Programa de Doctorado en Ciencias de la Salud

TROMBOS EN CAVIDADES CARDIACAS DERECHAS EN PACIENTES CON TROMBOEMBOLIA PULMONAR AGUDA SINTOMÁTICA. PRONÓSTICO Y TRATAMIENTO

TESIS DOCTORAL

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ESTRUCTURA

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Artículo 1

Deisy Barrios, Vladimir Rosa-Salazar, David Jiménez, Raquel Morillo, Alfonso Muriel, Jorge del Toro, Luciano López-Jiménez, Dominique Farge-Bancel, Roger Yusen, Manuel Monreal, RIETE investigators. Right heart thrombi in pulmonary embolism. Eur Respir J. 2016 Nov; 48(5): 1377-1385.

Artículo 2

Deisy Barrios, Vladimir Rosa-Salazar, Raquel Morillo, Rosa Nieto, Sara Fernández, José Luis Zamorano, Manuel Monreal, Adam Torbicki, Roger Yusen, David Jiménez. Prognostic significance of right heart thrombi in patients with acute symptomatic pulmonary embolism. Systematic review and meta-analysis. Chest. 2017 Feb; 151(2): 409-416.

Artículo 3

Deisy Barrios, Jeremy Chavant, David Jiménez, Laurent Bertoletti, Vladimir Rosa-Salazar, Alfonso Muriel, Alain Viallon, Carmen Fernández-Capitán, Roger Yusen, Manuel Monreal. Treatment of right heart thrombi associated with acute pulmonary embolism. Am J Med. 2017 May; 130(5): 588-595.

ABREVIATURAS Y ACRÓNIMOS

BNP: péptido natriurético cerebral

DVD: disfunción del ventrículo derecho

EPOC: enfermedad pulmonar obstructiva crónica

ETT: ecocardiografía transtorácica

ETV o ETEV: enfermedad tromboembólica venosa

FC: frecuencia cardiaca

FVC: filtro de vena cava

HBPM: heparina de bajo peso molecular

HNF: heparina no fraccionada

IC: intervalo de confianza

ICC: insuficiencia cardiaca congestiva

P: significación estadística

PESI: Pulmonary Embolism Severity Index

PESIs: PESI simplificada

RIETE: Registro Informatizado de Pacientes con Enfermedad TromboEmbólica

$SatO_2$: saturación de la hemoglobina por el oxígeno

TAS: tensión arterial sistólica

TC: tomografía computarizada

TCD: trombos en cavidades cardiacas derechas

TEP: tromboembolia de pulmón

TVP: trombosis venosa profunda

VD: ventrículo derecho

INTRODUCCIÓN

Generalidades

La tromboembolia pulmonar (**TEP**) representa un importante problema de salud pública y es potencialmente mortal. Consiste en el enclavamiento en las arterias pulmonares de un trombo in situ o procedente de otro lugar del sistema venoso profundo (1). Aunque, en la mayoría de las ocasiones, el embolo proviene de una trombosis venosa profunda (**TVP**) de las extremidades inferiores, este puede tener otras localizaciones como: extremidades superiores, venas prostáticas, renales, uterinas y cavidades cardiacas derechas, entre otras.

La enfermedad tromboembólica venosa (**ETEV)**, conformada por la TEP y/o la TVP, es una enfermedad multicausal influenciada por uno o varios factores etiológicos (**Tabla 1**). En presencia de estos factores (reversibles o permanentes), la ETEV es provocada (2,3), mientras que es no provocada (o idiopática), cuando no se evidencia causa que lo justifique (4). La presencia o ausencia de un factor de riesgo desencadenante influye en la decisión sobre la duración del tratamiento anticoagulante (4).

Entre los factores de riesgo para ETEV destacan la cirugía, inmovilización, anticonceptivos orales, terapia de sustitución hormonal, embarazo, o vuelos transatlánticos. Todas las neoplasias aumentan el riesgo de ETEV, aunque varían según el tipo de cáncer asociado; las neoplasias hematológicas y los tumores de pulmón, gastrointestinal, páncreas y cerebro se asocian con más frecuencia a ETEV (4).

