3. Una TACH de un solo cabezal informada como normal reduce la posibilidad de TEP, pero no excluye el diagnóstico (similar a centellograma de baja probabilidad). Si el nivel de sospecha es alto, debería completarse con otros estudios.
4. Una TACH *multislice* normal, según estudios recientes, descartaría la TEP sin necesidad de otros exámenes.

En cuanto a las embolias en vasos de pequeño calibre (subsegmentarios), constituyen entre el 10% y el 30% de las embolias pulmonares. Algunos autores ponen en duda su significación clínica, aunque es probable que su trascendencia clínica sea mayor en los pacientes con reserva cardiopulmonar disminuida.

Los nuevos equipos con cabezales múltiples mejoran mucho la posibilidad de diagnosticar trombos periféricos, evaluar su grado de organización (indicativo de su antigüedad) y además permiten obtener una angiografía del territorio de la vena cava inferior con la misma inyección de contraste.

Su valor es equivalente al de la arteriografía pulmonar.

8.12 Trombosis venosa profunda

Su diagnóstico es una manera indirecta de determinar la posibilidad de TEP, dado que el tratamiento es similar.

En presencia de TEP, la TVP detectada por flebografía se halla presente en el 50% a 70% de los enfermos. Además, el 50% de los enfermos con TVP presentan una TEP asintomática si se investiga. Y en los pacientes con TVP y clínica de TEP, esta última se confirma en el 90% de los casos.

El eco-Doppler de los miembros inferiores es el método diagnóstico más útil, fácil y accesible para arribar al diagnóstico de TVP; sin embargo:

1. Un eco-Doppler normal no excluye TEP en pacientes con centellograma o TACH no diagnóstica, pero reduce su probabilidad.
2. La ausencia de TVP diagnosticada por eco-Doppler se acompaña de un riesgo bajo de recurrencia de TEP.

8.13 Angiografía pulmonar (7, 25, 28)

Es el método patrón para el diagnóstico de TEP, pero es invasivo, no siempre está disponible y es relativamente costoso. Su realización está indicada en pacientes con riesgo alto y pruebas no invasivas negativas o dudosas cuando es necesario llegar al diagnóstico de certeza en pacientes graves o cuando se vaya a utilizar algún tratamiento local, mecánico y/o farmacológico. Puede ser negativa en alrededor del 1-5% de los pacientes que efectivamente han padecido una TEP.

9. RECOMENDACIONES DE MÉTODOS DIAGNÓSTICOS POR IMÁGENES

Flebotrombosis profunda

Clase I

- Venografía con contraste radiológico (A).
- Eco-Doppler venoso (A).
- Venografía asociada con la tomografía computarizada pulmonar helicoidal *multislice* (A).

Embolia pulmonar

Clase I

- Angiografía pulmonar (A).
- Tomografía computarizada helicoidal *multislice* (A).

Clase IIa

- Centellograma V/Q (A).
- Tomografía computarizada helicoidal *monoslice* (A).
- Eco-Doppler transesofágico (A).

10. ALGORITMO DIAGNÓSTICO – TERAPÉUTICO (32)

El diagnóstico de tromboembolia pulmonar no es tarea sencilla. Es una de las enfermedades que con más frecuencia se encuentra en la autopsia sin que se haya sospechado previamente y, a la vez, una en la que más diagnósticos empíricos y tratamientos innecesarios se realizan, lo que lleva al riesgo de complicaciones hemorrágicas. Además, dado que su incidencia es elevada, es una situación clínica con la que debemos enfrentarnos frecuentemente.

La creación de los algoritmos diagnósticos tiene el objetivo de esquematizar la trayectoria de los estudios para permitir más fácilmente la inclusión y la exclusión de los pacientes con esta patología, adaptarse al hospital en el que se realizan y ofrecer una relación costo-beneficio adecuada.

El punto inicial de cualquier estrategia diagnóstica es la sospecha clínica, la cual debe guiar el estudio a realizar. El dímero D (DD), el centellograma de ventilación/perfusión (V/Q), la tomografía computarizada helicoidal (TACH) y el ecocardiograma bidimensional son los estudios que deben realizarse a fin de establecer la estratificación del riesgo clínico.

Por supuesto, las conductas variarán si el paciente tiene signos de trombosis venosa profunda (TVP), lo cual determinará que el eco-Doppler de los miembros inferiores sea el estudio inicial dada su sensibilidad, su especificidad, facilidad de realización y menor costo.

10.1 Modelos de estratificación clínica

La sospecha clínica como paso inicial puede ser guiada por la experiencia clínica o reglada a través de esquemas preestablecidos. En este sentido, son varios los modelos que pueden implementarse en el enfoque inicial.

Modelos basados en puntajes

El esquema más utilizado ha sido el de Wells, que utilizó síntomas, signos, la presencia de otra alternativa

diagnóstica y la de factores de riesgo para clasificar a los enfermos como de baja, mediana o alta probabilidad de TEP (Tabla 7).

Con su esquema desarrollado para el departamento de emergencia, Wells encontró una prevalencia del 2% de TEP en el grupo de baja probabilidad (40% de los enfermos estudiados), del 19% en el de mediana (52% de los pacientes estudiados) y del 50% en el de alta probabilidad (8% de los pacientes).

En resumen, de acuerdo con distintos estudios, hay suficiente evidencia de que los parámetros clínicos utilizados en forma empírica, o estandarizada por reglas, permiten categorizar el riesgo de los pacientes. La prevalencia esperada de enfermedad es de alrededor del 10% en pacientes con baja probabilidad, del 25% en los de intermedia y del 60% en los de alta probabilidad clínica.

Situaciones especiales que modifican algunas de las conductas diagnósticas

1. Pacientes internados posquirúrgicos: generalmente tienen DD positivo (especificidad del 7% *versus* el 47% en pacientes externos).
2. Pacientes con cáncer: aun sin padecer ETE, el 85% tiene DD positivo.
3. Efecto de la edad en las pruebas: DD más positivo y V/Q más alterado en gerontes.
4. Tratamiento del TEP: la heparina reduce los niveles de DD, por lo que la sensibilidad de éste disminuye significativamente.
5. Alta probabilidad clínica: no alcanza con un DD negativo, aunque sea de alta sensibilidad.
6. La enfermedad cardíaca o vascular previa modifica el V/Q.

Basados en los estudios que hemos revisado, creemos que el último algoritmo publicado por Goldhaber en 2005 constituye una interesante propuesta para encarar esta entidad (Figura 2).

Tabla 7. Esquema propuesto por Wells para el diagnóstico presuntivo de TEP. Valor del puntaje y probabilidad preprueba (33)

	Puntaje
Cáncer activo	1,0
Hemoptisis	1,0
Cirugía reciente	1,5
TVP previa	1,5
FC > 100	1,5
Signos clínicos de TVP	3,0
Sin otro diagnóstico	3,0
Probabilidad preprueba	
Alta	≥ 6
Moderada	2,5-5,5
Baja	≤ 2

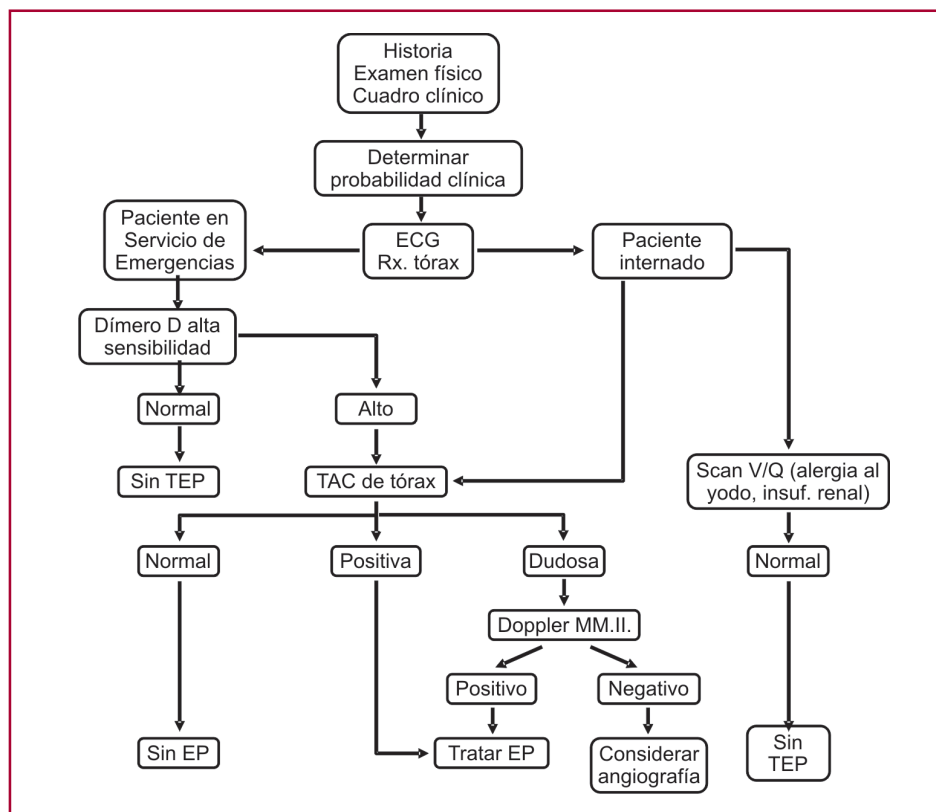


Fig. 2. Algoritmo diagnóstico. (Adaptado de Piazza G, Godhaber SZ. Acute Pulmonary Embolism Part I. Circulation 2006;114:e28-e32.)

11. TEP DE ALTO RIESGO (MASIVA) (34)

Por su trascendencia, merece una consideración especial. El concepto de TEP de alto riesgo o masiva actualmente es funcional y no anatómico. Se define como una TEP con hipotensión sistólica sostenida (menos de 90 mm Hg o una caída de más de 40 mm Hg en los hipertensos) por al menos 30 minutos, que no responde a la expansión con líquidos intravenosos y que no es explicable por otra patología concomitante (sepsis, hemorragia activa, arritmias).

Esta entidad, si no se trata en forma adecuada, tiene una mortalidad altísima en las primeras horas de evolución.

Estas embolias masivas achican el área de sección pulmonar, elevando la presión pulmonar, lo que provoca la dilatación aguda del ventrículo derecho. En los pacientes sin patología cardiopulmonar previa, la presión en la arteria pulmonar comienza a elevarse cuando la reducción del lecho pulmonar se aproxima al 50%. En cambio, en los que tienen reserva disminuida alcanza con que esta reducción sea del 25% o incluso menos en los más graves.

En pacientes sin hipertensión pulmonar previa no debe esperarse una presión sistólica pulmonar mayor de 50 mm Hg o una media superior a 40 mm Hg, ya que un ventrículo derecho no hipertrofiado difícilmente pueda superar estos valores. Cuando la obstrucción del lecho pulmonar alcanza el 75% (porcentaje que baja en los previamente enfermos), habitualmente el ventrículo derecho entra en falla y se produce un

desacople entre el consumo miocárdico de oxígeno y el aporte de las arterias coronarias, condicionado por la caída del volumen minuto, la disminución de la presión arterial y el aumento de la presión intramural, todo esto agravado si el enfermo tiene patología coronaria asociada. La muerte llega entonces como consecuencia de la sobrecarga sistólica inmanejable, asociada con isquemia y eventualmente infarto agudo del ventrículo derecho.

En la Figura 3 se puede apreciar la secuencia de eventos que llevan a la descompensación aguda del VD. La dilatación aguda del ventrículo derecho hace que el pericardio se transforme en restrictivo y el desplazamiento septal hacia la izquierda agrava el déficit de llenado del ventrículo izquierdo, con caída del volumen minuto y de la perfusión coronaria, en circunstancias en que el corazón derecho se encuentra sometido a una exigencia muy aumentada y con necesidad de flujo coronario máximo.

Estos conceptos explican el incremento de las troponinas en los pacientes más graves. (28)

12. TRATAMIENTO DE LA ENFERMEDAD TROMBOEMBÓLICA (35)

12.1 Paciente de alto riesgo (Figura 4)

Estos enfermos llegan a la Unidad de Cuidados Intensivos con compromiso hemodinámico y/o hipoxemia grave y requieren una actitud rápida y eficaz por parte del equipo médico. El primer paso es sostener las

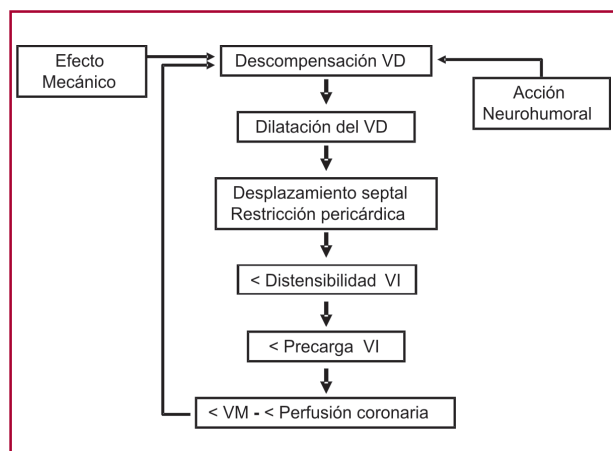


Fig. 3. Fisiopatología de la TEP masiva.

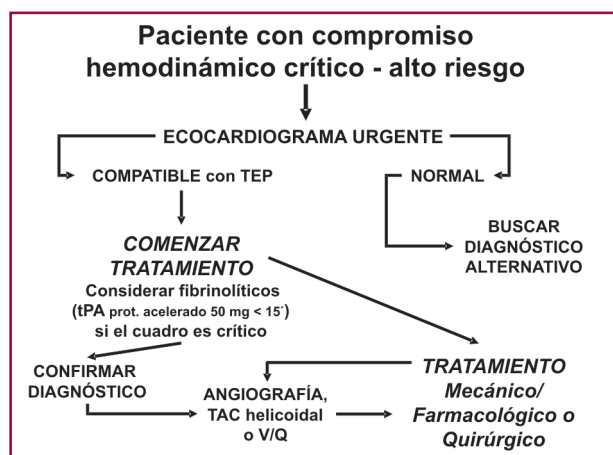


Fig. 4. Secuencia diagnóstico-terapéutica en el paciente con compromiso hemodinámico crítico.

funciones vitales. Hipovolemia y resistencias pulmonares aumentadas es una combinación muy peligrosa. Una expansión hídrica cuidadosa (500 a 1.000 cm³ en infusión rápida) puede sacar del shock a algunos enfermos en pocos minutos y es una de las primeras medidas a tomar. Debe evitarse expandir en exceso a estos enfermos, porque se corre el riesgo de dilatar aún más al ventrículo derecho desfalleciente.

El suplemento de oxígeno en concentraciones adecuadas también es fundamental. Los pacientes que a pesar de estas medidas iniciales permanecen en shock o muy hipóxicos deben ser ventilados mecánicamente sin dilación.

Si con estas medidas iniciales persiste el compromiso hemodinámico, agregamos agentes inotrópicos y/o vasoactivos siguiendo las normas para el tratamiento del shock cardiogénico.

Sin dudas, el tratamiento de fondo es la disolución o la fragmentación de los trombos. Cuando es posible, llevar al paciente al laboratorio de hemodinamia es la

opción preferida, para confirmar allí el diagnóstico y efectuar el tratamiento como hemos visto previamente. Si esto no es posible, optamos por la trombólisis por vía intravenosa, siguiendo los lineamientos previamente expuestos.

12.2 Paciente de bajo riesgo

a. Tratamiento anticoagulante (28)

La terapéutica anticoagulante es similar tanto para la TVP como para la TEP, ya que ambas son manifestaciones de la misma enfermedad.

Sin embargo, merecen considerarse algunas diferencias: en primer término, la mortalidad es significativamente mayor en los enfermos que han padecido TEP y, segundo, la recurrencia es tres veces mayor en los que han tenido una TEP *versus* los que solamente han tenido TVP. En tercer lugar, debe tomarse en cuenta la secuela pulmonar de los pacientes con TEP, ya que a mediano plazo alrededor del 4% desarrollarán hipertensión pulmonar importante. (36)

Este tratamiento tiene el objetivo de interrumpir la progresión de los fenómenos trombóticos, pero no actúa sobre los trombos ya formados. Sobre estos últimos actuará a mediano plazo la fibrinólisis endógena.

La anticoagulación con heparina en alguna de sus formas se mantiene actualmente por 5 días. Si no hay contraindicaciones, en el primero o el segundo día ya comenzamos con dicumarínicos por vía oral. Hacia el quinto día es habitual que tengamos una anticoagulación adecuada con estos últimos y estemos en condiciones de suspender la heparina.

En los pacientes con sospecha clínica de enfermedad tromboembólica, y en ausencia de contraindicaciones, se sugiere comenzar el tratamiento con algunas de las formas de heparina actualmente en uso, hasta que se pueda descartar o confirmar de manera fehaciente el diagnóstico.

b. Heparina no fraccionada

La anticoagulación con heparina no fraccionada (HNF) es el tratamiento clásico de la enfermedad tromboembólica. La ventaja de esta droga es su vida media corta. Su desventaja es que por su baja biodisponibilidad es difícil alcanzar tiempos útiles con rapidez. Se ha demostrado que cuanto mayor es la demora en obtener tiempos de anticoagulación adecuados, mayor es la posibilidad de progresión de la trombosis y también mayor la posibilidad de recidiva. Es por esto que se recomienda alcanzar tiempos útiles dentro de las 24 horas de comenzada la heparinización. El tratamiento se inicia con un bolo de 5.000 UI por vía intravenosa, seguido por un goteo de 15 a 18 UI/kg por hora (promedio 1.250 U/h), lo que hace un total, para individuos de peso promedio, de 25.200 a 30.240 UI por día, administrados por bomba de infusión continua. El objetivo es alcanzar rápidamente un KPTT de 1,5 a 2, cinco veces el basal. Se recomienda controlar el KPTT cada 2 a 4 horas hasta alcanzar el valor

deseado y luego, cada 24 horas. En base a los resultados, ajustamos las dosis de heparina siguiendo un nomograma. Hay varios en uso; el que proponemos es el que se muestra en la Tabla 8.

Continúa siendo la droga de elección para los pacientes hemodinámicamente inestables, para los que tienen mayor riesgo de sangrado, los más ancianos (según el estado general, pero se estima de 75 años en adelante), para los que presentan falla renal y para los que se prevé una cirugía a corto plazo.

Se desaconseja el empleo de la heparina en forma de bolos intermitentes, ya que esta metodología incrementa considerablemente el riesgo de sangrado.

Esta terapéutica no está exenta de complicaciones, de las que la más frecuente es el sangrado. Otro inconveniente inherente al uso de esta droga son: la ya mencionada variabilidad en su efecto, debido a su acción indirecta a través de la antitrombina III, y la resistencia que algunos pacientes tienen a ella, causada por su unión a proteínas plasmáticas, con liberación ulterior de forma no predecible.

Una complicación importante, que se observa en el 1% a 3% de los casos es la trombocitopenia autoinmune. Ésta suele aparecer entre el tercero y el quinto día del tratamiento. En ese momento está indicado efectuar un recuento de plaquetas, y si éstas caen por debajo de $100.000/\text{mm}^3$, o a la mitad o menos del valor basal, debe interrumpirse el tratamiento. Este riesgo es algo inferior cuando se emplean HBPM.

La FDA aprobó el uso de bivalirudina para pacientes que no pueden recibir heparina, básicamente para los que presentan cuadros de trombocitopenia por esta droga. Se administra con un bolo inicial de 0,10 mg/kg, seguido por una infusión de 0,25 mg/kg/h, ajustando la dosis para mantener un KPTT de dos veces el valor basal.

La otra droga que por su mecanismo de acción (actúa sobre el factor Xa y no sobre las plaquetas) tiene un riesgo de trombocitopenia mínimo o nulo es el fondaparinux; se administra por vía subcutánea y actualmente se encuentra disponible en nuestro medio.

c. Heparinas de bajo peso molecular (Tabla 9)

A diferencia de la heparina no fraccionada, que actúa inhibiendo a la trombina, las heparinas de bajo peso molecular (HBPM) actúan esencialmente sobre el factor Xa y en menor medida sobre la trombina. Por esta razón, el KPTT no se altera en forma significativa y no es un parámetro adecuado para evaluar su actividad. Con excepción de algunas situaciones especiales (insuficiencia renal, embarazo, obesidad extrema), no es necesario monitorizar la coagulación. Si fuera necesario, se debe medir el factor Xa.

Son más estables y predecibles y tienen menos incidencia de trombocitopenia autoinmune y de osteoporosis. Su efectividad es por lo menos similar a la de la HNF y en algunos estudios se considera superior, tanto en la prevención como en la terapéutica de la

Tabla 8. Nomograma para el manejo de la heparina intravenosa

KPTT (seg)	Bolo IV	Cambio de goteo
< 35	80 UI/kg	Aumentar el goteo 4 UI/kg/h
35-50	40 UI/kg	Aumentar goteo 2 UI/kg/h
51-70	———	Igual
71-90	———	Disminuir goteo 2 UI/kg/h
> 90	Suspender infusión 1 hora	Disminuir goteo 3 UI/kg/h

Tabla 9. HBPM y pentasacáridos en el tratamiento de la enfermedad tromboembólica

HBPM	Dosis recomendada
Enoxaparina	1 mg/kg s.c. cada 12 h (máximo 180 mg)
Nandroparina	85 UAXa/kg s.c. cada 12 h
Dalteparina	100 UAXa/kg s.c. cada 12 h
Pentasacáridos	
Fondaparinux	7,5 mg dosis única s.c./día

enfermedad tromboembólica. En los enfermos con cáncer se ha demostrado una disminución de la mortalidad.

Tienen las desventajas de una vida media más prolongada y que sólo son parcialmente inhibidas por la acción de la protamina. Por lo tanto, en pacientes con alto riesgo de sangrado y en los que pueden requerir una cirugía a corto plazo se prefiere continuar utilizando HNF, lo mismo que en los que presentan insuficiencia renal con una creatinina superior a 2,5 mg/dl.

Una vez suspendida, la HBPM cesa su efecto en aproximadamente 6 horas. (37, 38)

d. Pentasacáridos (Tabla 9)

En 2008 se aprobó por la FDA y en nuestro país el uso de fondaparinux para la prevención y el tratamiento de la enfermedad tromboembólica. Es una droga de síntesis con actividad anti-Xa pura, que se administra en dosis única de 2,5 mg/s.c./día para profilaxis y 7,5 mg para el tratamiento. Esta última es dosis fija para los enfermos cuyo peso se encuentra entre 50 y 100 kg. No necesita controles de laboratorio, salvo situaciones especiales.

Su vida media es de 17 horas, lo que permite una sola aplicación al día. No tiene antagonista específico.

e. Trombolíticos

La trombólisis parece, al menos teóricamente, como una opción formidable; lisa los trombos dentro del sistema venoso y los émbolos en el pulmón, con todo lo que esto significa en términos de mejoría hemodinámica.

mica y clínica inmediata. Sin embargo, sumando todos los estudios aleatorizados de trombolíticos *versus* placebo, solamente podemos contabilizar entre todos ellos poco más de 800 pacientes.

El estudio reciente más importante que evaluó el tratamiento con trombolíticos más heparina contra heparina sola fue el MAPPET. (39) La droga estudiada fue tPA y se incluyeron pacientes con disfunción ventricular derecha. El resultado fue favorable a los trombolíticos, pero el estudio recibió fuertes críticas metodológicas.

El registro ICOPER (40) que incluyó 2.454 pacientes, 304 de ellos con tratamiento trombolítico, no mostró que mejorara la sobrevida. En cambio, hubo una incidencia del 3% de sangrado intracraneano.

Un metaanálisis publicado en el año 2002 resume nueve publicaciones que incluyen un total de 461 participantes. De estos ensayos, solamente tres se hicieron con doble ciego.

La mayoría de estos estudios mostró una mejor y más rápida resolución de los trombos con los trombolíticos en relación con la heparina, especialmente dentro de las primeras 24 horas. Pero el resultado más importante de este metaanálisis fue que los trombolíticos no proveían ningún beneficio a la población general de enfermos con embolia pulmonar (riesgo relativo 0,63, 95% IC 0,32-1,93).

Hay un consenso de expertos para indicar este tratamiento a pacientes con compromiso hemodinámico grave, es decir, enfermos con tensión arterial sistólica inferior a 90 mm Hg o 40 mm Hg por debajo de su presión habitual si es que son hipertensos, y que no responden a la expansión en un lapso breve (30 a 60 minutos), y a los que requieren el empleo de drogas vasopresoras. También se acepta su empleo en enfermos con hipoxemia refractaria. Son pacientes cuya vida está en riesgo y en los que una rápida mejoría de la circulación pulmonar puede significar la diferencia entre la vida y la muerte.

También se sugiere su empleo en los enfermos en los que se visualizan por imágenes trombos en tránsito, especialmente cuando se asocian con foramen oval permeable.

Es motivo de debate si cabe su empleo en otras circunstancias, como el compromiso del ventrículo derecho o la embolia pulmonar grave en pacientes con reserva cardiopulmonar disminuida. En estos casos, la decisión se tomará en forma individual, contraponiendo los riesgos a los posibles beneficios. (28)

Todos los pacientes que han recibido trombolíticos deben quedar anticoagulados (si no surge alguna contraindicación) con HNF en goteo continuo, con los controles que se señalaron previamente. Si el paciente venía recibiendo heparina, la postura más recomendable es suspender la anticoagulación mientras se administra el trombolítico. Cuando se termina su infusión se verifica un KPTT al finalizarla y luego cada dos horas. La heparinización se reinicia cuando el KPTT baja de los 80 segundos.

En la Tabla 10 se describen los distintos regímenes terapéuticos que usamos habitualmente y en la Tabla 11, las principales contraindicaciones.

Los regímenes de administración prolongados (infusiones con duración mayor de 12 horas) se han abandonado por su menor efectividad y por el riesgo incrementado de sangrado.

Precauciones que deben tomarse en cuenta cuando se utilizan trombolíticos como tratamiento de la embolia pulmonar:

- Evitar dentro de lo posible procedimientos invasivos, como punciones en lugares no compresibles (p. ej., vena subclavia) o punciones arteriales.
- No se requieren controles de coagulación luego de su administración, ya que se emplean dosis fijas. Este tratamiento debe realizarse bajo control estricto, en un área de cuidado intensivo. Se recomienda suspender la infusión si durante el tratamiento se produce un deterioro del sensorio que hace sospechar sangrado intracerebral o aparecen signos sugestivos de sangrado intraabdominal.

Otro aspecto controversial es la vía de administración de los trombolíticos. Tradicionalmente se ha sostenido que la vía de administración intravenosa es tan eficaz como la infusión directa en la arteria pulmonar. Sin embargo, algunos estudios experimentales sugieren que en pacientes con embolias masivas, la aplicación del trombolítico mediante un catéter, directamente en la masa del trombo, en dosis más bajas (10% a 20% de la que se emplea por vía venosa),

Tabla 10. Regímenes de administración usados en nuestro medio

tPA	100 mg IV en dos horas de goteo continuo. Los primeros 10 mg pueden pasarse en bolo
Estreptoquinasa	1.500.000 unidades IV a pasar en 2 horas en goteo continuo
tPA	0,6 mg/kg IV con un máximo de 60 mg en 5 a 15 minutos, en pacientes en situación crítica

Tabla 11. Contraindicaciones para el uso de trombolíticos

Absolutas	Relativas
ACV hemorrágico	Diátesis hemorrágica o plaquetopenia < 100.000/mm ³
Neoplasia intracraneana	Hipertensión no controlada (sistólica > 180 mm Hg, diastólica > 110 mm Hg)
Cirugía o trauma craneal en los últimos 2 meses	ACV isquémico en los últimos 6 meses
Sangrado interno en los últimos 6 meses	Cirugía en los 10 días precedentes

podría derivar en un resultado mejor, con un riesgo de sangrado menor. Esta modalidad terapéutica se ha empleado en pequeños estudios en pacientes críticos, con resultados alentadores.

Ventana de tiempo: clásicamente se estima que hasta dos semanas después de producido el episodio agudo es posible mejorar la perfusión pulmonar mediante la lisis del trombo. En la práctica, la realidad nos dice que la mayoría de las muertes por TEP se producen dentro de las primeras horas.

f. Tratamiento mecánico y farmacológico en el laboratorio de hemodinamia

Hoy es poco frecuente que llevemos al laboratorio de hemodinamia a un paciente solamente para diagnosticar una embolia pulmonar.

En la mayoría de los casos adoptamos esta conducta frente a un enfermo con embolia pulmonar masiva, según criterio hemodinámico, con el objetivo de certificar rápidamente el diagnóstico y además destruir o fragmentar el trombo cuando está cabalgando en la bifurcación de la arteria pulmonar o en alguna de sus ramas proximales. Para este fin hay diversos modelos de catéteres diseñados especialmente, pero si se carece de ellos se pueden emplear catéteres angiográficos (p. ej., *pigtail*). En forma complementaria, el trombolítico, como ya hemos señalado, se puede infundir en la masa misma del trombo, en dosis del 10% al 20% de las de uso sistémico.

g. Embolectomía quirúrgica

Hasta hace muy poco, la embolectomía quirúrgica se empleaba excepcionalmente y en pacientes *in extremis*. La técnica de Trendelenburg se ha abandonado casi por completo y la mayoría de los procedimientos se efectúan con circulación extracorpórea y con una mortalidad muy elevada, aun en los grandes centros quirúrgicos del mundo. Últimamente, un grupo de investigadores de Boston ha resucitado esta técnica y ha publicado muy buenos resultados en pacientes con TEP grave, pero sin situación crítica. Creemos que por el momento ésta es una opción para grandes centros, con equipos quirúrgicos especialmente entrenados.

13. RECOMENDACIONES TERAPÉUTICAS

Clase I

Los pacientes con TEP se anticoagulan por 5 días y hasta que la RIN sea ≥ 2 durante como mínimo 24 horas, con alguna de las siguientes drogas:

- Heparina no fraccionada en goteo continuo (A).
- Heparinas de bajo peso molecular (A).
- Pentasacáridos: fondaparinux (A).

Los pacientes en shock y los que presenten dudas de la absorción de medicamentos por vía subcutánea deben recibir HNF por vía intravenosa.

Los pacientes con fuerte sospecha clínica de TEP pero sin diagnóstico de certeza deberían permanecer

anticoagulados hasta que se confirme el diagnóstico, siempre que no presenten contraindicaciones para recibir anticoagulantes (C).

Clase IIa

- Bivalirudina o fondaparinux para los pacientes que deben ser anticoagulados y que no pueden recibir heparina (B).

Clase I

- Fibrinolíticos para el shock (C).
- tPA 100 mg en dos horas.
- Estreptocinasa 1.500.000 unidades en 90 minutos.

Clase IIa

- Fibrinolíticos para la hipoxemia no controlable con asistencia respiratoria.
- Mecánica y alta fracción inspirada de O₂ (C).
- Fibrinolíticos para los pacientes con trombos en tránsito (C).
- Tratamiento mecánico asociado o no con fibrinolíticos en la TEP (A).
- Embolectomía quirúrgica (B).
- En caso de detención circulatoria inminente se ha recomendado la administración de 50 mg de tPA en bolo (en menos de 15 minutos) (C).

Clase IIb

- Fibrinolíticos para la TEP con compromiso ecográfico del ventrículo derecho, pero sin compromiso hemodinámico (B).

14. FILTROS EN LA VENA CAVA

Recomendaciones para la colocación de filtros en la vena cava

Clase I

- Pacientes con sangrado activo (C).
- Pacientes que siguen embolizando a pesar de una anticoagulación correcta (C).
- Pacientes que han sangrado en el transcurso de una anticoagulación correcta (C).

Otras indicaciones: evitar el riesgo de una nueva embolia en un paciente que ha padecido una TEP masiva, en pacientes con reserva cardíaca o pulmonar disminuida o en los que se ha efectuado una embolectomía quirúrgica o percutánea, son motivo de debate. En estas situaciones especiales se debe evaluar cada caso en particular y revisar las actualizaciones del tema, antes de tomar una conducta.

Excepcionalmente, también se han colocado filtros en la vena cava superior.

Recientemente han salido al mercado filtros removibles que pueden permanecer colocados durante 15 días, al cabo de los cuales se debería tomar la decisión de retirarlos o de dejarlos implantados en forma definitiva.

Actualmente son pocos los enfermos que reciben filtros en la vena cava (3% a 5%). Los estudios disponibles hasta el momento no han podido demostrar una disminución significativa de la mortalidad y sí en cambio un descenso moderado de la morbilidad a corto plazo.

15. TRATAMIENTO CON DICUMARÍNICOS

Este tratamiento nos permitirá continuar la anticoagulación a largo plazo y de esta forma evitar las recidivas. Su mecanismo de acción es la inhibición de los factores dependientes de la vitamina K. Debemos recordar que, aunque se prolongue el tiempo de protrombina, su efecto máximo recién se obtiene transcurridos cinco días desde el comienzo de su administración, que es cuando se inhiben efectivamente todos los factores involucrados en la cadena de la coagulación. Por eso, igual en la TEP que en la TVP, asociamos el dicumarínico elegido con heparina durante 4 o 5 días y luego continuamos solamente con dicumarínicos. No hay estudios confiables que nos indiquen por cuánto tiempo hay que seguir con este tratamiento anticoagulante. En consecuencia, se propone seguir, en líneas generales, las normas propuestas por el American College of Chest Physicians (Tabla 12).

No está determinada la conducta en pacientes con un primer evento y:

- Factor V de Leyden - homocistinemia - déficit de proteína C o S;
- Trombofilia de causa reversible (Hyers TM, et al. Chest 2001;169:176S).

Si se produce una hemorragia grave, debe tratarse de inmediato con concentrado de factores protrombóticos, y eventualmente plasma fresco (5 o 6 unidades). Si se administra vitamina K en dosis de 10 mg por vía parenteral, el efecto del dicumarínico se revertirá en un lapso de 6 a 12 horas, pero cuando se desee reiniciar este tratamiento se encontrará una resistencia relativa a él por 10 a 15 días.

16. RECOMENDACIONES PARA LA PREVENCIÓN SECUNDARIA

- En pacientes con TVP se recomienda la deambulación precoz, en la medida en que sea tolerada (Clase I -B-).
- Se recomienda comenzar con antagonistas de la vitamina K (dicumarínicos), en el primer día de tratamiento con heparina, y superponer ambas drogas por 3 a 5 días (Clase I -B-).
- Se recomienda mantener una RIN de 2 a 3 (Clase I -A-).
- En pacientes con dos o más episodios de ETE documentados se recomienda anticoagulación en forma indefinida (Clase II -A-).

Tabla 12. Duración del tratamiento anticoagulante

3-6 meses
Primer evento con una causa transitoria o reversible
6 meses
Primer evento de TVP idiopático
12 meses a toda la vida
Primer evento con neoplasia o hasta su resolución
– Anticuerpos anticardiolipina
– Recurrencia de un episodio idiopático
– Segundo evento con trombofilia

- Cuando la TVP responde a una causa transitoria reversible, se recomienda anticoagular con antagonistas de la vitamina K por 3 meses (Clase I -A-).
- Para pacientes con TVP y cáncer se recomienda el empleo de HBPM por 3 a 6 meses y luego anticoagulación por tiempo indefinido o hasta que el cáncer esté resuelto (Clase I -C-).
- En pacientes con anticuerpos antifosfolípidicos o que reúnen dos o más condiciones trombofílicas recomendamos tratamiento por 12 meses (Clase I -C-).
Se sugiere la posibilidad de tratamiento indefinido (Clase II -C-).
- Si la TVP es idiopática, debe considerarse la anticoagulación en forma indefinida (Clase II -A-).
- Cuando se indica anticoagulación por tiempo indefinido, esta indicación debe ser revisada periódicamente, tomando en cuenta en cada caso la relación riesgo-beneficio del tratamiento (Clase I -C-).

17. EMBARAZO

Las mujeres durante el embarazo y el puerperio y las que reciben tratamiento hormonal tienen un riesgo incrementado para padecer una enfermedad tromboembólica. El puerperio es el período de mayor riesgo, ya que éste se quintuplica en relación con el período de gestación y el riesgo de desarrollar TEP es quince veces mayor.

En la etapa diagnóstica se prefiere usar métodos que no interfieran con la gestación, pero si se considera necesario efectuar una TC helicoidal para establecer fehacientemente el diagnóstico, ésta debe realizarse con el cuidado de proteger al feto lo mejor posible.

En cuanto a la terapéutica, en la etapa aguda se procede a anticoagular con heparina de la misma forma que con los demás pacientes. Si hay riesgo de vida, se debe considerar también el empleo de trombolíticos (hay solamente comunicación de casos aislados, con buenos resultados). La terapéutica de mantenimiento se realiza habitualmente con HBPM, ya que los dicumarínicos son teratogénicos.

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Insuficiencia ventilatoria

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INFORMACIÓN: PARA PACIENTES

La insuficiencia ventilatoria es el aumento de la PaCO_2 (hipercapnia) que se produce cuando el aparato respiratorio ya no puede soportar la carga respiratoria. Las causas más frecuentes son las exacerbaciones agudas graves de asma y enfermedad pulmonar obstructiva crónica, la sobredosis de drogas que suprimen el estímulo respiratorio y enfermedades que producen debilidad de los músculos respiratorios (p. ej., síndrome de Guillain-Barré, miastenia grave, botulismo). Los hallazgos incluyen disnea, taquipnea y confusión. Puede llevar a la muerte. El diagnóstico se basa en los gases en sangre arterial y la observación del paciente; la radiografía de tórax y la evaluación clínica pueden ayudar a determinar la causa. El tratamiento varía con la enfermedad, pero suele incluir ventilación mecánica.

(Véase también [Generalidades sobre la ventilación mecánica](#).)

Fisiopatología

La hipercapnia se produce cuando la ventilación alveolar se reduce o no logra aumentar adecuadamente en respuesta a una elevación de la producción de CO_2 . La reducción de la ventilación alveolar se debe a una disminución de la ventilación minuto o un aumento en la ventilación del espacio muerto sin un aumento compensatorio apropiado de la ventilación minuto.

Puede haber insuficiencia ventilatoria cuando el aparato respiratorio soporta una carga excesiva (p. ej., las cargas de resistencia, las cargas elásticas pulmonares y de la pared torácica) frente a una competencia neuromuscular para conseguir un esfuerzo inspiratorio eficaz. Cuando aumenta la carga de la ventilación minuto (p. ej., como ocurre en la sepsis) un aparato respiratorio comprometido no puede cumplir con este aumento de la demanda (por causas, ver figura [El equilibrio entre la carga \(resistiva, elástica y ventilación minuto\) y la competencia neuromuscular \(impulso, transmisión y fuerza muscular\) determina la capacidad para sostener la ventilación alveolar](#)).

El **espacio muerto fisiológico** es la parte del árbol respiratorio que no participa en el intercambio de gases. Ésta incluye

- Espacio muerto anatómico (orofaringe, tráquea y vías aéreas)
- Espacio muerto alveolar (alvéolos ventilados pero no perfundidos)

Un espacio muerto fisiológico puede también resultar de un cortocircuito o una baja relación ventilación/perfusión (V/Q) si el paciente no pueden aumentar su ventilación minuto adecuadamente. El espacio muerto fisiológico es de un 30 a 40% del volumen corriente, pero aumenta a un 50% en pacientes intubados y a > 70% en embolia pulmonar masiva, enfisema grave y mal asmático. Así, para una ventilación minuto dada, cuanto mayor sea el espacio muerto, menor será la eliminación de CO_2 .

El aumento de la producción de dióxido de carbono, como ocurre en los procesos febriles, las sepsis, los traumatismos, las quemaduras, el hipertiroidismo y la hipertermia maligna, no es una causa primaria de insuficiencia ventilatoria pues los pacientes deben aumentar la ventilación para compensarlo. En estos casos, la insuficiencia ventilatoria se produce sólo cuando está comprometida la capacidad de compensación.

La hipercapnia disminuye el pH arterial ([acidosis respiratoria](#)). Una acidemia intensa ($\text{pH} < 7,2$) contribuye a la vasoconstricción arteriolar pulmonar, la dilatación vascular sistémica, la reducción de la contractilidad miocárdica, la hiperpotasemia, la hipotensión y la irritabilidad cardíaca, con el peligro de arritmias potencialmente mortales. Una hipercapnia aguda también produce vasodilatación cerebral y aumenta la presión intracraneana, un problema importante en pacientes con traumatismo craneano agudo. Con el tiempo, el amortiguamiento tisular y la compensación renal pueden corregir la acidemia. Sin embargo, puede haber aumentos bruscos de PaCO_2 más rápidos que los cambios compensatorios (la PaCO_2 aumenta 3 a 6 mmHg/min en un paciente con apnea total).

El equilibrio entre la carga (resistiva, elástica y ventilación minuto) y la competencia neuromuscular (impulso, transmisión y fuerza muscular) determina la capacidad para sostener la ventilación alveolar.

PEEP = presión de fin de espiración positiva.

Cargas elásticas de la pared torácica

Distensión abdominal
Ascitis
Obesidad
Derrame pleural
Neumotórax
Fractura costal
Tumor

Cargas elásticas pulmonares

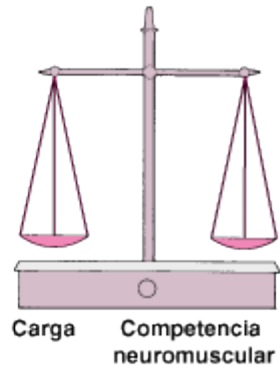
Edema alveolar
Atelectasias
Infección
AutoPEEP

Cargas de ventilación minuto

Exceso de calorías
Hipovolemia
Embolia pulmonar
Sepsis

Cargas resistivas

Broncoespasmo (p. ej., asma, bronquilitis, EPOC)
Edema, secreciones o esfacelo de las vías aéreas
Apnea obstructiva del sueño
Obstrucción de las vías aéreas superiores



Disminución del estímulo respiratorio

Lesión del tronco encefálico
Sobredosis de fármacos
Hipotiroidismo
Trastorno respiratorio del sueño

Deterioro de la neurotransmisión

Aminoglucósidos
Esclerosis lateral amiotrófica
Botulismo
Lesión en la médula espinal
Síndrome de Guillain-Barré
Miastenia grave
Bloqueantes neuromusculares
Lesión del nervio frénico

Debilidad muscular

Anomalías electrolíticas
Fatiga
Estados de hipoperfusión
Hipoxemia
Miopatías
Desnutrición

Signos y síntomas

El síntoma predominante de la insuficiencia ventilatoria es la **disnea**.

Los signos de insuficiencia ventilatoria incluyen el uso enérgico de los músculos respiratorios accesorios, taquipnea, taquicardia, diaforesis, ansiedad, disminución del volumen corriente, patrones respiratorios irregulares o en boqueadas y movimiento paradójico del abdomen.

Las manifestaciones del sistema nervioso central varían desde cambios de personalidad sutiles hasta una marcada confusión, obnubilación o coma. La hipercapnia crónica se tolera mejor que la aguda y tiene menos síntomas.

Diagnóstico

- Gases en sangre arterial
- Radiografía de tórax
- Pruebas para determinar la etiología

Debe sospecharse insuficiencia ventilatoria en pacientes con dificultad respiratoria, fatiga respiratoria visible o cianosis, o cambios en el sensorio y en aquellos con afecciones que producen debilidad neuromuscular. La taquipnea también es un problema; una frecuencia respiratoria > 28 a $30/\text{min}$ no puede sostenerse durante mucho tiempo, en particular en pacientes ancianos o debilitados.

Si se sospecha insuficiencia ventilatoria, debe realizarse análisis de gases en sangre arterial, oximetría de pulso continua y radiografía de tórax. Una acidosis respiratoria en gases en sangre arterial (p. ej., $\text{pH} < 7,35$ y $\text{PCO}_2 > 50$) confirma el diagnóstico. Los pacientes con insuficiencia ventilatoria crónica suelen tener PCO_2 elevada (p. ej., 60 a 90 mmHg) en situación basal, con un pH levemente acidémico. En estos pacientes, el principal marcador de hipoventilación aguda es el grado de acidemia en lugar de la PCO_2 .

Como los gases en sangre arterial pueden ser normales en pacientes con insuficiencia ventilatoria incipiente, algunos estudios de la función pulmonar puede realizarse en la cama del enfermo y ayudan a predecir esta situación, en especial en pacientes con debilidad neuromuscular, que pueden presentar una insuficiencia ventilatoria sin tener dificultad respiratoria notoria. Una capacidad vital < 10 a 15 mL/kg y una incapacidad para generar una fuerza inspiratoria negativa de $15 \text{ cm H}_2\text{O}$ sugieren insuficiencia ventilatoria inminente.

Una vez diagnosticada la insuficiencia ventilatoria, debe identificarse la causa. A veces una afección conocida existente (p. ej., coma, asma aguda, exacerbación de enfermedad pulmonar obstructiva crónica, mixedema, miastenia grave, botulismo) es una causa evidente. En otros casos, los antecedentes son sugestivos; un comienzo brusco de taquipnea e hipotensión luego de una cirugía sugiere una embolia pulmonar, y la presencia de signos de foco neurológico indican una causa en el sistema nervioso central o neuromuscular. Es posible evaluar la competencia neuromuscular midiendo la fuerza de los músculos inspiratorios (fuerza de inspiración negativa y fuerza de espiración positiva) y la transmisión neuromuscular (estudios de conducción nerviosa y

electromiografía) e investigando las causas de la disminución del estímulo (estudios toxicológicos, estudios por la imagen cerebrales y pruebas de función tiroidea).

Tratamiento

- Tratamiento de la causa
- A menudo, ventilación a presión positiva

El tratamiento de la insuficiencia ventilatoria se orienta a corregir el desequilibrio entre la fuerza del aparato respiratorio y su carga, y varía con la etiología. Los factores precipitantes evidentes (p. ej., broncoespasmo, tapón mucoso, cuerpos extraños) deben corregirse en la medida de lo posible.

Las 2 causas más frecuentes de insuficiencia ventilatoria son la exacerbación aguda del asma (estado de mal asmático) grave y la enfermedad pulmonar obstructiva crónica. La insuficiencia respiratoria debida a enfermedad pulmonar obstructiva crónica se denomina insuficiencia respiratoria crónica agudizada.