Otros factores que predisponen a la enfermedad tromboembólica son: trombosis previas, obesidad, hipercolesterolemia, hábito tabáquico, diabetes mellitus, hipertensión arterial, enfermedades mieloproliferativas crónicas como la policitemia, el síndrome antifosfolípido, la hiperhomocistinemia (5–7), las trombofilias hereditarias (como la mutación G1691A del gen del factor V [factor

V Leiden], la mutación G20210A del gen de la protrombina [factor II] y la mutación homocigota C677T en el gen de la metilentetrahidrofolato reductasa, el déficit de antitrombina, de proteína C y de proteína S, las disfibrinogenemias, la homocistinuria homocigota y las concentraciones elevadas de factor VIII determinadas por los grupos sanguíneos A o B) (8).

Varios estudios han demostrado que la presencia de trombofilia hereditaria o adquirida es significativamente mayor en pacientes con ETEV que en pacientes sin esta (9–11).

Tabla 1. Factores de riesgo para la enfermedad tromboembólica venosa

Riesgo alto	Riesgo moderado	Riesgo bajo
• Cirugía mayor • Politraumatismo • Prótesis o fractura de cadera o rodilla • Lesión espinal	• Inmovilización con órtesis de miembros inferiores • Parálisis de miembros inferiores • TEP o TVP previa • Embarazo o puerperio • Terapia hormonal sustitutiva • Trombofilia • Neoplasias • Catéteres o dispositivos venosos centrales • Tratamiento antipsicótico • Enfermedad inflamatoria intestinal • Enfermedades mieloproliferativas • Cirugía de rodilla • Quimioterapia	• Obesidad • Viajes prolongados (>6 horas) • Cirugía laparoscópica • Várices • Edad avanzada • Reposo en cama > 3 días • Edad avanzada

Pronóstico y tratamiento

La TEP tiene un amplio espectro de manifestaciones clínicas, desde la ausencia de síntomas (la llamada TEP incidental) hasta la inestabilidad hemodinámica (hipotensión y shock), lo que hace imprescindible una adecuada estratificación pronóstica para emplear las estrategias terapéuticas más adecuadas en función de la gravedad del paciente (12).

Algunos estudios revelan que hasta un 10% de los pacientes con TEP pueden debutar con compromiso hemodinámico (13). El tratamiento de elección en este grupo de pacientes es la fibrinolisis sistémica, si no hay contraindicaciones para su uso (4,14). Al otro lado del espectro, hay pacientes normotensos con TEP que se presentan con pocos síntomas. El tratamiento consiste en el uso de heparina de bajo peso molecular (**HBPM**), heparina no fraccionada (**HNF**) o fondaparinux como puente para la anticoagulación oral (acenocumarol, dabigatrán o edoxabán) o rivaroxabán o apixabán desde el momento del diagnóstico (12,15). Aunque estos pacientes son habitualmente ingresados y suelen evolucionar favorablemente, la mortalidad precoz oscila entre un 2 y un 8% (13). Por tanto, la estratificación de este grupo de pacientes normotensos resulta fundamental por 2 razones (4):

- Los pacientes de menor riesgo podrían ser tratados de forma ambulatoria.
- Los pacientes con mayor riesgo pueden beneficiarse de vigilancia hospitalaria intensiva y de formas más agresivas de tratamiento.

A lo largo de los años, se han desarrollado diferentes factores pronósticos para clasificar a los pacientes normotensos con TEP, dentro de las cuales se encuentran: la disfunción del ventrículo derecho (**DVD**) (valorada mediante ecocardiografía transtorácica o tomografía computarizada [**TC**] de tórax), la carga trombótica, el daño miocárdico (determinado por biomarcadores cardiacos, como el péptido natriurético cerebral [**BNP y NT-pro-BNP**], o las troponinas cardiacas), o las características clínicas del paciente (4,16).

Las escalas clínicas pronósticas son instrumentos útiles para seleccionar a pacientes de riesgo bajo con TEP aguda sintomática. La escala clínica más extensamente validada para identificar a pacientes con TEP de riesgo bajo es la Pulmonary Embolism Severity Index (**PESI)** (16,17). Este modelo clasifica a los pacientes con TEP en 5 clases (I-V) de riesgo de muerte por cualquier causa y complicaciones en los primeros 30 días después del diagnóstico. Incluye 11 variables clínicas habitualmente disponibles en el momento del diagnóstico de la TEP: edad, sexo masculino, cáncer, insuficiencia cardiaca, enfermedad pulmonar crónica, frecuencia cardiaca (**FC**) ≥110 latidos por minuto (**lpm**), tensión arterial sistólica (**TAS**) <100mmHg, frecuencia respiratoria ≥30 respiraciones por minuto (**rpm**), temperatura <36ºC, estado mental alterado y saturación de la hemoglobina (**$satO_2$**) <90%. El modelo asigna un número de puntos determinado a cada característica, y para cada paciente se calcula la puntuación total mediante la suma de estos puntos y la edad del paciente en años. El total de puntos asignados se corresponde con las clases de riesgo de la siguiente forma: ≤65 puntos, clase I, riesgo muy bajo; 66-85 puntos, clase II, riesgo bajo; 86-105 puntos, clase III, riesgo intermedio; 106-125 puntos, clase IV, riego alto; >125 puntos, clase V, riesgo muy alto (**Tabla 2**). En el estudio original, el modelo clasificó un 41% de los pacientes en las clases I y II, y un 59% en las clases III, IV y V. El 2% de los pacientes en las clases I y II (intervalo de confianza [**IC**] del 95%, 1,7-2,6%) y el 14% de los pacientes en las clases III-V (IC del 95%, 13,1-14,9%) fallecieron en los primeros 30 días después del diagnóstico de la TEP (16).

Posteriormente se derivó y validó externamente una versión simplificada de la escala **PESI** (12). La escala PESI simplificada (**PESIs**), en comparación con la original**,** es más sencilla de utilizar y tiene un menor número de variables (12,18): edad (>80 años vs. ≤80 años), historia de cáncer (sí/no), historia de enfermedad cardiopulmonar crónica (sí/no), frecuencia cardiaca (≥110 lpm vs. <110 lpm), TAS (<100 mmHg vs. ≥100 mmHg) y $satO_2$ (<90% vs. ≥90%). La escala PESIs clasifica los pacientes en riesgo bajo si no presentan ninguna de las variables, y en riesgo alto si presentan una o más variables (**Tabla 3**). En un metanálisis reciente, la sensibilidad de la escala PESIs fue de 0,92 (IC del 95%, 0,89-0,94) para la muerte por cualquier causa a corto plazo (19). Los criterios de HESTIA

se han validado para identificar aquellos pacientes con TEP candidatos a tratamiento ambulatorio (20). Incluyen las siguientes variables: inestabilidad hemodinámica (sí/no), necesidad de trombolisis o embolectomía (sí/no), alto riesgo de sangrado o sangrado activo (sí/no), necesidad de oxígeno suplementario por más de 24 horas para mantener satO_2 >90% (sí/no), diagnóstico de la TEP durante el tratamiento anticoagulante (sí/no), dolor severo con necesidad de analgesia intravenosa por más de 24 horas (sí/no), incapacidad (por razones médicas o sociales) para recibir con éxito el tratamiento en domicilio (sí/no), aclaramiento de creatinina <30mL/min (sí/no), insuficiencia hepática severa (sí/no), embarazo (sí/no), antecedentes de trombocitopenia inducida por heparina (sí/no). Un estudio de cohorte, prospectivo, multicéntrico y de brazo único utilizó los criterios de HESTIA para seleccionar pacientes que fueron tratados con nadroparina subcutánea una vez al día en su domicilio. De los 581 pacientes incluidos, 297 (51%) fueron tratados ambulatoriamente. De ellos 6 (2,0%, IC del 95%, 0,8-4,3%) pacientes sufrieron una ETEV recurrente (cinco TEP [1,7%] y una TVP [0,3%]), mientras que solo dos pacientes (0,7%; IC del 95%, 0,1-2,4%) experimentaron una hemorragia grave y tres pacientes (1,0%; IC del 95%, 0,2-2,9%) murieron (ninguno debido a la propia TEP) durante los 3 primeros meses de seguimiento. Este estudio proporcionó evidencia de que los criterios de HESTIA pueden identificar razonablemente a pacientes con riesgo bajo de complicaciones tras el diagnóstico de la TEP y que pueden tratarse de forma ambulatoria (20).