Estado asmático (mal asmático)

Debe tratarse al paciente en una unidad de cuidados intensivos con personal capacitado en el manejo de la vía aérea. (Véase también [Tratamiento de las exacerbaciones agudas del asma](#)).

La [ventilación con presión positiva no invasiva](#) puede reducir en forma inmediata el esfuerzo respiratorio y evitar la intubación endotraqueal hasta que el tratamiento farmacológico surta efecto. A diferencia de lo que ocurre en pacientes con enfermedad pulmonar obstructiva crónica, que reciben bien esta ventilación, en pacientes asmáticos la mascarilla aumenta la percepción de disnea, de modo que debe usarse con mucho cuidado, ajustando al principio solamente la presión espiratoria positiva de la vía aérea (EPAP) debido a que una de las principales funciones de la presión inspiratoria positiva de la vía aérea (IPAP) es aumentar el volumen corriente, y en estos pacientes, el volumen pulmonar de fin de espiración se aproxima a la capacidad pulmonar total (Véase también [Mecánica respiratoria](#)). Después de explicarle los beneficios al paciente, éste debe sostener la mascarilla contra su rostro mientras se aplica una presión moderada (presión positiva continua en la vía aérea [CPAP] de 3 a 5 cm H₂O). Una vez tolerada, se asegura la mascarilla en su lugar aumentando las presiones según la comodidad del paciente y para reducir el esfuerzo respiratorio evaluado según la frecuencia respiratoria y el uso de los músculos accesorios. Los ajustes finales son de IPAP 10 a 15 cm H₂O y EPAP 5 a 8 cm H₂O. Es preciso seleccionar cuidadosamente a los pacientes.

La ventilación mecánica convencional a través de [intubación endotraqueal](#) se indica en la insuficiencia respiratoria inminente que se establece clínicamente por la presencia de obnubilación, discurso monosilábico, postura decaída y respiración superficial. Un examen de gases en sangre arterial que muestra hipercapnia progresiva también es una indicación, aunque no es necesaria la confirmación de gases en sangre y no debe reemplazar el juicio del médico. Es preferible la intubación oral que la nasal debido a que puede utilizarse un tubo endotraqueal más grande, que disminuye la resistencia de la vía aérea y facilita la succión. A veces después de una intubación por estado asmático aparece una hipotensión y puede producirse un neumotórax (Ver también [Generalidades sobre la ventilación mecánica : Complicaciones y precauciones](#)). Estas complicaciones y su correspondiente mortalidad han disminuido significativamente gracias a una estrategia ventilatoria que prefiere limitar la hiperinsuflación dinámica más que alcanzar la eucapnia. En el estado asmático, una ventilación suficiente para lograr un pH normal produce típicamente hiperinsuflación grave. Para evitar una hiperinsuflación, los ajustes iniciales del respirador deben incluir un volumen corriente de 5 a 7 mL/kg y una frecuencia respiratoria de 10 a 18/min. Puede ser necesario un flujo inspiratorio elevado (p. ej., 70 a 120 L/min) con un patrón de onda cuadrada para facilitar el tiempo máximo en espiración. Es poco probable que se produzca una hiperinsuflación dinámica peligrosa mientras la presión meseta medida sea < 30 a 35 cm H₂O y la presión intrínseca positiva de fin de espiración ([PEEP intrínseca](#)) sea < 15 cm H₂O (aunque estas presiones pueden ser difíciles de medir debido a la actividad de los músculos inspiratorios y espiratorios). Una presión de meseta > 35 cm H₂O se maneja reduciendo el volumen corriente (asumiendo que la evaluación clínica no indique que la alta presión se debe a una disminución de la distensibilidad de la pared torácica o del abdomen) o la frecuencia respiratoria.

Aunque se puede reducir la presión pico en la vía aérea disminuyendo la velocidad máxima de flujo o cambiando la forma de las ondas a un perfil descendente, esto *no* debe hacerse. Aunque una alta velocidad de flujo requiere una alta presión para superar la resistencia de la vía aérea en el estado asmático, esta presión se disipa en las vías aéreas gruesas que contienen cartílago. Una velocidad de flujo más baja (p. ej., < 60 L/min) reduce el tiempo disponible para la espiración, y aumenta así el volumen de fin de espiración (y la PEEP intrínseca resultante) y permite un mayor volumen inspiratorio durante la siguiente respiración.

El uso de un volumen corriente bajo a menudo produce hipercapnia, que en cierto grado se permite para reducir la hiperinsuflación dinámica. Un pH arterial > 7,15 suele ser bien tolerado en términos fisiológicos, pero requiere grandes dosis de sedantes y opiáceos. Los bloqueantes neuromusculares deben evitarse después del período periintubatorio pues estos agentes, en combinación con corticoides, pueden causar una miopatía grave y ocasionalmente irreversible, en particular después de 24 h de uso combinado. La agitación del paciente debe manejarse con sedantes y no con parálisis, y lo ideal es ajustar la ventilación a las necesidades del paciente, de modo de reducir la necesidad de sedación.

La mayoría de los pacientes con estado de mal asmático mejoran lo suficiente como para ser destetados de la ventilación mecánica en 2 a 5 días, aunque una minoría experimenta una obstrucción grave y prolongada al flujo de aire. Véase [Desconexión de la ventilación mecánica](#) para obtener un análisis sobre el abordaje general.

Insuficiencia respiratoria crónica reagudizada

En los pacientes con insuficiencia respiratoria crónica reagudizada causada por [enfermedad pulmonar obstructiva crónica](#), el gasto de oxígeno de la respiración es varias veces mayor que el de aquellos sin enfermedad pulmonar de base. Este aumento de la carga respiratoria aparece en un marco de una competencia neuromuscular apenas adecuada, por lo que los pacientes se cansan fácilmente en el esfuerzo por mantener la ventilación. Estos pacientes presentan una insuficiencia respiratoria por lesiones aparentemente triviales, y la recuperación requiere la identificación sistemática y la corrección de estos factores precipitantes (véase también [Tratamiento de la exacerbación aguda de la enfermedad pulmonar obstructiva crónica](#)). Para restaurar el equilibrio entre la competencia neuromuscular y la carga, el médico debe reducir la obstrucción al flujo de aire y la hiperinsuflación dinámica con broncodilatadores y corticoides y tratar la infección con antibióticos. Bajos niveles séricos de K, fósforo y Mg pueden aumentar la debilidad muscular y frustrar la recuperación, y deben identificarse y tratarse.

La [ventilación con presión positiva no invasiva](#) es el tratamiento inicial de preferencia para muchos pacientes con insuficiencia respiratoria crónica agudizada, que disminuye la frecuencia de neumonía asociada con el respirador, la duración de la internación y la mortalidad comparadas con la intubación endotraqueal. Probablemente el 75% de los pacientes tratados con ventilación con presión positiva no invasiva no requieren intubación endotraqueal. Las ventajas incluyen la facilidad de administración y de retiro; una vez lograda la estabilización inicial, puede interrumpirse la ventilación temporalmente para permitir la alimentación oral en pacientes seleccionados. Las pruebas de respiración sin ayuda son fácilmente realizables, y la ventilación asistida puede reapplicarse en caso necesario. Los ajustes típicos son una IPAP de 10 a 15 cm H₂O y una EPAP de 5 a 8 cm H₂O, de acuerdo con el trabajo respiratorio según la sensación del paciente, la frecuencia respiratoria y el volumen corriente, y el uso de los músculos accesorios. En muchos pacientes, la EPAP aislada puede ser suficiente, lo cual es

beneficioso porque una de las funciones principales de la presión respiratoria positiva inspiratoria es aumentar el volumen corriente y, en estos pacientes, el volumen pulmonar al final de la espiración se aproxima a la capacidad pulmonar total (véase también [Mecánica respiratoria](#)). El deterioro (y la necesidad de intubación endotraqueal) se evalúa mejor clínicamente; los valores de gases en sangre arterial pueden resultar confusos. Si bien un empeoramiento de la hipercapnia típicamente indica un fracaso del tratamiento, la tolerancia de los pacientes a la hipercapnia es muy variable. Algunos pacientes con una $\text{PaCO}_2 > 100$ mmHg están alertas y conversan con ventilación a presión positiva no invasiva, mientras que otros requieren intubación a valores mucho más bajos.

La ventilación mecánica convencional en la insuficiencia respiratoria crónica agudizada tiene el objetivo de minimizar la hiperinsuflación dinámica y contrarrestar los efectos adversos de la [PEEP intrínseca](#) y hacer descansar los músculos respiratorios. Los ajustes iniciales recomendados son el modo asistida/controlada (A/C) con un volumen corriente de 5 a 7 mL/kg y una frecuencia respiratoria de 20 a 24/min, aunque algunos pacientes necesitan frecuencias iniciales más bajas para limitar la PEEP intrínseca. Esta PEEP intrínseca representa la carga umbral inspiratoria que debe ser superada por el paciente para poner en marcha el respirador, aumentando el esfuerzo respiratorio y evitando que el paciente dependa completamente del respirador. Para contrarrestar el efecto de la PEEP intrínseca, debe aplicarse PEEP externa a un nivel $\leq 85\%$ de la PEEP intrínseca (ajuste típico de 5 a 10 cm H₂O). Esta aplicación disminuye el esfuerzo respiratorio sin aumentar la hiperinsuflación dinámica. Debe utilizarse una alta velocidad de flujo inspiratoria para maximizar el tiempo de la espiración. Estos ajustes minimizan el riesgo de alcalosis secundaria a una ventilación inicial enérgica. Inmediatamente después de la intubación puede producirse una hipotensión (ver [Complicaciones y precauciones](#)).

La mayoría de los pacientes requieren un apoyo respiratorio completo durante 24 a 48 h antes de considerar una prueba de respiración espontánea. No se ha determinado si este tiempo terapéutico es necesario para poner en reposo los músculos respiratorios o para permitir que disminuya la hiperinsuflación y aumentar así la fuerza de los músculos respiratorios. Los pacientes a menudo duermen profundamente durante este período, y a diferencia de lo que ocurre en aquellos con asma, requieren poca sedación. El reposo adecuado no se consigue si no se presta la suficiente atención a los esfuerzos respiratorios del paciente. Este esfuerzo puede manifestarse por el uso de los músculos accesorios, una presión inadecuadamente baja en la vía aérea al comienzo o durante la inspiración, o fracasos frecuentes en la activación del respirador, que indican una elevada PEEP intrínseca o debilidad.

Otros tipos de insuficiencia respiratoria



Insuficiencia respiratoria hipoxémica aguda (AHRF, ARDS)



Cómo hacer ventilación con máscara ambú



Tratamiento de la exacerbación aguda de la enfermedad pulmonar obstructiva crónica

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Revisión de Temas: Liposucción Complicaciones y Prevención

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Resumen

La liposucción

Al igual que cualquier procedimiento quirúrgico, presenta riesgos inherentes.

El cirujano debe tener un conocimiento completo de las complicaciones mayores y menores asociadas con este procedimiento, así como de su prevención y tratamiento.

La selección adecuada del paciente, la elaboración completa de historia clínica, evaluación por parte del anestesiólogo, consentimiento informado y una técnica quirúrgica estandarizada que incluya un estricto control de líquidos administrados y eliminados, lidocaína infiltrada y monitoreo intra y postoperatorio, son factores que permiten disminuir las complicaciones asociadas con este procedimiento.

Summary

Liposuction as any surgical procedure has inherent risks.

Plastic surgeon should have a thorough understanding about its complications, prevention and management.

Dr. consulte los Estudios de Bioequivalencia AQUÍ

Adequate patient selection, careful medical record, informed consent, preoperative anesthesiologist assessment, and standardized surgical technique including strict evaluation of fluid replacement, lidocaine infiltration, trans and postoperative control, are factors helping to decrease complications related to lipoplasty.

Introducción en la liposucción

La liposucción paso de ser una novedad de finales de los años 70 a convertirse en el procedimiento mas comúnmente realizado por los cirujanos plásticos en la ultima década. Dujarrier en 1921 fue el primero en utilizar una cánula para remover tejido adiposo por razones cosméticas teniendo un desenlace desastroso en ese intento.

El interés en la remoción de grasa a través de pequeñas cánulas resurgió en los años 60 cuando Schrudde utilizó curetas afiladas ranuradas a presión negativa para la remoción de grasa.

En los años 80 se introdujeron las cánulas romas y a finales de esta década Klein presentó la técnica tumescente la cual minimiza la pérdida de líquidos. Zocchi en 1992 revolucionó la técnica con la asistencia del ultrasonido, (1,2,3,4).

La clave del éxito de la liposucción comienza con una adecuada selección del paciente, la realización de una historia clínica completa que valore antecedentes y factores de riesgo y la comunicación abierta acerca del procedimiento incluyendo los riesgos, complicaciones y limitaciones del mismo.

Aunque la liposucción se considera un procedimiento seguro tiene algunos riesgos inherentes al método mismo que en la mayoría de casos pueden evitarse con una técnica quirúrgica meticulosa y un análisis prequirúrgico cuidadoso.

Complicaciones menores de la liposucción

La literatura disponible destaca como complicaciones menores más frecuentes:

- Las irregularidades de contorno definidas mejor como una secuela más que como una verdadera complicación, pueden ocurrir en cualquier área tratada. Según algunos artículos, se ha reportado que la liposucción asistida por ultrasonido (LAU), presenta menores problemas de este tipo los cuales pueden evitarse llevando a cabo el procedimiento en forma ordenada, (5).
- La hipoestesia de la piel localizada sobre el área liposucionada es una secuela normal y esperada de la liposucción. Teóricamente la disestesia postoperatoria representa una neuritis inflamatoria transitoria que debe tratarse con antiinflamatorios y masajes desensibilizantes.
- Howard encontró una relación directa entre la amplitud de la energía del ultrasonido y el grado de lesión nerviosa en un estudio realizado con ratas en 1998, (5).
- Teóricamente todas áreas tratadas se edematizan por lo que deben utilizarse prendas compresivas durante el postoperatorio para disminuir la presentación de esta complicación, (6).
- Las equimosis serán inevitables en respuesta a la lesión de pequeños vasos, que en la mayoría de veces resolverán espontáneamente, sin embargo la coloración de hemosiderina puede ser permanente sin que exista tratamiento alguno para ella, (2,5,6).
- Puede ser frecuente el sangrado postoperatorio, lo cual puede evitarse mediante una adecuada infiltración del tejido con soluciones con epinefrina que por su efecto vasoconstrictor disminuyen el sangrado procedente de pequeñas lesiones vasculares. Se debe por lo tanto controlar cuidadosamente el material extraído.

- En el caso de aplicación de ultrasonido, este deberá usar únicamente en áreas infiltradas. También se ha relacionado la utilización de cánulas de titanio gastadas con el trauma tisular y el sangrado potencial, (5).
- La aparición de seromas se ha visto con mayor frecuencia con la utilización del ultrasonido. Son más frecuentes cuando se extraen grandes cantidades de grasa o cuando el procedimiento se combina con una cirugía abierta.
- Puede reducirse su frecuencia limitando el tiempo de exposición al ultrasonido y colocando drenaje en el postoperatorio, (7, 8).
- Afortunadamente la infección no es una complicación común en la liposucción y puede prevenirse con un adecuado lavado y esterilización de los equipos así como el empleo de una adecuada asepsia y antisepsia durante el procedimiento mismo.
- El germen mas frecuentemente involucrado es el Estafilococo áureas. Comúnmente se utilizan antibióticos profilácticos tales como las cefalosporinas de primera generación, (5).
- También se han reportado casos de fascitis necrotizante, siendo los microorganismos causales más frecuentes los anaerobios y el Estreptococo beta hemolítico.
- El tratamiento incluye la combinación de antibióticos de amplio espectro, el desbridamiento agresivo y la administración de oxígeno hiperbárico, (5).

La necrosis de piel

Es resultado, de una lesión bascular o térmica puede evitarse por completo si la técnica es realizada apropiadamente y respetando la anatomía.

La lesión térmica del espacio subcutáneo es un riesgo exclusivo dela liposucción asistida por ultrasonido que puede prevenirse teniendo en cuenta sus dos reglas cardinales: aplicar ultrasonido únicamente en el tejido infiltrado y mantener siempre la cánula en movimiento, (5,9).

- Debido al pequeño diámetro y longitud de las cánulas y a la naturaleza ciega del procedimiento existe el riesgo de dirigir la cánula dentro de planos tisulares indeseados, resultando en la perforación de una visera.
- Se consideran pacientes de alto riesgo para perforación intestinal aquellos con hernias de la pared abdominal; antecedente de cirugía abdominal incluyendo la laparoscopia, debido al neumoperitoneo.
- Por lo que debe enfatizarse en el examen físico la búsqueda de cicatrices abdominales y cualquier herniacion que alerte al cirujano sobre un riesgo de perforación.
- Incluso se ha recurrido a la tomografía y ecografía en pacientes en quienes el examen físico resulta dudoso como es el caso del paciente obeso, (5,10).

Trombosis venosa profunda

El embolismo pulmonar es una enfermedad común en nuestro medio hospitalario y una causa frecuente de muerte. La incidencia de trombosis venosa profunda es de aproximadamente 0.1 a 0.8% en pacientes sin profilaxis. Aunque existe poca información en cuanto a esta complicación en pacientes de cirugía estética, el riesgo parece ser bajo, (11).

Es un hecho que el embolismo pulmonar no tratado debe considerarse como un estado de enfermedad con mortalidad relativamente alta si no se diagnostica adecuadamente.

Las manifestaciones clínicas son variables e inespecíficas y puede o no haber signos o síntomas aún cuando exista una trombosis profunda extensa. Los síntomas pueden ser dolor o sensación de tirantez en la pierna, con o sin inflamación.

Dolor a la dorsiflexión pasiva del talón, signo de Homan y cuando se presenta el embolismo pulmonar puede haber dolor pleurítico, disnea, hemoptisis, taquicardia, taquipnea, alteración del estado mental o presentarse una descompensación respiratoria repentina en el periodo postoperatorio, (11,12).

Lea Tambien: Liposucción, Embolismo Graso

Factores de riesgo

El paso más importante en el diagnóstico de tromboembolismo pulmonar es la sospecha clínica.

Es fundamental considerar ante todo los factores de riesgo, dentro de los antecedentes de importancia se encuentran:

Antecedentes patológicos:

1. Varios defectos genéticos y adquiridos predisponen a los pacientes a desarrollar desórdenes de coagulación hemorrágica como son disfrinogenemia y anormalidades de los factores VIII, IX, y X
2. Estados de hipercoagulabilidad incluyendo protrombina anormal, antitrombina III normal o ausente, proteína C o S anormal, plaquetas anormales y síndrome antifosfolípido.
3. Pacientes con una historia previa de embolismo pulmonar, insuficiencia venosa crónica.
4. Obesidad
5. Trauma quirúrgico o no quirúrgico
6. Infección sistémica severa
7. Policitemia
8. Enfermedad del sistema nervioso central o periférico parálisis de miembros inferiores
9. Homocistinemia
10. Radioterapia especialmente de neoplasmas pélvicos
11. Mujeres que estén tomando anticonceptivos orales, o reemplazo hormonal tienen un riesgo más alto.
12. Embarazo.
13. Enfermedad cardíaca
14. Enfermedad cardíaca
15. Enfermedades que impliquen inmovilizaciones prolongadas

En los antecedentes familiares es importante la historia de eventos trombóticos o estados de hipercoagulabilidad. Estos factores son modificados adicionalmente por el cuidado general del paciente, duración y tipo de anestesia. Inmovilización perioperatoria, grado de deshidratación y presencia de sepsis. Por esto el riesgo individual está determinado por el tipo de cirugía y la acumulación de factores predisponentes.

El diagnóstico será, pues, el resultado de la suma de factores de riesgo, signos y síntomas, EKG, Rx de tórax, test de ventilación/perfusión, sin embargo, el examen más preciso para confirmar el diagnóstico es la arteriografía pulmonar.

Tabla No.1

TROMBOSIS VENOSA PROFUNDA	FACTORES DE RIESGO	RECOMENDACIONES
RIESGO BAJO	● [40 años No uso anticonceptivos orales o terapia hormonal. ● No enfermedad crónica, maligna o infección. ● No antecedentes familiares ● No antecedentes, insuficiencia venosa.	● Posición confortable en la mesa quirúrgica ● Flexión de la rodillas ● De ambulación temprana ● Medias de compresión graduada.

RIESGO MODERADO	● ≥ 40 años ● Uso de anticonceptivos orales o terapia hormonal ● Enfermedad crónica, maligna o infecciosa ● Historia familiar ● Procedimiento corto ● Cirugía abdominal o ginecológica conmitante	● Lo mismo que bajo riesgo ● Compresión neumática intermitente. ● Cambio de posición en la mesa-Heparina 5000uc/12h-HBPM 20mg/día 24h post-quirúrgico.
RIESGO ALTO	● Cualquier edad con procedimiento prolongado. ● Historia de uso hormonal ● Historia de enfermedad crónica maligna o infecciosa ● Antecedente familiar	● Igual que bajo riesgo ● Interconsulta a hematología prequirúrgico con ant. previo ● Considerar uso pre-quirúrgico heparina 500u/8h o BPM 40MG C/12H ● Compresión neumática intermitente y cambio frecuente de posición intraoperatoria

Profilaxis y manejo

En Octubre de 1998 la Sociedad Americana de Cirugía Plástica y Reconstructiva creó el "task force" en tromboembolismo pulmonar, el cual está conformado por varias recomendaciones. Teniendo en cuenta la historia clínica, el examen físico y los exámenes de laboratorio adecuados, el riesgo de trombosis venosa profunda se clasifica en bajo, moderado y alto, lo que determina un tratamiento profiláctico, (11, 13, 14) (Tabla No.1).

Las medidas profilácticas más comunes son:

1. Deambulación temprana: debe iniciarse antes de las 24 horas de forma gradual
2. Medias de compresión graduada: se ha observado que aumentan la velocidad de flujo sanguíneo venoso aunque no hay evidencia conclusiva que eviten o disminuyan la incidencia de embolismo pulmonar.
3. Compresión intermitente en miembros inferiores: aumentan el flujo venoso sanguíneo profundo y favorecen la actividad fibrinolítica
4. Anticoagulantes orales: no se recomienda el uso de aspirina como profilaxis. En pacientes de alto riesgo, en casos muy seleccionados, se puede usar la warfarina perioperatoria con INR de 2 a 3.
5. Heparina: se administra usualmente a dosis bajas de 5000U. subcutáneos 2 horas antes de cirugía y en el postoperatorio cada 8 o cada 12 horas según el riesgo.
6. Heparinas de bajo peso molecular (HBPM): se ha demostrado su mejor eficacia en la prevención de trombosis. Ejercen un buen efecto de prevención cuando se administran en las primeras 24 horas del postoperatorio.
7. En nuestro medio recomiendan enoxiparina 20 mg subcutáneos/día en riesgo moderado y 20 mg cada 12 horas en riesgo alto y la nadroparina a 40 U/kg 2 horas antes de la cirugía y una vez al día por tres días, (12,16,17).

Revisión Bibliográfica

PROFILAXIS PREOPERATORIA DE TROMBOSIS VENOSA PROFUNDA EN PACIENTES DE CIRUGÍA GENERAL

Preoperative prophylaxis of deep vein thrombosis in general surgery patients

Carlos Felipe Matute Martínez, Luis Enrique Sánchez-Sierra, Daniel Martín Barahona López¹, Luis Membreño Vásquez², Rafael Perdomo Vaquero³

RESUMEN

La tromboembolia venosa resulta de la alteración en uno de los componentes de la tríada de Virchow. Dentro de ella encontramos la trombosis venosa profunda y la embolia pulmonar, siendo la última una complicación potencialmente fatal. La tromboembolia venosa es una causa común de muerte prevenible en los pacientes hospitalizados; aproximadamente un tercio de las muertes relacionadas con esta patología ocurren después de una intervención quirúrgica. Con una detallada anamnesis se conocen las patologías y factores de riesgo previos, coadyuvando a trazar un plan profiláctico o terapéutico para cada caso. Según la complejidad del procedimiento quirúrgico, comorbilidades y factores de riesgo, se sugiere el uso de terapia profiláctica farmacológica y/o mecánica para prevenir la trombosis. Las recomendaciones en el tratamiento profiláctico actualmente son en base a la escala de Caprini y Rogers. **Objetivo:** Caracterizar el tratamiento profiláctico de la trombosis venosa profunda en pacientes de cirugía general. **Metodología:** Se realizó una revisión no sistemática de artículos publicados en revistas indizadas en base de datos nacionales e internacionales. Inicialmente se obtuvo el resumen y texto completo de las publicaciones mediante el uso de palabras claves para la búsqueda, finalizando con la aplicación de los criterios de selección. **Conclusión:** Los factores de riesgo para tromboembolia venosa se

deben considerar para clasificar el riesgo y establecer la profilaxis preoperatoria adecuada según el procedimiento y patología preexistente.

Palabras clave: Trombosis de la vena, embolia pulmonar, tromboembolia, embolia y trombosis, prevención y control.

ABSTRACT

Venous thromboembolism results from the alteration in one of the components of Virchow's triad. Within the thromboembolism we find the deep vein thrombosis and pulmonary embolism, being the latter one a potentially fatal complication. The venous thromboembolism is a common cause of preventable death in hospitalized patients. Approximately one third of this pathology related deaths occurs after surgery. With a detailed history, pathologies and previous risk factors should be known, helping to draw an appropriate prophylactic or therapeutic plan for each individual case. Depending on the complexity of the surgical procedure, comorbidities and associated risk factors, the use of pharmacological and/or mechanic prophylactic therapy is suggested to prevent thrombosis. The current recommendations in the prophylactic treatment are based on the Caprini and Rogers scales. **Objective:** Characterize the prophylactic treatment of deep vein thrombosis in general surgery patients. **Methodology:** a non-systematic review of articles published in indexed journals on national and international data bases was performed. Initially abstracts and full text publications were obtained by using keywords in the search, ending with the application of the selection criteria. **Conclusion:** Risk factors for venous thromboembolism should be taken into account to classify the risk and establish appropriate preoperative prophylaxis according to the procedure and pre-existing condition.

Key words: Venous thromboembolism, deep vein thrombosis, pulmonary embolism, general surgery, prophylaxis.

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INTRODUCCIÓN

La Trombosis Venosa Profunda (TVP) es una patología de alto impacto en la población hospitalaria debido a la inmovilización que presentan estos pacientes, lo cual favorece la formación de coágulos en el sistema venoso profundo, pudiendo progresar al embolismo pulmonar.

Los avances en la terapia antitrombotica han permitido prevenir las complicaciones originadas por la estadía hospitalaria. La TVP es definida por la University of Maryland Medical Center (2011) como “La formación de un coágulo sanguíneo dentro del sistema venoso profundo con mayor frecuencia en los miembros inferiores o piernas”, pero también puede ocurrir en otros lugares como brazos y abdomen.^(1,2)

Se considera que la incidencia de TVP es de 1-2 por 1000 habitantes por año;⁽²⁾ forma parte del complejo de enfermedad tromboembólica que incluye esta entidad y al tromboembolismo pulmonar⁽²⁻⁴⁾, caracterizados por cumplir con los tres componentes de la tríada de Virchow

(estasis, hipercoagulabilidad e injuria endotelial) que llevan a la formación del trombo.^(2,5-7)

La TVP y Embolia Pulmonar (EP) son la primera causa de muerte prevenibles en pacientes hospitalizados. La elevada incidencia de complicaciones secundaria a Tromboembolismo Venoso (TEV) puede ser fácilmente disminuida con la administración terapéutica o profiláctica de tratamiento para la trombosis. El apropiado uso de la profilaxis se basa en el conocimiento de factores de riesgo específicos para la TVP. Más que otro tipo de pacientes, el paciente quirúrgico acumula múltiples factores de riesgo, en especial aquel que se somete a procedimientos ortopédicos.^(6,8)

La terapia anticoagulante es efectiva, pero cuando su uso es innecesario provoca gastos, molestias y riesgo de hemorragia grave.⁽⁹⁾ En cirugía general los pacientes con riesgo moderado de TEV de 3.0% (Puntaje de Roger 10; Puntaje de Caprini 3-4) que no tienen alto riesgo de complicaciones por sangrado, se recomienda el uso de heparina de bajo peso molecular, bajas dosis de heparina no fraccionada o profilaxis mecánica, preferiblemente la compresión neumática intermitente.⁽¹⁰⁻¹³⁾ (Cuadro 1 y 2).

Cuadro 1. Escala de Caprini

1 Punto	2 Puntos	3 Puntos	5 Puntos
Edad 41 a 60 años	Edad de 61 a 74 años	Edad mayor a 75 años	ACV en el último mes
Cirugía menor	Cirugía artroscópica	Antecedentes de embolia venosa	Artroplastia electiva
IMC>25 Kg/m2	Cirugía abierta mayor de 45 minutos	Antecedentes familiares de embolia venosa	Fractura de cadera pelvis o pierna
Edema en miembros	Cirugía laparoscópica mayor de 45 minutos	Factor V de Leiden	Lesión espinal aguda en el último mes
Venas varicosas	Cáncer	Protrombina 20210A	
Embarazo o puerperio	Paciente encamado por más de 72 horas	Anticoagulante lúpico	
Historia de abortos espontáneos	Paciente inmovilizado	Anticuerpos anti-cardiolipina	
ACO	Acceso venoso central	Niveles séricos de homocisteína elevados	
Sepsis en el último mes		Trombocitopenia inducida por heparina	
Neumonía en el último mes o EPOC		Trombofilia congénita o adquirida	
Pruebas de función pulmonar anormales			
Infarto cardiaco			
Enfermedad Inflamatoria Intestinal			
Encamamiento			

Riesgo Muy Bajo 0 (deambulaci3n temprana), Riesgo Bajo 1-2 (compresi3n neum3nica intermitente), Riesgo Moderado 3-4 (heparina de bajo peso molecular o heparina no fraccionada +/- compresi3n neumática intermitente), Riesgo Alto 5+ (heparina de bajo peso molecular o heparina no fraccionada + compresi3n neumática intermitente); Abreviaciones: IMC, Índice de masa corporal; ACO, Anticonceptivos orales; EPOC, Enfermedad pulmonar obstructiva cr3nica; ACV, Accidente cerebro-vascular.

Fuente: Caprini JA. Thrombosis risk assessment as a guide to quality patient care. Dis Mon. 2005.

Cuadro 2. Medicamentos aprobados por la FDA para la profilaxis en TEV

Medicamento	Dosis	Dosis en falla renal	Comentario
Heparina no fraccionada	5000 UI SC cada 8-12 horas	Igual	Metanálisis han sugerido la dosis cada 8 horas, pero con aumento del riesgo de sangrado
Heparinas de bajo peso molecular			
Enoxaparina	40 mg SC cada día	30 mg SC cada día	La dosis de 30 mg no está aprobada en pacientes en hemodiálisis. Expertos recomiendan el uso de 30 mg cada 12 horas en pacientes con IMC mayor de 35 kg/m ²
Dalteparina	5000 UI SC cada día	dosis no específica	La dosis de 5000 UI cada día ha sido estudiada en pacientes en UCI con falla renal severa, pero la FDA no la ha aprobado para estos pacientes.
Pentasacáridos			
Fondaparinux	2.5 mg SC cada día	Dosis no aprobada	No administrar en pacientes con peso menor de 50 kg. Usar con precaución cuando el aclaramiento de creatinina sea de 30 a 50 ml/min. Es poco probable que cause trombocitopenia inducida por heparina.
Abreviaturas: TEV, tromboembolismo venoso; FDA, Food and Drug Administration; IMC, índice de masa corporal; UCI, unidad de cuidados intensivos; UI, Unidades Internacionales; SC, Subcutánea.			

Fuente: Stevens S.M, Douketis J.D, Deep Vein Thrombosis Prophylaxis in Hospitalized Medical Patients: Current recommendations, general rates of implementation and initiatives for improvement. Clin Chest Med. 2010.

La TVP es la formación de coágulos en el sistema venoso profundo, predominando en los miembros inferiores. Estos coágulos usualmente se forman en la vena poplítea y/o femoral, presentándose en ambos sexos, pero con mayor incidencia en mujeres de edad avanzada.⁽¹⁴⁾

Se debe considerar que la TVP es una complicación frecuente en pacientes encamados o inmovilizados, por lo que una tromboprofilaxis adecuada reduce significativamente la probabilidad de formación de trombos especialmente en miembros inferiores.^(15,16) Históricamente la tríada de Virchow ha aportado tres factores predisponentes: estasis sanguínea, lesión endotelial y alteraciones de la coagulación, investigaciones en los últimos años se han encaminado a la búsqueda de nuevos factores asociados a la aparición de estas patologías.⁽¹⁶⁾ El tratamiento antitrombotico permite la prevención de esta patología en pacientes que presenten situaciones de riesgo como cirugía reciente y estancia hospitalaria prolongada.⁽¹⁷⁾ La progresión de esta patología conduce a embolia pulmonar, definida como la impactación de un embolo en el sistema vascular pulmonar, proveniente del sistema venoso profundo.

Por lo antes mencionado se han considerado que ambos cuadros pertenecen a la misma patología.⁽³⁾

Esta revisión pretende caracterizar el tratamiento profiláctico de la trombosis venosa profunda en pacientes de cirugía general, estableciendo la etiología, aspectos clínicos y factores de riesgo relacionados.

METODOLOGÍA

En orden para actualizar y expandir los conocimientos se realizó una revisión no sistemática de artículos de investigación, artículos de revisión y literatura relacionada, usando bases de datos como PubMed, HINARI, SCOPUS, Sciences Direct y BVS-HN, utilizando los términos médicos tromboembolismo, trombosis venosa profunda, embolismo pulmonar, profilaxis y cirugía general en el idioma español e inglés. Se analizó el resumen y se obtuvo el texto completo de la publicación, finalizando con la aplicación de los criterios de selección.

Criterios de inclusión: artículos relacionados con el tema en discusión, artículos de estudio realizado en seres humanos vivos, publicados preferiblemente en los últimos cinco años y literatura mayor a cinco años relevante al tema de estudio. Fueron excluidos publicaciones de estudios experimentales, estudios desarrollados en animales y estudios no relacionados con la temática de la revisión.

DESARROLLO Y DISCUSIÓN

La incidencia de TVP en la población del hemisferio occidental es de 1-2 casos por cada 1000 habitantes, es poco frecuente en la población menor de 20 años, aumentando su incidencia conforme avanza la edad. Es conocido que un grupo en riesgo es la población recientemente sometida a cirugía, en especial una intervención quirúrgica ortopédica.^(3,4) La mayoría de pacientes que presentan TVP se encuentran hospitalizados, debido a que el tiempo prolongado en cama o inmovilización del paciente aumenta el riesgo de su padecimiento. La mayoría de casos de TVP permanecen asintomáticos; existen trombosis en el árbol vascular pulmonar en cerca del 50% de pacientes que presentan la patología a nivel de la porción proximal de las venas profundas.⁽¹⁸⁾ A pesar que generalmente los trombos son originados en las venas profundas de los miembros inferiores, existen raros casos de trombos con origen en las venas profundas del miembro superior, estos casos han venido en aumento debido al empleo de dispositivos y catéteres venosos centrales a través de estas venas.⁽¹⁹⁾

El empleo de heparinas de bajo peso molecular, así como también nuevos fármacos que actúan a nivel de los factores de coagulación ha permitido la reducción de esta patología en pacientes que presenten factores de riesgo. En pacientes quirúrgicos se recomienda su empleo previo a la intervención y posterior a la misma según lo amerite el caso del paciente.^(20,21)

En estudios a nivel nacional relacionados con TEV, se encontró el primero en 1950 desarrollado por el Dr. Hernán Corrales Padilla, médico dermatólogo, sobre el síndrome post-trombótico de los miembros inferiores, menciona que las varices son muy frecuentes y son tratadas de manera errónea por los cirujanos, cuando no han hecho aún el estudio clínico para descartar una tromboflebitis o una flebotrombosis profunda antigua, y

las várices en cuestión, que son netamente secundarias, pasan a ser un capítulo del síndrome post-trombótico de las extremidades inferiores, como lo llama Westermeyer “Insuficiencia crónica venosa profunda de Allen”. En 1956 se publicó un estudio sobre el sistema venoso de los miembros inferiores, este establece que hay que repetir hasta la saciedad como consecuencia de este concepto, que el varicoso no es un hipertenso venoso, sino que permanentemente tiene la tensión ortostática elevada, es decir, la tensión de un individuo parado, y no se beneficia de la descompresión que normalmente ocurre durante la marcha.^(22,23)

Es importante que el cirujano clínico investigue la frecuencia o incidencia real del embolismo pulmonar fatal, es probable que se han exagerado esos datos estadísticamente, al analizarlos en base a un determinado parámetro, por ejemplo: en relación al número de casos diagnosticados clínicamente como embolia pulmonar, esta es una patología relacionada con trombosis venosa profunda; en 1986 el Dr. Membreno cirujano y profesor de la Facultad de Ciencias Médicas realizó un estudio que reportó 3 muertes por embolia pulmonar en el período 1973-1977 y 3 muertes en el período 1980-1984.⁽²⁴⁾

La causa más frecuente de muerte post-operatoria en cirugías electivas es el tromboembolismo pulmonar (15%) y el tratamiento del tromboembolismo venoso ha demostrado reducir sus índices de mortalidad, uno de los tratamientos más efectivos es la colocación de un filtro de vena cava inferior.⁽²⁵⁾

Etiología

Los factores de riesgo de TVP asociados a la afectación de uno o más de los mecanismos de la tríada de Virchow aumentan la probabilidad de formar trombos, entre ellos se encuentran los procedimientos quirúrgicos; en cirugía mayor especialmente pelvis, abdomen, cadera y rodilla.^(1,2) (Cuadro 3); antecedentes personales de TVP y trombo embolismo pulmonar previo, esto aumenta el riesgo de un nuevo episodio de TVP hasta 5 veces^(2,26); hospitalización; un tercio de los casos ocurre en los 3 primeros meses de hospitalización.⁽²⁾ Embarazo y puerperio; confiere un estado de hipercoagulabilidad transitoria que representan una respuesta fisiológica para controlar la hemorragia que se produce durante el parto; sin embargo, esta respuesta puede progresar anormalmente a un estado patológico y aumentar el riesgo

de fenómenos tromboembólicos, con una incidencia general de 199.7 por cada 100,000 mujeres al año y riesgo relativo de 4.3.^(8,27) La mujer debe ser interrogada sobre el uso de anticonceptivos orales o terapia de reemplazo hormonal, debido que los preparados con altas y bajas dosis de estrógenos representan un riesgo para el desarrollo de TVP.

Antecedentes de cáncer u hallazgos que pueden sugerir una neoplasia subyacente, debido que las células tumorales pueden estimular la trombina y expresión de actividad procoagulante por tejidos sin alteración del huésped.^(2,27) Obesidad, se estima que un índice de masa corporal mayor de 30 kg/m² genera el doble de riesgo, al estar relacionado

con la inactividad física; vuelos de largo recorrido, ya que la combinación de inmovilidad y deshidratación predisponen a TVP.⁽²⁷⁾ Trombofilias; estas ocurren debido a mutaciones genéticas afectando la función de la antitrombina III, proteína C o proteína S, o en la ganancia de la función del factor V Leiden y la protrombina.^(22,23) Los altos niveles de factores de coagulación (factores VIII, IX y XI) y la hiperhomocisteinemia también han sido implicados en el riesgo de TVP.⁽²⁷⁾ Entre otros factores causales encontramos el trauma, insuficiencia cardíaca y la inmovilidad.⁽²⁾ También se ha planteado como probable causa la influencia de los cambios atmosféricos en la ocurrencia de la trombosis venosa profunda principalmente en las extremidades inferiores.⁽²⁸⁾

Cuadro 3. Estratificación de Riesgo para TEV

Categoría de riesgo AT9	Pacientes con cirugía mayor torácica o vascular		Pacientes con cirugía general (tiroides, TGI, urológica, mama o vascular)		Pacientes con cirugía plástica o reconstructiva		Otros pacientes quirúrgicos en riesgo	Riesgo estimado en ausencia de profilaxis mecánica o farmacológica %
	Escala de Rogers	Riesgo de TEV (%)	Escala de Caprini	Riesgo de TEV (%)	Escala de Caprini	Riesgo de TEV (%)		
Muy Bajo	<7	0.1	0	0	1-2	ND	Cirugía ambulatoria	<0.5
Bajo	7-10	0.4	1-2	0.7	3-4	0.6	Cirugía espinal sin enfermedad maligna	1.5
Medio	>10	1.5	3-4	1	5-6	1.3	Cirugía ginecológica, cirugía cardíaca, cirugía espinal por malignidad y mayoría de cirugías	3
Alto	ND	ND	≥5	1.9	7-8	2.7	Cirugía bariátrica, cirugía ginecológica por malignidad, neumonectomía, craneotomía, TEC, trauma espinal y otros traumas	6

Abreviatura: ND significa No disponible.

Fuente: Gould MK et al. Prevention of VTE in nonorthopedic surgical patients. Chest. 2012.

Aspectos clínicos

Si la TVP afecta a las venas proximales de los miembros inferiores la clínica suele ser más evidente, los síntomas clásicos de la TVP incluyen aumento de volumen o edema del miembro afectado, constituyendo el síntoma más específico; dolor en el miembro afectado, ocurre en el 50% de los pacientes, pero no es específico; eritema o cianosis en la extremidad afectada; sensibilidad en 75% de los casos; también podemos encontrar calor en el área de la trombosis.^(27,29)

El signo de Homans (dolor en la pantorrilla con la dorsiflexión de pie) es sugestivo pero de muy escasa especificidad y no es diagnóstico definitivo para TVP.^(2,27) El signo de Ollow (dolor a la palpación de un cordón venoso en la zona poplíteica) pueden ser más específicos, aunque la utilidad diagnóstica de estos métodos es escasa.⁽²⁾ El edema unilateral con fovea es importante, pues indica trombosis en el 70% de los pacientes, representando el síntoma más específico para TVP.^(27,29) No existe necesariamente

una correlación entre la ubicación de los síntomas y el sitio de la trombosis.⁽²⁾ La presentación clínica tiene un espectro muy variable, desde asintomático hasta manifestaciones más sugestivas.⁽²⁷⁾

Aproximadamente 46% de los pacientes con manifestaciones clínicas clásicas tienen un flebograma negativo y un 50% de casos con documentación por estudio de imagen de trombosis venosa tienen ausencia de síntomas.⁽²⁹⁾ La TVP incluye las siguientes complicaciones potenciales: embolia pulmonar (el 40% de los pacientes la presentan al momento del diagnóstico), embolia paradójica, TVP recurrente y síndrome posttrombótico.

Profilaxis según procedimiento y riesgo de tromboembolismo venoso

El puntaje de Caprini es un sistema de puntuación validado que muestra el aumento de incidencia de TEV por nivel de riesgo, utiliza los factores de riesgo para TEV y le asigna puntos, resultando en una puntuación con la que el cirujano puede medir el riesgo de hemorragia versus el riesgo de TEV y así determinar cuál profilaxis es la más apropiada para cada paciente (Cuadro 1).⁽³⁰⁾

Para cirugía general y abdominopélvica en los pacientes con riesgo muy bajo para TEV de 0.5%, puntaje de Rogers: 7; Puntaje de Caprini: 0, se recomienda la temprana deambulacion. Los pacientes con riesgo bajo de 1.5%, puntaje de Rogers: 7-10; puntaje de Caprini: 1-2, se recomienda profilaxis mecánica, preferiblemente la compresión neumática intermitente. En pacientes con riesgo moderado de 3.0%, puntaje de Rogers: 10; puntaje de Caprini: 3-4 (Cuadro 1), quienes no están en alto riesgo de complicaciones hemorrágicas graves, se sugiere heparinas de bajo peso molecular (Cuadro 2), dosis bajas de heparina no fraccionada o profilaxis mecánica preferiblemente la compresión neumática intermitente. Los pacientes con riesgo moderado y con alto riesgo de complicaciones hemorrágicas graves, o en los que se piensa que las consecuencias de sangrado pueden ser particularmente graves, se sugiere profilaxis mecánica, preferiblemente con compresión neumática intermitente. Los pacientes con riesgo alto de 6%, puntaje de Caprini: 7-8 (Cuadro 3), de TEV quienes no están en riesgo alto de complicaciones hemorrágicas, se recomienda el uso de heparina de bajo peso molecular o heparina no fraccionada de baja dosis. También se sugiere el uso de medias elásticas o compresión neumática intermitente como medida adyuvante.^(11,30)

Para cirugía general en los pacientes con alto riesgo en los cuales la heparina de bajo peso molecular (Cuadro 2) y la heparina no fraccionada está contraindicada, no está disponible o no presente alto riesgo de complicaciones hemorrágicas graves, se sugiere el uso de bajas dosis de aspirina, fondaparinux o compresión neumática intermitente. Los pacientes sometidos a cirugía general, cirugía abdominopélvica y torácica con alto riesgo de TEV en quienes presentan alto riesgo de complicaciones hemorrágicas graves, se sugiere el uso de profilaxis mecánica con compresión neumática intermitente hasta que el riesgo de sangrado disminuya y la profilaxis farmacológica pueda iniciarse. En los pacientes sometidos a cirugía torácica con moderado o alto riesgo para TEV y no están en alto riesgo de sangrado postoperatorio, se sugiere el uso de heparina no fraccionada de baja dosis, heparina de bajo peso molecular o profilaxis mecánica con compresión neumática intermitente.⁽¹¹⁾

En los pacientes con alto riesgo de TEV que se someterán a cirugías abdominales o pélvicas por cáncer que no presenten alto riesgo de complicaciones hemorrágicas graves, se recomienda profilaxis farmacológica de duración extendida (4 semanas) con heparina de bajo

peso molecular (dosis profiláctica máxima) o heparina no fraccionada cuando el procedimiento (laparotomía) es de gran magnitud. La profilaxis farmacológica debe iniciarse 12 horas antes del procedimiento y continuar al menos 7-10 días.^(11,31)

Para cirugía cardíaca en pacientes post-operados no complicados, se sugiere el uso de profilaxis mecánica con compresión neumática intermitente. En el caso que su estadía hospitalaria se prolongue no por razones quirúrgicas hemorrágicas, se sugiere el uso de heparina fraccionada de baja dosis o heparina de bajo peso molecular, más la profilaxis mecánica. En pacientes sometidos a craneotomía y cirugía espinal, se sugiere la profilaxis mecánica con compresión neumática intermitente junto con la profilaxis farmacológica. Cuando la terapia farmacológica está contraindicada se indica solamente la compresión neumática intermitente. En el caso que presente alto riesgo de TEV, se sugiere añadir la terapia farmacológica una vez se establezca una adecuada hemostasia y el riesgo de sangrado disminuya.^(11, 30)

Para paciente con trauma grave en alto riesgo de TEV, se sugiere la profilaxis mecánica con compresión neumática intermitente y farmacológica con heparina de bajo peso molecular. En el caso que la profilaxis farmacológica este contraindicada se sugiere la profilaxis mecánica hasta que el riesgo por sangrado disminuya o las contraindicaciones se resuelvan. En pacientes con trauma grave y con trastornos de la movilidad se recomienda la profilaxis farmacológica hasta el alta médica. En pacientes sometidos a cirugía general, abdominopélvico, espinal y trauma grave con alto riesgo de TEV, no se recomienda el filtro de vena cava inferior como prevención primaria. En todos los casos anteriores actualmente no se recomienda la supervisión periódica con ecografía por compresión venosa de manera rutinaria.^(11,30)

Diagnóstico

La TVP en extremidades inferiores usualmente comienza en la pantorrilla y se propaga proximalmente hacia la vena poplítea, vena femoral y vena iliaca. En extremidades inferiores se clasifican según su localización: distal a la vena poplítea y proximal a la vena poplítea.^(2,6) Es 10 veces más común que en extremidades superiores, está a menudo precipitada por la colocación de marcapasos, desfibriladores intracardiacos y catéteres

venosos centrales permanentes. La probabilidad de TVP en las extremidades superiores aumenta, así como aumenta el diámetro del catéter y el número de lúmenes. La trombosis venosa superficial usualmente aparece con eritema, aumento de la sensibilidad y un “cordón palpable”.⁽⁶⁾

El síntoma común es calambre en la parte inferior de la pantorrilla, que persiste y se intensifica durante varios días. Según el puntaje obtenido con la Escala de Wells, la probabilidad de padecer TVP se puede clasificar en poco probable (< 2) y probable (≥ 2) ó baja (0-1), moderada (1-2) y alta: ($\geq 2-3$). En pacientes con síntomas en ambas piernas, se utiliza la pierna con más síntomas. Pacientes con probabilidad baja a moderada de TVP o EP deben someterse a una evaluación diagnóstica inicial con el examen Dimero-D (DD), sin exámenes por imagen. Si el DD es negativo no se recomiendan más exámenes; si el DD es positivo se sugiere realizar un ultrasonido por compresión de las venas proximales en lugar de toda la pierna o venografía. En pacientes con probabilidad alta de TVP se debe omitir el DD e iniciar con exámenes por imagen, como ser el ultrasonido por compresión. Si el ultrasonido por compresión es negativo, se recomienda exámenes adicionales con DD en 1 semana. Si el ultrasonido por compresión de las venas proximales es positiva se sugiere tratar por TVP y no seguir realizando exámenes.^(6,7,9,32)

Dentro de los cuadros diferenciales se debe mencionar la celulitis y el quiste de Baker, el dolor repentino y severo de pantorrilla sugiere ruptura de quiste de Baker, mientras que la fiebre y escalofríos sugieren celulitis más que TVP. Los hallazgos clínicos, si están presentes, puede consistir en leve dolor a la palpación de la pantorrilla. Una TVP masiva a menudo se presenta en el muslo con un marcado edema, sensibilidad y eritema. Si la pierna está difusamente edematosa, la TVP es improbable, es más probable una exacerbación de la insuficiencia venosa debido al síndrome post-trombótico. La trombosis venosa de las extremidades superiores puede presentarse con asimetría en la fosa supraclavicular o en la circunferencia de los brazos superiores.⁽⁶⁾

Laboratorio

La función hemostática se valora con una revisión cuidadosa de la historia clínica del paciente (anamnesis y examen físico) y ciertas pruebas de laboratorio. La

anamnesis es útil para recabar datos relacionados con antecedentes de hemorragias, enfermedades asociadas, fármacos o drogas que alteren la hemostasia normal del paciente. Usualmente las pruebas de laboratorio iniciales son el recuento plaquetario, International Normalized Ratio (INR, por sus siglas en inglés), Tiempo de Protrombina (TP), Tiempo de Tromboplastina Parcial activado (TTPa) y DD.

Las plaquetas son fragmentos anucleados de los megacariocitos. El número normal circulante de plaquetas en el plasma varía entre 150,000 y 400,000/ μ L. Si las plaquetas no son consumidas por una reacción de coagulación, hasta un 30% de ellas son normalmente removidas por el bazo y tiene una vida media de 7 a 10 días.^(2,8)

Las plaquetas juegan un rol importante en la hemostasia formando un tapón hemostático y contribuyendo a la formación de trombina. Los recuentos elevados (>1,000,000/uL) se asocian a complicaciones trombóticas, en cambio su contraparte se asocia a complicaciones hemorrágicas. La severidad de cada evento es directamente proporcional al recuento plaquetario existente y su pronóstico varía según las complicaciones y procedimiento cruento realizado.⁽⁵⁾

Los tiempos de coagulación TP y TTP son variaciones de los tiempos de la recalcificación del plasma que se inicia con la adición de un agente tromboplástico. El reactivo de TP contiene tromboplastina y calcio, que cuando se añade al plasma, lleva a la formación del coágulo de fibrina. El TP mide la función de los factores I, II, V, VII y X. El factor VII es parte de la vía extrínseca y los factores restantes son parte de la vía común de la coagulación. El factor VII tiene la vida media más corta de los factores de coagulación y su síntesis es dependiente de la vitamina K. El TP es el más adecuado para detectar anomalías causadas por la deficiencia de vitamina K y tratamiento con warfarina.^(5,8)

Por las variaciones en la actividad de la tromboplastina, puede ser difícil de evaluar acertadamente el grado de anticoagulación basado solamente con el TP. Para tener en cuenta estas variaciones, el INR es ahora el método de elección para reportar los valores del PT. El International Sensitivity Index (ISI por sus siglas en inglés) es única para cada lote de tromboplastina y es proporcionado por el fabricante a cada laboratorio de hematología. El reactivo óptimo tiene un ISIS entre 1.3 - 1.5. El INR es

un número calculado derivado por la siguiente ecuación: $INR = (PT_{medido}/PT_{normal})^{ISI}$.^(5,6)

El Tiempo de TTPa contiene un sustituto de fosfolípido, un activador y calcio, el cual en presencia de plasma lleva a la formación del coágulo de fibrina. El TTPa mide la función de los factores I, II, y el V de la vía común y los factores VIII, IX, X y XII de la vía intrínseca. La terapia con heparina es a menudo monitorizada con el seguimiento de los valores de TTPa con un rango terapéutico de 1.5-2.5 del valor control. Las heparinas de bajo peso molecular inhiben selectivamente el factor Xa, elevando levemente el TTPa, pero la monitorización terapéutica de rutina no está recomendada.⁽⁵⁾

La activación del sistema de coagulación resulta en formación de fibrina, pero al activarse el sistema fibrinolítico, el coágulo es sustancialmente lisado liberando productos de degradación de fibrina en el torrente sanguíneo. El DD es un fragmento derivado de la fibrina que es liberado en la circulación cuando la fibrina entrelazada se rompe por el sistema fibrinolítico. Diferentes técnicas están disponibles para medir el nivel de DD, pero el Enzyme-Linked Immunosorbent Assay (ELISA por sus siglas en inglés) continúa siendo el estándar de oro.^(6,7,32)

Para una mejor evaluación de las interacciones complejas en un paciente con sangrado activo, muchos centros se han cambiado a las pruebas de viscoelasticidad de sangre entera como la tromboelastografía o tromboelastometría rotacional. La tromboelastografía mide las propiedades viscoelásticas de la sangre, ya que se induce a la coagulación en un entorno de baja cizalladura (que se asemeja a flujo venoso lento).⁽⁵⁾

Conclusiones

Los factores de riesgo para tromboembolismo venoso se deben tomar en cuenta para clasificar el riesgo y establecer la profilaxis preoperatoria adecuada según el procedimiento y patología preexistente. Actualmente el riesgo de TEV se clasifica según el puntaje de Caprini o Rogers en muy bajo riesgo, bajo riesgo, riesgo moderado y alto riesgo, eliminando el grupo de muy alto riesgo que anteriormente se utilizaba y agregando el grupo de muy bajo riesgo.

En pacientes con trauma severo sin contraindicaciones, se recomienda el uso de profilaxis mecánica hasta

restablecer una adecuada hemodinámica que permita el uso en conjunto de profilaxis farmacológica.

El tiempo intrahospitalario del paciente post-operado puede disminuirse estableciendo protocolos de atención que incluyan una correcta evaluación de factores de riesgo y tratamiento profiláctico para tromboembolismo venoso.

Se recomienda la elaboración de un estudio sobre la incidencia, manejo profiláctico y terapéutico de tromboembolismo venoso en los pacientes postquirúrgicos para actualizar los conocimientos a nivel nacional sobre el tema.

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2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS)

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SD For the Supplementary Data which include background information and detailed discussion of the data that have provided the basis for the Guidelines see <https://academic.oup.com/eurheartj/article-lookup/doi/10.1093/eurheartj/ehz405#supplementary-data>

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Abbreviations and acronyms

AcT	Right ventricular outflow Doppler acceleration time
AFE	Amniotic fluid embolism
ALT	Alanine aminotransferase
AMPLIFY	Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-line Therapy
ASPIRE	Aspirin to Prevent Recurrent Venous Thromboembolism trial
AV	Arteriovenous
b.i.d	Bis in die (twice a day)
BNP	B-type natriuretic peptide
BP	Blood pressure
BPA	Balloon pulmonary angioplasty
b.p.m	Beats per minute
CI	Confidence interval
CO	Cardiac output
CPET	Cardiopulmonary exercise testing
CPG	Committee for Practice Guidelines
CrCl	Creatinine clearance

CRNM	Clinically relevant non-major (bleeding)
CT	Computed tomogram/tomographic/tomography
CTED	Chronic thromboembolic disease
CTEPH	Chronic thromboembolic pulmonary hypertension
CTPA	Computed tomography pulmonary angiography/angiogram
CUS	Compression ultrasonography
CYP3A4	Cytochrome 3A4
DAMOVES	D-dimer, Age, Mutation, Obesity, Varicose veins, Eight [coagulation factor VIII], Sex
DASH	D-dimer, Age, Sex, Hormonal therapy
DVT	Deep vein thrombosis
ECMO	Extracorporeal membrane oxygenation
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ERS	European Respiratory Society
ESC	European Society of Cardiology
FAST	H-FABP, Syncope, Tachycardia (prognostic score)
FDA	US Food and Drug Administration
GUSTO	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries
HAS-BLED	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly
HERDOO2	Hyperpigmentation, Edema, or Redness in either leg; D-dimer level ≥ 250 $\mu\text{g/L}$; Obesity with body mass index ≥ 30 kg/m^2 ; or Older age, ≥ 65 years
H-FABP	Heart-type fatty acid-binding protein
HIV	Human immunodeficiency virus
HR	Hazard ratio
INR	International normalized ratio
IU	International units
i.v	Intravenous
IVC	Inferior vena cava
LA	Left atrium
LMWH	Low-molecular weight heparin(s)
LV	Left ventricle/ventricular
MRA	Magnetic resonance angiography
NCT	National clinical trial
NOAC(s)	Non-vitamin K antagonist oral anticoagulant(s)
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
OBRI	Outpatient Bleeding Risk Index
o.d	Omni die (once a day)
OR	Odds ratio
PAH	Pulmonary arterial hypertension
PAP	Pulmonary artery pressure
PE	Pulmonary embolism
PEA	Pulmonary endarterectomy
PEITHO	Pulmonary Embolism Thrombolysis trial
PERC	Pulmonary Embolism Rule-out Criteria
PERT	Pulmonary Embolism Response Team
PESI	Pulmonary Embolism Severity Index

P-gp	P-glycoprotein
PH	Pulmonary hypertension
PIOPED	Prospective Investigation On Pulmonary Embolism Diagnosis
PISAPED	Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis
PREPIC	Prevention of Recurrent Pulmonary Embolism by Vena Cava Interruption
PVR	Pulmonary vascular resistance
RA	Right atrium/atrial
RCT	Randomized controlled trial
RIETE	Registro Informatizado de la Enfermedad Tromboembolica venosa
RR	Relative risk
rtPA	Recombinant tissue-type plasminogen activator
RV	Right ventricle/ventricular
SaO ₂	Arterial oxygen saturation
SPECT	Single-photon emission computed tomography
sPESI	Simplified Pulmonary Embolism Severity Index
SURVET	Sulodexide in Secondary Prevention of Recurrent Deep Vein Thrombosis study
TAPSE	Tricuspid annular plane systolic excursion
TOE	Transoesophageal echocardiography/echocardiogram
TTE	Transthoracic echocardiography/echocardiogram
TV	Tricuspid valve
U	Unit
UFH	Unfractionated heparin
VKA(s)	Vitamin K antagonist(s)
V/Q	Ventilation/perfusion (lung scintigraphy)
VTE	Venous thromboembolism
VTE-BLEED	ActiVe cancer, male with uncontrolled hyperTension at baseline, anaEmia, history of BLEeding, agE ≥60 years, rEnal Dysfunction
WARFASA	Warfarin and Aspirin study

1 Preamble

Guidelines summarize and evaluate available evidence with the aim of assisting health professionals in proposing the best management strategies for an individual patient with a given condition. Guidelines and their recommendations should facilitate decision making of health professionals in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible health professional(s) in consultation with the patient and caregiver as appropriate.

A great number of guidelines have been issued in recent years by the European Society of Cardiology (ESC), as well as by other societies and organisations. Because of their impact on clinical practice, quality criteria for the development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC website (<http://www.escardio.org/Guidelines-&Education/Clinical-Practice-Guidelines/Guidelines-development/Writing-ESC-Guidelines>). The ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated.

The ESC carries out a number of registries which are essential to assess, diagnostic/therapeutic processes, use of resources and adherence to Guidelines. These registries aim at providing a better understanding of medical practice in Europe and around the world, based on data collected during routine clinical practice.

The guidelines are developed together with derivative educational material addressing the cultural and professional needs for cardiologists and allied professionals. Collecting high-quality observational data, at appropriate time interval following the release of ESC Guidelines, will help evaluate the level of implementation of the Guidelines, checking in priority the key end points defined with the ESC Guidelines and Education Committees and Task Force members in charge.

The Members of this Task Force were selected by the ESC, including representation from its relevant ESC sub-specialty groups, in order to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a comprehensive review of the published evidence for management of a given condition according to ESC Committee for Practice Guidelines (CPG) policy. A critical evaluation of diagnostic and therapeutic procedures was performed, including assessment of the risk–benefit ratio. The level of evidence and the strength of the recommendation of particular management options were weighed and graded according to predefined scales, as outlined in *Tables 1* and *2*.

The experts of the writing and reviewing panels provided declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. These forms were compiled into one file and can be found on the ESC website (<http://www.escardio.org/guidelines>). Any changes in declarations of interest that arise during the writing period were notified to the ESC and updated. The Task Force received its entire financial support from the ESC without any involvement from the healthcare industry.

The ESC CPG supervises and coordinates the preparation of new Guidelines. The Committee is also responsible for the endorsement process of these Guidelines. The ESC Guidelines undergo extensive review by the CPG and external experts. After appropriate revisions the Guidelines are approved by all the experts involved in the Task Force. The finalized document is approved by the CPG for publication in the *European Heart Journal*. The Guidelines were developed after careful consideration of the scientific and medical knowledge and the evidence available at the time of their dating.

The task of developing ESC Guidelines also includes the creation of educational tools and implementation programmes for the recommendations including condensed pocket guideline versions, summary slides, booklets with essential messages, summary cards for non-specialists and an electronic version for digital applications (smartphones, etc.). These versions are abridged and thus, for more detailed information, the user should always access to the full text version of the Guidelines, which is freely available via the ESC website and hosted on the EHJ website. The National Societies of the ESC are encouraged to endorse, translate and implement all ESC Guidelines. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Health professionals are encouraged to take the ESC Guidelines fully into account when exercising their clinical judgment, as well as in the

Table I Classes of recommendations

Classes of recommendations

	Definition	Wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended or is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/ efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

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Table 2 Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

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determination and the implementation of preventive, diagnostic or therapeutic medical strategies. However, the ESC Guidelines do not override in any way whatsoever the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient’s health condition and in consultation with that patient or the patient’s caregiver where appropriate and/or necessary. It is also the health professional’s responsibility to verify the rules and regulations applicable in each country to drugs and devices at the time of prescription.

2 Introduction

2.1 Why do we need new Guidelines on the diagnosis and management of pulmonary embolism?

This document follows the previous ESC Guidelines focusing on the clinical management of pulmonary embolism (PE), published in 2000, 2008, and 2014. Many recommendations have been retained or their validity has been reinforced; however, new data have extended or

modified our knowledge in respect of the optimal diagnosis, assessment, and treatment of patients with PE. These new aspects have been integrated into previous knowledge to suggest optimal and—whenever possible—objectively validated management strategies for patients with suspected or confirmed PE. To limit the length of the printed text, additional information, tables, figures, and references are available as [supplementary data](#) on the ESC website (www.escardio.org).

These Guidelines focus on the diagnosis and management of acute PE in adult patients. For further details specifically related to the diagnosis and management of deep vein thrombosis (DVT), the reader is referred to the joint consensus document of the ESC Working Groups of Aorta and Peripheral Vascular Diseases, and Pulmonary Circulation and Right Ventricular Function.¹

2.2 What is new in the 2019 Guidelines?

2.2.1 New/revised concepts in 2019

Diagnosis
D-dimer cut-off values adjusted for age or clinical probability can be used as an alternative to the fixed cut-off value.
Updated information is provided on the radiation dosage when using CTPA and a lung scan to diagnose PE (Table 6).
Risk assessment
A clear definition of haemodynamic instability and high-risk PE is provided (Table 4).
Assessment of PE severity and early PE-related risk is recommended, in addition to comorbidity/aggravating conditions and overall death risk.
A clear word of caution that RV dysfunction may be present, and affect early outcomes, in patients at 'low risk' based on clinical risk scores.
Treatment in the acute phase
Thoroughly revised section on haemodynamic and respiratory support for high-risk PE (Section 6.1).
A dedicated management algorithm is proposed for high-risk PE (Supplementary Figure 1).
NOACs are recommended as the first choice for anticoagulation treatment in a patient eligible for NOACs; VKAs are an alternative to NOACs.
The risk-adjusted management algorithm (Figure 6) was revised to take into consideration clinical PE severity, aggravating conditions/comorbidity, and the presence of RV dysfunction.
Chronic treatment after the first 3 months
Risk factors for VTE recurrence have been classified according to high, intermediate, or low recurrence risk (Table 11).
Potential indications for extended anticoagulation are discussed, including the presence of a minor transient or reversible risk factor for the index PE, any persisting risk factor, or no identifiable risk factor.
Terminology such as 'provoked' vs. 'unprovoked' PE/VTE is no longer supported by the Guidelines, as it is potentially misleading and not helpful for decision-making regarding the duration of anticoagulation.

Continued

VTE recurrence scores are presented and discussed in parallel with bleeding scores for patients on anticoagulation treatment (Supplementary Tables 13 and 14 respectively).

A reduced dose of apixaban or rivaroxaban for extended anticoagulation should be considered after the first 6 months of treatment.

PE in cancer

Edoxaban or rivaroxaban should be considered as an alternative to LMWH, with a word of caution for patients with gastrointestinal cancer due to the increased bleeding risk with NOACs.

PE in pregnancy

A dedicated diagnostic algorithm is proposed for suspected PE in pregnancy (Figure 7).

Updated information is provided on radiation absorption related to procedures used for diagnosing PE in pregnancy (Table 12).

Long-term sequelae

An integrated model of patient care after PE is proposed to ensure optimal transition from hospital to community care.

Recommendations on patient care have been extended to the entire spectrum of post-PE symptoms and functional limitation, not only CTEPH.

A new comprehensive algorithm is proposed for patient follow-up after acute PE (Figure 8).

CTEPH = Chronic thromboembolic pulmonary hypertension; CTPA = computed tomography pulmonary angiography; LMWH = low-molecular weight heparin; NOAC(s) = non-vitamin K antagonist oral anticoagulant(s); PE = pulmonary embolism; RV = right ventricular; VKA(s) = vitamin K antagonist(s); VTE = venous thromboembolism.

2.2.2 Changes in recommendations 2014–19

Recommendations	2014	2019
Rescue thrombolytic therapy is recommended for patients who deteriorate haemodynamically.	IIa	I
Surgical embolectomy or catheter-directed treatment should be considered as alternatives to rescue thrombolytic therapy for patients who deteriorate haemodynamically.	IIb	IIa
D-dimer measurement and clinical prediction rules should be considered to rule out PE during pregnancy or the post-partum period.	IIb	IIa
Further evaluation may be considered for asymptomatic PE survivors at increased risk for CTEPH.	III	IIb

CTEPH = Chronic thromboembolic pulmonary hypertension; PE = pulmonary embolism.

Coloured columns indicate classes of recommendation (see Table 1 for colour coding).

2.2.3 Main new recommendations 2019

Diagnosis	
A D-dimer test, using an age-adjusted cut-off or adapted to clinical probability, should be considered as an alternative to the fixed cut-off level.	IIa
If a positive proximal CUS is used to confirm PE, risk assessment should be considered to guide management.	IIa
V/Q SPECT may be considered for PE diagnosis.	IIb
Risk assessment	
Assessment of the RV by imaging or laboratory biomarkers should be considered, even in the presence of a low PESI or a sPESI of 0.	IIa
Validated scores combining clinical, imaging, and laboratory prognostic factors may be considered to further stratify PE severity.	IIb
Treatment in the acute phase	
When oral anticoagulation is initiated in a patient with PE who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is the recommended form of anticoagulant treatment.	I
Set-up of multidisciplinary teams for management of high-risk and selected cases of intermediate-risk PE should be considered, depending on the resources and expertise available in each hospital.	IIa
ECMO may be considered, in combination with surgical embolectomy or catheter-directed treatment, in refractory circulatory collapse or cardiac arrest.	IIb
Chronic treatment and prevention of recurrence	
Indefinite treatment with a VKA is recommended for patients with antiphospholipid antibody syndrome.	I
Extended anticoagulation should be considered for patients with no identifiable risk factor for the index PE event.	IIa
Extended anticoagulation should be considered for patients with a persistent risk factor other than antiphospholipid antibody syndrome.	IIa
Extended anticoagulation should be considered for patients with a minor transient/reversible risk factor for the index PE event.	IIa
A reduced dose of apixaban or rivaroxaban should be considered after the first 6 months.	IIa
PE in cancer	
Edoxaban or rivaroxaban should be considered as an alternative to LMWH, with the exception of patients with gastrointestinal cancer.	IIa
PE in pregnancy	
Amniotic fluid embolism should be considered in a pregnant or post-partum woman, with unexplained haemodynamic instability or respiratory deterioration, and disseminated intravascular coagulation.	IIa

Continued

Thrombolysis or surgical embolectomy should be considered for pregnant women with high-risk PE.	IIa
NOACs are not recommended during pregnancy or lactation.	III
Post-PE care and long-term sequelae	
Routine clinical evaluation is recommended 3–6 months after acute PE.	I
An integrated model of care is recommended after acute PE to ensure optimal transition from hospital to ambulatory care.	I
It is recommended that symptomatic patients with mismatched perfusion defects on a V/Q scan >3 months after acute PE are referred to a pulmonary hypertension/CTEPH expert centre, taking into account the results of echocardiography, natriuretic peptide, and/or cardiopulmonary exercise testing.	I

CPET = cardiopulmonary exercise testing; CTEPH = Chronic thromboembolic pulmonary hypertension; CUS = compression ultrasonography; ECMO = extracorporeal membrane oxygenation; LMWH = low-molecular weight heparin; NOAC(s) = non-vitamin K antagonist oral anticoagulant(s); PE = pulmonary embolism; PESI = Pulmonary Embolism Severity Index; RV = right ventricular; SPECT = single-photon emission computed tomography; sPESI = simplified Pulmonary Embolism Severity Index; VKA(s) = vitamin K antagonist(s); V/Q = ventilation/perfusion (lung scintigraphy).

Coloured columns indicate classes of recommendation (see Table 1 for colour coding).

3 General considerations

3.1 Epidemiology

Venous thromboembolism (VTE), clinically presenting as DVT or PE, is globally the third most frequent acute cardiovascular syndrome behind myocardial infarction and stroke.² In epidemiological studies, annual incidence rates for PE range from 39–115 per 100 000 population; for DVT, incidence rates range from 53–162 per 100 000 population.^{3,4} Cross-sectional data show that the incidence of VTE is almost eight times higher in individuals aged ≥80 years than in the fifth decade of life.³ In parallel, longitudinal studies have revealed a rising tendency in annual PE incidence rates^{4–7} over time. Together with the substantial hospital-associated, preventable, and indirect annual expenditures for VTE (an estimated total of up to €8.5 billion in the European Union),⁸ these data demonstrate the importance of PE and DVT in ageing populations in Europe and other areas of the world. They further suggest that VTE will increasingly pose a burden on health systems worldwide in the years to come.

PE may cause ≤300 000 deaths per year in the US, ranking high among the causes of cardiovascular mortality.³ In six European countries with a total population of 454.4 million, more than 370 000 deaths were related to VTE in 2004, as estimated on the basis of an epidemiological model.⁹ Of these patients, 34% died suddenly or within a few hours of the acute event, before therapy could be initiated or take effect. Of the other patients, death resulted from acute PE that was diagnosed after death in 59% and only 7% of patients who died early were correctly diagnosed with PE before death.⁹

Time trend analyses in European, Asian, and North American populations suggest that case fatality rates of acute PE may be decreasing.^{4–7,10,11} Increased use of more effective therapies and interventions, and possibly better adherence to guidelines,^{12,13} has most likely exerted a significant positive effect on the prognosis of PE in recent years. However, there is also a tendency towards overdiagnosis of (subsegmental or even non-existent) PE in the modern era,¹⁴ and this might in turn lead to a false drop in case fatality rates by inflating the denominator, i.e. the total number of PE cases.

Figure 1 summarizes the existing data on global trends in PE, highlighting increasing incidence rates in parallel with decreasing case fatality rates over an ~15 year period.

In children, studies have reported an annual incidence of VTE of between 53–57 per 100 000 among hospitalized patients,^{19,20} and between 1.4–4.9 per 100 000 in the community overall.^{21,22}

3.2 Predisposing factors

There is an extensive collection of predisposing environmental and genetic factors for VTE; a list of predisposing (risk) factors is shown in Table 3. VTE is considered to be a consequence of the interaction between patient-related—usually permanent—risk factors and setting-related—usually temporary—risk factors. Since categorization of temporary and permanent risk factors for VTE is important for assessing the risk of recurrence, and consequently for decision-making on chronic anticoagulation, it is discussed in more detail in section 8 of these Guidelines.

Major trauma, surgery, lower-limb fractures and joint replacements, and spinal cord injury are strong provoking factors for VTE.^{23,24} Cancer is a well-recognized predisposing factor for VTE. The risk of VTE varies with different types of cancer;^{25,26} pancreatic cancer, haematological malignancies, lung cancer, gastric cancer, and brain cancer carry the highest risk.^{27,28} Moreover, cancer

is a strong risk factor for all-cause mortality following an episode of VTE.²⁹

Oestrogen-containing oral contraceptive agents are associated with an elevated VTE risk, and contraceptive use is the most frequent VTE risk factor in women of reproductive age.^{30–32} More specifically, combined oral contraceptives (containing both an oestrogen and a progestogen) are associated with an approximately two- to six-fold increase in VTE risk over baseline.^{32,33} In general, the absolute VTE risk remains low in the majority of the >100 million combined oral contraceptive users worldwide;³⁴ however, VTE risk factors, including severe inherited thrombophilia (discussed in section 8),³⁵ increase this risk. Third-generation combined oral contraceptives, containing progestogens such as desogestrel or gestodene, are associated with a higher VTE risk than the second-generation combined oral contraceptives, which contain progestogens such as levonorgestrel or norgestrel.^{36,37} On the other hand, hormone-releasing intrauterine devices and some progesterone-only pills (used at contraceptive doses) are not associated with a significant increase in VTE risk,^{33,38} consequently, and following counselling and full risk assessment, these options are often proposed to women with a personal or strong family history of VTE.

In post-menopausal women who receive hormone replacement therapy, the risk of VTE varies widely depending on the formulation used.³⁹

Infection is a common trigger for VTE.^{23,40,41} Blood transfusion and erythropoiesis-stimulating agents are also associated with an increased risk of VTE.^{23,42}

In children, PE is usually associated with DVT and is rarely unprovoked. Serious chronic medical conditions and central venous lines are considered likely triggers of PE.⁴³

VTE may be viewed as part of the cardiovascular disease continuum, and common risk factors—such as cigarette smoking, obesity, hypercholesterolaemia, hypertension, and diabetes

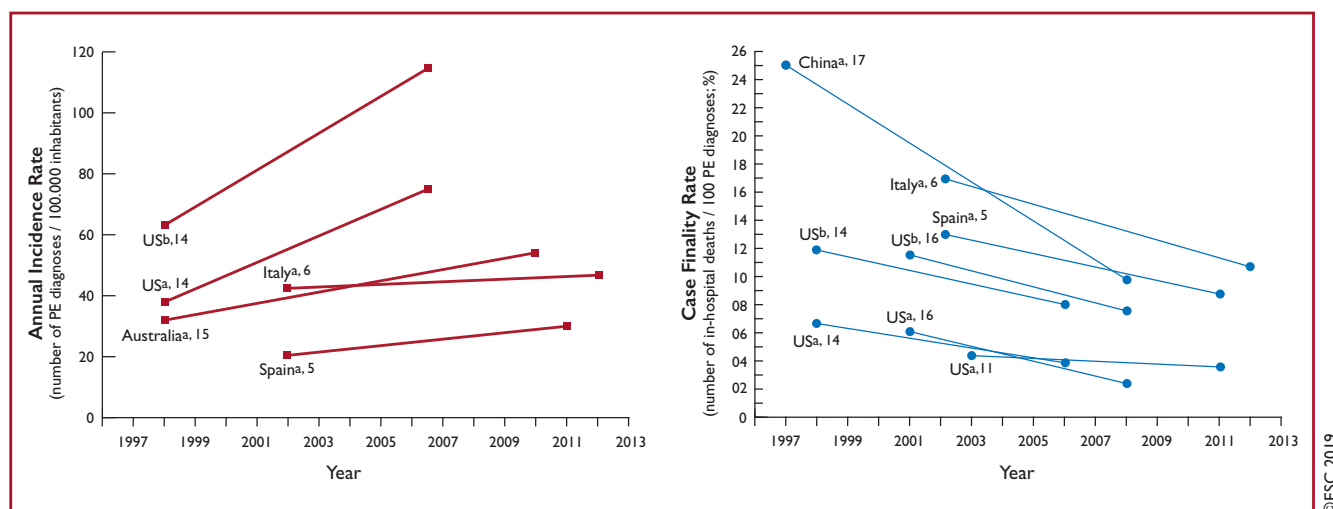


Figure 1 Trends in annual incidence rates (left panel) and case fatality rates (right panel) of pulmonary embolism around the world, based on data retrieved from various references.^{5,6,11,14–17} Reproduced with permission from JACC 2016;67:976-90. PE = pulmonary embolism; US = United States.

^aPE listed as principal diagnosis.

^bAny listed code for PE was considered.

Table 3 Predisposing factors for venous thromboembolism (data modified from Rogers et al.²³ and Anderson and Spencer²⁴)

Strong risk factors (OR > 10)
Fracture of lower limb
Hospitalization for heart failure or atrial fibrillation/flutter (within previous 3 months)
Hip or knee replacement
Major trauma
Myocardial infarction (within previous 3 months)
Previous VTE
Spinal cord injury
Moderate risk factors (OR 2–9)
Arthroscopic knee surgery
Autoimmune diseases
Blood transfusion
Central venous lines
Intravenous catheters and leads
Chemotherapy
Congestive heart failure or respiratory failure
Erythropoiesis-stimulating agents
Hormone replacement therapy (depends on formulation)
In vitro fertilization
Oral contraceptive therapy
Post-partum period
Infection (specifically pneumonia, urinary tract infection, and HIV)
Inflammatory bowel disease
Cancer (highest risk in metastatic disease)
Paralytic stroke
Superficial vein thrombosis
Thrombophilia
Weak risk factors (OR < 2)
Bed rest >3 days
Diabetes mellitus
Arterial hypertension
Immobility due to sitting (e.g. prolonged car or air travel)
Increasing age
Laparoscopic surgery (e.g. cholecystectomy)
Obesity
Pregnancy
Varicose veins

HIV = human immunodeficiency virus; OR = odds ratio; VTE = venous thromboembolism.

mellitus^{44–47}—are shared with arterial disease, notably atherosclerosis.^{48–51} However, this may be an indirect association mediated, at least in part, by the complications of coronary artery disease and, in the case of smoking, cancer.^{52,53} Myocardial infarction and heart failure increase the risk of PE.^{54,55} Conversely, patients with VTE have an increased risk of subsequent myocardial infarction and stroke, or peripheral arterial embolization.⁵⁶

3.3 Pathophysiology and determinants of outcome

Acute PE interferes with both circulation and gas exchange. Right ventricular (RV) failure due to acute pressure overload is considered the primary cause of death in severe PE. Pulmonary artery pressure (PAP) increases if >30–50% of the total cross-sectional area of the pulmonary arterial bed is occluded by thromboemboli.⁵⁷ PE-induced vasoconstriction, mediated by the release of thromboxane A2 and serotonin, contributes to the initial increase in pulmonary vascular resistance (PVR) after PE.⁵⁸ Anatomical obstruction and hypoxic vasoconstriction in the affected lung area lead to an increase in PVR, and a proportional decrease in arterial compliance.⁵⁹

The abrupt increase in PVR results in RV dilation, which alters the contractile properties of the RV myocardium via the Frank–Starling mechanism. The increase in RV pressure and volume leads to an increase in wall tension and myocyte stretch. The contraction time of the RV is prolonged, while neurohumoral activation leads to inotropic and chronotropic stimulation. Together with systemic vasoconstriction, these compensatory mechanisms increase PAP, improving flow through the obstructed pulmonary vascular bed and thus temporarily stabilizing systemic blood pressure (BP). However, the extent of immediate adaptation is limited, as a non-preconditioned, thin-walled RV is unable to generate a mean PAP >40 mmHg.

Prolongation of RV contraction time into early diastole in the left ventricle (LV) leads to leftward bowing of the interventricular septum.⁶⁰ The desynchronization of the ventricles may be exacerbated by the development of right bundle branch block. As a result, LV filling is impeded in early diastole, and this may lead to a reduction in the cardiac output (CO), and contribute to systemic hypotension and haemodynamic instability.⁶¹

As described above, excessive neurohumoral activation in PE can be the result of both abnormal RV wall tension and circulatory shock. The finding of massive infiltrates of inflammatory cells in the RV myocardia of patients who died within 48 h of acute PE may be explained by high levels of epinephrine released as a result of the PE-induced ‘myocarditis’.⁶² This inflammatory response might explain the secondary haemodynamic destabilization that sometimes occurs 24–48 h after acute PE, although early recurrence of PE may be an alternative explanation in some of these cases.

Finally, the association between elevated circulating levels of biomarkers of myocardial injury and an adverse early outcome indicates that RV ischaemia is of pathophysiological significance in the acute phase of PE.^{63,64} Although RV infarction is uncommon after PE, it is likely that the imbalance between oxygen supply and demand can result in damage to cardiomyocytes, and further reduce contractile forces. Systemic hypotension is a critical element in this process, leading to impairment of the coronary driving pressure to the overloaded RV.

The detrimental effects of acute PE on the RV myocardium and the circulation are summarized in Figure 2.

Respiratory failure in PE is predominantly a consequence of haemodynamic disturbances.⁶⁶ Low CO results in desaturation of the mixed venous blood. Zones of reduced flow in obstructed

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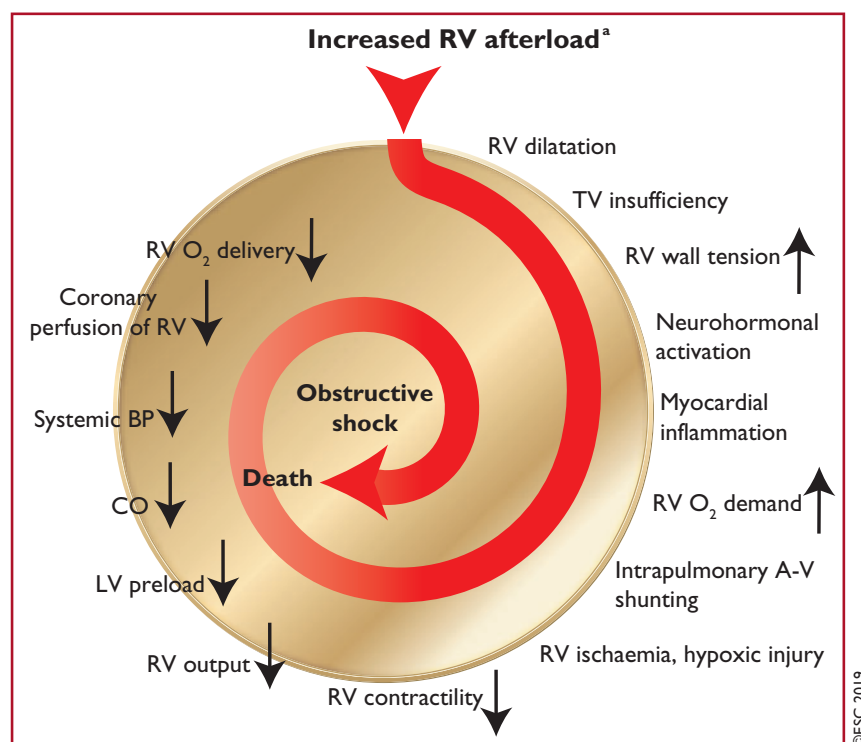


Figure 2 Key factors contributing to haemodynamic collapse and death in acute pulmonary embolism (modified from Konstantinides et al.⁶⁵ with permission). A-V = arterio-venous; BP = blood pressure; CO = cardiac output; LV = left ventricular; O₂ = oxygen; RV = right ventricular; TV = tricuspid valve.

^aThe exact sequence of events following the increase in RV afterload is not fully understood.

Table 4 Definition of haemodynamic instability, which delineates acute high-risk pulmonary embolism (one of the following clinical manifestations at presentation)

(1) Cardiac arrest	(2) Obstructive shock ^{68–70}	(3) Persistent hypotension
Need for cardiopulmonary resuscitation	Systolic BP < 90 mmHg or vasopressors required to achieve a BP ≥ 90 mmHg despite adequate filling status	Systolic BP < 90 mmHg or systolic BP drop ≥ 40 mmHg, lasting longer than 15 min and not caused by new-onset arrhythmia, hypovolaemia, or sepsis
	And	
	End-organ hypoperfusion (altered mental status; cold, clammy skin; oliguria/anuria; increased serum lactate)	

BP = blood pressure.

pulmonary arteries, combined with zones of overflow in the capillary bed served by non-obstructed pulmonary vessels, result in ventilation/perfusion mismatch, which contributes to hypoxaemia. In about one-third of patients, right-to-left shunting through a patent foramen ovale can be detected by echocardiography; this is caused by an inverted pressure gradient between the right atrium (RA) and left atrium, and may lead to severe hypoxaemia, and an increased risk of paradoxical embolization and stroke.⁶⁷ Finally, even if they do not affect haemodynamics, small distal emboli may create areas of alveolar haemorrhage resulting in haemoptysis, pleuritis, and pleural effusion, which is usually mild. This clinical

presentation is known as ‘pulmonary infarction’. Its effect on gas exchange is normally mild, except in patients with pre-existing cardiorespiratory disease.

In view of the above pathophysiological considerations, acute RV failure, defined as a rapidly progressive syndrome with systemic congestion resulting from impaired RV filling and/or reduced RV flow output,⁶⁸ is a critical determinant of clinical severity and outcome in acute PE. Accordingly, clinical symptoms, and signs of overt RV failure and haemodynamic instability, indicate a high risk of early (in-hospital or 30 day) mortality. High-risk PE is defined by haemodynamic instability and encompasses the forms of clinical presentation shown in Table 4.

As an immediately life-threatening situation, high-risk PE requires an emergency diagnostic (upon suspicion) and therapeutic (upon confirmation or if the level of suspicion is sufficiently high) strategy, as outlined in section 7. However, the absence of haemodynamic instability does not exclude beginning (and possibly progressing) RV dysfunction, and thus an elevated PE-related early risk. In this large population, further assessment (outlined in sections 5 and 7) is necessary to determine the level of risk and adjust management decisions accordingly.

4 Diagnosis

The increased awareness of venous thromboembolic disease and the ever-increasing availability of non-invasive imaging tests, mainly computed tomography (CT) pulmonary angiography (CTPA), have generated a tendency for clinicians to suspect and initiate a diagnostic workup for PE more frequently than in the past. This changing attitude is illustrated by the rates of PE confirmation among patients undergoing diagnostic workup: these were as low as 5% in recent North American diagnostic studies, in sharp contrast to the approximately 50% prevalence reported back in the early 1980s.⁷¹ Therefore, it is critical that, when evaluating non-invasive diagnostic strategies for PE in the modern era, it is ensured that they are capable of safely excluding PE in contemporary patient populations with a rather low pre-test probability of the disease.⁷² Conversely, a positive test should have an adequate specificity to set the indication for anticoagulant treatment.

4.1 Clinical presentation

The clinical signs and symptoms of acute PE are non-specific. In most cases, PE is suspected in a patient with dyspnoea, chest pain, pre-syncope or syncope, or haemoptysis.^{73–75} Haemodynamic instability is a rare but important form of clinical presentation, as it indicates central or extensive PE with severely reduced haemodynamic reserve. Syncope may occur, and is associated with a higher prevalence of haemodynamic instability and RV dysfunction.⁷⁶ Conversely, and according to the results of a recent study, acute PE may be a frequent finding in patients presenting with syncope (17%), even in the presence of an alternative explanation.⁷⁷

In some cases, PE may be asymptomatic or discovered incidentally during diagnostic workup for another disease.

Dyspnoea may be acute and severe in central PE; in small peripheral PE, it is often mild and may be transient. In patients with pre-existing heart failure or pulmonary disease, worsening dyspnoea may be the only symptom indicative of PE. Chest pain is a frequent symptom of PE and is usually caused by pleural irritation due to distal emboli causing pulmonary infarction.⁷⁸ In central PE, chest pain may have a typical angina character, possibly reflecting RV ischaemia, and requiring differential diagnosis from an acute coronary syndrome or aortic dissection.

In addition to symptoms, knowledge of the predisposing factors for VTE is important in determining the clinical probability of the disease, which increases with the number of predisposing factors present; however, in 40% of patients with PE, no predisposing factors are found.⁷⁹ Hypoxaemia is frequent, but ≤40% of patients have normal arterial oxygen saturation (SaO₂) and 20% have a

Table 5 The revised Geneva clinical prediction rule for pulmonary embolism

Items	Clinical decision rule points	
	Original version ⁹¹	Simplified version ⁸⁷
Previous PE or DVT	3	1
Heart rate		
75–94 b.p.m.	3	1
≥95 b.p.m.	5	2
Surgery or fracture within the past month	2	1
Haemoptysis	2	1
Active cancer	2	1
Unilateral lower-limb pain	3	1
Pain on lower-limb deep venous palpation and unilateral oedema	4	1
Age >65 years	1	1
Clinical probability		
Three-level score		
Low	0–3	0–1
Intermediate	4–10	2–4
High	≥11	≥5
Two-level score		
PE-unlikely	0–5	0–2
PE-likely	≥6	≥3

b.p.m. = beats per minute; DVT = deep vein thrombosis; PE = pulmonary embolism.

normal alveolar–arterial oxygen gradient.^{80,81} Hypocapnia is also often present. A chest X-ray is frequently abnormal and, although its findings are usually non-specific in PE, it may be useful for excluding other causes of dyspnoea or chest pain.⁸² Electrocardiographic changes indicative of RV strain—such as inversion of T waves in leads V1–V4, a QR pattern in V1, a S1Q3T3 pattern, and incomplete or complete right bundle branch block—are usually found in more severe cases of PE;⁸³ in milder cases, the only abnormality may be sinus tachycardia, present in 40% of patients. Finally, atrial arrhythmias, most frequently atrial fibrillation, may be associated with acute PE.

4.2 Assessment of clinical (pre-test) probability

The combination of symptoms and clinical findings with the presence of predisposing factors for VTE allows the classification of patients with suspected PE into distinct categories of clinical or pre-test probability, which correspond to an increasing actual prevalence of confirmed PE. This pre-test assessment can be done either by implicit (empirical) clinical judgement or by using prediction rules. As the post-test (i.e. after an imaging test) probability of PE depends not only on the characteristics of the diagnostic test itself but also on the pre-test probability, this is a key step in all diagnostic algorithms for PE.

The value of empirical clinical judgement has been confirmed in several large series.^{84,85} Clinical judgement usually includes

commonplace tests such as chest X-rays and electrocardiograms for differential diagnosis. However, as clinical judgement lacks standardization, several explicit clinical prediction rules have been developed. Of these, the most frequently used prediction rules are the revised Geneva rule (Table 5) and the Wells rule (see Supplementary Data Table 1).⁸⁶ Both prediction rules have been simplified in an attempt to increase their adoption into clinical practice;^{87,88} the simplified versions have been externally validated.^{89,90}

Regardless of the score used, the proportion of patients with confirmed PE can be expected to be ~10% in the low-probability category, 30% in the moderate-probability category, and 65% in the high-probability category.⁹² When the two-level classification is used, the proportion of patients with confirmed PE is ~12% in the PE-unlikely category and 30% in the PE-likely category.⁹² A direct prospective comparison of these rules confirmed a similar diagnostic performance.⁸⁹

4.3 Avoiding overuse of diagnostic tests for pulmonary embolism

Searching for PE in every patient with dyspnoea or chest pain may lead to high costs and complications of unnecessary tests. The Pulmonary Embolism Rule-out Criteria (PERC) were developed for emergency department patients with the purpose of selecting, on clinical grounds, patients whose likelihood of having PE is so low that diagnostic workup should not even be initiated.⁹³ They comprise eight clinical variables significantly associated with an absence of PE: age < 50 years; pulse < 100 beats per minute; SaO₂ > 94%; no unilateral leg swelling; no haemoptysis; no recent trauma or surgery; no history of VTE; and no oral hormone use. The results of a prospective validation study,⁹⁴ and those of a randomized non-inferiority management study,⁹⁵ suggested safe exclusion of PE in patients with low clinical probability who, in addition, met all criteria of the PERC rule. However, the low overall prevalence of PE in these studies^{94,95} does not support the generalizability of the results.

4.4 D-dimer testing

D-dimer levels are elevated in plasma in the presence of acute thrombosis because of simultaneous activation of coagulation and fibrinolysis. The negative predictive value of D-dimer testing is high, and a normal D-dimer level renders acute PE or DVT unlikely. On the other hand, the positive predictive value of elevated D-dimer levels is low and D-dimer testing is not useful for confirmation of PE. D-dimer is also more frequently elevated in patients with cancer,^{96,97} in hospitalized patients,^{89,98} in severe infection or inflammatory disease, and during pregnancy.^{99,100} Accordingly, the number of patients in whom D-dimer must be measured to exclude one PE (number needed to test) rises from 3 in the general population of an emergency department to ≥10 in the specific situations listed above.

As a number of D-dimer assays are available, clinicians should become aware of the diagnostic performance of the test used in their own hospital. The quantitative enzyme-linked immunosorbent assay (ELISA) or ELISA-derived assays have a diagnostic sensitivity of ≥95%, and can be used to exclude PE in patients with either low or intermediate pre-test probability. In the emergency department, a negative ELISA D-dimer can, in combination with clinical probability, exclude the disease without further testing in ~30% of patients with suspected PE.^{101–103} Outcome studies have shown that the 3 month thrombo-

embolic risk was <1% in patients with low or intermediate clinical probability who were left untreated on the basis of a negative test result.¹⁰⁴

4.4.1 Age-adjusted D-dimer cut-offs

The specificity of D-dimer in suspected PE decreases steadily with age to ~10% in patients >80 years of age.¹⁰⁵ The use of age-adjusted cut-offs may improve the performance of D-dimer testing in the elderly. A multinational prospective management study evaluated a previously validated age-adjusted cut-off (age × 10 µg/L, for patients aged >50 years) in a cohort of 3346 patients.¹⁰⁶ Patients with a normal age-adjusted D-dimer value did not undergo CTPA; they were left untreated and followed for a 3 month period. Among the 766 patients who were ≥75 years of age, 673 had a non-high clinical probability. Use of the age-adjusted (instead of the 'standard' 500 µg/L) D-dimer cut-off increased the number of patients in whom PE could be excluded from 6.4 to 30%, without additional false-negative findings.¹⁰⁶

4.4.2 D-dimer cut-offs adapted to clinical probability

A prospective management trial used the 'YEARS' clinical decision rule, which consists of three clinical items of the Wells score (see Supplementary Data Table 1)—namely signs of DVT, haemoptysis, and PE more likely than an alternative diagnosis—plus D-dimer concentrations.¹⁰⁷ PE was considered to be excluded in patients without clinical items and D-dimer levels <1000 ng/mL, or in patients with one or more clinical items and D-dimer levels <500 ng/mL. All other patients underwent CTPA. Of the 2946 patients (85%) in whom PE was ruled out at baseline and who were left untreated, 18 [0.61%, 95% confidence interval (CI) 0.36–0.96%] were diagnosed with symptomatic VTE during the 3 month follow-up. CTPA was avoided in 48% of the included patients using this algorithm, compared to 34% if the Wells rule and a fixed D-dimer threshold of 500 ng/mL would have been applied.¹⁰⁷

4.4.3 Point-of-care D-dimer assays

In certain situations, notably in community or primary care medicine, 'on-the-spot' D-dimer testing may have advantages over referring a patient to a central laboratory for D-dimer testing. This may particularly apply to remote areas where access to healthcare is limited.^{108,109} However, point-of-care assays have a lower sensitivity and negative predictive value compared with laboratory-based D-dimer tests. In a systematic review and meta-analysis, sensitivity of point-of-care D-dimer assays was 88% (95% CI 83–92%) whereas conventional laboratory-based D-dimer testing had a sensitivity of at least 95%.¹¹⁰ As a result, point-of-care D-dimer assays should only be used in patients with a low pre-test probability. In these situations, PE could be ruled out in 46% of patients with suspected PE without proceeding to imaging tests (with a failure rate of 1.5%), as suggested by a prospective study in Dutch primary care.¹¹¹

4.5 Computed tomographic pulmonary angiography

Multidetector CTPA is the method of choice for imaging the pulmonary vasculature in patients with suspected PE. It allows adequate visualization of the pulmonary arteries down to the subsegmental level.^{112–114} The Prospective Investigation On Pulmonary Embolism Diagnosis (PIOPED) II study observed a sensitivity of 83% and a

Table 6 Imaging tests for diagnosis of pulmonary embolism

	Strengths	Weaknesses/limitations	Radiation issues ^a
CTPA	● Readily available around the clock in most centres ● Excellent accuracy ● Strong validation in prospective management outcome studies ● Low rate of inconclusive results (3–5%) ● May provide alternative diagnosis if PE excluded ● Short acquisition time	● Radiation exposure ● Exposure to iodine contrast: ○ limited use in iodine allergy and hyperthyroidism ○ risks in pregnant and breastfeeding women ○ contraindicated in severe renal failure ● Tendency to overuse because of easy accessibility ● Clinical relevance of CTPA diagnosis of subsegmental PE unknown	● Radiation effective dose 3–10 mSv^b ● Significant radiation exposure to young female breast tissue
Planar V/Q scan	● Almost no contraindications ● Relatively inexpensive ● Strong validation in prospective management outcome studies	● Not readily available in all centres ● Interobserver variability in interpretation ● Results reported as likelihood ratios ● Inconclusive in 50% of cases ● Cannot provide alternative diagnosis if PE excluded	● Lower radiation than CTPA, effective dose ~2 mSv^b
V/Q SPECT	● Almost no contraindications ● Lowest rate of non-diagnostic tests (<3%) ● High accuracy according to available data ● Binary interpretation ('PE' vs. 'no PE')	● Variability of techniques ● Variability of diagnostic criteria ● Cannot provide alternative diagnosis if PE excluded ● No validation in prospective management outcome studies	● Lower radiation than CTPA, effective dose ~2 mSv^b
Pulmonary angiography	● Historical gold standard	● Invasive procedure ● Not readily available in all centres	● Highest radiation, effective dose 10–20 mSv^b

CTPA = computed tomographic pulmonary angiography; mGy = milligray; mSv = millisieverts; PE = pulmonary embolism; SPECT = single-photon emission computed tomography; V/Q = ventilation/perfusion (lung scintigraphy).
^aIn this section, effective radiation dose is expressed in mSv [dose in mSv = absorbed dose in mGy × radiation weighting factor (1.0 for X-rays) × tissue weighting factor]. This reflects the effective doses of all organs that have been exposed, that is, the overall radiation dose to the body from the imaging test. Compare with Table 12, in which the absorbed radiation dose is expressed in mGy to reflect the radiation exposure to single organs or to the foetus.
^bFor comparison, the whole-body effective dose of a chest X-ray examination is 0.1 mSv.¹⁴¹

specificity of 96% for (mainly four-detector) CTPA in PE diagnosis.¹¹⁵ PLOPED II also highlighted the influence of pre-test clinical probability on the predictive value of multidetector CTPA. In patients with a low or intermediate clinical probability of PE, a negative CTPA had a high negative predictive value for PE (96 and 89%, respectively), but its negative predictive value was only 60% if the pre-test probability was high. Conversely, the positive predictive value of a positive CTPA was high (92–96%) in patients with an intermediate or high clinical probability, but much lower (58%) in patients with a low pre-test likelihood of PE.¹¹⁵ Therefore, clinicians should consider further testing in case of discordance between clinical judgement and the CTPA result.

Several studies have provided evidence in favour of CTPA as a stand-alone imaging test for excluding PE. Taken together, the available data suggest that a negative CTPA result is an adequate criterion for the exclusion of PE in patients with low or intermediate clinical probability of PE. On the other hand, it remains controversial whether patients with a negative CTPA and a high clinical probability should be further investigated.

Chronic thromboembolic pulmonary hypertension (CTEPH) is a potentially fatal late sequela of PE, but pre-existing CTEPH should not

be missed in patients investigated for suspected acute PE. Signs of pre-existing CTEPH on CTPA are listed in Supplementary Data Table 2; the diagnosis and management of CTEPH is discussed in section 10.

The major strengths, weaknesses/limitations, and radiation issues related to the use of CTPA in the diagnosis of PE are summarized in Table 6.

4.6 Lung scintigraphy

The planar ventilation/perfusion [V/Q (lung scintigraphy)] scan is an established diagnostic test for suspected PE. Perfusion scans are combined with ventilation studies, for which multiple tracers such as xenon-133 gas, krypton-81 gas, technetium-99m-labelled aerosols, or technetium-99m-labelled carbon microparticles (Technegas) can be used. The purpose of the ventilation scan is to increase specificity: in acute PE, ventilation is expected to be normal in hypoperfused segments (mismatched). Being a lower-radiation and contrast medium-sparing procedure, the V/Q scan may preferentially be applied in outpatients with a low clinical probability and a normal chest X-ray, in young (particularly female) patients, in pregnant women, in patients

with history of contrast medium-induced anaphylaxis, and patients with severe renal failure.¹¹⁶

Planar lung scan results are frequently classified according to the criteria established in the PIOPED study.¹¹⁷ These criteria were the subject of debate and have been revised.^{118,119} To facilitate communication with clinicians, a three-tier classification is preferable: normal scan (excluding PE), high-probability scan (considered diagnostic of PE in most patients), and non-diagnostic scan.^{120–122} Prospective clinical outcome studies suggested that it is safe to withhold anticoagulant therapy in patients with a normal perfusion scan. This was confirmed by a randomized trial comparing the V/Q scan with CTPA.¹²² An analysis from the PIOPED II study suggested that a high-probability V/Q scan could confirm PE, although other sources suggest that the positive predictive value of a high-probability lung scan is not sufficient to confirm PE in patients with a low clinical probability.^{123,124}

Performing only a perfusion scan might be acceptable in patients with a normal chest X-ray; any perfusion defect in this situation would be considered a mismatch. The high frequency of non-diagnostic scans is a limitation because they indicate the necessity for further diagnostic testing. Various strategies to overcome this problem have been proposed, notably the incorporation of clinical probability. Although the use of perfusion scanning and chest X-ray with the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISAPED) criteria may be associated with a low rate of inconclusive results, the sensitivity appears too low to exclude PE and thus this approach may be less safe than CTPA.^{123,125}

Several studies suggest that data acquisition in single-photon emission CT (SPECT) imaging, with or without low-dose CT, may decrease the proportion of non-diagnostic scans to as low as 0–5%.^{121,126–128} However, most studies reporting on the accuracy of SPECT are limited by their retrospective design^{129,130} or the inclusion of SPECT itself in the reference standard,¹²⁷ and only one study used a validated diagnostic algorithm.¹³¹ The diagnostic criteria for SPECT also varied; most studies defined PE as one or two subsegmental perfusion defects without ventilation defects, but these criteria are infrequently used in clinical practice. In addition, the optimal scanning technique (perfusion SPECT, V/Q SPECT, perfusion SPECT with non-enhanced CT, or V/Q SPECT with non-enhanced CT) remains to be defined. Finally, few outcome studies are available, and with incomplete follow-up.¹³² Large-scale prospective studies are needed to validate SPECT techniques.

The major strengths, weaknesses/limitations, and radiation issues related to the use of V/Q scan and V/Q SPECT in the diagnosis of PE are summarized in Table 6.

4.7 Pulmonary angiography

For several decades, pulmonary angiography was the 'gold standard' for the diagnosis or exclusion of acute PE, but it is now rarely performed as less-invasive CTPA offers similar diagnostic accuracy.¹³³ The diagnosis of acute PE is based on direct evidence of a thrombus in two projections, either as a filling defect or as amputation of a pulmonary arterial branch.¹³⁴ Thrombi as small as 1–2 mm within the subsegmental arteries can be visualized by digital subtraction angiography, but there is substantial interobserver variability at this level.^{135,136}

Pulmonary angiography is not free of risk. In a study of 1111 patients, procedure-related mortality was 0.5%, major non-fatal

complications occurred in 1%, and minor complications in 5%.¹³⁷ The majority of deaths occurred in patients with haemodynamic compromise or respiratory failure. The amount of contrast agent should be reduced and non-selective injections avoided in patients with haemodynamic compromise.¹³⁸

The major strengths, weaknesses/limitations, and radiation issues related to the use of pulmonary angiography in the diagnosis of PE are summarized in Table 6.

4.8 Magnetic resonance angiography

Magnetic resonance angiography (MRA) has been evaluated for several years regarding suspected PE. However, the results of large-scale studies^{139,140} show that this technique, although promising, is not yet ready for clinical practice due to its low sensitivity, the high proportion of inconclusive MRA scans, and its low availability in most emergency settings. The hypothesis that a negative MRA, combined with the absence of proximal DVT on compression ultrasonography (CUS), may safely rule out clinically significant PE is currently being investigated in an ongoing multicentre outcome study [Clinicaltrials.gov National Clinical Trial (NCT) number 02059551].

4.9 Echocardiography

Acute PE may lead to RV pressure overload and dysfunction, which can be detected by echocardiography. Given the peculiar geometry of the RV, there is no individual echocardiographic parameter that provides fast and reliable information on RV size or function. This is why echocardiographic criteria for the diagnosis of PE have differed between studies. Because of the reported negative predictive value of 40–50%, a negative result cannot exclude PE.^{124,142,143} On the other hand, signs of RV overload or dysfunction may also be found in the absence of acute PE, and may be due to concomitant cardiac or respiratory disease.¹⁴⁴

Echocardiographic findings of RV overload and/or dysfunction are graphically presented in Figure 3. RV dilation is found in ≥25% of patients with PE on transthoracic echocardiography (TTE) and is useful for risk stratification of the disease.¹⁴⁵ More specific echocardiographic findings were reported to retain a high positive predictive value for PE even in the presence of pre-existing cardiorespiratory disease. Thus, the combination of a pulmonary ejection acceleration time (measured in the RV outflow tract) <60 ms with a peak systolic tricuspid valve gradient <60 mmHg ('60/60' sign), or with depressed contractility of the RV free wall compared to the 'echocardiographic' RV apex (McConnell sign), is suggestive of PE.¹⁴⁶ However, these findings are present in only ~12 and 20% of unselected PE patients, respectively.¹⁴⁵ Detection of echocardiographic signs of RV pressure overload helps to distinguish acute PE from RV free wall hypokinesia or akinesia due to RV infarction, which may mimic the McConnell sign.¹⁴⁷ It should be noted that in ~10% of PE patients, echocardiography can show potentially misleading incidental findings such as significant LV systolic dysfunction or valvular heart disease.¹⁴⁵ Decreased tricuspid annular plane systolic excursion (TAPSE) may also be present in PE patients.^{148,149} Echocardiographic parameters of RV function derived from Doppler tissue imaging and wall strain assessment may also be affected by the presence of acute PE (Figure 3). However, they probably have low sensitivity as stand-alone findings, as they were reported to be normal in haemodynamically stable patients despite the presence of PE.^{150,151}

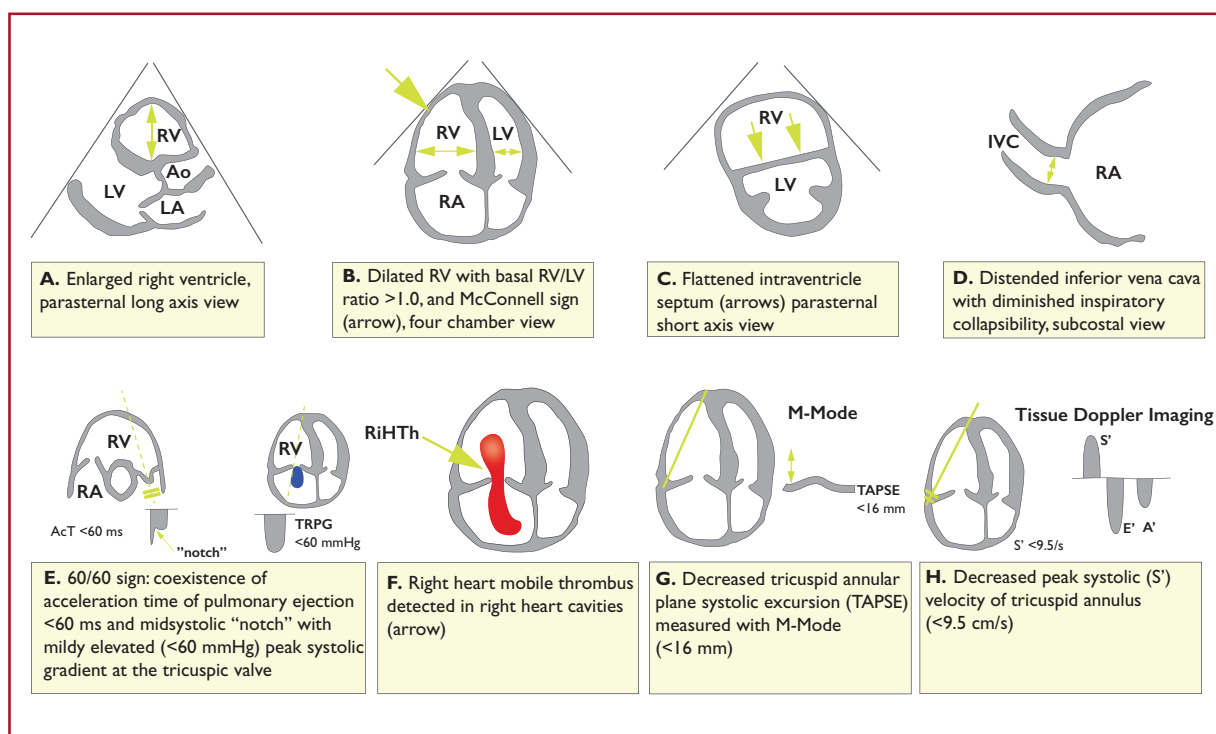


Figure 3 Graphic representation of transthoracic echocardiographic parameters in the assessment of right ventricular pressure overload. A' = peak late diastolic (during atrial contraction) velocity of tricuspid annulus by tissue Doppler imaging; AcT = right ventricular outflow Doppler acceleration time; Ao = aorta; E' = peak early diastolic velocity of tricuspid annulus by tissue Doppler imaging; IVC = inferior vena cava; LA = left atrium; LV = left ventricle; RA = right atrium; RiHTh = right heart thrombus (or thrombi); RV = right ventricle/ventricular; S' = peak systolic velocity of tricuspid annulus by tissue Doppler imaging; TAPSE = tricuspid annular plane systolic excursion; TRPG = tricuspid valve peak systolic gradient.

Echocardiographic examination is not mandatory as part of the routine diagnostic workup in haemodynamically stable patients with suspected PE,¹²⁴ although it may be useful in the differential diagnosis of acute dyspnoea. This is in contrast to suspected high-risk PE, in which the absence of echocardiographic signs of RV overload or dysfunction practically excludes PE as the cause of haemodynamic instability. In the latter case, echocardiography may be of further help in the differential diagnosis of the cause of shock, by detecting pericardial tamponade, acute valvular dysfunction, severe global or regional LV dysfunction, aortic dissection, or hypovolaemia.¹⁵² Conversely, in a haemodynamically compromised patient with suspected PE, unequivocal signs of RV pressure overload, especially with more specific echocardiographic findings (60/60 sign, McConnell sign, or right-heart thrombi), justify emergency reperfusion treatment for PE if immediate CT angiography is not feasible in a patient with high clinical probability and no other obvious causes for RV pressure overload.¹⁵²

Mobile right-heart thrombi are detected by TTE or transoesophageal echocardiography (TOE), or by CT angiography, in <4% of unselected patients with PE.^{153–155} Their prevalence may reach 18% among PE patients in the intensive care setting.¹⁵⁶ Mobile right-heart thrombi essentially confirm the diagnosis of PE and are associated with high early mortality, especially in patients with RV dysfunction.^{155,157–159}

In some patients with suspected acute PE, echocardiography may detect increased RV wall thickness or tricuspid insufficiency jet velocity beyond values compatible with acute RV pressure overload (>3.8 m/s or a tricuspid valve peak systolic gradient >60 mmHg).¹⁶⁰ In these

cases, chronic thromboembolic (or other) pulmonary hypertension (PH) should be included in the differential diagnosis.

4.10 Compression ultrasonography

In the majority of cases, PE originates from DVT in a lower limb, and only rarely from upper-limb DVT (mostly following venous catheterization). In a study using venography, DVT was found in 70% of patients with proven PE.¹⁶¹ Nowadays, lower-limb CUS has largely replaced venography for diagnosing DVT. CUS has a sensitivity >90% and a specificity of ~95% for proximal symptomatic DVT.^{162,163} CUS shows a DVT in 30–50% of patients with PE,^{162–164} and finding a proximal DVT in patients suspected of having PE is considered sufficient to warrant anticoagulant treatment without further testing.¹⁶⁵ However, patients in whom PE is indirectly confirmed by the presence of a proximal DVT should undergo risk assessment for PE severity and the risk of early death.

In the setting of suspected PE, CUS can be limited to a simple four-point examination (bilateral groin and popliteal fossa). The only validated diagnostic criterion for DVT is incomplete compressibility of the vein, which indicates the presence of a clot, whereas flow measurements are unreliable. A positive proximal CUS result has a high positive predictive value for PE. The high diagnostic specificity (96%) along with a low sensitivity (41%) of CUS in this setting was shown by a recent meta-analysis.^{165,166} CUS is a useful procedure in the diagnostic strategy of patients with CT contraindications. The probability of a positive proximal CUS in suspected PE is higher in patients with signs and symptoms related to the leg veins than in asymptomatic patients.^{162,163}

4.11 Recommendations for diagnosis

Recommendations	Class ^a	Level ^b
Suspected PE with haemodynamic instability		
In suspected high-risk PE, as indicated by the presence of haemodynamic instability, bedside echocardiography or emergency CTPA (depending on availability and clinical circumstances) is recommended for diagnosis. ¹⁶⁹	I	C
It is recommended that i.v. anticoagulation with UFH, including a weight-adjusted bolus injection, be initiated without delay in patients with suspected high-risk PE.	I	C
Suspected PE without haemodynamic instability		
The use of validated criteria for diagnosing PE is recommended. ¹²	I	B
Initiation of anticoagulation is recommended without delay in patients with high or intermediate clinical probability of PE while diagnostic workup is in progress.	I	C
Clinical evaluation		
It is recommended that the diagnostic strategy be based on clinical probability, assessed either by clinical judgement or by a validated prediction rule. ^{89,91,92,103,134,170–172}	I	A
D-dimer		
Plasma D-dimer measurement, preferably using a highly sensitive assay, is recommended in outpatients/emergency department patients with low or intermediate clinical probability, or those that are PE-unlikely, to reduce the need for unnecessary imaging and irradiation. ^{101–103,122,164,171,173,174}	I	A
As an alternative to the fixed D-dimer cut-off, a negative D-dimer test using an age-adjusted cut-off (age × 10 µg/L, in patients aged >50 years) should be considered for excluding PE in patients with low or intermediate clinical probability, or those that are PE-unlikely. ¹⁰⁶	IIa	B
As an alternative to the fixed or age-adjusted D-dimer cut-off, D-dimer levels adapted to clinical probability ^c should be considered to exclude PE. ¹⁰⁷	IIa	B
D-dimer measurement is not recommended in patients with high clinical probability, as a normal result does not safely exclude PE, even when using a highly sensitive assay. ^{175,176}	III	A
CTPA		
It is recommended to reject the diagnosis of PE (without further testing) if CTPA is normal in a patient with low or intermediate clinical probability, or who is PE-unlikely. ^{101,122,164,171}	I	A
It is recommended to accept the diagnosis of PE (without further testing) if CTPA shows a segmental or more proximal filling defect in a patient with intermediate or high clinical probability. ¹¹⁵	I	B
It should be considered to reject the diagnosis of PE (without further testing) if CTPA is normal in a patient with high clinical probability or who is PE-likely. ¹⁷¹	IIa	B
Further imaging tests to confirm PE may be considered in cases of isolated subsegmental filling defects. ¹¹⁵	IIb	C
CT venography is not recommended as an adjunct to CTPA. ^{115,164}	III	B
V/Q scintigraphy		
It is recommended to reject the diagnosis of PE (without further testing) if the perfusion lung scan is normal. ^{75,122,134,174}	I	A
It should be considered to accept that the diagnosis of PE (without further testing) if the V/Q scan yields high probability for PE. ¹³⁴	IIa	B
A non-diagnostic V/Q scan should be considered as exclusion of PE when combined with a negative proximal CUS in patients with low clinical probability, or who are PE-unlikely. ^{75,122,174}	IIa	B

Continued

V/Q SPECT		
V/Q SPECT may be considered for PE diagnosis. ^{121,126–128}	IIb ^d	B
Lower-limb CUS		
It is recommended to accept the diagnosis of VTE (and PE) if a CUS shows a proximal DVT in a patient with clinical suspicion of PE. ^{164,165}	I	A
If CUS shows only a distal DVT, further testing should be considered to confirm PE. ¹⁷⁷	IIa	B
If a positive proximal CUS is used to confirm PE, assessment of PE severity should be considered to permit risk-adjusted management. ^{178,179}	IIa	C
MRA		
MRA is not recommended for ruling out PE. ^{139,140}	III	A

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CT = computed tomographic; CTPA = computed tomography pulmonary angiography/angiogram; CUS = compression ultrasonography; DVT = deep vein thrombosis; i.v. = intravenous; MRA = magnetic resonance angiography; PE = pulmonary embolism; SPECT = single-photon emission computed tomography; UFH = unfractionated heparin; V/Q = ventilation/perfusion (lung scintigraphy); VTE = venous thromboembolism.

^aClass of recommendation.

^bLevel of evidence.

^cD-dimer cut-off levels adapted to clinical probability according to the YEARS model (signs of DVT, haemoptysis, and whether an alternative diagnosis is less likely than PE) may be used. According to this model, PE is excluded in patients without clinical items and D-dimer levels <1000 µg/L, or in patients with one or more clinical items and D-dimer levels <500 µg/L. ¹⁰⁷

^dLow level of recommendation in view of the limitations summarized in Table 5.

In patients admitted to the emergency department with haemodynamic instability and suspicion of PE, a combination of venous ultrasound with cardiac ultrasound may further increase specificity. Conversely, an echocardiogram without signs of RV dysfunction and a normal venous ultrasound excluded PE with a high (96%) negative predictive value in one study. ¹⁶⁷

For further details on the diagnosis and management of DVT, the reader is referred to the joint consensus document of the ESC Working Groups of Aorta and Peripheral Vascular Diseases, and Pulmonary Circulation and Right Ventricular Function. ¹

4.12 Computed tomography venography

When using CTPA, it is possible to image the deep veins of the legs during the same acquisition. ¹¹⁵ However, this approach has not been widely validated and the added value of venous imaging is limited. ¹⁶⁴ Moreover, using CT venography is associated with increased radiation doses. ¹⁶⁸

5 Assessment of pulmonary embolism severity and the risk of early death

Risk stratification of patients with acute PE is mandatory for determining the appropriate therapeutic management approach. As described in section 3.3, initial risk stratification is based on clinical symptoms and signs of haemodynamic instability (Table 4), which indicate a high risk of early death. In the large remaining group of patients with PE who present without haemodynamic instability, further (advanced) risk stratification requires the assessment of two sets of prognostic criteria: (i) clinical, imaging, and laboratory indicators of PE severity, mostly related to the presence of RV dysfunction; and (ii) presence of comorbidity and any other aggravating conditions that may adversely affect early prognosis.

5.1 Clinical parameters of pulmonary embolism severity

Acute RV failure, defined as a rapidly progressive syndrome with systemic congestion resulting from impaired RV filling and/or reduced RV flow output, ⁶⁸ is a critical determinant of outcome in acute PE. Tachycardia, low systolic BP, respiratory insufficiency (tachypnoea and/or low SaO₂), and syncope, alone or in combination, have been associated with an unfavourable short-term prognosis in acute PE.

5.2 Imaging of right ventricular size and function

5.2.1 Echocardiography

Echocardiographic parameters used to stratify the early risk of patients with PE are graphically presented in Figure 3, and their prognostic values are summarized in Supplementary Data Table 3. Of these, an RV/LV diameter ratio ≥1.0 and a TAPSE <16 mm are the findings for which an association with unfavourable prognosis has most frequently been reported. ¹⁴⁸

Overall, evidence for RV dysfunction on echocardiography is found in ≥25% of unselected patients with acute PE. ¹⁴⁵ Systematic reviews and meta-analyses have suggested that RV dysfunction on echocardiography is associated with an elevated risk of short-term mortality in patients who appear haemodynamically stable at presentation, ^{180,181} but its overall positive predictive value for PE-related death was low (<10%) in a meta-analysis. ¹⁸⁰ This weakness is partly related to the fact that echocardiographic parameters have proved difficult to standardize. ^{148,180} Nevertheless, echocardiographic assessment of the morphology and function of the RV is widely recognized as a valuable tool for the prognostic assessment of normotensive patients with acute PE in clinical practice.

In addition to RV dysfunction, echocardiography can identify right-to-left shunt through a patent foramen ovale and the presence of right heart thrombi, both of which are associated with increased

mortality in patients with acute PE.^{67,158} A patent foramen ovale also increases the risk of ischaemic stroke due to paradoxical embolism in patients with acute PE and RV dysfunction.^{182,183}

5.2.2 Computed tomographic pulmonary angiography

CTPA parameters used to stratify the early risk of patients with PE are summarized in Supplementary Data Table 3. Four-chamber views of the heart by CT angiography can detect RV enlargement (RV end-diastolic diameter and RV/LV ratio measured in the transverse or four-chamber view) as an indicator of RV dysfunction. The prognostic value of an enlarged RV is supported by the results of a prospective multicentre cohort study in 457 patients.¹⁸⁴ In that study, RV enlargement (defined as an RV/LV ratio ≥ 0.9) was an independent predictor of an adverse in-hospital outcome, both in the overall population with PE [hazard ratio (HR) 3.5, 95% CI 1.6–7.7] and in haemodynamically stable patients (HR 3.8, 95% CI 1.3–10.9).¹⁸⁴ A meta-analysis of 49 studies investigating >13 000 patients with PE confirmed that an increased RV/LV ratio of ≥ 1.0 on CT was associated with a 2.5-fold increased risk for all-cause mortality [odds ratio (OR) 2.5, 95% CI 1.8–3.5], and with a five-fold risk for PE-related mortality (OR 5.0, 95% CI 2.7–9.2).¹⁸⁵

Mild RV dilation (RV/LV slightly above 0.9) on CT is a frequent finding (>50% of haemodynamically stable PE patients¹⁸⁶), but it probably has minor prognostic significance. However, increasing RV/LV diameter ratios are associated with rising prognostic specificity,^{187,188} even in patients considered to be at 'low' risk on the basis of clinical criteria.¹⁸⁶ Thus, RV/LV ratios ≥ 1.0 (instead of 0.9) on CT angiography may be more appropriate to indicate poor prognosis.

Apart from RV size and the RV/LV ratio, CT may provide further prognostic information based on volumetric analysis of the heart chambers^{189–191} and assessment of contrast reflux to the inferior vena cava (IVC).^{185,192,193}

5.3 Laboratory biomarkers

5.3.1 Markers of myocardial injury

Elevated plasma troponin concentrations on admission may be associated with a worse prognosis in the acute phase of PE. Cardiac troponin I or T elevation are defined as concentrations above the normal limits, and thresholds depend on the assay used; an overview of the cut-off values has been provided by a meta-analysis.¹⁹⁴ Of patients with acute PE, between 30 (using conventional assays)^{194,195} and 60% (using high-sensitivity assays)^{196,197} have elevated cardiac troponin I or T concentrations. A meta-analysis showed that elevated troponin concentrations were associated with an increased risk of mortality, both in unselected patients (OR 5.2, 95% CI 3.3–8.4) and in those who were haemodynamically stable at presentation (OR 5.9, 95% CI 2.7–13.0).¹⁹⁵

On their own, increased circulating levels of cardiac troponins have relatively low specificity and positive predictive value for early mortality in normotensive patients with acute PE. However, when interpreted in combination with clinical and imaging findings, they may improve the identification of an elevated PE-related risk and the further prognostic stratification of such patients (Supplementary Data Table 4). At the other end of the severity spectrum, high-sensitivity troponin assays possess a high negative predictive value in the setting of acute PE.¹⁹⁷ For example, in a

prospective multicentre cohort of 526 normotensive patients, high-sensitivity troponin T concentrations <14 pg/mL had a negative predictive value of 98% for excluding an adverse in-hospital clinical outcome.⁶³ Age-adjusted high-sensitivity troponin T cut-off values (≥ 14 pg/mL for patients aged <75 years and ≥ 45 pg/mL for those ≥ 75 years) may further improve the negative predictive value of this biomarker.¹⁹⁶

Heart-type fatty acid-binding protein (H-FABP), an early and sensitive marker of myocardial injury, provides prognostic information in acute PE, both in unselected^{198,199} and normotensive patients.^{200,201} In a meta-analysis investigating 1680 patients with PE, H-FABP concentrations ≥ 6 ng/mL were associated with an adverse short-term outcome (OR 17.7, 95% CI 6.0–51.9) and all-cause mortality (OR 32.9, 95% CI 8.8–123.2).²⁰²

5.3.2 Markers of right ventricular dysfunction

RV pressure overload due to acute PE is associated with increased myocardial stretch, which leads to the release of B-type natriuretic peptide (BNP) and N-terminal (NT)-proBNP. Thus, the plasma levels of natriuretic peptides reflect the severity of RV dysfunction and haemodynamic compromise in acute PE.²⁰³ A meta-analysis found that 51% of 1132 unselected patients with acute PE had elevated BNP or NT-proBNP concentrations on admission; these patients had a 10% risk of early death (95% CI 8.0–13%) and a 23% (95% CI 20–26%) risk of an adverse clinical outcome.²⁰⁴

Similar to cardiac troponins (see above), elevated BNP or NT-proBNP concentrations possess low specificity and positive predictive value (for early mortality) in normotensive patients with PE,²⁰⁵ but low levels of BNP or NT-proBNP are capable of excluding an unfavourable early clinical outcome, with high sensitivity and a negative predictive value.¹⁸⁰ In this regard, an NT-proBNP cut-off value <500 pg/mL was used to select patients for home treatment in a multicentre management study.²⁰⁶ If emphasis is placed on increasing the prognostic specificity for an adverse early outcome, higher cut-off values ≥ 600 pg/mL might be more appropriate.²⁰⁷

5.3.3 Other laboratory biomarkers

Lactate is a marker of imbalance between tissue oxygen supply and demand, and consequently of severe PE with overt or imminent haemodynamic compromise. Elevated arterial plasma levels ≥ 2 mmol/L predict PE-related complications, both in unselected²⁰⁸ and in initially normotensive^{209,210} PE patients.

Elevated serum creatinine levels and a decreased (calculated) glomerular filtration rate are related to 30 day all-cause mortality in acute PE.²¹¹ Elevated neutrophil gelatinase-associated lipocalin and cystatin C, both indicating acute kidney injury, are also of prognostic value.²¹²

A recent meta-analysis investigating 18 616 patients with acute PE found that hyponatraemia predicted in-hospital mortality (OR 5.6, 95% CI 3.4–9.1).²¹³

Vasopressin is released upon endogenous stress, hypotension, and low CO. Its surrogate marker, copeptin, has been reported to be useful for risk stratification of patients with acute PE.^{214,215} In a single-centre derivation study investigating 268 normotensive PE patients, copeptin levels ≥ 24 pmol/L were associated with a 5.4-fold (95% CI 1.7–17.6) increased risk of an adverse outcome.²¹⁶ These results

were confirmed in 843 normotensive PE patients prospectively included in three European cohorts.²¹⁷

5.4 Combined parameters and scores for assessment of pulmonary embolism severity

In patients who present without haemodynamic instability, individual baseline findings may not suffice to determine and further classify PE severity and PE-related early risk when used as stand-alone parameters. As a result, various combinations of the clinical, imaging, and laboratory parameters described above have been used to build prognostic scores, which permit a (semi)quantitative assessment of early PE-related risk of death. Of these, the Bova^{218–221} and the H-FABP (or high-sensitivity troponin T), Syncope, Tachycardia (FAST) scores^{219,222,223} have been validated in cohort studies (see Supplementary Data Table 4). However, their implications for patient management remain unclear. To date, only a combination of RV dysfunction on an echocardiogram (or CTPA) with a positive cardiac troponin test has directly been tested as a guide for early therapeutic decisions (anticoagulation plus reperfusion treatment vs. anticoagulation alone) in a large randomized controlled trial (RCT) of PE patients presenting without haemodynamic instability.²²⁴

5.5 Integration of aggravating conditions and comorbidity into risk assessment of acute pulmonary embolism

In addition to the clinical, imaging, and laboratory findings, which are directly linked to PE severity and PE-related early death, baseline parameters related to aggravating conditions and comorbidity are necessary to assess a patient's overall mortality risk and early outcome. Of the clinical scores integrating PE severity and comorbidity, the Pulmonary Embolism Severity Index (PESI) (Table 7) is the one that has been most extensively validated to date.^{225–228} The principal strength of the PESI lies in the reliable identification of patients at low risk for 30 day mortality (PESI classes I and II). One randomized trial employed a low PESI as the principal inclusion criterion for home treatment of acute PE.¹⁷⁸

In view of the complexity of the original PESI, which includes 11 differently weighed variables, a simplified version (sPESI; Table 7) has been developed and validated.^{229–231} As with the original version of the PESI, the strength of the sPESI lies in the reliable identification of patients at low risk for 30 day mortality. The prognostic performance of the sPESI has been confirmed in observational cohort studies,^{227,228} although this index has not yet been prospectively used to guide therapeutic management of low-risk PE patients.

The diagnosis of concomitant DVT has been identified as an adverse prognostic factor, being independently associated with death within the first 3 months after acute PE.²³² In a meta-analysis investigating 8859 patients with PE, the presence of concomitant DVT was confirmed as a predictor of 30 day all-cause mortality (OR 1.9, 95% CI 1.5–2.4), although it did not predict PE-related adverse outcomes at 90 days.²³³ Thus, concomitant DVT can be regarded as an indicator of significant comorbidity in acute PE.

Table 7 Original and simplified Pulmonary Embolism Severity Index

Parameter	Original version ²²⁶	Simplified version ²²⁹
Age	Age in years	1 point (if age >80 years)
Male sex	+10 points	–
Cancer	+30 points	1 point
Chronic heart failure	+10 points	1 point
Chronic pulmonary disease	+10 points	
Pulse rate ≥110 b.p.m.	+20 points	1 point
Systolic BP <100 mmHg	+30 points	1 point
Respiratory rate >30 breaths per min	+20 points	–
Temperature <36°C	+20 points	–
Altered mental status	+60 points	–
Arterial oxyhaemoglobin saturation <90%	+20 points	1 point
Risk strata ^a		
Class I: ≤65 points very low 30 day mortality risk (0–1.6%) Class II: 66–85 points low mortality risk (1.7–3.5%)		0 points = 30 day mortality risk 1.0% (95% CI 0.0–2.1%)
Class III: 86–105 points moderate mortality risk (3.2–7.1%) Class IV: 106–125 points high mortality risk (4.0–11.4%) Class V: >125 points very high mortality risk (10.0–24.5%)		≥1 point(s) = 30 day mortality risk 10.9% (95% CI 8.5–13.2%)

BP = blood pressure; b.p.m. = beats per minute; CI = confidence interval.
^aBased on the sum of points.

5.6 Prognostic assessment strategy

The classification of PE severity and the risk of early (in-hospital or 30 day) death is summarized in Table 8. Risk assessment of acute PE begins upon suspicion of the disease and initiation of the diagnostic workup. At this early stage, it is critical to identify patients with (suspected) high-risk PE. This clinical setting necessitates an emergency

Table 8 Classification of pulmonary embolism severity and the risk of early (in-hospital or 30 day) death

Early mortality risk		Indicators of risk			
		Haemodynamic instability ^a	Clinical parameters of PE severity and/or comorbidity: PESI class III–V or sPESI $\geq$ I	RV dysfunction on TTE or CTPA ^b	Elevated cardiac troponin levels ^c
High		+	(+) ^d	+	(+)
Intermediate	Intermediate–high	–	+ ^e	+	+
	Intermediate–low	–	+ ^e	One (or none) positive	
Low		–	–	–	Assessment optional; if assessed, negative

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BP = blood pressure; CTPA = computed tomography pulmonary angiography; H-FABP = heart-type fatty acid-binding protein; NT-proBNP = N-terminal pro B-type natriuretic peptide; PE = pulmonary embolism; PESI = Pulmonary Embolism Severity Index; RV = right ventricular; sPESI = simplified Pulmonary Embolism Severity Index; TTE = transthoracic echocardiogram.

^aOne of the following clinical presentations (Table 4): cardiac arrest, obstructive shock (systolic BP <90 mmHg or vasopressors required to achieve a BP $\geq$ 90 mmHg despite an adequate filling status, in combination with end-organ hypoperfusion), or persistent hypotension (systolic BP <90 mmHg or a systolic BP drop $\geq$ 40 mmHg for >15 min, not caused by new-onset arrhythmia, hypovolaemia, or sepsis).

^bPrognostically relevant imaging (TTE or CTPA) findings in patients with acute PE, and the corresponding cut-off levels, are graphically presented in Figure 3, and their prognostic value is summarized in Supplementary Data Table 3.

^cElevation of further laboratory biomarkers, such as NT-proBNP $\geq$ 600 ng/L, H-FABP $\geq$ 6 ng/mL, or copeptin $\geq$ 24 pmol/L, may provide additional prognostic information. These markers have been validated in cohort studies but they have not yet been used to guide treatment decisions in randomized controlled trials.

^dHaemodynamic instability, combined with PE confirmation on CTPA and/or evidence of RV dysfunction on TTE, is sufficient to classify a patient into the high-risk PE category. In these cases, neither calculation of the PESI nor measurement of troponins or other cardiac biomarkers is necessary.

^eSigns of RV dysfunction on TTE (or CTPA) or elevated cardiac biomarker levels may be present, despite a calculated PESI of I–II or an sPESI of 0.²³⁴ Until the implications of such discrepancies for the management of PE are fully understood, these patients should be classified into the intermediate-risk category.

diagnostic algorithm (Figure 4) and immediate referral for reperfusion treatment, as explained in section 7, and displayed in Figure 6 and Supplementary Data Figure 1. Testing for laboratory biomarkers such as cardiac troponins or natriuretic peptides is not necessary for immediate therapeutic decisions in patients with high-risk PE.

In the absence of haemodynamic instability at presentation, further risk stratification of PE is recommended, as it has implications for early discharge vs. hospitalization or monitoring of the patient (explained in section 7). Table 8 provides an overview of the clinical, imaging, and laboratory parameters used to distinguish intermediate- and low-risk PE. The PESI is—in its original or simplified form—the most extensively validated and most broadly used clinical score to date, as it integrates baseline indicators of the severity of the acute PE episode with aggravating conditions and the comorbidity of the patient. Overall, a PESI of class I–II or an sPESI of 0 is a reliable predictor of low-risk PE.

In addition to clinical parameters, patients in the intermediate-risk group who display evidence of both RV dysfunction (on echocardiography or CTPA) and elevated cardiac biomarker levels in the circulation (particularly a positive cardiac troponin test) are classified into the intermediate-high-risk category. As will be discussed in more detail in section 7, close monitoring is recommended in these cases to permit the early detection of haemodynamic decompensation or collapse, and consequently the need for rescue reperfusion therapy.¹⁷⁹ Patients in whom the RV appears normal on echocardiography or

CTPA, and/or who have normal cardiac biomarker levels, belong to the intermediate-low-risk category. As an alternative approach, use of further prognostic scores combining clinical, imaging, and laboratory parameters may be considered to semi-quantitatively assess the severity of the PE episode, and distinguish intermediate-high-risk and intermediate-low-risk PE. Supplementary Data Table 4 lists the scores most frequently investigated for this purpose in observational (cohort) studies; however, none of them has been used in RCTs to date.

A recent meta-analysis included 21 cohort studies with a total of 3295 patients with ‘low-risk’ PE based on a PESI of I–II or an sPESI of 0.²³⁴ Overall, 34% (95% CI 30–39%) of them were reported to have signs of RV dysfunction on echocardiography or CTPA. Data on early mortality were provided in seven studies (1597 patients) and revealed an OR of 4.19 (95% CI 1.39–12.58) for death from any cause in the presence of RV dysfunction; elevated cardiac troponin levels were associated with a comparable magnitude of risk elevation.²³⁴ Early all-cause mortality rates (1.8% for RV dysfunction and 3.8% for elevated troponin levels²³⁴) were in the lower range of those previously reported for patients with intermediate-risk PE.²³⁵ Until the clinical implications of such discrepancies are clarified, patients with signs of RV dysfunction or elevated cardiac biomarkers, despite a low PESI or an sPESI of 0, should be classified into the intermediate-low-risk category.

5.7 Recommendations for prognostic assessment

Recommendations	Class ^a	Level ^b
Initial risk stratification of suspected or confirmed PE, based on the presence of haemodynamic instability, is recommended to identify patients at high risk of early mortality. ^{218,219,235}	I	B
In patients without haemodynamic instability, further stratification of patients with acute PE into intermediate- and low-risk categories is recommended. ^{179,218,219,235}	I	B
In patients without haemodynamic instability, use of clinical prediction rules integrating PE severity and comorbidity, preferably the PESI or sPESI, should be considered for risk assessment in the acute phase of PE. ^{178,226,229}	IIa	B
Assessment of the RV by imaging methods ^c or laboratory biomarkers ^d should be considered, even in the presence of a low PESI or a negative sPESI. ²³⁴	IIa	B
In patients without haemodynamic instability, use of validated scores combining clinical, imaging, and laboratory PE-related prognostic factors may be considered to further stratify the severity of the acute PE episode. ^{218–223}	IIb	C

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PE = pulmonary embolism; PESI = Pulmonary Embolism Severity Index; RV = right ventricle; sPESI = simplified Pulmonary Embolism Severity Index.
^aClass of recommendation.
^bLevel of evidence.
^cTransthoracic echocardiography or computed tomography pulmonary angiography.
^dCardiac troponins or natriuretic peptides.

6 Treatment in the acute phase

6.1 Haemodynamic and respiratory support

6.1.1 Oxygen therapy and ventilation

Hypoxaemia is one of the features of severe PE, and is mostly due to the mismatch between ventilation and perfusion. Administration of supplemental oxygen is indicated in patients with PE and SaO₂ <90%. Severe hypoxaemia/respiratory failure that is refractory to conventional oxygen supplementation could be explained by right-to-left shunt through a patent foramen ovale or atrial septal defect.⁶⁷ Further oxygenation techniques should also be considered, including high-flow oxygen (i.e. a high-flow nasal cannula)^{236,237} and mechanical ventilation (non-invasive or invasive) in cases of extreme instability (i.e. cardiac arrest), taking into consideration that correction of hypoxaemia will not be possible without simultaneous pulmonary reperfusion.

Patients with RV failure are frequently hypotensive or are highly susceptible to the development of severe hypotension during induction of anaesthesia, intubation, and positive-pressure ventilation. Consequently, intubation should be performed only if the patient is unable to tolerate or cope with non-invasive ventilation. When feasible, non-invasive ventilation or oxygenation through a high-flow nasal cannula should be preferred; if mechanical ventilation is used, care should be taken to limit its adverse haemodynamic effects. In particular, positive intrathoracic pressure induced by mechanical ventilation may reduce venous return and worsen low CO due to RV failure in patients with high-risk PE; therefore, positive end-expiratory pressure should be applied with caution. Tidal volumes of approximately 6 mL/kg lean body weight should be used in an attempt to keep the end-inspiratory plateau pressure <30 cm H₂O. If intubation is needed, anaesthetic drugs more prone to cause hypotension should be avoided for induction.

6.1.2 Pharmacological treatment of acute right ventricular failure

Acute RV failure with resulting low systemic output is the leading cause of death in patients with high-risk PE. The principles of acute right heart failure management have been reviewed in a statement from the Heart Failure Association and the Working Group on Pulmonary Circulation and Right Ventricular Function of the ESC.⁶⁸ An overview of the current treatment options for acute RV failure is provided in Table 9.

If the central venous pressure is low, modest (≤500 mL) fluid challenge can be used as it may increase the cardiac index in patients with acute PE.²³⁸ However, volume loading has the potential to over-distend the RV and ultimately cause a reduction in systemic CO.²³⁹ Experimental studies suggest that aggressive volume expansion is of no benefit and may even worsen RV function.²⁴⁰ Cautious volume loading may be appropriate if low arterial pressure is combined with an absence of elevated filling pressures. Assessment of central venous pressure by ultrasound imaging of the IVC (a small and/or collapsible IVC in the setting of acute high-risk PE indicates low volume status) or, alternatively, by central venous pressure monitoring may help guide volume loading. If signs of elevated central venous pressure are observed, further volume loading should be withheld.

Use of vasopressors is often necessary, in parallel with (or while waiting for) pharmacological, surgical, or interventional reperfusion treatment. Norepinephrine can improve systemic haemodynamics by bringing about an improvement in ventricular systolic interaction and coronary perfusion, without causing a change in PVR.²⁴⁰ Its use should be limited to patients in cardiogenic shock. Based on the results of a small series, the use of dobutamine may be considered for patients with PE, a low cardiac index, and normal BP; however, raising the cardiac index may aggravate the ventilation/perfusion mismatch by further redistributing flow from (partly) obstructed to unobstructed vessels.²⁴¹ Although experimental data suggest that

Table 9 Treatment of right ventricular failure in acute high-risk pulmonary embolism

Strategy	Properties and use	Caveats
Volume optimization		
Cautious volume loading, saline, or Ringer's lactate, ≤ 500 mL over 15–30 min	Consider in patients with normal–low central venous pressure (due, for example, to concomitant hypovolaemia)	Volume loading can over-distend the RV, worsen ventricular interdependence, and reduce CO ²³⁹
Vasopressors and inotropes		
Norepinephrine, 0.2–1.0 $\mu\text{g/kg/min}$ ^a ²⁴⁰	Increases RV inotropy and systemic BP, promotes positive ventricular interactions, and restores coronary perfusion gradient	Excessive vasoconstriction may worsen tissue perfusion
Dobutamine, 2–20 $\mu\text{g/kg/min}$ ²⁴¹	Increases RV inotropy, lowers filling pressures	May aggravate arterial hypotension if used alone, without a vasopressor; may trigger or aggravate arrhythmias
Mechanical circulatory support		
Veno–arterial ECMO/extracorporeal life support ^{251,252,258}	Rapid short-term support combined with oxygenator	Complications with use over longer periods (>5–10 days), including bleeding and infections; no clinical benefit unless combined with surgical embolectomy; requires an experienced team

CO = cardiac output; BP = blood pressure; ECMO = extracorporeal membrane oxygenation; RV = right ventricle/ventricular.

^aEpinephrine is used in cardiac arrest.

levosimendan may restore RV–pulmonary arterial coupling in acute PE by combining pulmonary vasodilation with an increase in RV contractility,²⁴² no evidence of clinical benefit is available.

Vasodilators decrease PAP and PVR, but may worsen hypotension and systemic hypoperfusion due to their lack of specificity for the pulmonary vasculature after systemic [intravenous (i.v.)] administration. Although small clinical studies have suggested that inhalation of nitric oxide may improve the haemodynamic status and gas exchange of patients with PE,^{243–245} no evidence for its clinical efficacy or safety is available to date.²⁴⁶

6.1.3 Mechanical circulatory support and oxygenation

The temporary use of mechanical cardiopulmonary support, mostly with veno–arterial extracorporeal membrane oxygenation (ECMO), may be helpful in patients with high-risk PE, and circulatory collapse or cardiac arrest. Survival of critically ill patients has been described in a number of case series,^{247–252} but no RCTs testing the efficacy and safety of these devices in the setting of high-risk PE have been conducted to date. Use of ECMO is associated with a high incidence of complications, even when used for short periods, and the results depend on the experience of the centre as well as patient selection. The increased risk of bleeding related to the need for vascular access should be considered, particularly in patients undergoing thrombolysis. At present, the use of ECMO as a stand-alone technique with anticoagulation is controversial^{247,252} and additional therapies, such as surgical embolectomy, have to be considered.

A few cases suggesting good outcomes with use of the Impella® catheter in patients in shock caused by acute PE have been reported.^{253,254}

6.1.4 Advanced life support in cardiac arrest

Acute PE is part of the differential diagnosis of cardiac arrest with non-shockable rhythm against a background of pulseless electrical

activity. In cardiac arrest presumably caused by acute PE, current guidelines for advanced life support should be followed.^{255,256} The decision to treat for acute PE must be taken early, when a good outcome is still possible. Thrombolytic therapy should be considered; once a thrombolytic drug is administered, cardiopulmonary resuscitation should be continued for at least 60–90 min before terminating resuscitation attempts.²⁵⁷

6.2 Initial anticoagulation

6.2.1 Parenteral anticoagulation

In patients with high or intermediate clinical probability of PE (see section 4), anticoagulation should be initiated while awaiting the results of diagnostic tests. This is usually done with subcutaneous, weight-adjusted low-molecular weight heparin (LMWH) or fondaparinux (Supplementary Data Table 5), or i.v. unfractionated heparin (UFH). Based on pharmacokinetic data (Supplementary Data Table 6),²⁵⁹ an equally rapid anticoagulant effect can also be achieved with a non-vitamin K antagonist oral anticoagulant (NOAC), and phase III clinical trials have demonstrated the non-inferior efficacy of a single-oral drug anticoagulation strategy using higher doses of apixaban for 7 days or rivaroxaban for 3 weeks.^{259–261}

LMWH and fondaparinux are preferred over UFH for initial anticoagulation in PE, as they carry a lower risk of inducing major bleeding and heparin-induced thrombocytopenia.^{262–265} Neither LMWH nor fondaparinux need routine monitoring of anti-Xa levels. Use of UFH is nowadays largely restricted to patients with overt haemodynamic instability or imminent haemodynamic decompensation in whom primary reperfusion treatment will be necessary. UFH is also recommended for patients with serious renal impairment [creatinine clearance (CrCl) ≤ 30 mL/min] or severe obesity. If LMWH is prescribed in patients with CrCl 15–30 mL/min, an adapted dosing scheme should be used. The

dosing of UFH is adjusted based on the activated partial thromboplastin time (Supplementary Data Table 7).²⁶⁶

6.2.2 Non-vitamin K antagonist oral anticoagulants

NOACs are small molecules that directly inhibit one activated coagulation factor, which is thrombin for dabigatran and factor Xa for apixaban, edoxaban, and rivaroxaban. The characteristics of NOACs used in the treatment of acute PE are summarized in Supplementary Data Table 6. Owing to their predictable bioavailability and pharmacokinetics, NOACs can be given at fixed doses without routine laboratory monitoring. Compared with vitamin K antagonists (VKAs), there are fewer interactions when NOACs are given concomitantly with other drugs.²⁵⁹ In the phase III VTE trials, the dosages of dabigatran, rivaroxaban, and apixaban were not reduced in patients with mild–moderate renal dysfunction (CrCl between 30–60 mL/min), whereas edoxaban was given at a 30 mg dose in these patients. Patients with CrCl <25 mL/min were excluded from the trials testing apixaban, whereas patients with CrCl <30 mL/min were excluded from those investigating rivaroxaban, edoxaban, and dabigatran (Supplementary Data Table 8).

Phase III trials on the treatment of acute VTE (Supplementary Data Table 8), as well as those on extended treatment beyond the first 6 months (see section 8), demonstrated the non-inferiority of NOACs compared with the combination of LMWH with VKA for the prevention of symptomatic or lethal VTE recurrence, along with significantly reduced rates of major bleeding.²⁶⁷ The different drug regimens tested in these trials are displayed in Supplementary Data Table 8. In a meta-analysis, the incidence rate of the primary efficacy outcome was 2.0% for NOAC-treated patients and 2.2% for VKA-treated patients [relative risk (RR) 0.88, 95% CI 0.74–1.05].²⁶⁸ Major bleeding occurred in 1.1% of NOAC-treated patients and 1.7% of VKA-treated patients for an RR of 0.60 (95% CI 0.41–0.88). Compared with VKA-treated patients, critical site major bleeding occurred less frequently in NOAC-treated patients (RR 0.38, 95% CI 0.23–0.62); in particular, there was a significant reduction in intracranial bleeding (RR 0.37, 95% CI 0.21–0.68) and in fatal bleeding (RR 0.36, 95% CI 0.15–0.87) with NOACs compared with VKAs.²⁶⁸

Suggestions for the anticoagulation management of PE in specific clinical situations, for which conclusive evidence is lacking, are presented in Supplementary Data Table 9.

Practical guidance for clinicians regarding the handling of NOACs and the management of emergency situations related to their use are regularly updated by the European Heart Rhythm Association.²⁵⁹

6.2.3 Vitamin K antagonists

VKAs have been the gold standard in oral anticoagulation for more than 50 years. When VKAs are used, anticoagulation with UFH, LMWH, or fondaparinux should be continued in parallel with the oral anticoagulant for ≥ 5 days and until the international normalized ratio (INR) value has been 2.0–3.0 for 2 consecutive days. Warfarin may be started at a dose of 10 mg in younger (e.g. aged <60 years) otherwise healthy patients and at a dose ≤ 5 mg in older patients.²⁶⁹ The daily dose is adjusted according to the INR over the next 5–7 days, aiming for an INR level of 2.0–3.0. Pharmacogenetic testing may increase the precision of warfarin dosing.^{270,271} When used in addition to clinical parameters, pharmacogenetic testing improves

anticoagulation control and may be associated with a reduced risk of bleeding, but does not reduce the risk of thromboembolic events or mortality.²⁷²

The implementation of a structured anticoagulant service (most commonly, anticoagulant clinics) appears to be associated with increased time in the therapeutic range and improved clinical outcome, compared with control of anticoagulation by the general practitioner.^{273,274} Finally, in patients who are selected and appropriately trained, self-monitoring of VKA is associated with fewer thromboembolic events and increased time in the therapeutic range compared with usual care.²⁷⁵

6.3 Reperfusion treatment

6.3.1 Systemic thrombolysis

Thrombolytic therapy leads to faster improvements in pulmonary obstruction, PAP, and PVR in patients with PE, compared with UFH alone; these improvements are accompanied by a reduction in RV dilation on echocardiography.^{276–279} The greatest benefit is observed when treatment is initiated within 48 h of symptom onset, but thrombolysis can still be useful in patients who have had symptoms for 6–14 days.²⁸⁰ Unsuccessful thrombolysis, as judged by persistent clinical instability and unchanged RV dysfunction on echocardiography after 36 h, has been reported in 8% of high-risk PE patients.²⁸¹

A meta-analysis of thrombolysis trials that included (but were not confined to) patients with high-risk PE, defined mainly as the presence of cardiogenic shock, indicated a significant reduction in the combined outcome of mortality and recurrent PE (Supplementary Data Table 10). This was achieved with a 9.9% rate of severe bleeding and a 1.7% rate of intracranial haemorrhage.²⁸²

In normotensive patients with intermediate-risk PE, defined as the presence of RV dysfunction and elevated troponin levels, the impact of thrombolytic treatment was investigated in the Pulmonary Embolism Thrombolysis (PEITHO) trial.¹⁷⁹ Thrombolytic therapy was associated with a significant reduction in the risk of haemodynamic decompensation or collapse, but this was paralleled by an increased risk of severe extracranial and intracranial bleeding.¹⁷⁹ In the PEITHO trial, 30 day death rates were low in both treatment groups, although meta-analyses have suggested a reduction in PE-related and overall mortality of as much as 50–60% following thrombolytic treatment in the intermediate-risk category (Supplementary Data Table 10).^{282,283}

The approved regimens and doses of thrombolytic agents for PE, as well as the contraindications to this type of treatment, are shown in Table 10. Accelerated i.v. administration of recombinant tissue-type plasminogen activator (rtPA; 100 mg over 2 h) is preferable to prolonged infusions of first-generation thrombolytic agents (streptokinase and urokinase). Preliminary reports on the efficacy and safety of reduced-dose rtPA^{284,285} need confirmation by solid evidence before any recommendations can be made in this regard. UFH may be administered during continuous infusion of alteplase, but should be discontinued during infusion of streptokinase or urokinase.⁶⁵ Reteplase,²⁸⁶ desmoteplase,²⁸⁷ or tenecteplase^{179,278,279} have also been investigated; at present, none of these agents are approved for use in acute PE.

It remains unclear whether early thrombolysis for (intermediate- or high-risk) acute PE has an impact on clinical symptoms, functional

Table 10 Thrombolytic regimens, doses, and contraindications

Molecule	Regimen	Contraindications to fibrinolysis
rtPA	100 mg over 2 h 0.6 mg/kg over 15 min (maximum dose 50 mg) ^a	Absolute History of haemorrhagic stroke or stroke of unknown origin Ischaemic stroke in previous 6 months Central nervous system neoplasm Major trauma, surgery, or head injury in previous 3 weeks Bleeding diathesis Active bleeding Relative Transient ischaemic attack in previous 6 months Oral anticoagulation Pregnancy or first post-partum week Non-compressible puncture sites Traumatic resuscitation Refractory hypertension (systolic BP >180 mmHg) Advanced liver disease Infective endocarditis Active peptic ulcer
Streptokinase	250 000 IU as a loading dose over 30 min, followed by 100 000 IU/h over 12–24 h Accelerated regimen: 1.5 million IU over 2 h	
Urokinase	4400 IU/kg as a loading dose over 10 min, followed by 4400 IU/kg/h over 12–24 h	
	Accelerated regimen: 3 million IU over 2 h	

BP = blood pressure; IU = international units; rtPA, recombinant tissue-type plasminogen activator.

^aThis is the accelerated regimen for rtPA in pulmonary embolism; it is not officially approved, but it is sometimes used in extreme haemodynamic instability such as cardiac arrest.

limitation, or CTEPH at long-term follow-up. A small randomized trial of 83 patients suggested that thrombolysis might improve functional capacity at 3 months compared with anticoagulation alone.²⁷⁸ In the PEITHO trial,¹⁷⁹ mild persisting symptoms, mainly dyspnoea, were present in 33% of the patients at long-term (at 41.6 ± 15.7 months) clinical follow-up.²⁸⁸ However, the majority of patients (85% in the tenecteplase arm and 96% in the placebo arm) had a low or intermediate probability—based on the ESC Guidelines definition²⁸⁹—of persisting or new-onset PH at echocardiographic follow-up.²⁸⁸ Consequently, the findings of this study do not support a role for thrombolysis with the aim of preventing long-term sequelae (section 10) after intermediate-risk PE, although they are limited by the fact that clinical follow-up was available for only 62% of the study population.

6.3.2 Percutaneous catheter-directed treatment

Mechanical reperfusion is based on the insertion of a catheter into the pulmonary arteries via the femoral route. Different types of catheters (summarized in Supplementary Data Table 11) are used for mechanical fragmentation, thrombus aspiration, or more commonly a pharmacomechanical approach combining mechanical or ultrasound fragmentation of the thrombus with *in situ* reduced-dose thrombolysis.

Most knowledge about catheter-based embolectomy is derived from registries and pooled results from case series.^{290,291} The overall procedural success rates (defined as haemodynamic stabilization, correction of hypoxia, and survival to hospital discharge) of percutaneous catheter-based therapies reported in these studies have reached 87%;²⁹² however, these results may be subject to publication bias. One RCT compared conventional heparin-based

treatment and a catheter-based therapy combining ultrasound-based clot fragmentation with low-dose *in situ* thrombolysis in 59 patients with intermediate-risk PE. In that study, ultrasound-assisted thrombolysis was associated with a larger decrease in the RV/LV diameter ratio at 24 h, without an increased risk of bleeding.²⁹³ Data from two prospective cohort studies^{294,295} and a registry,²⁹⁶ with a total of 352 patients, support the improvement in RV function, lung perfusion, and PAP in patients with intermediate- or high-risk PE using this technique. Intracranial haemorrhage was rare, although the rate of Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) severe and moderate bleeding complications was 10% in one of these cohorts.²⁹⁴ These results should be interpreted with caution, considering the relatively small numbers of patients treated, the lack of studies directly comparing catheter-directed with systemic thrombolytic therapy, and the lack of data from RCTs on clinical efficacy outcomes.

6.3.3 Surgical embolectomy

Surgical embolectomy in acute PE is usually carried out with cardiopulmonary bypass, without aortic cross-clamping and cardioplegic cardiac arrest, followed by incision of the two main pulmonary arteries with the removal or suction of fresh clots. Recent reports have indicated favourable surgical results in high-risk PE, with or without cardiac arrest, and in selected cases of intermediate-risk PE.^{297–300} Among 174 322 patients hospitalized between 1999 and 2013 with a diagnosis of PE in New York state, survival and recurrence rates were compared between patients who underwent thrombolysis ($n = 1854$) or surgical embolectomy ($n = 257$) as first-line therapy.²⁹⁷ Overall, there

was no difference between the two types of reperfusion treatment regarding 30 day mortality (15 and 13%, respectively), but thrombolysis was associated with a higher risk of stroke and re-intervention at 30 days. No difference was found in terms of 5 year actuarial survival, but thrombolytic therapy was associated with a higher rate of recurrent PE requiring readmission compared with surgery (7.9 vs. 2.8%). However, the two treatments were not randomly allocated in this observational retrospective study, and the patients referred for surgery may have been selected. An analysis of the Society of Thoracic Surgery Database with multicentre data collection, including 214 patients submitted for surgical embolectomy for high- ($n = 38$) or intermediate-risk ($n = 176$) PE, revealed an in-hospital mortality rate of 12%, with the worst outcome (32%) in the group experiencing pre-operative cardiac arrest.²⁹⁹

Recent experience appears to support combining ECMO with surgical embolectomy, particularly in patients with high-risk PE with or without the need for cardiopulmonary resuscitation. Among patients who presented with intermediate-risk PE ($n = 28$), high-risk PE without cardiac arrest ($n = 18$), and PE with cardiac arrest ($n = 9$), the in-hospital and 1 year survival rates were 93 and 91%, respectively.³⁰⁰

6.4 Multidisciplinary pulmonary embolism teams

The concept of multidisciplinary rapid-response teams for the management of ‘severe’ (high-risk and selected cases of intermediate-risk) PE emerged in the USA, with increasing acceptance by the medical community and implementation in hospitals in Europe and worldwide. Set-up of PE response teams (PERTs) is encouraged, as they address the needs of modern systems-based healthcare.³⁰¹ A PERT brings together a team of specialists from different disciplines including, for example, cardiology, pulmonology, haematology, vascular medicine, anaesthesiology/intensive care, cardiothoracic surgery, and (interventional) radiology. The team convenes in real time (face-to-face or via web conference) to enhance clinical decision-making. This allows the formulation of a treatment plan and facilitates its immediate implementation.³⁰¹ The exact composition and operating mode of a PERT are not fixed, depending on the resources and expertise available in each hospital for the management of acute PE.

6.5 Vena cava filters

The aim of vena cava interruption is to mechanically prevent venous clots from reaching the pulmonary circulation. Most devices in current use are inserted percutaneously and can be retrieved after several weeks or months, or left in place over the long-term, if needed. Potential indications include VTE and absolute contraindication to anticoagulant treatment, recurrent PE despite adequate anticoagulation, and primary prophylaxis in patients with a high risk of VTE. Other potential indications for filter placement, including free-floating thrombi, have not been confirmed in patients without contraindications to therapeutic anticoagulation.

Only two phase III randomized trials have compared anticoagulation with or without vena cava interruption in patients with proximal DVT, with or without associated PE.^{302–304} In the Prevention of Recurrent Pulmonary Embolism by Vena Cava Interruption (PREPIC) study, insertion of a permanent vena cava

filter was associated with a significant reduction in the risk of recurrent PE and a significant increase in the risk of DVT, without a significant difference in the risk of recurrent VTE or death.^{303,304} The PREPIC-2 trial randomized 399 patients with PE and venous thrombosis to receive anticoagulant treatment, with or without a retrievable vena cava filter. In this study, the rate of recurrent VTE was low in both groups and did not differ between groups.³⁰² A systematic review and meta-analysis of published reports on the efficacy and safety of vena cava filters included 11 studies, with a total of 2055 patients who received a filter vs. 2149 controls.³⁰⁵ Vena cava filter placement was associated with a 50% decrease in the incidence of PE and an ~70% increase in the risk of DVT over time. Neither all-cause mortality nor PE-related mortality differed between patients with or without filter placement.

The broad indication for placement of a venous filter in patients with recent (<1 month) proximal DVT and an absolute contraindication to anticoagulant treatment is based mainly on the perceived high risk of recurrent PE in this setting, and the lack of other treatment options.

Complications associated with vena cava filters are common and can be serious. A systematic literature review revealed penetration of the venous wall in 1699 (19%) of 9002 procedures; of these cases, 19% showed adjacent organ involvement and ≥8% were symptomatic.³⁰⁶ Lethal complications were rare (only two cases), but 5% of the patients required major interventions such as surgical removal of the filter, endovascular stent placement or embolization, endovascu-

6.6 Recommendations for acute-phase treatment of high-risk pulmonary embolism^a

Recommendations	Class ^b	Level ^c
It is recommended that anticoagulation with UFH, including a weight-adjusted bolus injection, be initiated without delay in patients with high-risk PE.	I	C
Systemic thrombolytic therapy is recommended for high-risk PE. ²⁸²	I	B
Surgical pulmonary embolectomy is recommended for patients with high-risk PE, in whom thrombolysis is contraindicated or has failed. ^{d 281}	I	C
Percutaneous catheter-directed treatment should be considered for patients with high-risk PE, in whom thrombolysis is contraindicated or has failed. ^d	IIa	C
Norepinephrine and/or dobutamine should be considered in patients with high-risk PE.	IIa	C
ECMO may be considered, in combination with surgical embolectomy or catheter-directed treatment, in patients with PE and refractory circulatory collapse or cardiac arrest. ^{d 252}	IIIb	C

ECMO = extracorporeal membrane oxygenation; PE = pulmonary embolism; UFH = unfractionated heparin.
^aSee Table 4 for definition of high-risk PE. After haemodynamic stabilization of the patient, continue with anticoagulation treatment as in intermediate- or low-risk PE (section 6.7).
^bClass of recommendation.
^cLevel of evidence.
^dIf appropriate expertise and resources are available on-site.

6.7 Recommendations for acute-phase treatment of intermediate- or low-risk pulmonary embolism

Recommendations	Class ^a	Level ^b
Initiation of anticoagulation		
Initiation of anticoagulation is recommended without delay in patients with high or intermediate clinical probability of PE, ^c while diagnostic workup is in progress.	I	C
If anticoagulation is initiated parenterally, LMWH or fondaparinux is recommended (over UFH) for most patients. ^{262,309–311}	I	A
When oral anticoagulation is started in a patient with PE who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a VKA. ^{260,261,312–314}	I	A
When patients are treated with a VKA, overlapping with parenteral anticoagulation is recommended until an INR of 2.5 (range 2.0–3.0) is reached. ^{315,316}	I	A
NOACs are not recommended in patients with severe renal impairment, ^d during pregnancy and lactation, and in patients with antiphospholipid antibody syndrome. ^{260,261,312–314}	III	C
Reperfusion treatment		
Rescue thrombolytic therapy is recommended for patients with haemodynamic deterioration on anticoagulation treatment. ²⁸²	I	B
As an alternative to rescue thrombolytic therapy, surgical embolectomy ^e or percutaneous catheter-directed treatment ^e should be considered for patients with haemodynamic deterioration on anticoagulation treatment.	IIa	C
Routine use of primary systemic thrombolysis is not recommended in patients with intermediate- or low-risk PE. ^{c,f 179}	III	B

CrCl = creatinine clearance; INR = international normalized ratio; LMWH = low-molecular weight heparin; NOAC(s) = non-vitamin K antagonist oral anticoagulant(s); PE = pulmonary embolism; UFH = unfractionated heparin; VKA = vitamin K antagonist.

^aClass of recommendation.

^bLevel of evidence.

^cSee Table 8 for definition of the PE severity and PE-related risk.

^dDabigatran is not recommended in patients with CrCl <30 mL/min. Edoxaban should be given at a dose of 30 mg once daily in patients with CrCl of 15–50 mL/min and is not recommended in patients with CrCl <15 mL/min. Rivaroxaban and apixaban are to be used with caution in patients with CrCl 15–29 mL/min, and their use is not recommended in patients with CrCl <15 mL/min.

^eIf appropriate expertise and resources are available on-site.

^fThe risk-to-benefit ratios of surgical embolectomy or catheter-directed procedures have not yet been established in intermediate- or low-risk PE.

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6.8 Recommendations for multidisciplinary pulmonary embolism teams

Recommendation	Class ^a	Level ^b
Set-up of a multidisciplinary team and a programme for the management of high- and (in selected cases) intermediate-risk PE should be considered, depending on the resources and expertise available in each hospital.	IIa	C

PE = pulmonary embolism.

^aClass of recommendation.

^bLevel of evidence.

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6.9 Recommendations for inferior vena cava filters

Recommendations	Class ^a	Level ^b
IVC filters should be considered in patients with acute PE and absolute contraindications to anticoagulation.	IIa	C
IVC filters should be considered in cases of PE recurrence despite therapeutic anticoagulation.	IIa	C
Routine use of IVC filters is not recommended. ^{302–304}	III	A

IVC = inferior vena cava; PE = pulmonary embolism.

^aClass of recommendation.

^bLevel of evidence.

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6.10 Recommendations for early discharge and home treatment

Recommendation	Class ^a	Level ^b
Carefully selected patients with low-risk PE should be considered for early discharge and continuation of treatment at home, if proper outpatient care and anticoagulant treatment can be provided. ^{c 178,206,317–319}	IIa	A

PE = pulmonary embolism.

^aClass of recommendation.

^bLevel of evidence.

^cSee section 7 and Figure 6 for further guidance on defining low-risk PE and decision-making.

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lar retrieval of the permanent filter, or percutaneous nephrostomy or ureteral stent placement.³⁰⁶ Further reported complications include filter fracture and/or embolization, and DVT occasionally extending up to the vena cava.^{303,307,308}

7 Integrated risk-adapted diagnosis and management

7.1 Diagnostic strategies

Various combinations of clinical assessments, plasma D-dimer measurements, and imaging tests have been proposed and validated for PE

diagnosis. These strategies have been tested in patients presenting with suspected PE in the emergency department or during their hospital stay,^{101,164,171,320} and more recently in the primary care setting.¹¹¹ Withholding of anticoagulation without adherence to evidence-based diagnostic strategies was associated with a significant increase in the number of VTE episodes and sudden cardiac death at 3 month follow-up.¹² The most straightforward diagnostic algorithms for suspected PE—with and without haemodynamic instability—are presented in Figures 4 and 5, respectively. However, it is recognized that the diagnostic approach for suspected PE may vary, depending on the availability of, and expertise in, specific tests in various hospitals and clinical settings.

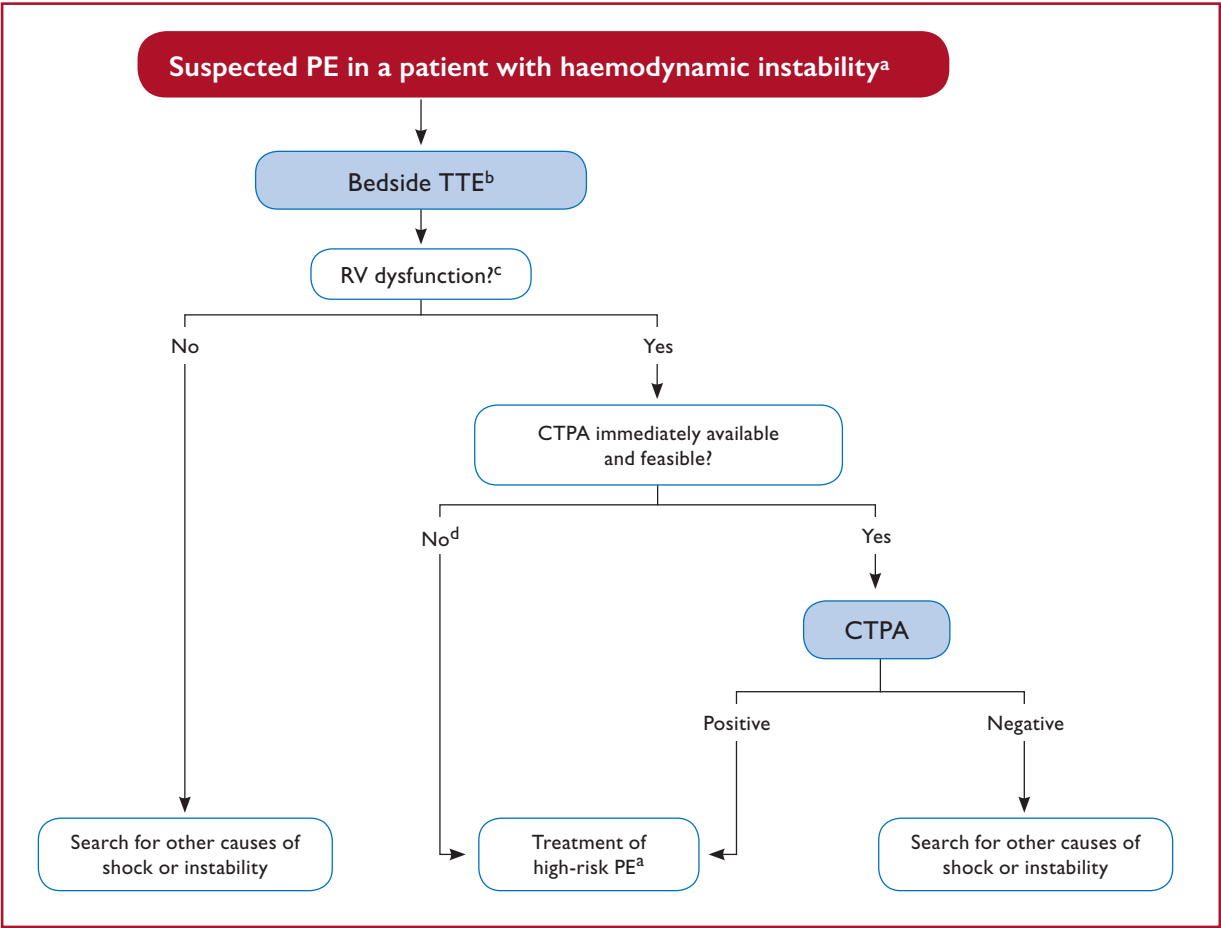
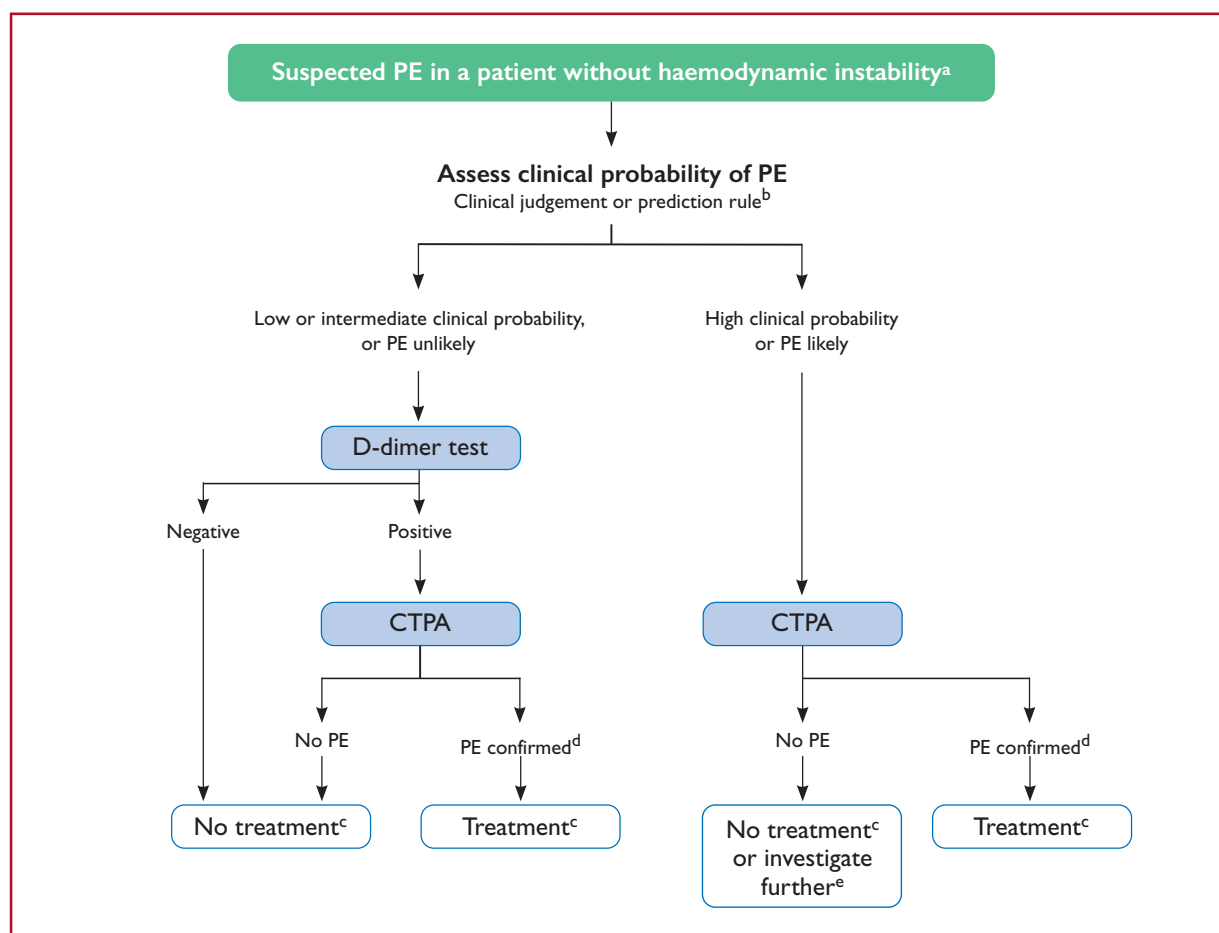


Figure 4 Diagnostic algorithm for patients with suspected high-risk pulmonary embolism presenting with haemodynamic instability. CTPA = computed tomography pulmonary angiography; CUS = compression ultrasonography; DVT = deep vein thrombosis; LV = left ventricle; PE = pulmonary embolism; RV = right ventricle; TOE = transoesophageal echocardiography; TTE = transthoracic echocardiogram. ^aSee Table 4 for definition of haemodynamic instability and high-risk PE. ^bAncillary bedside imaging tests may include TOE, which may detect emboli in the pulmonary artery and its main branches; and bilateral venous CUS, which may confirm DVT and thus VTE. ^cIn the emergency situation of suspected high-risk PE, this refers mainly to a RV/LV diameter ratio >1.0; the echocardiographic findings of RV dysfunction, and the corresponding cut-off levels, are graphically presented in Figure 3, and their prognostic value summarized in Supplementary Data Table 3. ^dIncludes the cases in which the patient’s condition is so critical that it only allows bedside diagnostic tests. In such cases, echocardiographic findings of RV dysfunction confirm high-risk PE and emergency reperfusion therapy is recommended



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Figure 5 Diagnostic algorithm for patients with suspected pulmonary embolism without haemodynamic instability.

CTPA = computed tomography pulmonary angiography/angiogram; PE = pulmonary embolism.

^aThe proposed diagnostic strategy for pregnant women with suspected acute PE is discussed in section 9.

^bTwo alternative classification schemes may be used for clinical probability assessment, i.e. a three-level scheme (clinical probability defined as low, intermediate, or high) or a two-level scheme (PE unlikely or PE likely). When using a moderately sensitive assay, D-dimer measurement should be restricted to patients with low clinical probability or a PE-unlikely classification, while highly sensitive assays may also be used in patients with intermediate clinical probability of PE due to a higher sensitivity and negative predictive value. Note that plasma D-dimer measurement is of limited use in suspected PE occurring in hospitalized patients.

^cTreatment refers to anticoagulation treatment for PE.

^dCTPA is considered diagnostic of PE if it shows PE at the segmental or more proximal level.

^eIn case of a negative CTPA in patients with high clinical probability, investigation by further imaging tests may be considered before withholding PE-specific treatment.

The diagnostic strategy for suspected acute PE in pregnancy is discussed in section 9.

7.1.1 Suspected pulmonary embolism with haemodynamic instability

The proposed strategy is shown in Figure 4. The clinical probability is usually high and the differential diagnosis includes cardiac tamponade, acute coronary syndrome, aortic dissection, acute valvular dysfunction, and hypovolaemia. The most useful initial test in this situation is bedside TTE, which will yield evidence of acute RV dysfunction if acute PE is the cause of the patient's haemodynamic decompensation. In a highly unstable patient, echocardiographic evidence of RV dysfunction is sufficient to prompt immediate reperfusion without further testing. This decision may be strengthened by

the (rare) visualization of right heart thrombi.^{155,157,321,322} Ancillary bedside imaging tests include TOE, which may allow direct visualization of thrombi in the pulmonary artery and its main branches, especially in patients with RV dysfunction. TOE should be cautiously performed in hypoxaemic patients. Moreover, bedside CUS can detect proximal DVT. As soon as the patient is stabilized using supportive treatment, final confirmation of the diagnosis by CT angiography should be sought.

For unstable patients admitted directly to the catheterization laboratory with suspected acute coronary syndrome, pulmonary angiography may be considered as a diagnostic procedure after the acute coronary syndrome has been excluded, provided that PE is a probable diagnostic alternative and particularly if percutaneous catheter-directed treatment is a therapeutic option.

7.1.2 Suspected pulmonary embolism without haemodynamic instability

7.1.2.1 Strategy based on computed tomographic pulmonary angiography

The proposed strategy based on CTPA is shown in *Figure 5*. In patients admitted to the emergency department, measurement of plasma D-dimer is the logical first step following the assessment of clinical probability and allows PE to be ruled out in ~30% of outpatients. D-dimer should not be measured in patients with a high clinical probability of PE, owing to a low negative predictive value in this population.³²³ It is also less useful in hospitalized patients because the number that needs to be tested to obtain a clinically relevant negative result is high.

In most centres, multidetector CTPA is the second-line test in patients with an elevated D-dimer level and the first-line test in patients with a high clinical probability of PE. CTPA is considered to be diagnostic of PE when it shows a clot at least at the segmental level of the pulmonary arterial tree. False-negative results of CTPA have been reported in patients with a high clinical probability of PE;¹¹⁵ however, such discrepancies are infrequent and the 3 month thromboembolic risk was low in these patients.¹⁷¹ Accordingly, both the necessity of performing further tests and the nature of these tests remain controversial in these clinical situations.

7.1.2.2 Strategy based on ventilation/perfusion scintigraphy

In hospitals in which V/Q scintigraphy is readily available, it is a valid option for patients with an elevated D-dimer and a contraindication to CTPA. Also, V/Q scintigraphy may be preferred over CTPA to avoid unnecessary radiation, particularly in younger patients and in female patients in whom thoracic CT might raise the lifetime risk of breast cancer.³²⁴ V/Q lung scintigraphy is diagnostic (with either normal- or high-probability findings) in ~30–50% of emergency ward patients with suspected PE.^{75,122,134,325} The proportion of diagnostic V/Q scans is higher in patients with a normal chest X-ray, and this might support the use of a V/Q scan as a first-line imaging test for PE in younger patients, depending on local availability.³²⁶ The number of patients with inconclusive findings may further be reduced by taking into account clinical probability. Thus, patients with a non-diagnostic lung scan and low clinical probability of PE have a low prevalence of confirmed PE,^{124,325} and the negative predictive value of this combination is further increased by the absence of a DVT on lower-limb CUS. If a high-probability lung scan is obtained from a patient with low clinical probability of PE, confirmation by other tests should be considered.

7.2 Treatment strategies

7.2.1 Emergency treatment of high-risk pulmonary embolism

The algorithm for a risk-adjusted therapeutic approach to acute PE is shown in *Figure 6*; an emergency management algorithm specifically for patients with suspected acute high-risk PE is proposed in Supplementary Data *Figure 1*. Primary reperfusion treatment, in most cases systemic thrombolysis, is the treatment of choice for patients with high-risk PE. Surgical pulmonary embolectomy or percutaneous catheter-directed treatment are alternative reperfusion options in patients with contraindications to thrombolysis, if expertise with either of these methods and the appropriate resources are available on-site.

Following reperfusion treatment and haemodynamic stabilization, patients recovering from high-risk PE can be switched from

parenteral to oral anticoagulation. As patients belonging to this risk category were excluded from the phase III NOAC trials, the optimal time point for this transition has not been determined by existing evidence but should instead be based on clinical judgement. The specifications concerning the higher initial dose of apixaban or rivaroxaban (for 1 and 3 weeks after PE diagnosis, respectively), or the minimum overall period (5 days) of heparin anticoagulation before switching to dabigatran or edoxaban, must be followed (see Supplementary Data *Table 8* for tested and approved regimens).

7.2.2 Treatment of intermediate-risk pulmonary embolism

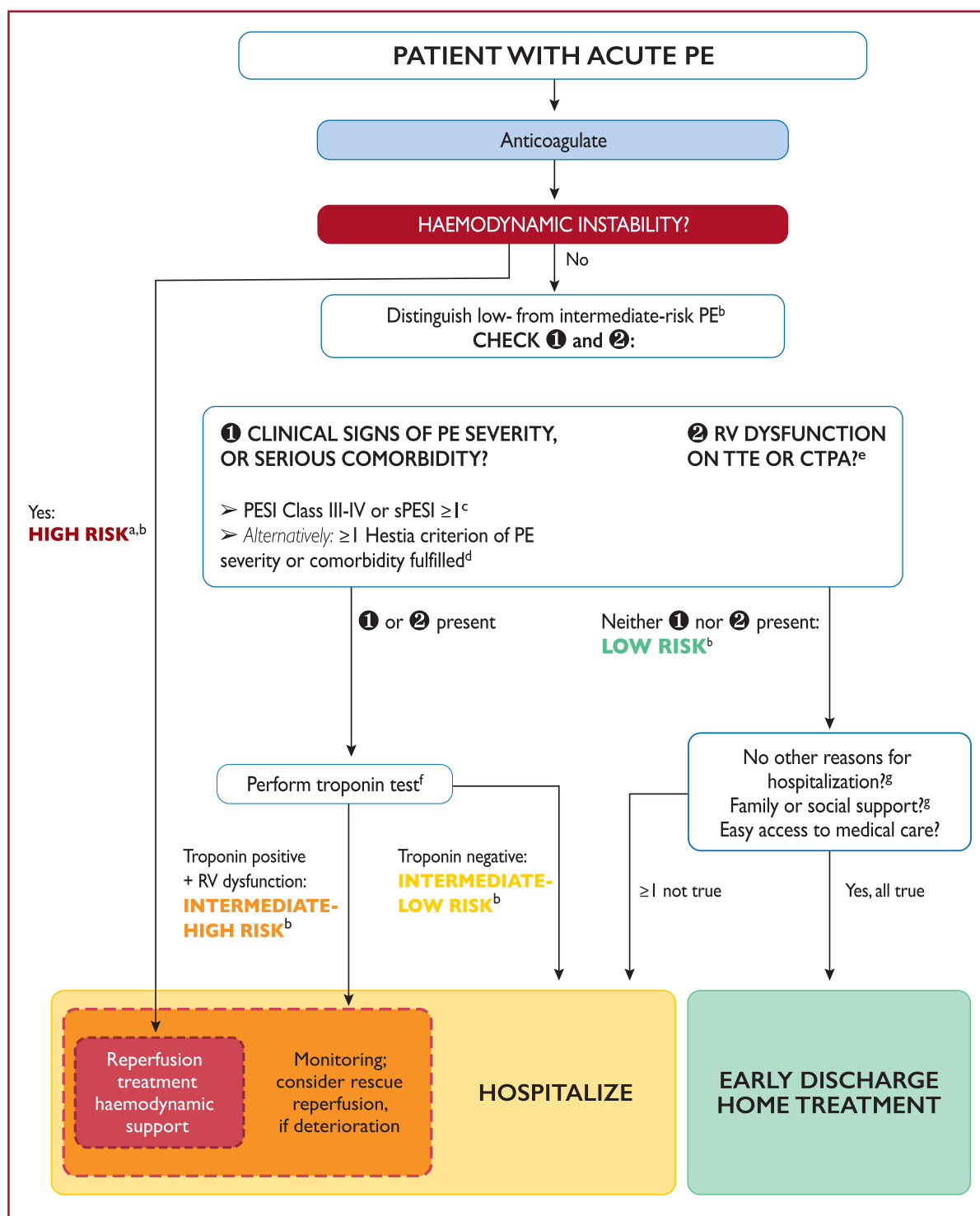
For most cases of acute PE without haemodynamic compromise, parenteral or oral anticoagulation (without reperfusion techniques) is adequate treatment. As shown in *Figure 6*, normotensive patients with at least one indicator of elevated PE-related risk, or with aggravating conditions or comorbidity, should be hospitalized. In this group, patients with signs of RV dysfunction on echocardiography or CTPA (graphically presented in *Figure 3*), accompanied by a positive troponin test, should be monitored over the first hours or days due to the risk of early haemodynamic decompensation and circulatory collapse.¹⁷⁹ Routine primary reperfusion treatment, notably full-dose systemic thrombolysis, is not recommended, as the risk of potentially life-threatening bleeding complications appears too high for the expected benefits from this treatment.¹⁷⁹ Rescue thrombolytic therapy or, alternatively, surgical embolectomy or percutaneous catheter-directed treatment should be reserved for patients who develop signs of haemodynamic instability. In the PEITHO trial, the mean time between randomization and death or haemodynamic decompensation was 1.79 ± 1.60 days in the placebo (heparin-only) arm.¹⁷⁹ Therefore, it appears reasonable to leave patients with intermediate-high-risk PE on LMWH anticoagulation over the first 2–3 days and ensure that they remain stable before switching to oral anticoagulation. As mentioned in the previous section, the specifications concerning the increased initial dose of apixaban or rivaroxaban, or the minimum overall period of heparin anticoagulation before switching to dabigatran or edoxaban, must be followed.

Suggestions for the anticoagulation and overall management of acute PE in specific clinical situations, for which conclusive evidence is lacking, are presented in Supplementary Data *Table 9*.

7.2.3 Management of low-risk pulmonary embolism: triage for early discharge and home treatment

As a general rule, early discharge of a patient with acute PE and continuation of anticoagulant treatment at home should be considered if three sets of criteria are fulfilled: (i) the risk of early PE-related death or serious complications is low (*section 5*); (ii) there is no serious comorbidity or aggravating condition(s) (see *section 5*) that would mandate hospitalization; and (iii) proper outpatient care and anticoagulant treatment can be provided, considering the patient's (anticipated) compliance, and the possibilities offered by the healthcare system and social infrastructure.

Randomized trials and prospective management cohort studies that investigated the feasibility and safety of early discharge, and home treatment, of PE adhered to these principles, even though



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Figure 6 Central Illustration. Risk-adjusted management strategy for acute pulmonary embolism.

CTPA = computed tomography pulmonary angiography/angiogram; PE = pulmonary embolism; PESI = Pulmonary Embolism Severity Index; RV = right ventricular; sPESI = simplified Pulmonary Embolism Severity Index; TTE = transthoracic echocardiogram.

^aSee also emergency management algorithm shown in the online Supplementary Data.

^bRefer to Table 8 for definition of high, intermediate-high-, intermediate-low-, and low-risk PE.

^cCancer, heart failure and chronic lung disease are included in the PESI and sPESI (Table 7).

^dSee Supplementary Data Table 12 for the Hestia criteria.

^ePrognostically relevant imaging (TTE or CTPA) findings in patients with acute PE, are graphically presented in Figure 3.

^fA cardiac troponin test may already have been performed during initial diagnostic work-up.

^gIncluded in the Hestia criteria.

slightly different criteria or combinations thereof were used to ensure the above three requirements.

The Hestia exclusion criteria (Supplementary Data Table 12) represent a checklist of clinical parameters or questions that can be obtained/answered at the bedside. They integrate aspects of PE severity, comorbidity, and the feasibility of home treatment. If the answer to one or more of the questions is 'yes', then the patient cannot be discharged early. In a single-arm management trial that used these criteria to select candidates for home treatment, the 3 month rate of recurrent VTE was 2.0% (0.8–4.3%) in patients with acute PE who were discharged within 24 h.³¹⁷ In a subsequent non-inferiority trial that randomized 550 patients to direct discharge based on the Hestia criteria alone vs. additional NT-proBNP testing and discharge if levels were ≤ 500 pg/mL, the primary outcome (30 day PE- or bleeding-related mortality, cardiopulmonary resuscitation, or admission to an intensive care unit) was very low in both arms. The results suggest no incremental value of natriuretic-peptide testing in patients who are eligible for home treatment based on the Hestia criteria, although the study was not powered to exclude this possibility.³¹⁸

The PESI and its simplified form, the sPESI (Table 7), also integrate clinical parameters of PE severity and comorbidity to permit assessment of overall 30 day mortality. Compared with the Hestia criteria, the PESI is more standardized, but it contains a less-comprehensive list of aggravating conditions; moreover, the sPESI excludes all patients with cancer from the low-risk category (compare Table 7 with Supplementary Data Table 12). The PESI was not primarily developed as a tool to select candidates for home treatment, but it has been used—in combination with additional feasibility criteria—in a trial of 344 patients randomized to inpatient vs. outpatient treatment of PE.¹⁷⁸ One (0.6%) patient in each treatment group died within 90 days.¹⁷⁸

In patients who were included in prospective cohort studies and treated at home, with or without a short hospitalization period, the 3 month rates of thromboembolic recurrence, major bleeding, and death were 1.75, 1.43, and 2.83%, respectively.³²⁷

In summary, the currently available evidence indicates that both the Hestia rule and the PESI or sPESI appear capable of reliably identifying patients who are (i) at low PE-related risk, and (ii) free of serious comorbidity. Consequently, either may be used for clinical triage according to local experience and preference. If a PESI- or sPESI-based approach is chosen, it must be combined with assessment of the feasibility of early discharge and home treatment; this assessment is already integrated into the Hestia criteria.

A more difficult decision related to immediate or early discharge is whether the exclusion of intermediate-risk PE on clinical grounds alone is adequate, or whether the assessment of RV dysfunction or myocardial injury (see section 5) by an imaging test or a laboratory biomarker is necessary to provide maximal safety for the patient in this 'vulnerable' early period. A systematic review and meta-analysis of cohort studies suggested that the prognostic sensitivity is increased further when clinical criteria (e.g. PESI or sPESI) are combined with imaging findings, or laboratory biomarker levels.²³⁴ A multicentre prospective management trial tested this hypothesis, investigating the efficacy and safety of early discharge, and ambulatory rivaroxaban treatment, in patients selected by clinical criteria and an absence of RV dysfunction.

Overall, ~20% of the screened unselected patients with PE were included. At the predefined interim analysis of 525 patients (50% of the planned population), the 3 month rate of symptomatic or fatal recurrent VTE was 0.6% (one-sided upper 99.6% CI 2.1%), permitting the early rejection of the null hypothesis and termination of the trial. Major bleeding occurred in six (1.2%) of the patients in the safety population. There were no PE-related deaths.³¹⁹ In view of the existing evidence—and taking into consideration (i) the catastrophic scenario of early death if a patient with acute PE is falsely judged to be at low risk on clinical grounds alone and discharged 'too early' (as described in a prematurely terminated trial³²⁸), and (ii) the ease and minimal additional effort of assessing RV size and function at presentation by echocardiography, or on the CTPA performed to diagnose the PE event itself³²⁹ (section 5)—it is wise to exclude RV dysfunction and right heart thrombi if immediate or early (within the first 24–48 h) discharge of the patient is planned.

8 Chronic treatment and prevention of recurrence

The aim of anticoagulation after acute PE is to complete the treatment of the acute episode and prevent recurrence of VTE over the long-term. Current drugs and regimens for the initial phase, and the first months of anticoagulant treatment, are described in section 6.

Most of the randomized studies focusing on long-term anticoagulation for VTE have included patients with DVT, with or without PE; only two randomized studies have specifically focused on patients with PE.^{330,331} The incidence of recurrent VTE does not appear to depend on the clinical manifestation of the first event (i.e. it is similar after PE and after proximal DVT). However, in patients who have had a PE, VTE more frequently recurs as PE, while in patients who have had a DVT, it tends to recur more frequently as DVT.³³² As a consequence, the case fatality rate of recurrent VTE in patients who have previously had a PE is twice as high as that of VTE recurrence after DVT.^{333,334}

Landmark clinical trials have evaluated various durations of anticoagulant treatment with VKAs for VTE.^{330,331,335–337} The findings of these studies permit the following conclusions. First, all patients with PE should receive ≥ 3 months of anticoagulant treatment. Second, after withdrawal of anticoagulant treatment, the risk of recurrence is expected to be similar if anticoagulants are stopped after 3–6 months compared with longer treatment periods (e.g. 12–24 months). Third, extended oral anticoagulant treatment reduces the risk for recurrent VTE by $\leq 90\%$, but this benefit is partially offset by the risk of bleeding.

Oral anticoagulants are highly effective in preventing recurrent VTE during treatment, but they do not eliminate the risk of subsequent recurrence after the discontinuation of treatment.^{330,331} Based on this fact on the one hand, and considering the bleeding risk of anticoagulation treatment on the other, the clinically important question is how to best select candidates for extended or indefinite anticoagulation. Involvement of the patient in the decision-making process is crucial to optimize and maintain treatment adherence.

Table 11 Categorization of risk factors for venous thromboembolism based on the risk of recurrence over the long-term

Estimated risk for long-term recurrence ^a	Risk factor category for index PE ^b	Examples ^b
Low (<3% per year)	Major transient or reversible factors associated with >10-fold increased risk for the index VTE event (compared to patients without the risk factor)	• Surgery with general anaesthesia for >30 min • Confined to bed in hospital (only “bathroom privileges”) for ≥3 days due to an acute illness, or acute exacerbation of a chronic illness • Trauma with fractures
Intermediate (3–8% per year)	Transient or reversible factors associated with ≤10-fold increased risk for first (index) VTE	• Minor surgery (general anaesthesia for <30 min) • Admission to hospital for <3 days with an acute illness • Oestrogen therapy/contraception • Pregnancy or puerperium • Confined to bed out of hospital for ≥3 days with an acute illness • Leg injury (without fracture) associated with reduced mobility for ≥3 days • Long-haul flight
	Non-malignant persistent risk factors	• Inflammatory bowel disease • Active autoimmune disease
	No identifiable risk factor	
High (>8% per year)		• Active cancer • One or more previous episodes of VTE in the absence of a major transient or reversible factor • Antiphospholipid antibody syndrome

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PE = pulmonary embolism; VTE = venous thromboembolism.

^aIf anticoagulation is discontinued after the first 3 months (based on data from Baglin et al.³⁴⁰ and Iorio et al.³⁴¹).^bThe categorization of risk factors for the index VTE event is in line with that proposed by the International Society on Thrombosis and Haemostasis.³³⁸ The present Guidelines avoid terms such as ‘provoked’, ‘unprovoked’, or ‘idiopathic’ VTE.

8.1 Assessment of venous thromboembolism recurrence risk

The risk for recurrent VTE after discontinuation of treatment is related to the features of the index PE (or, in the broader sense, VTE) event. A study, which followed patients after a first episode of acute PE, found that the recurrence rate after discontinuation of treatment was ~2.5% per year after PE associated with transient risk factors, compared with 4.5% per year after PE occurring in the absence of known cancer, known thrombophilia, or any transient risk factor.³³¹ Similar observations were made in other prospective studies in patients with DVT.³³⁷ Advancing the concept further, randomized anticoagulation trials over the past 15 years, which have focused on secondary VTE prevention, have classified patients into distinct groups based on their risk of VTE recurrence after discontinuation of anticoagulant treatment. In general, these groups are: (i) patients in whom a strong (major) transient or reversible risk factor, most commonly major surgery or trauma, can be identified as being responsible for the acute (index) episode; (ii) patients in whom the index episode might be partly explained by the presence of a weak (minor) transient or reversible risk factor, or if a non-malignant risk factor for thrombosis persists; (iii) patients in whom the index episode occurred in the

absence of any identifiable risk factor (the present Guidelines avoid terms such as ‘unprovoked’ or ‘idiopathic’ VTE); (iv) patients with one or more previous episodes of VTE, and those with a major persistent pro-thrombotic condition such as antiphospholipid antibody syndrome; and (v) patients with active cancer.³³⁸

Table 11 shows examples of transient/reversible and persistent risk factors for VTE, classified by the risk of long-term recurrence. As active cancer is a major risk factor for recurrence of VTE, but also for bleeding while on anticoagulant treatment,³³⁹ section 8.4 is specifically dedicated to the management of PE in patients with cancer.

Overall, assessment of the VTE recurrence risk after acute PE, in the absence of a major transient or reversible risk factor, is a complex issue. Beyond the examples listed in Table 11, patients who are carriers of some forms of hereditary thrombophilia, notably those with confirmed deficiency of antithrombin, protein C, or protein S, and patients with homozygous factor V Leiden or homozygous prothrombin G20210A mutation, are often candidates for indefinite anticoagulant treatment after a first episode of PE occurring in the absence of a major reversible risk factor. In view of these possible implications, testing for thrombophilia (including antiphospholipid

antibodies and lupus anticoagulant)³⁴² may be considered in patients in whom VTE occurs at a young age (e.g. aged <50 years) and in the absence of an otherwise identifiable risk factor, especially when this occurs against the background of a strong family history of VTE. In such cases, testing may help to tailor the regimen and dose of the anticoagulant agent over the long-term. On the other hand, no evidence of a clinical benefit of extended anticoagulant treatment is currently available for carriers of heterozygous factor V Leiden or prothrombin 20210A mutation.

A number of risk prediction models have been developed for the assessment of the risk of recurrence in an individual patient (Supplementary Data Table 13).^{343,344} The clinical value and, in particular, the possible therapeutic implications of these models in the NOAC era are unclear.

8.2 Anticoagulant-related bleeding risk

Incidence estimates from cohort studies conducted more than 15 years ago reported an ~3% annual incidence of major bleeding in patients treated with VKAs.³⁴⁵ Meta-analyses of phase III studies focusing on the first 3–12 months of anticoagulant treatment showed an ~40% reduction in the risk for major bleeding with NOACs compared with VKAs.³⁴⁶ The risk of major bleeding is higher in the first month of anticoagulant treatment, and then declines and remains stable over time. Based on currently available evidence, risk factors include: (i) advanced age (particularly >75 years); (ii) previous bleeding (if not associated with a reversible or treatable cause) or anaemia; (iii) active cancer; (iv) previous stroke, either haemorrhagic or ischaemic; (v) chronic renal or hepatic disease; (vi) concomitant antiplatelet therapy or non-steroidal anti-inflammatory drugs (to be avoided, if possible); (vii) other serious acute or chronic illness; and (viii) poor anticoagulation control.

Existing bleeding risk scores and their current validation status are reviewed in Supplementary Data Table 14. The patient's bleeding risk should be assessed, either by implicit judgement after evaluating individual risk factors or by the use of a bleeding risk score, at the time of initiation of anticoagulant treatment. It should be reassessed periodically (e.g. once a year in patients at low risk, and every 3 or 6 months in patients at high risk for bleeding). Bleeding risk assessment should be used to identify and treat modifiable bleeding risk factors, and it may influence decision-making on the duration and regimen/dose of anticoagulant treatment after acute PE.

8.3 Regimens and treatment durations with non-vitamin K antagonist oral anti-coagulants, and with other non-vitamin K antagonist antithrombotic drugs

All patients with PE should be treated with anticoagulants for ≥3 months.³⁴⁷ Beyond this period, the balance between the risk of VTE recurrence and that of bleeding, which has been used to select candidates for extended anticoagulation after a first VTE event in the VKA era, is currently being revisited based on the lower bleeding rates with NOACs. However, despite the improved safety of these drugs compared with VKAs, treatment

with NOACs is not without risk. Phase III clinical trials on the extended treatment of VTE have shown that the rate of major bleeding may be ~1%, and that of clinically relevant non-major (CRNM) bleeding as high as 6%. Bleeding rates may be higher in everyday clinical practice.^{348,349}

The NOAC trials that focused on extended VTE treatment are summarized in Supplementary Data Table 15. In all studies, patients with PE made up approximately one-third of the entire study population, while the remaining two-thirds were patients with proximal DVT but no clinically overt PE. Patients needed to have completed the initial and long-term anticoagulation phase to be included in the extended studies.

Dabigatran was compared with warfarin or placebo in two different studies (Supplementary Data Table 15).³⁵⁰ In these studies, dabigatran was non-inferior to warfarin for the prevention of confirmed recurrent symptomatic VTE or VTE-related death, and more effective than placebo for the prevention of symptomatic recurrent VTE or unexplained death.³⁵⁰ The rate of major bleeding was 0.9% with dabigatran compared to 1.8% with warfarin (HR 0.52, 95% CI 0.27–1.02).³⁵⁰

Rivaroxaban was compared with placebo or aspirin in two different studies in patients who had completed 6–12 months of anticoagulation treatment for a first VTE event (Supplementary Data Table 15). Treatment with rivaroxaban [20 mg once a day (o.d.)] reduced recurrent VTE by ~80%, with a 6.0% incidence of major or CRNM bleeding as compared to 1.2% with placebo.³⁵¹ Rivaroxaban given at a dose of 20 or 10 mg o.d. was compared with aspirin (100 mg o.d.) in 3365 patients.³⁵² Both doses of rivaroxaban reduced symptomatic recurrent fatal or non-fatal VTE by ~70% in comparison with aspirin. No significant differences in the rates of major or CRNM bleeding were shown between either dose of rivaroxaban and aspirin.³⁵²

Patients with VTE were randomized to receive two different doses of apixaban [2.5 or 5 mg twice a day (bis in die: b.i.d.)] or placebo after 6–12 months of initial anticoagulation (Supplementary Data Table 15).³⁵³ Both doses of apixaban reduced the incidence of symptomatic recurrent VTE or death from any cause compared with placebo, with no safety concerns.³⁵³

Patients at high bleeding risk—based on the investigator's judgement, the patient's medical history, and the results of laboratory examinations—were excluded from the extension studies mentioned above; this was also the case for studies on extended anticoagulation with VKAs.^{330,331} This fact should be taken into account during triage of a patient for extended anticoagulation with one of the above regimens.

In a randomized, open-label study in high-risk patients with antiphospholipid syndrome (testing triple positive for lupus anticoagulant, anticardiolipin, and anti-β2-glycoprotein I), rivaroxaban was associated with an increased rate of thromboembolic and major bleeding events compared with warfarin (HR for the composite primary outcome 6.7; 95% CI 1.5–30.5).³⁵⁴ At present, NOACs are not an alternative to VKAs for patients with antiphospholipid syndrome.

In two trials with a total of 1224 patients, extended therapy with aspirin (after termination of standard oral anticoagulation) was

associated with a 30–35% reduction in the risk of recurrence compared with placebo (Supplementary Data Table 15).^{355,356} However, more recently, another trial demonstrated the superiority of anticoagulation with rivaroxaban, either 20 or 10 mg o.d., over aspirin for secondary prophylaxis of VTE recurrence.³⁵²

A randomized, placebo controlled study evaluated sulodexide (2 × 250 lipasemic unit capsules b.i.d.) for the prevention of recurrence

in 615 patients with a first VTE event without an identifiable risk factor, who had completed 3–12 months of oral anticoagulant treatment (Supplementary Data Table 15).³⁵⁷ Sulodexide reduced the risk of recurrence by ~50% with no apparent increase in bleeding events. However, only 8% of patients in this study had PE as the index VTE event.³⁵⁷

8.4 Recommendations for the regimen and duration of anticoagulation after pulmonary embolism in patients without cancer

Recommendations	Class ^a	Level ^b
Therapeutic anticoagulation for ≥ 3 months is recommended for all patients with PE. ³⁴⁷	I	A
Patients in whom discontinuation of anticoagulation after 3 months is recommended		
For patients with first PE/VTE secondary to a major transient/reversible risk factor, discontinuation of therapeutic oral anticoagulation is recommended after 3 months. ^{331,340,341}	I	B
Patients in whom extension of anticoagulation beyond 3 months is recommended		
Oral anticoagulant treatment of indefinite duration is recommended for patients presenting with recurrent VTE (that is, with at least one previous episode of PE or DVT) not related to a major transient or reversible risk factor. ³⁵⁸	I	B
Oral anticoagulant treatment with a VKA for an indefinite period is recommended for patients with antiphospholipid antibody syndrome. ³⁵⁹	I	B
Patients in whom extension of anticoagulation beyond 3 months should be considered^{c,d}		
Extended oral anticoagulation of indefinite duration should be considered for patients with a first episode of PE and no identifiable risk factor. ^{330,331,347,351–353}	IIa	A
Extended oral anticoagulation of indefinite duration should be considered for patients with a first episode of PE associated with a persistent risk factor other than antiphospholipid antibody syndrome. ^{330,352,353}	IIa	C
Extended oral anticoagulation of indefinite duration should be considered for patients with a first episode of PE associated with a minor transient or reversible risk factor. ^{330,331,352}	IIa	C
NOAC dose in extended anticoagulation^e		
If extended oral anticoagulation is decided after PE in a patient without cancer, a reduced dose of the NOACs apixaban (2.5 mg b.i.d.) or rivaroxaban (10 mg o.d.) should be considered after 6 months of therapeutic anticoagulation. ^{352,353}	IIa	A
Extended treatment with alternative antithrombotic agents		
In patients who refuse to take or are unable to tolerate any form of oral anticoagulants, aspirin or sulodexide may be considered for extended VTE prophylaxis. ^{355–357}	IIb	B
Follow-up of the patient under anticoagulation		
In patients who receive extended anticoagulation, it is recommended that their drug tolerance and adherence, hepatic and renal ^f function, and bleeding risk be reassessed at regular intervals. ²⁵⁹	I	C

b.i.d. = bis in die (twice a day); DVT = deep vein thrombosis; NOAC(s) = non-vitamin K antagonist oral anticoagulant(s); o.d. = omni die (once a day); PE = pulmonary embolism; VKA = vitamin K antagonist; VTE = venous thromboembolism.

^aClass of recommendation.

^bLevel of evidence.

^cThe patient's bleeding risk should be assessed (see Supplementary Data Table 14 for prediction models) to identify and treat modifiable bleeding risk factors, and it may influence decision-making on the duration and regimen/dose of anticoagulant treatment.

^dRefer to Supplementary Data Table 9 for therapeutic decisions in specific clinical situations.

^eIf dabigatran or edoxaban is chosen for extended anticoagulation after PE, the dose should remain unchanged, as reduced-dose regimens were not investigated in dedicated extension trials.^{313,350}

^fEspecially for patients receiving NOACs.

8.5 Management of pulmonary embolism in patients with cancer

Five RCTs compared LMWH vs. conventional VTE treatment (heparin followed by VKA) in the treatment of VTE in cancer-associated thrombosis.^{360–364} In 2003, a significant reduction in VTE recurrence was reported with LMWH compared with conventional (VKA) treatment without an increase in bleeding complications.³⁶² In a more recent trial, long-term administration of tinzaparin failed to achieve a statistically significant reduction in overall VTE recurrence over conventional treatment (HR 0.65, 95% CI 0.41–1.03); however, the overall rate of recurrent VTE in the control arm was lower than that previously observed, probably as a result of the recruitment of patients with a lower cancer-specific thrombotic risk.³⁶⁰ Overall, LMWHs were found to decrease the risk of recurrent VTE by 40% with a risk of major bleeding complications similar to that of VKAs.³⁶⁵ Accordingly, LMWHs have become the standard of care. However, these agents are associated with a relevant cost and burden for patients. In addition, the absolute rate of recurrent VTE while on LMWH remains high (7–9%) compared with that observed in non-cancer patients with VTE on conventional treatment (1.5–3%).³⁶⁵

NOACs could make the treatment of VTE easier and more convenient in patients with cancer, due to their oral administration in fixed-dose regimens and their lower cost compared with LMWH. However, only 3–9% of patients included in phase III studies with NOACs for the treatment of VTE had concomitant cancer.^{260,261,312,314,351} A randomized, open-label trial compared edoxaban with LMWH in the secondary prevention of VTE in 1050 patients with cancer-associated thrombosis (mostly symptomatic or asymptomatic PE).³⁶⁶ Edoxaban (60 mg o.d., reduced to 30 mg in subjects with moderate renal impairment, low body weight, or concomitant need for strong inhibitors of glycoprotein-P) was started after 5 days of LMWH and treatment was given for ≥ 6 months. Edoxaban was non-inferior to dalteparin in the prevention of VTE recurrence or major bleeding over 12 months after randomization (HR 0.97, 95% CI 0.70–1.36). Major bleeding occurred in 6.9% of the patients in the edoxaban arm and 4.0% in the dalteparin arm (difference in risk 2.9 percentage points, 95% CI 0.1–5.6). This difference appears to have been mainly accounted for by the high rate of bleeding in patients with gastrointestinal cancer allocated to the edoxaban group.³⁶⁶ Similar results were reported by a randomized, open-label pilot trial comparing rivaroxaban with dalteparin in 406 patients with VTE and cancer, 58% of whom had metastases.³⁶⁷ A significant decrease in the risk of recurrent VTE was observed with rivaroxaban (HR 0.43, 95% CI 0.19–0.99). The 6 month cumulative rate of major bleeding, which was mostly gastrointestinal, was 6% (95% CI 3–11%) for rivaroxaban and 4% (95% CI 2–8%) for dalteparin (HR 1.83, 95% CI 0.68–4.96). Corresponding rates of CRNM bleeds were 13% (95% CI 9–19%) and 4% (95% CI 2–9%), respectively (HR 3.76, 95% CI 1.63–8.69).³⁶⁷

Based on the currently available evidence, as described above, patients with acute PE and cancer, particularly those with gastrointestinal cancer, should be encouraged to continue LMWH for ≥ 3 –6 months. This also applies to patients in whom oral treatment is unfeasible due to problems of intake or absorption, and to those with

severe renal impairment. In all other cases, especially in patients with an anticipated low risk of bleeding and without gastrointestinal tumours, the choice between LMWH and edoxaban or rivaroxaban is left to the discretion of the physician, and the patient's preference.

Owing to the high risk for recurrence, patients with cancer should receive indefinite anticoagulation after a first episode of VTE. Although existing evidence is limited, it is conceivable that once cancer is cured the risk for recurrence decreases and anticoagulation can be stopped. However, the definition of cured cancer is not always clear. The risk of recurrence of PE in cancer was assessed in a cohort study of 543 patients and was validated in an independent set of 819 patients.³⁶⁸ The proposed score to predict the risk of recurrence included breast cancer (minus 1 point), Tumour Node Metastasis stage I or II (minus 1 point), and female sex, lung cancer, and previous VTE (plus 1 point each). Patients with a score ≤ 0 were at low risk ($\leq 4.5\%$) and those with a score ≥ 1 were at high ($\geq 19\%$) risk of VTE recurrence over the first 6 months.³⁶⁸

After the first 3–6 months, extended anticoagulation may consist of continuation of LMWH or transition to an oral anticoagulant. Two cohort studies have assessed the safety of extended treatment with LMWH (≤ 12 months) in cancer-associated thrombosis.^{369,370} In both studies, the incidence of bleeding complications was higher in the first months and then reached a plateau that remained unchanged after the sixth month. In the absence of conclusive evidence, the decision to continue with LMWH or to change to VKA or a NOAC should be made on a case-by-case basis after consideration of the success of anticancer therapy, the estimated risk of recurrence of VTE, the bleeding risk, and the preference of the patient. Periodic reassessment of the risk-to-benefit ratio of continued anticoagulant treatment is mandatory.

As mentioned in section 5, venous filters are principally indicated when anticoagulation is impossible due to active haemorrhage or an excessive bleeding risk. However, the risk of VTE recurrence in the absence of anticoagulation is particularly high in patients with cancer, and the insertion of a filter should not delay the initiation of anticoagulation as soon as it is safe to do so. There is no evidence to support the use of venous filters as an adjunct to anticoagulation treatment in patients with cancer.

A number of studies have reported that a proportion of patients presenting with PE in the absence of identifiable risk factors develop cancer within the first year after diagnosis.³⁷¹ Consequently, the optimal strategy to achieve early diagnosis of these occult cancers was investigated. Two large randomized trials failed to show that comprehensive CT of the abdomen or ^{18}F deoxy-fluoro-glucose positron emission tomography were able to detect more cancers than limited screening in patients with an unprovoked VTE.^{372,373} Therefore, based on current evidence, the search for occult cancer after an episode of VTE may be restricted to careful history taking, physical examination, basic laboratory tests, and a chest X-ray (if no CTPA was performed to diagnose PE).^{372,374,375}

In patients with cancer, incidental PE should be managed in the same manner as symptomatic PE, whether it involves segmental or more proximal branches, multiple subsegmental vessels, or a single subsegmental vessel in association with detectable DVT.^{376,377}

8.6 Recommendations for the regimen and the duration of anticoagulation after pulmonary embolism in patients with active cancer

Recommendations	Class ^a	Level ^b
For patients with PE and cancer, weight-adjusted subcutaneous LMWH should be considered for the first 6 months over VKAs. ^{360–363}	IIa	A
Edoxaban should be considered as an alternative to weight-adjusted subcutaneous LMWH in patients without gastrointestinal cancer. ³⁶⁶	IIa	B
Rivaroxaban should be considered as an alternative to weight-adjusted subcutaneous LMWH in patients without gastrointestinal cancer. ³⁶⁷	IIa	C
For patients with PE and cancer, extended anticoagulation (beyond the first 6 months) ^c should be considered for an indefinite period or until the cancer is cured. ³⁷⁸	IIa	B
In patients with cancer, management of incidental PE in the same manner as symptomatic PE should be considered, if it involves segmental or more proximal branches, multiple subsegmental vessels, or a single subsegmental vessel in association with proven DVT. ^{376,377}	IIa	B

DVT = deep vein thrombosis; LMWH = low-molecular weight heparin; PE = pulmonary embolism; VKAs = vitamin K antagonists.

^aClass of recommendation.

^bLevel of evidence.

^cRefer to Supplementary Data Table 9 for further guidance on therapeutic decisions after the first 6 months.

9 Pulmonary embolism and pregnancy

9.1 Epidemiology and risk factors for pulmonary embolism in pregnancy

Acute PE remains one of the leading causes of maternal death in high-income countries.^{379,380} For example, in the UK and Ireland, thrombosis and thromboembolism were the most common causes of direct maternal death (death resulting from the pregnancy rather than pre-existing conditions) in the triennium 2013–15, resulting in 1.13 mortalities per 100 000 maternities (<https://www.npeu.ox.ac.uk/mbrance-uk>). VTE risk is higher in pregnant women compared with non-pregnant women of similar age; it increases during pregnancy and reaches a peak during the post-partum period.³⁸¹ The baseline pregnancy-related risk increases further in the presence of additional VTE risk factors, including *in vitro* fertilization: in a cross-sectional study derived from a Swedish registry, the HR for VTE following *in vitro* fertilization was 1.77 (95% CI 1.41–2.23) overall and 4.22 (95% CI 2.46–7.20) during the first trimester.³⁸² Other important and common risk factors include prior VTE, obesity, medical comorbidities, stillbirth, pre-eclampsia, post-partum haemorrhage, and caesarean section; documented risk assessment is therefore essential.³⁸³

The recommendations provided in these Guidelines are in line with those included in the 2018 ESC Guidelines on the management of cardiovascular diseases during pregnancy.³⁸⁴

9.2 Diagnosis of pulmonary embolism in pregnancy

9.2.1 Clinical prediction rules and D-dimers

Diagnosis of PE during pregnancy can be challenging as symptoms frequently overlap with those of normal pregnancy. The overall

prevalence of confirmed PE is low among women investigated for the disease, between 2 and 7%.^{385–388} D-dimer levels continuously increase during pregnancy,^{389,390} and levels are above the threshold for VTE ‘rule-out’ in almost one-quarter of pregnant women in the third trimester.³⁹⁰ The results of a multinational prospective management study of 441 pregnant women presenting to emergency departments with clinically suspected PE suggest that a diagnostic strategy—based on the assessment of clinical probability, D-dimer measurement, CUS, and CTPA—may safely exclude PE in pregnancy.³⁸⁸ In that study, PE exclusion on the basis of a negative D-dimer result (without imaging) was possible in 11.7% of the 392 women with a non-high pre-test probability (Geneva) score, a rate that was reduced to 4.2% in the third trimester.³⁸⁸ A further prospective management study evaluated a combination of a pregnancy-adapted YEARS algorithm with D-dimer levels in 498 women with suspected PE during pregnancy. PE was ruled out without CTPA in women deemed to be at low PE risk according to the combination of the algorithm and D-dimer results. At 3 months, only one woman with PE excluded on the basis of the algorithm developed a popliteal DVT (0.21%, 95% CI 0.04–1.2) and no women developed PE.³⁹¹

9.2.2 Imaging tests

A proposed algorithm for the investigation of suspected PE in women who are pregnant, or ≤ 6 weeks post-partum, is shown in Figure 7. Both maternal and foetal radiation exposure are low using modern imaging techniques (Table 12).^{385,392–398} For V/Q scans and CTPA, foetal radiation doses are well below the threshold associated with foetal radiation complications (which is 50–100 mSv).^{399,400} In the past, CTPA has been reported to cause high radiation exposure to the breast;^{395,401} however, CT technology has evolved, and several techniques can now reduce radiation exposure without compromising image quality. These

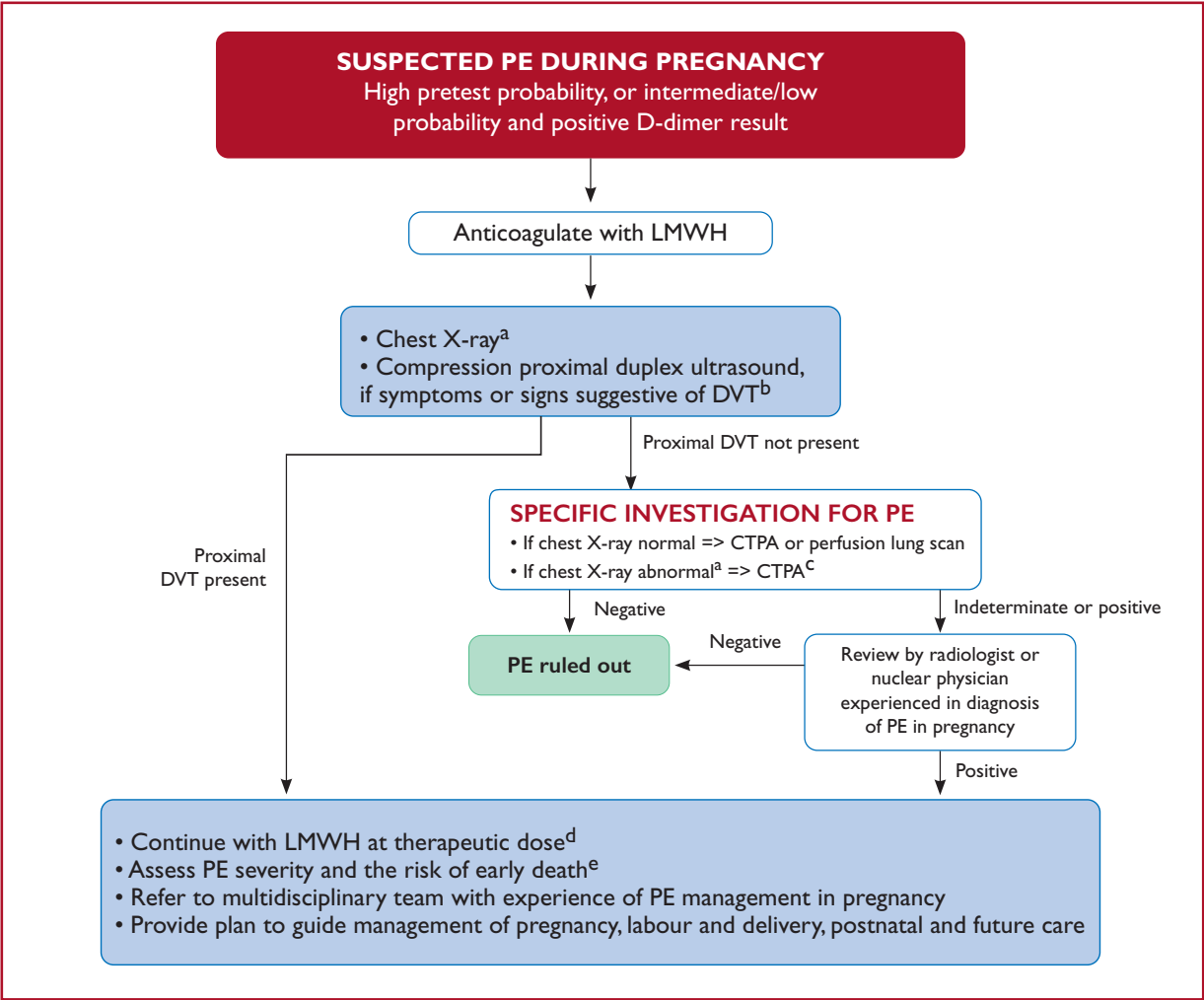


Figure 7 Diagnostic workup and management of suspected pulmonary embolism during pregnancy, and up to 6 weeks post-partum. CTPA = computed tomography pulmonary angiography; CUS = compression ultrasonography; DVT = deep vein thrombosis; LMWH = low-molecular-weight heparin; PE = pulmonary embolism.

^aIf chest X-ray abnormal, consider also alternative cause of chest symptoms.

^bDVT in pelvic veins may not be ruled out by CUS. If the entire leg is swollen, or there is buttock pain or other symptoms suggestive of pelvic thrombosis, consider magnetic resonance venography to rule out DVT.

^cCTPA technique must ensure very low foetal radiation exposure (see Table 12).

^dPerform full blood count (to measure haemoglobin and platelet count) and calculate creatinine clearance before administration. Assess bleeding risk and ensure absence of contra-indications.

^eSee Table 8.

include reducing the anatomical coverage of the scan,³⁹³ reducing the kilovoltage, using iterative reconstructive techniques, and reducing the contrast-monitoring component of the CTPA.^{392,393} Modern CTPA imaging techniques may therefore expose the maternal breast to median doses as low as 3–4 mGy (Table 12).³⁹² The effect on maternal cancer risk with modern CTPA techniques is negligible (lifetime cancer risk is reportedly increased by a factor of 1.0003–1.0007); avoiding CTPA on the grounds of maternal cancer risk is therefore not justified.³⁹⁴

A normal perfusion scan and a negative CTPA appear equally safe for ruling out PE in pregnancy, as suggested by retrospective series.^{385,386,402–404} Inconclusive results can be a problem (4–33% of investigations),^{385,386,405} especially late in pregnancy.⁴⁰⁵ A recent survey of 24 sites in the UK, representing a population of 15.5 million, revealed a similar rate of inadequate or indeterminate CTPA and scintigraphy scans, suggesting that the initial choice of imaging is best determined by local expertise and resources.⁴⁰⁶

V/Q SPECT is associated with low foetal and maternal radiation exposure, and has promise in PE diagnosis in pregnancy.⁴⁰⁷ However,

Table 12 Estimated amounts of radiation absorbed in procedures used to diagnose pulmonary embolism (based on various references^{385,392–398})

Test	Estimated foetal radiation exposure (mGy) ^a	Estimated maternal radiation exposure to breast tissue (mGy) ^a
Chest X-ray	<0.01	<0.1
Perfusion lung scan with technetium-99m-labelled albumin		
Low dose: ~40 MBq	0.02–0.20	0.16–0.5
High dose: ~200 MBq	0.20–0.60	1.2
Ventilation lung scan	0.10–0.30	<0.01
CTPA	0.05–0.5	3–10

CTPA = computed tomography pulmonary angiography; mGy = milligray; MBq = megabecquerel; PE = pulmonary embolism.

^aIn this section, absorbed radiation dose is expressed in mGy to reflect the radiation exposure to single organs, or the foetus, as a result of various diagnostic techniques. Compare with Table 6, in which effective radiation dose is expressed in millisieverts to reflect the effective doses of all organs that have been exposed.

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further evaluation of this technique is required before its widespread incorporation into diagnostic algorithms. For MRA, the long-term effects of gadolinium contrast on the foetus are not known. In non-pregnant patients, technically inadequate images are frequently obtained and the rate of inconclusive scan results is high.¹⁴⁰ Therefore, use of this technique for diagnosing or ruling out PE during pregnancy cannot be recommended at present. Conventional pulmonary angiography involves significantly higher radiation exposure of the foetus (2.2–3.7 mSv) and should be avoided during pregnancy.⁴⁰⁰

Overdiagnosis of PE is a potential pitfall that can have significant, lifelong implications for a pregnant woman, including the risk of bleeding at the time of delivery, the withholding of oestrogen contraception, and the requirement for thromboprophylaxis during future pregnancies. Consequently, avoiding PE overdiagnosis in pregnancy is as important as not missing a PE diagnosis.

9.3 Treatment of pulmonary embolism in pregnancy

LMWH is the treatment of choice for PE during pregnancy.³⁸⁴ In contrast to VKAs and NOACs, LMWH does not cross the placenta, and consequently does not confer a risk of foetal haemorrhage or teratogenicity. Moreover, while UFH is also safe in pregnancy, LMWH has more predictable pharmacokinetics and a more favourable risk profile.^{408–411} Although no RCT has evaluated the optimal dose of LMWH for the treatment of PE during pregnancy, currently published data favour similar dosing to non-pregnant patients, either with o.d. or b.i.d. regimens based on early pregnancy weight.^{408,410} For the majority of patients receiving LMWH treatment for PE during pregnancy,^{412,413} it remains uncertain whether using serial measurements of plasma anti-activated coagulation factor X activity to guide dosing may be of clinical benefit. It is important to bear in mind that: (i) LMWH has a predictable pharmacokinetic profile, (ii) data on optimal

anti-activated coagulation factor levels are lacking, and (iii) the assay itself has limitations.⁴¹⁴ In addition, there are no solid data on the clinical benefit vs. harm of frequent, weight-based dose adjustments of LMWH during pregnancy. Thus, anti-activated coagulation factor X monitoring may be reserved for specific high-risk circumstances such as recurrent VTE, renal impairment, and extremes of body weight.

The use of UFH has been associated with heparin-induced thrombocytopenia and bone loss. It remains uncertain whether, and to what extent, the risk of bone loss is increased with LMWH use. In a recent observational cohort study, in which bone mineral density was measured by dual-energy X-ray absorptiometry 4–7 years after the last delivery in 152 women (92 of whom received prolonged LMWH during pregnancy), lumbar spine bone mineral density was similar in LMWH-treated women and controls following adjustment for potential confounders. No osteoporosis or osteoporotic fractures were reported.⁴¹⁵

Fondaparinux may be considered if there is an allergy or adverse response to LMWH, although solid data are lacking and minor transplacental passage has been demonstrated.⁴¹⁶ VKAs cross the placenta and are associated with a well-defined embryopathy during the first trimester. Administration of VKAs in the third trimester can result in foetal and neonatal haemorrhage, as well as placental abruption. Warfarin may be associated with central nervous system anomalies in the foetus throughout pregnancy. NOACs are contraindicated in pregnant patients.⁴¹⁷

The management of labour and delivery requires particular attention. In women receiving therapeutic LMWH, strong consideration should be given to planned delivery in collaboration with the multidisciplinary team to avoid the risk of spontaneous labour while fully anticoagulated. The incidence of spinal haematoma after regional anaesthesia is unknown in pregnant women under anticoagulation treatment. If regional analgesia is considered for a woman receiving therapeutic LMWH, ≥24 h should have elapsed since the last LMWH dose before insertion of a spinal or epidural needle (assuming normal renal function and including risk assessment at extremes of body weight).

In high-risk situations, for example in patients with recent PE, it is recommended that LMWH be converted to UFH ≥36 h prior to delivery. The UFH infusion should be stopped 4–6 h prior to anticipated delivery and the activated partial thromboplastin time should be normal (i.e. not prolonged) prior to regional anaesthesia.⁴¹⁸

Data are limited on the optimal timing of post-partum reinstitution of LMWH.^{419,420} Timing will depend upon the mode of delivery and an assessment of the thrombotic vs. bleeding risk by a multidisciplinary team. LMWH should not be given for ≥4 h after removal of the epidural catheter; the decision on timing and dose should consider whether the epidural insertion was traumatic, and take into account the risk profile of the woman. For example, an interim dose of a prophylactic LMWH dose may be considered post-operatively (after caesarean section), once at least 4 h have elapsed since epidural catheter removal, and allowing for an interval of ≥8–12 h between the prophylactic and the next therapeutic dose. Close collaboration between the obstetrician, the anaesthesiologist, and the attending physician is recommended.

Anticoagulant treatment should be administered for ≥6 weeks after delivery and with a minimum overall treatment duration of 3 months. LMWH and warfarin can be given to breastfeeding mothers; the use of NOACs is not recommended.⁴¹⁷

High-risk, life-threatening PE during pregnancy is a rare, but potentially devastating, event. A recent systematic review included 127 cases of severe PE during pregnancy (and until 6 weeks post-partum) treated with thrombolysis, thrombectomy, and/or ECMO.⁴²¹ Both high- and intermediate-risk PE cases were included, and 23% of women experienced cardiac arrest. Reported survival rates were 94 and 86% following thrombolysis and surgical thrombectomy, respectively; however, these favourable rates may reflect reporting bias. Following thrombolysis, major bleeding occurred in 18 and 58% of cases during pregnancy and in the post-partum period, respectively.⁴²¹ Finally, foetal deaths occurred in 12 and 20% of the cases following thrombolysis and thrombectomy, respectively.⁴²¹ Thrombolytic treatment should not be used peri-partum, except in the setting of life-threatening PE. Typically, UFH is used in the acute treatment of high-risk PE.

Although the indications for vena cava filters are similar to those for non-pregnant patients (discussed in section 6), there is limited experience with their use in pregnancy and the risk associated with the procedure may be increased.

Suggestions for the anticoagulation management of PE in specific clinical situations (also) related to pregnancy, for which conclusive evidence is lacking, are presented in Supplementary Data Table 9.

9.3.1 Role of a multidisciplinary pregnancy heart team

A team of multidisciplinary colleagues should collaborate in the planning of ante-, peri-, and post-partum care pathways for women with cardiovascular diseases, including PE. As many members as possible of this team should have expertise in the management of PE during pregnancy and the post-partum period. Jointly agreed, written care pathways should be available (if timelines permit) for effective communication (an example is shown in Figure 7).

9.4 Amniotic fluid embolism

Amniotic fluid embolism (AFE) is a rare condition that occurs during pregnancy or shortly after delivery. It remains one of the leading causes of direct maternal death (i.e. death resulting from the pregnancy rather than from pre-existing conditions) in high-income countries.⁴²² Diagnosis of AFE is challenging, being primarily a clinical diagnosis of exclusion. Awareness of AFE, prompt diagnosis, and aggressive life support are of critical importance. AFE is characterized by unexplained sudden cardiovascular or respiratory deterioration, often accompanied by disseminated intravascular coagulation,⁴²² and occurring during pregnancy or after delivery.^{423,424} The reported incidence is approximately 2–7 per 100 000 maternities, with a mortality rate of 0.5–6 deaths per 100 000 deliveries.^{422,425,426} Reported case fatality rates vary, reflecting the challenges in making the diagnosis and the rarity of AFE. In a retrospective Californian study including more than 3.5 million deliveries, a case fatality rate of 13% was reported, as in other US and Canadian studies.⁴²⁵ Similarly, a case fatality rate of 19% was reported in a recent prospective UK population-based study with validated case criteria.⁴²² Recent literature have suggested that risk factors for AFE may include pre-existing cardiac, cerebrovascular, and renal disorders, placenta previa, polyhydramnios, stillbirth, chorioamnionitis, hypertensive disorders, instrumental delivery, and caesarean section.^{422,425} Management of AFE is supportive, and

9.5 Recommendations for pulmonary embolism in pregnancy

Recommendations	Class ^a	Level ^b
Diagnosis		
Formal diagnostic assessment with validated methods is recommended if PE is suspected during pregnancy or in the post-partum period. ^{388,391}	I	B
D-dimer measurement and clinical prediction rules should be considered to rule out PE during pregnancy or the post-partum period. ^{388,391}	IIa	B
In a pregnant patient with suspected PE (particularly if she has symptoms of DVT), venous CUS should be considered to avoid unnecessary irradiation. ³⁸⁸	IIa	B
Perfusion scintigraphy or CTPA (with a low-radiation dose protocol) should be considered to rule out suspected PE in pregnant women; CTPA should be considered as the first-line option if the chest X-ray is abnormal. ^{385,386}	IIa	C
Treatment		
A therapeutic, fixed dose of LMWH based on early pregnancy body weight is the recommended therapy for PE in the majority of pregnant women without haemodynamic instability. ^{408,410}	I	B
Thrombolysis or surgical embolectomy should be considered for pregnant women with high-risk PE. ⁴²¹	IIa	C
Insertion of a spinal or epidural needle is not recommended, unless ≥24 h have passed since the last therapeutic dose of LMWH.	III	C
Administration of LMWH is not recommended within 4 h of removal of an epidural catheter.	III	C
NOACs are not recommended during pregnancy or lactation.	III	C
Amniotic fluid embolism		
Amniotic fluid embolism should be considered in a pregnant or post-partum woman with otherwise unexplained cardiac arrest, sustained hypotension, or respiratory deterioration, especially if accompanied by disseminated intravascular coagulation. ^{422,425,426}	IIa	C

CTPA = computed tomography pulmonary angiography; CUS = compression ultrasonography; DVT = deep vein thrombosis; LMWH = low-molecular weight heparin; NOACs = non-vitamin K antagonist oral anticoagulants; PE = pulmonary embolism.
^aClass of recommendation.
^bLevel of evidence.

based on high-quality emergency care following the recognition and diagnosis of the condition, with prompt treatment of bleeding and coagulopathy.⁴²³ Awareness of AFE should be integral to the education of involved physicians and to emergency algorithms.

10 Long-term sequelae of pulmonary embolism

The patency of the pulmonary arterial bed is restored in the majority of PE survivors within the first few months following the acute episode; therefore, no routine follow-up CTPA imaging is needed in such patients treated for PE.⁴²⁷ However, in other patients, thrombi become persistent and organized, which in rare cases may result in CTEPH, a potentially life-threatening obstructing vasculopathy. The rarity of this condition is in contrast to the relatively large number of patients who report persisting dyspnoea or poor physical performance over several months after acute PE. Thus, the aims of an efficient follow-up strategy after PE should be to: (i) provide appropriate care (exercise rehabilitation, treatment of comorbidity, behavioural education, and modification of risk factors) to patients with persisting symptoms, and (ii) ensure early detection of CTEPH to refer the patient for further diagnostic workup and specific treatment.

10.1 Persisting symptoms and functional limitation after pulmonary embolism

Cohort studies conducted over the past decade (summarized in Klok *et al.*⁴²⁸) have revealed that persisting or deteriorating dyspnoea, and poor physical performance, are frequently present 6 months to 3 years after an acute PE episode. The proportion of patients claiming that their health status is worse at 6 month follow-up than it was at the time of PE diagnosis varies widely, ranging between 20 and 75%.^{429–431} The following baseline parameters and findings could be identified as predictors of exertional dyspnoea at long-term follow-up after PE: advanced age, cardiac or pulmonary comorbidity, higher body mass index, and history of smoking;⁴²⁹ higher systolic PAP and RV dysfunction at diagnosis;^{430,432,433} and residual pulmonary vascular obstruction at discharge.⁴³⁴

More recently, a prospective cohort study enrolled 100 patients at five Canadian hospitals between 2010 and 2013, and followed them over 1 year.⁴³⁵ As many as 47% of the patients had reduced maximal aerobic capacity, defined as peak oxygen consumption <80% of the predicted value on cardiopulmonary exercise testing (CPET). This functional outcome was associated with significantly worse generic health-related quality of life and dyspnoea scores, as well as with a significantly reduced 6 min walk distance.⁴³⁵ Independent predictors of reduced functional exercise capacity and quality of life over time included female sex, higher body mass index, history of lung disease, higher pulmonary artery systolic pressures on the 10 day echocardiogram, and higher main pulmonary artery diameter on the baseline CTPA.⁴³⁶ Of note, pulmonary function tests and echocardiographic results at follow-up were largely within normal limits, both in patients with and without reduced maximal aerobic capacity.⁴³⁵ Lack of an association between exercise impairment, and persistent RV dilation or dysfunction, was also reported by a study of 20 survivors of massive or submassive PE.⁴³⁷

Taken together, older and more recent cohort studies have suggested that muscle deconditioning, particularly in the presence of excess body weight and cardiopulmonary comorbidity, is largely responsible for the frequently reported dyspnoea and signs of exercise limitation after acute PE. This also means that, at least in the majority of cases, poor physical performance after PE does not

appear to be attributable to 'large' residual thrombi, or persisting/progressive PH and RV dysfunction. Ongoing prospective studies in large numbers of patients may help to better identify predictors of functional and/or haemodynamic impairment after acute PE, and their possible implications for shaping follow-up programmes.⁴³⁸

As mentioned in section 6, it remains unclear whether early reperfusion treatment, notably thrombolysis, has an impact on clinical symptoms, functional limitation, or persistent (or new-onset) PH at long-term follow-up after PE. Consequently, prevention of long-term PE sequelae is, at present, no justification for thrombolytic treatment in the acute phase of PE.

10.2 Chronic thromboembolic pulmonary hypertension

10.2.1 Epidemiology, pathophysiology, and natural history

CTEPH is a disease caused by the persistent obstruction of pulmonary arteries by organized thrombi, leading to flow redistribution and secondary remodelling of the pulmonary microvascular bed. CTEPH has been reported with a cumulative incidence of between 0.1 and 9.1% in the first 2 years after a symptomatic PE event; the large margin of error is due to referral bias, the paucity of early symptoms, and the difficulty of differentiating acute PE from symptoms of pre-existing CTEPH.^{439,440} A prospective, multicentre, observational screening survey for the detection of CTEPH included patients with acute PE from 11 centres in Switzerland, from March 2009 to November 2016. Screening for possible CTEPH was performed at 6, 12, and 24 months using a stepwise algorithm that included a phone-based dyspnoea survey, TTE, right heart catheterization, and radiological confirmation of CTEPH. Of 508 patients assessed for CTEPH screening over 2 years, CTEPH incidence following PE was 3.7 per 1000 patient-years, with a 2 year cumulative incidence of 0.79%.⁴⁴¹ In Germany, the incidence of CTEPH in 2016 was estimated at 5.7 per million adult population.⁴⁴²

The hallmark of CTEPH is fibrotic transformation of a pulmonary arterial thrombus, causing fixed mechanical obstruction of pulmonary arteries and leading to overflow of the open pulmonary arterial bed. Together with collateral supply from systemic arteries downstream of pulmonary arterial occlusions, this contributes to microvascular remodelling causing a progressive increase in PVR.⁴⁴³ Owing to this complex pathophysiology, there is no clear correlation between the degree of mechanical obstruction found at imaging and haemodynamics, which can deteriorate in the absence of recurrent PE.⁴⁴⁴

Two historical trials assessed survival in patients with CTEPH before the availability of surgical treatment. In both studies, mean PAP >30 mmHg was related to poor survival, similar to that reported for idiopathic pulmonary arterial hypertension.^{445,446}

The most frequently cited risk factors and predisposing conditions for CTEPH are shown in Table 13. In an international registry, a history of acute PE was reported by 75% of patients.⁴⁴⁷ Associated conditions and comorbidities included thrombophilic disorders, particularly antiphospholipid antibody syndrome and high coagulation factor VIII levels, cancer, a history of splenectomy, inflammatory bowel disease, ventriculo-atrial shunts, and infection of chronic i.v. lines and devices such as implantable pacemakers.

Table 13 Risk factors and predisposing conditions for chronic thromboembolic pulmonary hypertension^{447–449}

Findings related to the acute PE event (obtained at PE diagnosis)	Concomitant chronic diseases and conditions predisposing to CTEPH (documented at PE diagnosis or at 3–6 month follow-up)
Previous episodes of PE or DVT	Ventriculo-atrial shunts
Large pulmonary arterial thrombi on CTPA	Infected chronic i.v. lines or pacemakers
Echocardiographic signs of PH/RV dysfunction ^a	History of splenectomy
CTPA findings suggestive of pre-existing chronic thromboembolic disease ^b	Thrombophilic disorders, particularly antiphospholipid antibody syndrome and high coagulation factor VIII levels
	Non-O blood group
	Hypothyroidism treated with thyroid hormones
	History of cancer
	Myeloproliferative disorders
	Inflammatory bowel disease
	Chronic osteomyelitis

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CTEPH = Chronic thromboembolic pulmonary hypertension; CTPA = computed tomographic pulmonary angiography; DVT = deep vein thrombosis; i.v. = intravenous; LV = left ventricular; PE = pulmonary embolism; PH = pulmonary hypertension; RV = right ventricular.
^aEchocardiographic criteria of RV dysfunction are graphically presented in Figure 3, and their prognostic value summarized in Supplementary Data Table 3. On CTPA (four-chamber views of the heart), RV dysfunction is defined as RV/LV diameter ratio >1.0.
^bDirect and indirect vascular signs, as well as lung parenchymal findings, are summarized in Supplementary Data Table 2.

10.2.2 Clinical presentation and diagnosis

Diagnosing CTEPH is difficult. Algorithms for predicting⁴⁵⁰ or ruling out CTEPH^{451,452} are limited by a lack of specificity. The clinical characteristics of patients enrolled in an international CTEPH registry have shown that the median age at diagnosis is 63 years and that both sexes are equally affected; paediatric cases are rare.⁴⁴⁷ Clinical symptoms and signs are non-specific or absent in early CTEPH, with signs of right heart failure only becoming evident in advanced disease. Thus, early diagnosis remains a challenge in CTEPH, with a median time of 14 months between symptom onset and diagnosis in expert centres.⁴⁵³ When present, the clinical symptoms of CTEPH may resemble those of acute PE or of pulmonary arterial hypertension; in the latter context, oedema and haemoptysis occur more often in CTEPH, while syncope is more common in pulmonary arterial hypertension.⁴⁵³

The diagnosis of CTEPH is based on findings obtained after at least 3 months of effective anticoagulation, to distinguish this condition from acute PE. The diagnosis requires a mean PAP of ≥25 mmHg along with a pulmonary arterial wedge pressure of ≤15 mmHg, documented at right heart catheterization in a patient with mismatched perfusion defects on V/Q lung scan. Specific diagnostic signs for CTEPH on multidetector CT angiography or conventional pulmonary cineangiography include ring-like stenoses, webs, slits, and chronic total occlusions.²⁸⁹

Some patients may present with normal pulmonary haemodynamics at rest despite symptomatic disease. If other causes of exercise limitation are excluded, these patients are considered as having chronic thromboembolic disease (CTED). Identification of patients with chronic thromboembolism without PH, who may have an indication for surgical or interventional treatment, requires particular expertise and should be done in CTEPH referral centres. Among 1019 patients who were submitted to pulmonary endarterectomy (PEA) in a UK referral centre, 42 patients did not have pulmonary

hypertension at rest but showed functional improvement after the operation.⁴⁵⁴

Planar V/Q lung scan is a suitable first-line imaging modality for CTEPH as it has 96–97% sensitivity and 90–95% specificity for the diagnosis.⁴⁵⁵ SPECT seems less sensitive than planar V/Q scanning if assessed at a level of individual segmental arteries, but it is unlikely to miss clinically relevant CTEPH in an individual patient. In contrast to CTEPH, abnormal mismatched perfusion defects sometimes found in pulmonary arterial hypertension and pulmonary veno-occlusive disease typically have a non-segmental pattern.

CTPA is gaining ground as a diagnostic modality in CTEPH,⁴⁵⁶ but it should not be used as a stand-alone test to exclude the disease.⁴⁵⁵ Newer diagnostic tests include dual-energy CT, which allows the simultaneous assessment of patency of the pulmonary arteries and of lung perfusion, probably at a cost of some increase in radiation delivered to the patient. Magnetic resonance imaging of the pulmonary vasculature is still considered inferior to CT.⁴⁵⁷ Cone-beam CT,⁴⁵⁸ angiography,⁴⁵⁹ intravascular ultrasound, and optical coherence tomography are more suitable for the characterization of lesions during interventional treatment than for diagnosis. High-resolution CT scan of the chest may assist in the differential diagnosis of CTEPH, showing emphysema, bronchial, or interstitial lung disease, as well as infarcts, and vascular and thoracic wall malformations. Perfusion inequalities manifesting as a mosaic parenchymal pattern are frequently found in CTEPH, but may also be observed in ≤12% of patients with other causes of PH. Differential diagnosis of CTEPH should also include pulmonary arteritis, pulmonary angiosarcoma, tumour embolism, parasites (hydatid cyst), foreign body embolism, and congenital or acquired pulmonary artery stenoses.²⁸⁹

10.2.3 Surgical treatment

Surgical PEA is the treatment of choice for operable CTEPH. In contrast to surgical embolectomy for acute PE, treatment of CTEPH

necessitates a true bilateral endarterectomy through the medial layer of the pulmonary arteries. It requires deep hypothermia and intermittent circulatory arrest, without a need for cerebral perfusion.^{460,461} In-hospital mortality is currently as low as 4.7%⁴⁶² and is even lower in high-volume single centres.⁴⁶³ The majority of patients experience substantial relief from symptoms and near-normalization of haemodynamics.^{461–464} Owing to the complexity of both the surgical technique and peri-procedural management, PEA is performed in specialized centres. Eligibility for surgery requires a decision taken during a dedicated meeting of a multidisciplinary CTEPH team including experienced surgeons for PEA, interventional radiologists or cardiologists, radiologists experienced in pulmonary vascular imaging, and clinicians with expertise in PH. The CTEPH team should confirm the diagnosis, assess the surgical accessibility of chronic post-thrombotic obstructions ('surgical operability'), and consider the risks related to comorbidities ('medical operability'). The operability of patients with CTEPH is determined by multiple factors that cannot easily be standardized. These are related to the suitability of the patient, the expertise of the surgical team, and available resources. General criteria include pre-operative New York Heart Association (NYHA) functional class and the surgical accessibility of thrombi in the main, lobar, or segmental pulmonary arteries.⁴⁶² Advanced age *per se* is no contraindication for surgery. There is no haemodynamic threshold or measure of RV dysfunction that can be considered to preclude PEA.

Data from the international CTEPH registry, set up in 27 centres to evaluate the long-term outcome and outcome predictors in 679 operated and not-operated patients, showed estimated survival at 3 years of 89% in operated and 70% in not-operated patients.⁴⁶⁵ Mortality was associated with NYHA functional class, RA pressure, and a history of cancer.⁴⁶⁵ In this prospective registry, the long-term prognosis of operated patients was better than the outcome of not-operated patients.⁴⁶⁵ Additional correlates of mortality were bridging therapy with pulmonary vasodilators, post-operative PH, surgical complications, and additional cardiac procedures in operated patients, and comorbidities such as coronary disease, left heart failure, and chronic obstructive pulmonary disease in not-operated patients.⁴⁶⁵ A recent report identified mean PAP ≥ 38 mmHg and PVR ≥ 425 dyn $\cdot$ s $\cdot$ cm⁻⁵ as determinants of poor prognosis in survivors of surgical treatment for CTEPH.⁴⁶⁶

Post-operative ECMO is recommended as the standard of care in PEA centres.⁴⁶¹ Early post-operative reperfusion oedema may require veno-arterial ECMO, and severe persistent PH may be bridged to emergency lung transplantation with ECMO. After PEA, patients should be followed in CTEPH centres to exclude persistent or recurrent PH, with at least one haemodynamic assessment to be considered at 6–12 months after the intervention.

10.2.4 Balloon pulmonary angioplasty

Over the past decade, balloon pulmonary angioplasty (BPA) has emerged as an effective treatment for technically inoperable CTEPH. It allows dilatation of obstructions down to subsegmental vessels, which are inaccessible to surgery. BPA is a stepwise procedure requiring several (usually 4–10) separate sessions. This is necessary to engage all under-perfused lung segments, while limiting the contrast burden and radiation delivered per session. Navigation in distal

pulmonary arteries requires particular expertise, as the complexity and individual variability of the pulmonary arterial tree greatly exceeds that of other vascular beds. Complications include wire- and balloon-induced injury, which may result in intrapulmonary bleeding, haemoptysis, and reperfusion lung injury. Usually, bleeding resolves spontaneously, but sometimes it has to be controlled by transient balloon inflation proximal to the site of perforation; in rare cases it requires embolization. Mild hypoxaemia is frequent and can be controlled by oxygen delivery. Mechanical ventilation or ECMO is rarely needed.

The largest published registry to date included 249 patients with a mean age of 61.5 years, who were treated with BPA between 2004 and 2013 in seven Japanese centres.⁴⁶⁷ Mean PAP decreased from 43 to 24 mmHg after terminating BPA sessions, and this result was maintained in 196 patients who underwent follow-up right heart catheterization. Complications occurred in 36% of the patients, including pulmonary injury (18%), haemoptysis (14%), and pulmonary artery perforation (2.9%). After BPA, 30 day mortality was 2.6% and overall survival was 97% at 1 year.⁴⁶⁷

While most of the BPA procedures are performed in technically inoperable patients, this method has also been used for sequential treatment for PH persisting after PEA. Few 'rescue' BPA interventions performed in unstable patients remaining on ECMO after PEA were ineffective.⁴⁶⁸

10.2.5 Pharmacological treatment

Optimal medical treatment for CTEPH consists of anticoagulants, as well as diuretics and oxygen in cases of heart failure or hypoxaemia. Lifelong oral anticoagulation with VKAs is recommended, and also after successful PEA or BPA. No data exist on the efficacy and safety of NOACs.

Pulmonary microvascular disease in CTEPH has provided the rationale for also testing drugs that have been approved for pulmonary arterial hypertension for this indication. Based on available data, medical treatment of CTEPH with targeted therapy is now justified for technically inoperable patients,^{469,470} as well as for patients with PH persisting after PEA.⁴⁶⁹ To date, the only drug approved for inoperable CTEPH or persistent/recurrent PH after PEA is riociguat, an oral stimulator of soluble guanylate cyclase.⁴⁶⁹ In a prospective randomized trial of 261 patients with inoperable CTEPH or persistent/recurrent PH after PEA, treatment with riociguat significantly increased 6 min walking distance and reduced PVR.⁴⁶⁹ In a similar population of 157 patients, the dual endothelin antagonist bosentan showed a positive effect on haemodynamics, but no improvement was observed in exercise capacity and the primary outcome was not met.⁴⁷¹ Another dual endothelin antagonist, macitentan, was found to significantly improve PVR and 6 min walking distance compared to placebo in a phase II trial focusing on inoperable patients with CTEPH.⁴⁷⁰ Currently, riociguat is being tested in trials addressing its efficacy and safety: (i) as bridging therapy for patients scheduled to undergo PEA (NCT 03273257) and (ii) in comparison to BPA (NCT 02634203).

Overall, the effects on clinical worsening of drugs tested with RCTs in patients with CTEPH have not yet been clarified. Furthermore, no data exist on medical treatment in technically operable patients with prohibitive comorbidities or those refusing surgery.

Off-label combination of drugs approved for pulmonary arterial hypertension has been proposed for CTEPH patients presenting with severe haemodynamic compromise, but only limited prospective data are available to date.⁴⁷⁰

Medical therapy is not indicated in symptomatic survivors of acute PE with documented post-thrombotic obstructions but an absence of PH at right heart catheterization at rest (CTED).

10.3 Strategies for patient follow-up after pulmonary embolism

Figure 8 displays a proposed follow-up strategy for survivors of acute PE following discharge from hospital. Evaluation of the patients 3–6 months after the acute PE episode is recommended to assess the persistence (or new onset) and severity of dyspnoea or functional limitation, and to check for possible signs of VTE recurrence, cancer,

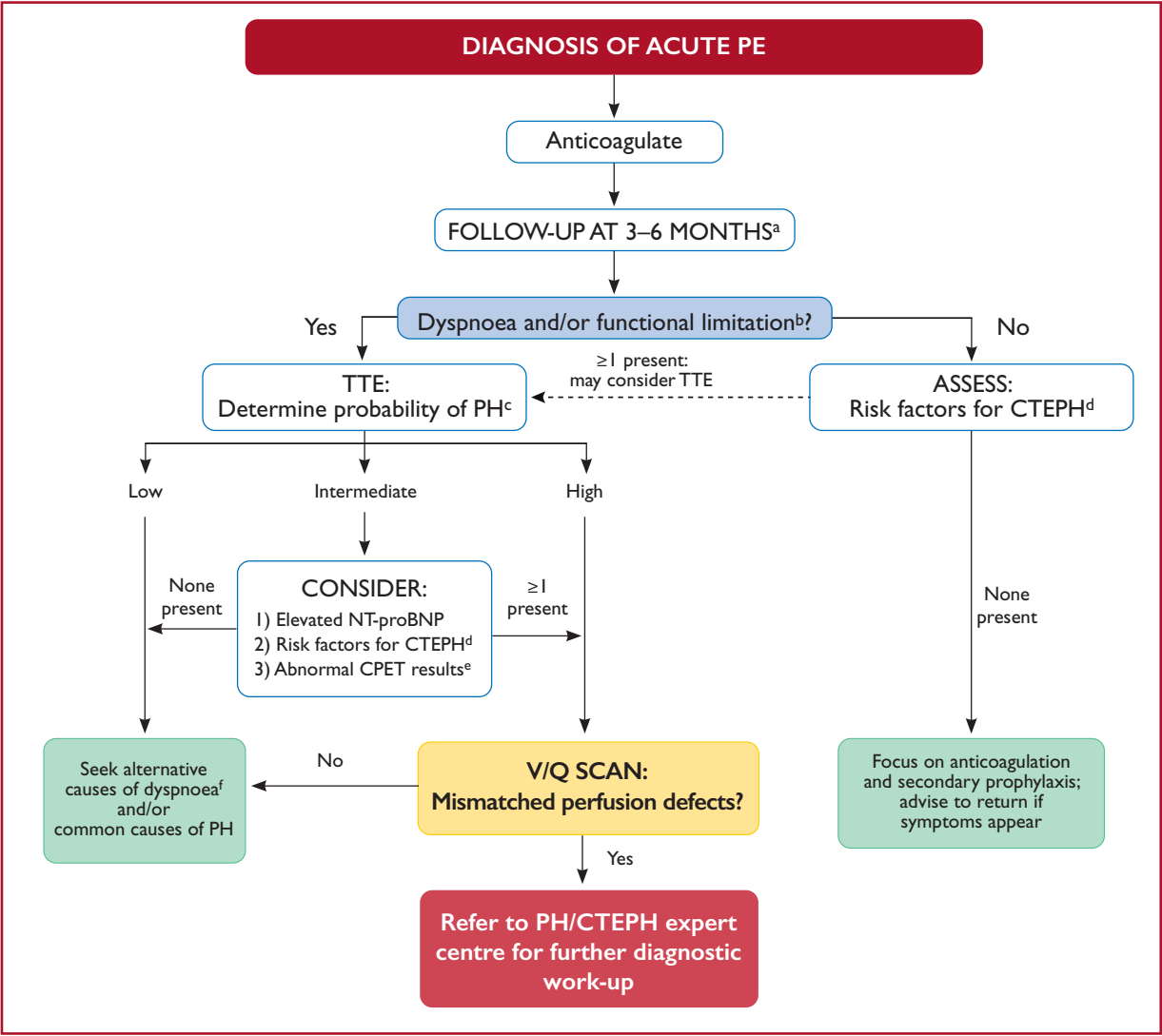


Figure 8 Follow-up strategy and diagnostic workup for long-term sequelae of pulmonary embolism. CPET = cardiopulmonary exercise testing; CTEPH = chronic thromboembolic pulmonary hypertension; NT-proBNP = N-terminal pro B-type natriuretic peptide; PE = pulmonary embolism; PH = pulmonary hypertension; TTE = transthoracic echocardiography/echocardiogram; V/Q = ventilation/perfusion (lung scintigraphy).

^aAssess the persistence (or new onset) and severity of dyspnoea or functional limitation, and also check for possible signs of VTE recurrence, cancer, or bleeding complications of anticoagulation.

^bThe Medical Research Council scale can be used to standardize the evaluation of dyspnoea;¹⁶⁰ alternatively, the World Health Organization functional class can be determined (Supplementary Data Table 16).²⁸⁹

^cAs defined by the ESC/ERS guidelines on the diagnosis and treatment of Pulmonary Hypertension (Supplementary Data Tables 17 and 18).²⁸⁹

^dRisk factors and predisposing conditions for CTEPH are listed in Table 13.

^eCardiopulmonary exercise testing, if appropriate expertise and resources are available on site; abnormal results include, among others, reduced maximal aerobic capacity (peak oxygen consumption), increased ventilatory equivalent for carbon dioxide, and reduced end-tidal carbon dioxide pressure.

^fConsider CPET in the diagnostic work-up.

or bleeding complications of anticoagulation. The severity of dyspnoea can be assessed using the Medical Research Council scale;¹⁶⁰ alternatively, the World Health Organization functional class can be determined (Supplementary Data Table 16).²⁸⁹

In patients complaining of persisting dyspnoea and poor physical performance, TTE should be considered as the next step to assess the probability of (chronic) PH and thus possible CTEPH. The criteria and levels of PH probability are defined by current ESC Guidelines,²⁸⁹ and are listed in Supplementary Data Tables 17 and 18. Patients with a high echocardiographic probability of PH, or those with intermediate probability combined with elevated NT-proBNP levels or risk factors/predisposing conditions for CTEPH, such as those listed in Table 13, should be considered for a V/Q scan.

If mismatched perfusion defects are found on the V/Q scan, referral to a PH or CTEPH expert centre for further diagnostic workup is indicated. If, on the other hand, the V/Q scan is normal and the patient's symptoms remain unexplained, CPET may be performed. By providing evidence of reduced maximal aerobic capacity, CPET supports the need for further follow-up visits and helps to identify candidates for pulmonary rehabilitation, exercise, or weight-reduction programmes.^{435,436} CPET may also be helpful in patients with suspected CTEPH and coexisting left heart and/or respiratory disease; in such cases, it can help to establish the main limiting factor and thus set priorities for the treatment strategy.⁴⁷²

For patients who report as free of dyspnoea or functional limitation at 3–6-month follow-up after acute PE but have risk factors/predisposing conditions for CTEPH (Table 13), further follow-up visits may be scheduled and the patient must be advised to return if symptoms appear. Alternatively, TTE may be considered to assess the probability of PH (Figure 8).

Apart from the recommended screening and diagnostic measures, an integrated model of patient care after PE should be provided, taking into consideration the infrastructure and possibilities offered by each country's health system. The model should include appropriately qualified nurses, interdisciplinary working with physicians in the care of both in-hospital and ambulatory PE patients, standardized treatment protocols adapted to the capacities of each hospital, and bidirectional referral pathways between general practice and the hospital. Such models ensure smooth transitions between hospital specialists and practitioners; provide continuity, and easy access to care along with information and education; and respect the patients' preferences, and those of their families and social environment. In this context, nurse-led care models to deliver follow-up have been shown to be effective after acute coronary syndrome,⁴⁷³ in primary care-based management of chronic diseases,⁴⁷⁴ and in community based self-management initiatives.⁴⁷⁵ A recently published study investigated the care of 42 patients followed at a pulmonary arterial hypertension (PAH)/CTEPH nurse-led outpatient clinic and showed positive results.⁴⁷⁶ During patient follow-up visits, appropriately qualified nurses screen for signs and symptoms indicating VTE recurrence or complications of treatment, and assess adherence to medication. Nurses work collaboratively with patients using behavioural frameworks and motivational interviewing, to identify and modify associated risk factors (smoking cessation, diet, physical activity, and exercise). In addition, they promote self-management skills such as

10.4 Recommendations for follow-up after acute pulmonary embolism

Recommendations	Class ^a	Level ^b
Routine clinical evaluation ^c of patients 3–6 months after the acute PE episode is recommended. ^{288,352,353,437}	I	B
An integrated model of patient care after PE (involving hospital specialists, appropriately qualified nurses, and primary care physicians) is recommended to ensure optimal transition from hospital to community care.	I	C
In symptomatic patients with mismatched perfusion defects persisting on V/Q scan ^d beyond 3 months after acute PE, referral to a PH/CTEPH expert centre is recommended, after taking into account the results of echocardiography, natriuretic peptide levels, and/or CPET. ⁴⁷⁷	I	C
Further diagnostic evaluation ^e should be considered in patients with persistent or new-onset dyspnoea/exercise limitation after PE.	IIa	C
Further diagnostic evaluation ^e may be considered in asymptomatic patients with risk factors for CTEPH. ^{f 447–449,478}	IIb	C

CPET = cardiopulmonary exercise testing; CT = computed tomography; CTEPH = Chronic thromboembolic pulmonary hypertension; PE = pulmonary embolism; PH = pulmonary hypertension; V/Q = ventilation/perfusion (lung scintigraphy).

^aClass of recommendation.

^bLevel of evidence.

^cFor symptoms suggesting recurrence, bleeding, malignancy, or persistent or new-onset exercise limitation, and to decide on extension of anticoagulant treatment.

^dAlternatively, dual-energy CT may be used, if appropriate expertise and resources are available on-site.

^eAs proposed in the algorithm shown in Figure 8.

^fRisk factors and predisposing conditions for CTEPH are listed in Table 13.

the use of compression stockings, safe increase in mobility, increased awareness of signs of recurrence, or complications.

11 Non-thrombotic pulmonary embolism

This section is included in the [Supplementary Data](#) available online on the EHJ and ESC websites (www.escardio.org/guidelines).

12 Key messages

The ESC Task Force has selected 10 simple key messages and rules to guide physicians in the diagnosis and management of PE:

- (1) In patients presenting with haemodynamic instability, perform bedside TTE as a fast, immediate step to differentiate suspected high-risk PE from other acute life-threatening situations.

- (2) If you suspect acute PE, institute anticoagulation therapy as soon as possible, while the diagnostic workup is ongoing, unless the patient is bleeding or has absolute contraindications to this therapy.
- (3) Use recommended, validated diagnostic algorithms for PE, including standardized assessment of (pre-test) clinical probability and D-dimer testing. They help to avoid unnecessary, expensive, and potentially harmful imaging tests and exposure to ionizing radiation.
- (4) If the CTPA report suggests single subsegmental PE, consider the possibility of a false-positive finding. Discuss the findings again with the radiologist and/or seek a second opinion to avoid misdiagnosis, and unnecessary, potentially harmful anticoagulation treatment.
- (5) Confirmation of PE in a patient, without haemodynamic instability, must be followed by further risk assessment involving clinical findings, evaluation of the size and/or function of the RV, and laboratory biomarkers as appropriate. This information will help you to decide on the need for reperfusion treatment or monitoring for patients at elevated risk, or consider the option of early discharge and continuation of anticoagulation on an ambulatory basis for patients at low risk.
- (6) As soon as you diagnose (or strongly suspect) high-risk PE, select the best reperfusion option (systemic thrombolysis, surgical embolectomy, or catheter-directed treatment) considering the patient's risk profile, and the resources and expertise available at your hospital. For patients with intermediate-high-risk PE, reperfusion is not first-line treatment, but you should prospectively plan the management strategy with your team to have a contingency plan ready if the situation deteriorates.
- (7) Prefer anticoagulation with a NOAC over the 'traditional' LMWH-VKA regimen unless the patient has contraindication(s) to this type of drug.
- (8) Always remember that, with the exception of acute PE provoked by a strong transient/reversible risk factor, there is a lifelong risk of VTE recurrence after a first episode of PE. Consequently, re-examine the patient after the first 3–6 months of anticoagulation, weigh the benefits vs. risks of continuing treatment, and decide on the extension and dose of anticoagulant therapy, also considering the patient's preference. Remember to recommend regular follow-up examinations, e.g. at yearly intervals.
- (9) If you suspect PE in a pregnant patient, consider diagnostic pathways and algorithms including CTPA or V/Q lung scan, which can be used safely during pregnancy.
- (10) After acute PE, patients should not be lost to follow-up. Apart from checking for possible signs of VTE recurrence, cancer, or bleeding complications of anticoagulation, ask the patient if there is persisting or new-onset dyspnoea or functional limitation. If yes, implement a staged diagnostic workup to exclude CTEPH or chronic thromboembolic disease, and to detect/treat comorbidity or 'simple' deconditioning. Follow-up imaging is not routinely recommended in an asymptomatic patient, but it may be considered in patients with risk factors for development of CTEPH.

13 Gaps in the evidence

Diagnosis

- The optimal method to adjust (based on the patient's age or in combination with clinical probability) the D-dimer threshold, permitting the exclusion of PE while reducing the number of unnecessary imaging tests to a minimum, remains to be determined.
- The diagnostic value and clinical significance of isolated subsegmental contrast-filling defects in the modern CTPA era remain controversial.
- No robust data exist to guide the decision on whether to treat incidental PE with anticoagulants compared with a strategy of watchful waiting.
- For patients presenting with non-traumatic chest pain, the benefits vs. risks of 'triple rule-out' (for coronary artery disease, PE, and aortic dissection) CT angiography need further evaluation before such an approach can be routinely recommended.

Assessment of pulmonary embolism severity and the risk of early death

- The optimal, clinically most relevant combination (and cut-off levels) of clinical and biochemical predictors of early PE-related death remain to be determined, particularly with regard to identifying possible candidates for reperfusion treatment among patients with intermediate-risk PE.
- The need for assessment of the RV status in addition to clinical parameters, to classify a patient with acute symptomatic PE as being at low vs. intermediate risk, needs to be confirmed by further prospective management (cohort) studies.

Treatment in the acute phase

- The clinical benefits vs. risks of reduced-dose thrombolysis and catheter-based reperfusion modalities in patients with intermediate-high-risk PE should be evaluated in prospective randomized trials.
- The place of ECMO in the management of acute high-risk PE awaits support by additional evidence from prospective management (cohort) studies.
- The optimal anticoagulant drug(s) and regimen in patients with renal insufficiency and CrCl <30 mL/min remain unclear.
- The criteria for selecting patients for early discharge and outpatient treatment of PE, and particularly the need for assessment of the RV status with imaging methods and/or laboratory markers in addition to calculating a clinical score, need to be further validated in prospective cohort studies.

Chronic treatment and prevention of recurrence

- The clinical value and the possible therapeutic implications of models or scores assessing the risk of VTE recurrence, and the risk of bleeding under anticoagulation, need to be revisited in the NOAC era.
- The effectiveness of extended treatment with a reduced dose, or apixaban or rivaroxaban, should be confirmed in patients with a high risk of recurrent PE.

- The evidence supporting the efficacy and safety of NOACs for the treatment of PE in patients with cancer needs to be extended by further studies.
- In patients with cancer, the anticoagulant regimen and dose after the first 6 months should be clarified and prospectively tested.
- The optimal time for discontinuing anticoagulant treatment after an episode of acute PE in patients with cancer is yet to be determined.

Pulmonary embolism and pregnancy

- Diagnostic algorithms for PE in pregnancy, using modern radiological imaging techniques and low radiation doses, need to be prospectively tested in adequately powered cohort studies.
- Controversy persists on the optimal LMWH dose and regimen for the treatment of PE during pregnancy.
- NOACs are not allowed in pregnancy. However, if exposure to these drugs occurs during pregnancy despite this warning, any possible effects on the foetus should be recorded to provide

more precise information on the risks and complications of these drugs, and adapt the instructions to physicians in the future.

Long-term sequelae of pulmonary embolism

- The optimal follow-up strategy, including the spectrum of diagnostic tests that may be necessary, in patients with persisting symptoms and functional limitation after acute PE needs to be defined and prospectively validated.
- In the absence of persisting symptoms or functional limitation after acute PE, the criteria for identifying patients whose risk of developing CTEPH may be sufficiently high to justify further diagnostic workup require further elaboration and validation in prospective cohort studies.

14 'What to do' and 'what not to do' messages from the Guidelines

Diagnosis	Class ^a
In suspected high-risk PE, perform bedside echocardiography or emergency CTPA (depending on availability and clinical circumstances) for diagnosis.	I
In suspected high-risk PE, initiate intravenous anticoagulation with UFH without delay, including a weight-adjusted bolus injection.	I
In suspected PE without haemodynamic instability, use validated diagnostic criteria.	I
In suspected PE without haemodynamic instability, initiate anticoagulation in case of high or intermediate clinical probability, while diagnostic workup is in progress.	I
Base the diagnostic strategy on clinical probability, using either clinical judgement or a validated prediction rule.	I
Measure D-dimers in plasma, preferably with a highly sensitive assay, in outpatients/emergency department patients with low or intermediate clinical probability, or who are PE-unlikely.	I
Reject the diagnosis of PE (without further testing) if CTPA is normal in a patient with low or intermediate clinical probability, or if the patient is PE-unlikely.	I
Reject the diagnosis of PE (without further testing) if the perfusion lung scan is normal.	I
Accept the diagnosis of PE if CTPA shows a segmental or more proximal filling defect in a patient with intermediate or high clinical probability.	I
Accept the diagnosis of VTE if CUS shows a proximal DVT in a patient with clinical suspicion of PE.	I
Do not measure D-dimers in patients with high clinical probability, as a normal result does not safely exclude PE.	III
Do not perform CT venography as an adjunct to CTPA.	III
Do not perform MRA to rule out PE.	III
Risk assessment	
Stratify patients with suspected or confirmed PE, based on the presence of haemodynamic instability, to identify those at high risk of early mortality.	I
In patients without haemodynamic instability, further stratify PE into intermediate- and low-risk categories.	I
Treatment in the acute phase	
Administer systemic thrombolytic therapy to patients with high-risk PE.	I
Surgical pulmonary embolectomy for patients with high-risk PE, in whom recommended thrombolysis is contraindicated or has failed.	I
If anticoagulation is initiated parenterally in a patient without haemodynamic instability, prefer LMWH or fondaparinux over UFH.	I

Continued

When oral anticoagulation is initiated in a patient with PE who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), prefer a NOAC.	I
As an alternative to a NOAC, administer a VKA, overlapping with parenteral anticoagulation until an INR of 2.5 (range 2.0–3.0) has been reached.	I
Administer rescue thrombolytic therapy to a patient with haemodynamic deterioration on anticoagulation treatment.	I
Do not use NOACs in patients with severe renal impairment or in those with antiphospholipid antibody syndrome.	III
Do not routinely administer systemic thrombolysis as primary treatment in patients with intermediate- or low-risk PE.	III
Do not routinely use inferior vena cava filters.	III
Chronic treatment and prevention of recurrence	
Administer therapeutic anticoagulation for ≥ 3 months to all patients with PE.	I
Discontinue therapeutic oral anticoagulation after 3 months in patients with first PE secondary to a major transient/reversible risk factor.	I
Continue oral anticoagulant treatment indefinitely in patients presenting with recurrent VTE (at least one previous episode of PE or DVT) that is not related to a major transient or reversible risk factor.	I
Continue oral anticoagulant treatment with a VKA indefinitely in patients with antiphospholipid antibody syndrome.	I
In patients who receive extended anticoagulation, reassess drug tolerance and adherence, hepatic and renal function, and the bleeding risk at regular intervals.	I
PE in pregnancy	
Perform formal diagnostic assessment with validated methods if PE is suspected during pregnancy or in the post-partum period.	I
Administer therapeutic, fixed doses of LMWH, based on early pregnancy weight, in the majority of pregnant women without haemodynamic instability.	I
Do not insert a spinal or epidural needle within 24 h since the last LMWH dose.	III
Do not administer LMWH within 4 h of removal of an epidural catheter.	III
Do not use NOACs during pregnancy or lactation.	III
Post-PE care and long-term sequelae	
Routinely re-evaluate patients 3–6 months after acute PE.	I
Implement an integrated model of care after acute PE, in order to ensure optimal transition from hospital to ambulatory care.	I
Refer symptomatic patients with mismatched perfusion defects on V/Q lung scan beyond 3 months after acute PE to a pulmonary hypertension/CTEPH expert centre, taking into account the results of echocardiography, natriuretic peptide, and/or cardiopulmonary exercise testing.	I

CT = computed tomography; CTPA = computed tomographic pulmonary angiography/angiogram; CTEPH = Chronic thromboembolic pulmonary hypertension; CUS = compression ultrasonography; DVT = deep vein thrombosis; INR = international normalized ratio; LMWH = low-molecular weight heparin; MRA = magnetic resonance angiography; NOAC(s) = non-vitamin K antagonist oral anticoagulant(s); PE = pulmonary embolism; UFH = unfractionated heparin; VKA = vitamin K antagonist; V/Q = ventilation/perfusion (lung scintigraphy); VTE = venous thromboembolism.

^aClass of recommendation.

15 Supplementary data

[Supplementary Data](#) with additional Web Supplementary Tables complementing the full text, as well as *section 11* on non-thrombotic PE, are available on the *European Heart Journal* website and via the ESC website at www.escardio.org/guidelines.

16 Appendix

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Tromboprofilaxis en cirugía plástica: ¿cuándo, cómo y por qué?

Thromboprophylaxis in plastic surgery: why, when and how?

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RESUMEN

Casi todos los pacientes quirúrgicos cuentan con factores de riesgo para presentar enfermedad tromboembólica venosa. Por lo anterior surgió la necesidad de realizar una revisión de la literatura con el objetivo de responder a las siguientes preguntas: ¿cuándo, cómo y por qué es necesaria la tromboprofilaxis en la práctica de la cirugía plástica? Después de realizar la revisión se concluyó que la escala de Caprini 2005 es la más adecuada para estratificar el riesgo de tromboembolia en pacientes de cirugía plástica. Se adoptó un diagrama de flujo con el cual podemos decidir el tipo de profilaxis necesaria. Así mismo se especifica cuáles son los fármacos, dosis, duración e indicaciones. Nuestra sugerencia para quimioprofilaxis es el uso de enoxaparina 40 mg subcutánea cada 24 horas en pacientes que así lo ameriten según su estratificación. Se explican cuáles son las contraindicaciones para los diversos métodos de profilaxis y por último se concluye que el uso de enoxaparina, empleada como se sugiere en el protocolo, no incrementa el riesgo de sangrado mayor que requiera de reintervención.

ABSTRACT

Almost every surgical patient has enough risk factors to develop venous thromboembolic disease. Therefore, a review of the medical literature was needed to answer the following questions: when, how and why is thromboprophylaxis needed in plastic surgery? After thorough research we concluded that Caprini's 2005 scale was the best for thromboembolic risk stratification in plastic surgery patients. A flow chart was then devised to determine the prophylactic therapy needed. The medications, dosages, duration of treatment and instructions are specified. Evidence suggests that 40 mg of enoxaparin administered subcutaneously every 24 hours in patients in need, according to their risk score, are adequate. The contraindications of the wide array of prophylactic treatments are explained, and lastly we concluded that enoxaparin used as shown in the guidelines does not increase the risk of a major bleeding event requiring an additional surgery.

INTRODUCCIÓN

Prácticamente todos los pacientes quirúrgicos cuentan con factores de riesgo para presentar enfermedad tromboembólica venosa. Por lo anterior es importante responder las siguientes preguntas: cuándo, cómo y por qué es necesaria la tromboprofilaxis en la práctica de la cirugía plástica.

Este trabajo tiene como objetivo responder las preguntas anteriores, basándose en la evidencia que la literatura actual nos ofrece, así como exponer los riesgos y beneficios de dicha práctica, además de proponer un pro-

toloco que norme el proceder diario de todo cirujano plástico.

¿Por qué utilizar tromboprofilaxis en cirugía plástica?

La enfermedad tromboembólica venosa se presenta como un espectro que puede iniciar desde una trombosis venosa profunda hasta terminar con una tromboembolia pulmonar fatal.

En una encuesta realizada a miembros de la Sociedad Americana de Cirujanos Plásticos (ASPS, por sus siglas en inglés) se evidenció que únicamente el 48.7% de los cirujanos

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que realizan ritidectomías, 43.7% que realizan liposucciones y 60.8% de los que realizan procedimientos combinados utilizan de manera rutinaria la tromboprofilaxis.¹

Dentro de la cirugía plástica, la incidencia de tromboembolia venosa es mayor en pacientes sometidos a reconstrucción de cabeza y cuello (0-27%). En segundo lugar se encuentran los pacientes con quemaduras (0-23%) y en tercero, aquellos a los que se realiza una abdominoplastia (0-4.23%). Por otra parte, los más afectados por tromboembolia pulmonar son los pacientes a los que se les practicó liposucción (0-23%), abdominoplastia combinada con otro procedimiento (0.2-9.3%) y quemados (0-4.35%).² Por último, es importante mencionar que la tromboembolia pulmonar es la principal causa de muerte posterior a una liposucción.¹

En pacientes de cirugía general, la incidencia de trombosis venosa profunda fluctúa entre el 16 y 30% con una incidencia de tromboembolia pulmonar clínicamente significativa del 1.6% y una mortalidad del 0.1% al 0.8%. La trombosis venosa profunda, por lo general, se origina en las venas de la pierna; sin un tratamiento adecuado, hasta el 20% se propagará de manera proximal, ocasionando hasta en el 50% de los pacientes una tromboembolia pulmonar. El 10% de estos casos son fatales de manera inmediata y 5% son mortales a mediano plazo, debido a disfunción ventricular derecha o hipertensión pulmonar resultante. La tromboembolia pulmonar genera 200,000 muertes anuales en los Estados Unidos.³

Hasta el 50% de las trombosis venosas profundas inician en el periodo intraoperatorio; de las anteriores, el 50% se pueden resolver espontáneamente en las próximas 72 horas. La tromboprofilaxis facilita la lisis de coágulos y promueve la prevención de nuevas trombosis. Aproximadamente 25% de las trombosis de la pierna que no reciben tratamiento se extenderán a venas proximales dentro de la primera semana de evolución. El periodo de mayor riesgo para una tromboembolia pulmonar fatal comprende de 3 a 7 días posteriores al evento quirúrgico. El 10% provocará la muerte dentro de la primera hora del inicio de los síntomas. El riesgo de tromboembolia es muy alto en las primeras dos semanas posteriores a la cirugía

y permanece elevado por aproximadamente 2 a 3 meses. Hasta el 50% de los pacientes diagnosticados con tromboembolia pulmonar desarrollarán disfunción ventricular derecha.¹

La trombosis venosa profunda/tromboembolia pulmonar representa un riesgo latente en la práctica de nuestra profesión. Asimismo, y como se expondrá más adelante, el empleo sistemático de la tromboprofilaxis provee un beneficio claro para nuestros pacientes, reduciendo de manera significativa el índice de eventos trombóticos.^{1,4}

¿Cuándo utilizar tromboprofilaxis en pacientes de cirugía plástica?

Estratificación del riesgo de tromboembolia

Existen múltiples herramientas e índices para la estratificación del riesgo tromboembólico en el paciente quirúrgico; sin embargo, la mayoría fueron creados y validados para pacientes de cirugía general u ortopedia.⁵

Pannucci y cols, realizaron un estudio para la validación del índice de Caprini del 2005 concluyendo que este último es efectivo en la estratificación del riesgo en pacientes de cirugía plástica.⁷

Es importante estandarizar el índice de estratificación que se utilizará por los cirujanos plásticos para evitar una sobre o infraestimación del riesgo trombótico de los pacientes al utilizar otros índices, por ejemplo, el mencionado por Poor y cols (índice de Davison),⁸ o inclusive el propuesto por Caprini en el 2010, en el cual se puede incurrir en una sobreestimación del riesgo según las guías propuestas por la ASPS.⁹ Dicho organismo otorga un nivel de evidencia II y un grado de recomendación B para el uso del índice de Caprini 2005 en pacientes de cirugía plástica.^{1,9}

Llenando el formato de Caprini 2005 obtendremos una puntuación total, la cual normará la conducta a seguir. Dicho formato se debe llenar tanto para pacientes hospitalizados como para procedimientos de corta estancia bajo anestesia general con un grado de recomendación B.⁹

Las siguientes recomendaciones, según la puntuación obtenida por el paciente,

aplican para aquellos que serán sometidos a procedimientos quirúrgicos mayores a 60 minutos, bajo anestesia general, en cualquiera de los siguientes escenarios: cirugía de contorno corporal, abdominoplastia, reconstrucción mamaria, procedimientos en miembros inferiores y procedimientos relacionados a cáncer en cabeza y cuello.⁹

Puntuación

0 puntos: • No se requiere de tromboprofilaxis mecánica ni farmacológica. Se sugiere deambulación temprana. Grado de recomendación: 2C.¹⁰

1-2 puntos: • Se sugiere tromboprofilaxis mecánica, de preferencia con dispositivos de compresión neumática intermitente. Grado de recomendación: 2C.

3-4 puntos: • Si el paciente **No** presenta riesgo de complicaciones por sangrado mayor, se recomienda el uso de heparina de bajo peso molecular, heparina no fraccionada a dosis bajas (Grado 2B) o profilaxis mecánica de preferencia con dispositivos de compresión neumática intermitente (Grado 2C).
• Si el paciente está en riesgo de complicaciones por sangrado mayor, se recomienda el uso de profilaxis mecánica de preferencia con dispositivos de compresión neumática intermitente (Grado 2C).

≥ 5 puntos: • Si el paciente **No** presenta riesgo de complicaciones por sangrado mayor, se recomienda el uso de heparina de bajo peso molecular o heparina no fraccionada a dosis bajas (Grado 1B). Además se debe agregar profilaxis mecánica de preferencia con dispositivos de compresión neumática intermitente (Grado 2C).

• Si la heparina de bajo peso molecular o la heparina no fraccionada a dosis bajas se encuentran contraindicadas o no se encuentran disponibles, siempre y cuando no haya riesgo de complicaciones por sangrado mayor, se recomienda el uso de aspirina a bajas dosis (Grado 2C) o profilaxis mecánica de preferencia con dispositivos de compresión neumática intermitente (Grado 2C).¹⁰

≥ 7 puntos: Se recomienda el uso de heparina de bajo peso molecular o heparina no fraccionada a dosis bajas (Grado 1B). Además se debe agregar profilaxis mecánica de preferencia con dispositivos de compresión neumática intermitente (Grado 2C).

En pacientes de cirugía electiva, se debe considerar reducir el riesgo tromboembólico con estrategias como: reducir el tiempo quirúrgico, discontinuar la terapia de reemplazo hormonal, bajar de peso e iniciar movilización temprana postoperatoria (Grado C).

Se debe considerar fuertemente el uso extendido (cuatro semanas) de heparina de bajo peso molecular en el periodo postoperatorio (Grado B).⁹

*Viajeros de larga distancia:

Para pacientes que viajan por avión largas distancias (> 6 horas) y que cuentan con un riesgo aumentado de trombosis (incluyendo trombosis previa, cirugía o trauma reciente, malignidad activa, embarazo, estrógenos, edad avanzada, movilidad limitada, obesidad severa, trombofilias) se sugiere:

- Ambulación frecuente, ejercicios de pantorrilla y sentarse en un asiento amplio si es posible (Grado 2C)
- Uso de medias elásticas por debajo de la rodilla que provean de una presión de 15 a 30 mmHg a nivel del tobillo (Grado 2C).
- No se recomienda el uso de aspirina o anticoagulantes (Grado 2C).¹⁰

¿Cómo utilizar la tromboprofilaxis en pacientes de cirugía plástica?

Métodos mecánicos de tromboprofilaxis

Las medias de compresión graduada son un método pasivo que funciona incrementando la velocidad del flujo venoso, mejorando la función valvular y reduciendo la distensión de la pared venosa. Se menciona una reducción del 65% de trombosis venosa profunda con este método. Los dispositivos de compresión neumática intermitente funcionan disminuyendo la estasis venosa mediante un bombeo activo de la sangre, estimulación de la actividad fibrinolítica en las venas al reducir el activador uno de plasminógeno e incrementar la liberación del activador tisular de plasminógeno. Se menciona una reducción del 60% de riesgo de trombosis venosa profunda.¹¹

Los métodos mecánicos son medios que han demostrado reducir el riesgo de trombosis venosa profunda; sin embargo, no en la misma medida que la profilaxis farmacológica. Es importante mencionar que no hay estudios que demuestren de manera definitiva que los métodos mecánicos reduzcan el riesgo de trombosis venosa profunda proximal, tromboembolia pulmonar y tromboembolia pulmonar fatal, las cuales son las complicaciones que más nos interesa evitar.^{10,11} No obstante, se ha demostrado un incremento de cuatro veces en la probabilidad de presentar complicaciones cutáneas con el uso de medias elásticas, tales como ulceraciones, ámpulas y necrosis cutánea.¹⁰

Métodos farmacológicos de tromboprofilaxis

Heparinas

La heparina de bajo peso molecular y la heparina no fraccionada a bajas dosis son el método efectivo más utilizado para la prevención de la trombosis venosa profunda y tromboembolia pulmonar. Ambas inactivan dos factores de la cascada de coagulación: Factor Xa y Factor IIa (trombina). Una de las ventajas de la heparina de bajo peso molecular es su menor índice de unión a proteínas plasmáticas, lo cual le confiere una mayor biodisponibilidad. Por lo anterior, esta última tiene un efecto más predecible, requiere de un menor número de dosis diarias y no necesita de estudios para monitorización y ajuste de dosis. Por último, la heparina de bajo peso molecular tiene un menor índice en la incidencia de sangrado y hematoma en comparación con la heparina no fraccionada a bajas dosis.¹¹

La heparina no fraccionada a bajas dosis reduce en un 47% la incidencia de tromboembolia pulmonar fatal, en un 41% la tromboembolia pulmonar no fatal, y ocasiona un incremento del 57% en la incidencia de sangrado mayor no fatal. La heparina de bajo peso molecular reduce el riesgo de embolia pulmonar y trombosis venosa en un 70%.¹⁰

Fármacos no heparínicos

Existen múltiples fármacos en investigación, los cuales actúan solamente en uno de los pasos del proceso de la coagulación (iniciación, propagación o formación de fibrina) a diferencia de las heparinas que actúan en dos puntos simultáneamente. Un ejemplo es el fondaparinux, el cual actúa únicamente sobre el Factor Xa (inhibición indirecta) y es el único anticoagulante de nueva generación aprobado por la FDA con disponibilidad en nuestro medio.¹¹ No se ha logrado encontrar una diferencia significativa en eficacia ni en riesgo de sangrado al comparar fondaparinux con heparina de bajo peso molecular.

Cuando se compara el uso de métodos farmacológicos con mecánicos se obtiene una incidencia 80% mayor de trombosis venosa profunda en pacientes que sólo utilizan métodos mecánicos.

Asimismo, se reporta un índice 57% menor de sangrado mayor en este último grupo.¹⁰

La evidencia sugiere que el uso combinado de heparina (no fraccionada o de bajo peso molecular) junto con métodos mecánicos, aumenta la efectividad de la tromboprofilaxis comparado con utilizarlos por separado (Nivel de evidencia II).⁹

¿Cuándo utilizar la tromboprofilaxis en pacientes de cirugía plástica?

Raskob y Hirsh, en su reporte de controversias en el tiempo de inicio de la tromboprofilaxis farmacológica, mencionan que no se requiere el inicio preoperatorio de esta última para lograr una adecuada prevención en la formación de trombos. Por el contrario, si se inicia dentro de las dos horas anteriores a la cirugía, puede aumentar el riesgo de sangrado mayor.¹²

El inicio de la tromboprofilaxis farmacológica seis horas después de la cirugía ha demostrado ser efectivo y sin riesgo de sangrado asociado.^{12,13} Por el contrario, si se administra en un tiempo menor a seis horas después de la cirugía, se ha asociado a eventos de sangrado mayor sin aumentar la efectividad antitrombótica.^{12,14}

En las guías publicadas en 2012 por Gould y cols,¹⁰ se menciona que para disminuir el riesgo de eventos de sangrado mayor, la tromboprofilaxis farmacológica se puede aplicar 12 horas antes del procedimiento quirúrgico. En dichas guías se recomienda administrar la heparina de bajo peso molecular 12 horas antes o después del procedimiento quirúrgico.¹⁰

La ASPS propone en sus guías publicadas en 2012 la administración de heparina de bajo peso molecular, iniciando 6 a 8 horas antes del evento quirúrgico. Dicho comité concluye que no existe evidencia suficiente para establecer una recomendación sólida sobre el inicio, dosis o duración de la tromboprofilaxis.⁹

Podemos observar que el tiempo correcto de administración es un tema controvertido dentro del campo de la cirugía plástica, por lo que únicamente se debe enfatizar que no se debe administrar ni menos de seis horas antes del procedimiento ni menos de seis horas después del mismo, para evitar el riesgo de eventos de sangrado mayor.

Dosis de enoxaparina como quimioprofilaxis en cirugía plástica

En las guías de la ASPS se menciona que la dosis habitualmente utilizada de enoxaparina oscila entre los 30 y 60 mg diarios; sin embargo, no hay suficiente evidencia para emitir una recomendación sólida al respecto.⁹

Duración de la quimioprofilaxis en cirugía plástica

El riesgo de trombosis venosa profunda permanece elevado, al menos, durante 12 semanas después de la cirugía.¹⁰

En pacientes con un índice de Caprini 2005 mayor de 3, resulta efectivo el uso de quimioprofilaxis por un período de una semana sin aumentar el riesgo de sangrado (Nivel de evidencia I).

En pacientes con un índice de Caprini 2005 mayor de siete, se recomienda el uso extendido de quimioprofilaxis por un período de cuatro semanas para obtener una reducción efectiva en el riesgo de trombosis venosa profunda, sin aumentar el riesgo de hematoma o complicaciones secundarias a sangrado (Nivel de evidencia I).⁹

Riesgo de sangrado con el uso de quimioprofilaxis en cirugía plástica

Panucci y cols. reportaron que la tromboprofilaxis con enoxaparina (40 mg subcutáneo cada 24 horas o 30 mg subcutáneo cada 12 horas en pacientes con índice de masa corporal (IMC) > 40 kg/m², administrada 6 a 8 horas después de la cirugía, no se asocia con un incremento en el índice de hematoma que requiera de revisión quirúrgica (Nivel de evidencia: II).¹⁵

Existen estudios con un menor grado de evidencia, como el presentado por Dini y cols., en el cual se administró rivaroxaban (inhibidor selectivo del Factor Xa) por vía oral 8 horas antes del procedimiento. Dicho estudio fue suspendido por la presencia de complicaciones relacionadas a sangrado.¹⁶

Pontelli y cols. reportan que no hay diferencia significativa con respecto a la incidencia de hematoma, seroma, infección y dehiscencia entre los pacientes que reciben profilaxis con

métodos mecánicos y a los que se agrega el uso de enoxaparina.¹⁷ Resultados similares fueron reportados por Seruya y cols.¹⁸

Por último, en las guías de la ASPS, se menciona que el uso de quimioprofilaxis postoperatoria con heparina de bajo peso molecular, heparina no fraccionada o fondaparinux por un periodo de una semana o hasta cuatro semanas en casos selectos, no incrementa significativamente el riesgo de sangrado (Nivel de evidencia: I).⁹

Contraindicaciones para los métodos de tromboprofilaxis

Seruya y cols. en su publicación de educación médica continua para tromboprofilaxis en cirugía plástica mencionan los puntos importantes a considerar cuando se utiliza quimioprofilaxis y dispositivos de compresión neumática.

Para la quimioprofilaxis existen factores que incrementan el riesgo de sangrado, por lo que en presencia de uno de ellos, se deberá considerar el uso de métodos mecánicos y no el uso de los métodos farmacológicos.¹

Dichos factores son los siguientes:

1. Sangrado activo.
2. Paciente cursa con, o cuenta con el antecedente de trombocitopenia inducida por heparina.
3. Cuenta plaquetaria menor a 100,000/mm³.
4. Paciente que se encuentra bajo anticoagulación oral o inhibidores de plaquetas.
5. Depuración de creatinina anormal.

Los siguientes factores se deben considerar para evitar el uso de dispositivos de compresión neumática:

1. Enfermedad arterial periférica severa.
2. Insuficiencia cardíaca congestiva.
3. Trombosis venosa aguda superficial y/o profunda.

Protocolo sugerido

Pannucci y cols. describen su experiencia en la implementación de un protocolo de tromboprofilaxis en un servicio de cirugía plástica. Encontraron que al cabo de nueve meses de

uso, el 90% de los involucrados adoptó dicho protocolo por los beneficios que implica para los pacientes.¹⁹

Se ha descrito en este trabajo la necesidad de implementar un protocolo de tromboprofilaxis en nuestra especialidad, así mismo se ha descrito la manera de hacerlo con el máximo nivel de evidencia científica con el que se cuenta a la fecha de ser elaborado el presente texto.

En el *cuadro 1* se muestra un comparativo de cuatro estudios relacionados con tromboprofilaxis en cirugía plástica.

Se sugiere imprimir las dos páginas para estratificar el riesgo con el índice de Caprini 2005 (*Figura 1*) y en el reverso las recomendaciones adecuadas para cada paciente (*Figura 2*).

DISCUSIÓN

Broughton y cols.,³ reportan en su encuesta masiva a cirujanos plásticos las incidencias de eventos tromboembólicos así como la baja utilización de tromboprofilaxis rutinaria. Es evidente la importancia que toma esta patología en nuestra práctica clínica, así como la ausencia de protocolos de tromboprofilaxis que deberán ser adoptados por la mayoría de nuestros colegas.

El objetivo de este protocolo fue incluir únicamente datos y recomendaciones con un alto nivel de evidencia. Actualmente la autoridad mundial en protocolos de tromboprofilaxis son las guías publicadas por Gould y cols.¹⁰ En el medio de la cirugía plástica y reconstructiva, la referencia con mayor evidencia científica, son las guías publicadas por la ASPS elaboradas por Murphy y cols.⁹ Estas últimas dos publicaciones fueron la fuente principal de los datos y recomendaciones propuestas en nuestro protocolo. Desafortunadamente existen algunos puntos que permanecerán en controversia por falta de evidencia sólida. Sin embargo, consideramos que el protocolo presentado es el que incluye la más alta evidencia disponible en la actualidad. Es importante mencionar que hemos excluido de nuestro protocolo el uso de heparina no fraccionada a bajas dosis con la finalidad de facilitar la administración de la quimioprofilaxis, evitando el cálculo de dosis individuales y la necesidad de monitorización continua del efecto anticoagulante como sucede con este

fármaco. Por lo anterior se decidió proponer la estandarización de la aplicación de heparina de bajo peso molecular a una dosis y duración uniforme.

El primer punto de controversia es la escala que se debe utilizar para la estratificación del riesgo de tromboembolia en pacientes de cirugía plástica. Como podemos observar, en

Cuadro I. Adaptado de Murphy RX Jr, Alderman A, Gutowski K et al. Evidence based practices for thromboembolism prevention: summary of the ASPS venous thromboembolism task force report. *Plast Reconstr Surg.* 2012; 130(1): 168e-175e.

	Estudio de prevención de tromboembolismo	Universidad de Texas	Hospital de la Universidad de Georgetown	Centro Médico ASAN, Korea
	Pannucci et al.	Hatef et al.	Seruya M et al.	Kim et al.
Pacientes	Cirugías múltiples, anestesia general, estancia de al menos una noche	Pacientes de cirugía de contorno corporal	Reconstrucción de cabeza, cuello, mama o abdomen	Reconstrucción mamaria inmediata con TRAM
Escala de riesgo Protocolo	Caprini 2005	Caprini-Davidson	Caprini-Davidson	Ninguna
	Estratificación: Caprini 2005 ≥ 3	Estratificación: Moderado, alto y el más alto	Estratificación: Caprini 2005 > 4	Estratificación: Ninguna
	Fármaco: Enoxaparina	Fármaco: Enoxaparina	Fármaco: Enoxaparina	Fármaco: Enoxaparina
	Dosis: IMC < 40 : 40 mg c/24 h. IMC > 40 : 30 mg c/12 h	Dosis: 30 mg	Dosis: 40 mg	Dosis: 40 a 60 mg
	Administración: Primera dosis 6 a 8 h postop y terminar cuando el paciente se da de alta	Administración: 49 pacientes recibieron primera dosis preop, 88 intraop o postop inmediato	Administración: Primera dosis 12 h postop. Después c 24 h. Medidas adicionales: medias de compresión y dispositivos de compresión neumática	Administración: una hora preop después de cada 24 h
	Duración: variada	Duración: variada	Duración: variada. Promedio 7.4 días	Duración: 7 días
Resultados	La enoxaparina postoperatoria protegió contra tromboembolia venosa sin incrementar el riesgo de reintervención por hematoma	La enoxaparina redujo significativamente el riesgo de tromboembolismo en pacientes sometidos a abdominoplastia circular. Se asoció a incremento en incidencia de hematoma y sangrado postop que requirió de transfusión	La profilaxis mecánica más heparina de bajo peso molecular fue efectiva en prevenir tromboembolismo sin incrementar el riesgo de sangrado y hematoma	La enoxaparina fue efectiva en prevenir tromboembolismo sin incrementar las complicaciones derivadas de sangrado tales como transfusión y hematoma

nuestro protocolo se propone el uso del índice de Caprini 2005, el cual es aceptado para su uso en pacientes de cirugía plástica, como lo menciona Panucci⁷ y Murphy,⁹ con un nivel

de evidencia II. Existen autores y escalas de estratificación que han tratado de incluir factores de riesgo específicos a nuestra práctica. Por ejemplo, tratar de cuantificar el riesgo de

Servicio de Cirugía Plástica y Reconstructiva
Formato de Prevención de TVP/TEP

Datos del paciente: Nombre: _____ Ficha: _____ Diagnóstico: _____ Cirugía programada: _____		Fecha: _____ Edad: _____ Sexo: _____ Tipo de anestesia: _____ Gral ☐ Otra ☐
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Índice para la estratificación de riesgo de tromboembolia
Caprini 2005

Cada factor representa 1 punto

Edad 41-60 años	☐
Plan: Cirugía menor	☐
Antecedentes de cirugía mayor en el último mes	☐
Venas varicosas	☐
Antecedente de enfermedad inflamatoria intestinal	☐
Piernas inflamadas en este momento	☐
Obesidad (IMC > 25)	☐
Infarto agudo al miocardio	☐
Insuficiencia cardíaca congestiva en el último mes	☐
Sepsis en el último mes	☐
Enfermedad pulmonar seria en el último mes (incluyendo neumonía)	☐
Función pulmonar anormal (EPOC)	☐
Paciente actualmente en reposo en cama	☐

Cada factor representa 2 puntos

Edad 60-74 años	☐
Cirugía artroscópica	☐
Presencia de malignidad (presente o previa)	☐
Cirugía mayor (> 45 minutos)	☐
Cirugía laparoscópica (> 45 minutos)	☐
Pacientes confinado a cama (> 72 horas)	☐
Uso de yeso inmovilizador en el último mes	☐
Presencia de acceso venoso central	☐

Cada factor representa 3 puntos

Edad > 75 años	☐
Antecedentes de TVP/TEP	☐
Historia familiar de trombosis	☐
Factor V de Leiden	☐
Presencia de protrombina 20210A	☐
Homocisteína sérica elevada	☐
Anticoagulante lúpico	☐
Anticuerpos anticardiolipina	☐
Trombocitopenia inducida por heparina	☐
Otra trombofilia congénita o adquirida	☐
Cuál:	

Cada factor representa 5 puntos

Artroplastia mayor electiva de extremidad inferior	☐
Fractura de cadera, pelvis o pierna en el último mes	☐
Evento vascular cerebral en el último mes	☐
Mieloma múltiple	☐
Lesión aguda de médula espinal (parálisis) en el último mes	☐

Sólo para mujeres

(cada una representa 1 punto)

Uso de anticonceptivos orales o terapia de reemplazo hormonal	☐
Embarazo o período postparto en el último mes	☐
Historia de abortos espontáneos recurrentes (≥ 3), parto prematuro con toxemia o infante con restricción del crecimiento	☐

Puntaje total:

Formato llenado por: _____ Nombre: _____ Firma: _____

Figura 1.

Adaptado de Panucci CJ, Bailey SH, Dreszer G et al. Validation of the Caprini risk assessment model in plastic and reconstructive surgery patients. *J Am Coll Surg.* 2011; 212 (1): 105-112.

pendiendo del número de litros de liposucción que se extraerán. Otro ejemplo es la asignación arbitraria de riesgo en caso de realizar un colgajo libre, como el propuesto por Hatef y cols.⁶ Sin embargo, ninguna de estas publicaciones

presenta un nivel de evidencia adecuado, con la posibilidad de sobreestimar el riesgo de tromboembolia. Inclusive, se menciona que la escala de Caprini 2010 sobreestima los riesgos en la población de pacientes de cirugía plástica,



Figura 2.

Adaptado de: Murphy RX Jr, Alderman A, Gutowski K et al. Evidence based practices for thromboembolism prevention: summary of the ASPS venous thromboembolism task force report. *Plast Reconstr Surg.* 2012; 130(1): 168e-175e y de Seruya M, Baker S. Venous thromboembolism: prophylaxis in plastic surgery patients. *Plast Reconstr Surg* 2008; 122 (3 Suppl): 1-9.

por lo que no se utilizó como herramienta de estratificación en el protocolo sugerido por la Asociación Americana de Cirujanos Plásticos.⁹

La evidencia actual es sólida en cuanto al uso de heparina no fraccionada o heparinas de bajo peso molecular; no obstante, no podemos descartar que en un futuro cercano se apruebe, con un nivel sólido de evidencia, alguno de los fármacos que se encuentran en investigación que permitirán reducir los efectos adversos, facilitar la vía de administración y obtener una anticoagulación más predecible.

En cuanto a la dosis, fármaco de elección y duración del mismo, no hay evidencia suficiente para emitir una recomendación.⁹ Sin embargo, con la evidencia actual, se puede concluir que las heparinas de bajo peso molecular tienen un perfil farmacológico superior a las heparinas no fraccionadas, debido a que su administración es más sencilla y su efecto es predecible. En nuestro país, la enoxaparina es la heparina de bajo peso molecular más comúnmente utilizada y la farmacéutica recomienda una dosis de 40 mg cada 24 horas como profilaxis. Esta dosis coincide con el promedio utilizado en los grandes estudios de cirugía plástica.^{1,9} En cuanto a la duración, es importante considerar la extensión de la quimioprofilaxis por cuatro semanas cuando el paciente cuenta con más de siete puntos en la escala de Caprini 2005, ya que estos pacientes pueden desarrollar eventos tardíos de trombosis en el postoperatorio.⁹

Por último, es importante desmentir el mito de un riesgo de sangrado mayor que requiera de re-intervención, cuando se utiliza quimioprofilaxis de acuerdo al protocolo establecido.

Es indiscutible el número creciente de casos diagnosticados de enfermedad tromboembólica en la práctica del cirujano plástico. Tratándose de un problema real de salud, es imperativo establecer un protocolo de estratificación de riesgo y profilaxis para dicha patología.

CONCLUSIONES

Los pacientes de cirugía plástica y reconstructiva se encuentran en riesgo de presentar enfermedad tromboembólica. Los más afectados por tromboembolia pulmonar son los pacientes a los que se les practica liposucción y abdomi-

noplastia combinada con otros procedimientos. Es imperativo utilizar un protocolo para la estratificación del riesgo y la profilaxis de esta patología. El índice de Caprini 2005 es la escala más adecuada para la estimación de dicho riesgo. Se prefiere el uso de los dispositivos de compresión neumática sobre las medias de compresión. El uso de heparina no fraccionada o heparina de bajo peso molecular en pacientes seleccionados disminuye significativamente la incidencia de enfermedad tromboembólica. Es importante documentar los factores que pudieran contraindicar el uso de quimioprofilaxis y/o de los métodos mecánicos. El uso de quimioprofilaxis con las heparinas antes mencionadas conforme al protocolo establecido no incrementa el riesgo de sangrado mayor que requiera de cirugía de revisión.

CONFLICTOS DE INTERÉS

Los autores niegan conflictos de interés con los fármacos mencionados en el artículo.

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Research Article

Venous Thromboembolism following Elective Aesthetic Plastic Surgery: A Longitudinal Prospective Study in 1254 Patients

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Background. Venous thromboembolism (VTE) is a disorder with short-term mortality and long-term morbidity. Healthy patients submitted to elective aesthetic plastic surgeries (EAPS) have risk factors to develop VTE not well established yet. The objective of this study was to examine the incidence and risk factors for VTE in these patients. **Methods.** Longitudinal, prospective (minimum follow-up of 3 months), observational study. Comprehensive information on patient characteristics and surgeries performed was obtained. Preoperative, intraoperative, and postoperative risk factors were analyzed for their association with VTE. **Results.** A total of 1254 patients were included in the study. Postoperative VTE occurred in 17 (1.35%) of patients. VTE was more frequent in patients more than 40 years old (82.3%). Smoking, patients with 2 or 3 pregnancies, and hormone replacement therapy, and oral contraceptives use presents higher levels of VTE. In this study we have not found any correlation between liposuction, augmentation mammoplasty, mastopexy, and rhinoplasty as an isolated risk factor for VTE. **Conclusions.** The incidence of VTE in patients undergoing EAPS was 1.35%. Patients with more than 40 years of age, tobacco users, patients with 2 or more pregnancies, and hormone replacement therapy or oral contraceptives use presents higher levels of VTE.

1. Introduction

The significant increase in the popularity of aesthetic plastic surgeries in recent years has led to an increase in the number and types of complications associated with these procedures [1]. The postoperative occurrence of venous thromboembolism (VTE) is one of the most feared among these complications [2].

VTE, including deep venous thrombosis (DVT) and pulmonary embolus (PE), is a disorder with short-term mortality and long-term morbidity. The majority of PE deaths occur within hours of the embolic phenomenon, even when the event occurs in the hospital, often secondary to unrecognized DVT [3]. VTE carries the risk of sudden mortality but also notable morbidity, including the postthrombotic syndrome and pulmonary hypertension with progression to right heart failure [4].

Healthy patients submitted to elective aesthetic plastic surgeries (EAPS) have risk factors to develop VTE not well established yet, and there is no consensus regarding the use of VTE prophylaxis among them [5, 6]. In 2008, VTE risk

stratification and prevention were identified by the Plastic Surgery Foundation Research Oversight Committee as the top patient safety research priority in this specialty [7]. Around 7% of plastic surgeons report a patient death from postoperative PE [8]. Unfortunately, we do not have, to date, a specific study of VET regarding only patients of aesthetic surgery.

In order to further understand the risk factors and incidence of VTE, the objective of this study was to examine the incidence and risk factors for VTE in patients undergoing EAPS.

2. Methods

This is a longitudinal, prospective (minimum follow-up of 3 months), observational study conducted at a private day hospital between January 2006 and June 2013 with consecutive patients of two plastic surgeons. All participants provided written and informed consent prior to study initiation and patient enrolment. This study is in accordance with the 2000 Edinburgh, Scotland Revision of the Declaration of Helsinki,

TABLE 1: Risk factors of VTE studied.

Risk factor	Total	With VTE	Without VTE	P value
Age 41 or older	882/1254 (70.3%)	14/17 (82.3%)	743/882 (84.2%)	NS
Hormone therapy	714/1254 (56.9%)	15/17 (88.3%)	699/1237 (56.5%)	0.009
Smoking	504/1254 (40.2%)	5/17 (29.4%)	499/1237 (40.4%)	0.005
Varicose veins	132/1254 (10.5%)	1/17 (0.6%)	131/1237 (10.6%)	NS
Two or three pregnancies	67/1254 (5.3%)	2/17 (11.8%)	65/1237 (5.2%)	0.041
Surgery $\geq$ 2 h	155/1254 (12.4%)	1/17 (0.6%)	154/1237 (12.4%)	NS
General anesthesia	27/1254 (2.2%)	0/17 (0%)	27/1237 (2.2%)	NS
Liposuction	1007/1254 (80.3%)	13/17 (76.5%)	994/1237 (80.4%)	NS

applicable ICH guidelines, and Guidelines on Research Practice and is registered at the Brazilian Ministry of Health under the number 1111-1161-1277. Comprehensive information on patient characteristics, surgery performed, anesthesia type, surgery length, contraceptive or postmenopausal hormone replacement use, and comorbidities was obtained. A comprehensive summary of complications was also included for each patient. Preoperative, intraoperative, and postoperative risk factors were analyzed for their association with VTE. In addition, other complications associated with VTE were surveyed too.

The inclusion criteria were EAPS in ambulatory center, blood tests, and electrocardiogram with normal results before the surgery. The exclusion criteria were patients with any personal or familial history of VTE, blood dyscrasias, multiple surgeries, length of hospital stay greater than 24 h, and American Society of Anesthesiologists (ASA) physical status classification system 3 or higher.

Patients presenting clinical symptoms of VTE in the follow-up were screened by D-dimer assay. D-dimer testing is sensitive but not specific for identifying DVT; its use lowered the proportion of patients who needed ultrasonography. For patients with positive results, compression ultrasonography of the proximal veins in the symptomatic legs was conducted for suspected DVT and spiral computerized tomography for suspected PE.

All patients in this study did not receive chemoprophylaxis for VTE. We used intermittent pneumatic leg compression to enhance blood flow in the deep veins of the legs. This method is virtually free of side effects and is particularly useful in patients at high risk of bleeding, such as those undergoing plastic surgery. We also indicated early mobilization of patients as soon as possible after surgery.

In the statistical analysis, numerical variables were presented as mean (SD). The *t*-test was used to compare values of continuous variables between patients in whom VTE developed versus those in whom VTE did not develop whereas categorical variables were compared with the χ^2 test. For all analyses, a *P* < 0.05 was considered significant. Multivariate logistic regression analysis was used to identify the following risk factors of VTE. The odds ratio (OR) and 95% confidence interval (CI) for each independent variable are presented in the final regression model presented. For the statistical analysis, the statistical software SPSS 19.0 (SPSS Inc., Chicago, IL, USA) was used.

TABLE 2: Multivariate logistic regression analysis of VTE risks factors.

Variable	Odds ratio	95% confidence interval	P value
Age > 40	0.504	0.335–0.756	0.000
Hormone therapy use	2.373	1.259–4.471	0.009
Nonsmoking	0.629	0.445–0.890	0.005
Two or three pregnancies	1.661	0.990–2.789	0.042

3. Results

A total of 1729 patients meet the initial inclusion criteria; among those 358 were excluded by the exclusion criteria, and 117 were lost to follow-up. So, 1254 patients were included in the final study with 3 or more months of follow-up. Of these patients, 864 (68.9%) were female and 390 (31.1%) male, and average age was 44.3 ± 16.2 years (range 15 to 72). Patients younger than 40 years constituted only approximately 29.7% of the total population. Postoperative VTE occurred in 17 (1.35%) of patients. Liposuction as the sole operative procedure was performed in 1007 (80.3%) of patients and mastopexy in 48 (3.8%); isolated breast augmentation was done in 132 (10.5%) and rhinoplasty in 67 (5.4%) patients. We did not find any difference in VTE incidence regarding the type of operative procedure.

In nearly 68.4% VTE occurred within the first 4 days after the surgery, with a mean delay of 3.8 ± 1.5 (median 3 days). Preoperative and intraoperative risk factors were presented in Table 1. VTE was more frequent in patients more than 40 years old (82.3%). Smoking, patients with 2 or 3 pregnancies, and hormone replacement therapy or oral contraceptives use presents higher levels of VTE. Preoperative diagnosis of lower limb varicose veins was not associated with a higher incidence of VTE (*P* = 0.237). Intraoperatively, patients who have surgeries lasting 2 or more hours, general anesthesia use, and liposuction procedures were not associated with an increased frequency of VTE. Multivariate analysis identified 4 independent factors as predictors of VTE as showed in Table 2.

4. Discussion

Many healthcare providers are under the false impression that this life-threatening illness is not a problem in their hospital or among their patients. While it is true that an individual plastic surgeon will normally see relatively few patients with this disease, it is clear that DVT is an important public health problem. The development of VTE and PE poses a small but significant risk for surgical patients and may result in death or debilitating consequences [4]. In our study VTE occurred in 1.35% of the patients. Most of the information used in VTE studies comes from reconstructive surgery. It is important to evaluate patients doing aesthetic procedures also. The results presented in this paper probably will stimulate further studies to allow comparisons.

Very little information exists on the incidence of VTE in the ambulatory surgery setting, especially amongst EAPS patients. However, the larger body of medical literature points to numerous intrinsic and transient risk factors that predispose a patient to VTE and PE [9, 10]. Patients with familial history of preoperative VTE, blood dyscrasias, multiple surgeries, length of hospital stay greater than 24 h, and ASA 3 or higher were excluded in our study because, according to the hospital policies, in these patients chemoprophylaxis for VTE must be performed.

These include a personal or family history of the disorders, venous insufficiency, chronic heart failure, obesity (body mass index 30 kg/m^2), standing for more than 6 hours per day, history of more than two pregnancies, current pregnancy, violent effort or muscular trauma, deterioration in general condition, confinement to a bed and/or armchair, long-distance travel, infectious disease, use of general anesthesia during surgery, and performance of abdominoplasty with or without another procedure [11, 12].

In our study the use of oral contraceptive or hormone replacement therapy increases the risk of VTE. Literature shows that women with a current or recent history of contraceptive or postmenopausal hormone replacement use are also at increased risk for VTE and PE, especially if they have the factor V Leiden mutation; deficiencies in antithrombin, protein C, or protein S; or elevated levels of factor VIIIc. Not only have heritable mutations in coagulation factor V and/or prothrombin (i.e., G20210A) been associated with an increased risk of thromboembolism, particularly in white individuals, but also they have been shown to correlate with placental thrombosis during pregnancy, which itself is an acquired hypercoagulable state. The most definite of these pregnancy complications include stillbirth and preterm delivery and possibly recurrent miscarriage [13, 14].

In our study patients with 40 years of age or more showed a significant higher risk to develop VTE. A classic study showed that those patients are at an increased risk of VTE compared with younger patients, with the risk approximately doubling with each decade thereafter [15].

Smoking was also a risk factor to develop VET in our study. In a recent meta-analysis, involving approximately 4 million participants and more than 35,000 patients with VTE from 32 observational studies, a slightly increased risk of VTE for smokers was found compared with nonsmokers. The risk

of developing VTE was greater for current smokers than for former smokers, and a dose-response relationship was found for daily smoking and pack-years smoked [16].

Much is said about liposuction risks; in this study we have not found any correlation between liposuction, augmentation mammoplasty, mastopexy, and rhinoplasty as an isolated risk factor for VTE. Despite the lack of reliable, comprehensive reporting of deaths and complications resulting from cosmetic surgeries, published data demonstrate that the risks associated with liposuction compare favorably with those from most general surgical procedures. A significant lack of literature documenting cosmetic breast surgery and rhinoplasty risks is observed, which should be of concern to both patients and physicians [17–20].

Study Implications. Having identified which patients are at risk of venous thromboembolism, the next choice for the physician is to select the most appropriate prophylactic measure for the patient's circumstances. The ideal primary prophylaxis should be effective, free from clinically important side effects, and well accepted by patients, nurses, and medical staff. It should be easy to administer, be relatively inexpensive, and require minimal monitoring.

Over the years, the available methods of thromboprophylaxis have been refined and improved to give maximum risk reduction for patients liable to suffer postoperative thrombosis. In principle, all prophylaxis is directed either at suppressing activation of blood coagulation or at increasing venous blood flow in the leg veins. There are two general types of prophylaxis—mechanical methods and pharmacological agents.

Ultimately, the decision to provide chemoprophylaxis should be made when the patient is initially admitted. Patients with age higher than 40 years old, who are smoking, with 2 or 3 pregnancies, and in hormone use at admission should be considered for early VTE prophylaxis using both mechanical and pharmacologic means.

5. Conclusion

The incidence of VTE in patients undergoing EAPS in this study was 1.35%. VTE was more frequent in patients more than 40 years old (82.3%). Smoking, patients with 2 or 3 pregnancies, and hormone replacement therapy or oral contraceptives use presents higher levels of VTE. In this study we have not found any correlation between liposuction, augmentation mammoplasty, mastopexy, and rhinoplasty as an isolated risk factor for VTE.

Disclosure

This study has not received any supporting funds. All authors do not have any commercial associations or financial disclosures that might pose or create a conflict of interests with information presented in this study. Level of evidence: II.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper. None of the authors

has a financial interest in any of the products, devices, or drugs mentioned in this paper.

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EAN
ESCUELA
DE ADMINISTRACIÓN
DE NEGOCIOS

ESPECIALIZACIÓN EN ADMINISTRACIÓN HOSPITALARIA

ACTA No.422

En la ciudad de Bogotá, D.C., el día 18 del mes de diciembre de 2003, se llevó a cabo el Acto de Graduación, presidido por el Rector, Doctor **RICARDO AVELLANEDA**, en el cual la **ESCUELA DE ADMINISTRACIÓN DE NEGOCIOS – EAN**, legalmente autorizada para el efecto y previo juramento de rigor, otorga a **HERNÁN SEPÚLVEDA MARTÍNEZ**, identificado(a) con la Cédula de Ciudadanía No.79,445,101 expedida en Bogotá, D.E., quien cumplió con todos los requisitos exigidos por la Ley y los Reglamentos de la institución, el título de **ESPECIALISTA EN ADMINISTRACIÓN HOSPITALARIA**, mediante el Diploma No.422 que lo(a) acredita como tal, anotado en el Libro de Registros de Graduandos No.1, Folio No.029, Registro No.422.

Para constancia se expide y firma la presente Acta por los que en ella intervinieron en la ciudad de Bogotá, D.C., el día 18 del mes de diciembre de 2003.

RICARDO AVELLANEDA
Rector

JORGE ENRIQUE SILVA DUARTE
Vicerrector Académico

CLAUDIA LILIANA MUÑOZ MAYA
Secretario Académico

UNIVERSIDAD NACIONAL DE COLOMBIA
FACULTAD DE
Medicina

ACTA DE GRADO NUMERO 91

EL CONSEJO DIRECTIVO DE LA FACULTAD DE *Medicina*

EN SU SESION DEL DIA 12 DE *Febrero* DE 1998

ACTA No. 04 CONSIDERANDO QUE :

Hernán Sepúlveda Martínez

C.C. No. 79.445.101 de Bogotá D.C.

CUMPLIO SATISFACTORIAMENTE TODOS LOS REQUISITOS EXIGIDOS POR LOS
ACUERDOS Y REGLAMENTOS DE LA UNIVERSIDAD RESUELVE OTORGARLE EL
TITULO DE :

Especialista en Cirugia General

EN NOMBRE Y REPRESENTACION DE LA UNIVERSIDAD NACIONAL Y DE LA
REPUBLICA DE COLOMBIA Y PREVIO EL JURAMENTO DE RIGOR, EL DECANO
DE LA FACULTAD HIZO ENTREGA DEL DIPLOMA CORRESPONDIENTE
REGISTRADO AL FOLIO No. 191 L. 1

ACUERDO N° 33 A DE 1.973 - CONSEJO SUPERIOR UNIVERSITARIO

EN TESTIMONIO DE LO ANTERIOR SE FIRMA LA PRESENTE ACTA DE GRADO
EN LA CIUDAD DE *Stafé de Bta* A LOS 12 DIAS DEL MES DE *Marzo* DE 1998

Campesano
PRESIDENTE DEL CONSEJO
DIRECTIVO

Secretario
SECRETARIO DEL CONSEJO
DIRECTIVO

0006535



MINSALUD



TODOS POR UN
NUEVO PAÍS
PAZ EQUIDAD EDUCACIÓN

IDENTIFICACIÓN ÚNICA DEL TALENTO HUMANO EN SALUD

RODRIGO ARTURO CHAPARRO ESPINOSA

C.C o C.E. 74862059

Profesión u Ocupación

MEDICO CIRUJANO

Especialidad

ANESTESIOLOGIA

Institución de Educación

U.P.T.C.

Ciudad TUNJA

Fecha de expedición diploma

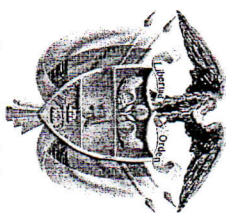
Fecha de inscripción RETHUS

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13/06/2008

21/04/2016





Libertad y Orden

Universidad Militar Nueva Granada

En consideración a que:

Rodrigo Arturo Chaparro Espinosa

U.C. 74.862.059 expedida en Bogotá

ha cumplido en

Hospital Universitario Clínica San Rafael

con todos los requisitos exigidos, le confiere el título de

Especialista en Anestesiología

En constancia se firma el presente Diploma en Bogotá, D.C.

a los 17 días del mes de Marzo de 2016.

Rector

Acta de Inscripción PG-1016-UMNG
Registro PG-1016

Jefe División Registro y Control Académico

Vicerrector Académico

Director

Decano de la Facultad

Registro Oficial
Anotado al folio 28 Libro 08
Folios 03 Año 2016
Bogotá, D.C. República de Colombia

LA UNIVERSIDAD NACIONAL DE COLOMBIA



FACULTAD DE Medicina

TENIENDO EN CUENTA QUE

Hernán Sepúlveda Martínez
C.C. 79.445.101 de Bogotá D.C.

CUMPLIO SATISFACTORIAMENTE
TODOS LOS REQUISITOS REGLAMENTARIOS DEL PROGRAMA
DE ESTUDIOS PARA GRADUADOS LE CONFIERE EL TÍTULO DE

Especialista en Cirugía General

EN LA CIUDAD DE Bogotá a 12 de Marzo DE 1998


RECTOR DE LA UNIVERSIDAD


DECANO DE LA FACULTAD


SECRETARIO GENERAL DE LA UNIVERSIDAD


SECRETARIO DE LA FACULTAD



ALCALDÍA MAYOR
DE BOGOTÁ D.C.



SECRETARÍA DE SALUD

CERTIFICADO DE INSCRIPCION

HERNAN
SEPULVEDA MARTINEZ

C.C. 79445101

MEDICO(A)

Expedicion

24/01/2011