Wicki y colaboradores (21) realizaron un estudio prospectivo que incluyó 296 pacientes ambulatorios diagnosticados de TEP aguda sintomática e identificaron seis predictores independientes, evaluados en el momento de la presentación, de eventos adversos (muerte, recurrencia tromboembólica y sangrado mayor) durante los primeros tres meses de tratamiento (escala de Ginebra). Estos seis predictores son: cáncer, insuficiencia cardiaca, historia de TVP previa, TAS <100 mmHg, PaO_2 <8kPa y la presencia de TVP concomitante objetivada mediante ecografía-doppler venosa de miembros inferiores. Para cada paciente, la puntuación de riesgo de la escala de Ginebra se obtiene por la suma de puntos por la presencia de cáncer e hipotensión (dos puntos por cada uno) y un punto por la presencia de cada uno de los otros predictores. Los pacientes con una

puntuación ≤2 son asignados a la categoría de riesgo bajo, y aquellos con una puntuación ≥3 a la categoría de riesgo alto (**Tabla 4**). El modelo clasificó un 61% de los pacientes de riesgo bajo y un 39% de los pacientes de riesgo alto. El 2% de los pacientes de riesgo bajo (IC del 95%, 0,1-4,4%) y el 26% de los pacientes de riesgo alto (IC del 95%, 17,0-35,3%) presentaron un evento adverso en los tres primeros meses después del diagnóstico de la TEP.

Posteriormente, la escala de Ginebra ha sido validada de forma retrospectiva por Nendaz y colaboradores en 199 pacientes consecutivos diagnosticados de TEP aguda sintomática. Ciento cincuenta y nueve pacientes (80%) fueron clasificados de riesgo bajo. Ocho de ellos (5%, IC del 95%, 2,6-9,6%) experimentaron un evento adverso durante los tres primeros meses de seguimiento (un sangrado fatal, cuatro sangrados no fatales, una recurrencia en forma de TVP y dos muertes por cáncer), comparado con 11 pacientes en el grupo de riesgo alto (27,5%; IC del 95%, 16,1-42,8%) (22).

Se ha publicado un estudio que comparó las escalas de riesgo PESI y Ginebra para predecir la mortalidad a 30 días en 599 pacientes consecutivos ambulatorios diagnosticados de TEP. La escala PESI clasificó una proporción menor de pacientes de riesgo bajo o muy bajo (36%; IC del 95%, 32-40%), en comparación con la escala de Ginebra (84%; IC del 95%, 81-87%) ($p < 0,0001$). Los pacientes clasificados de riesgo bajo por la escala PESI tuvieron menor mortalidad que los pacientes clasificados de riesgo bajo con la escala de Ginebra (0,9% vs. 5,6%; $p < 0,0001$) (23).

Todos estos modelos pronósticos identifican de forma fiable a un grupo de pacientes con TEP y riesgo bajo de muerte por cualquier causa en los 3 primeros meses después del diagnóstico. Este grupo de paciente podría beneficiarse de un ingreso hospitalario corto o incluso del tratamiento ambulatorio de la enfermedad, lo que mejora su calidad de vida y disminuye el gasto sanitario (24).

Para la identificación de pacientes con TEP de riesgo intermedio-alto (pacientes hemodinámicamente estables con riesgo alto de complicaciones) se recomienda la combinación de variables clínicas que reflejan la situación hemodinámica del

paciente, pruebas de imagen para identificar la presencia o ausencia de DVD, y biomarcadores para identificar la presencia o ausencia de isquemia miocárdica.

Los marcadores bioquímicos cardiacos, fundamentalmente la troponina y el BNP**,** han emergido como herramientas prometedoras para la estratificación de los pacientes con TEP. Jiménez y colaboradores realizaron un metanálisis de estudios que incluían pacientes normotensivos con TEP agudo para evaluar el pronóstico (en términos de mortalidad por cualquier causa) de la elevación de troponina cardiaca. La elevación de los niveles de troponina se asociaba a mayor mortalidad (odds ratio [**OR**], 4,3; IC del 95%, 2,1-8,5). Sin embargo, la magnitud de esta asociación no es suficiente como para justificar la escalada de tratamiento (25).

Se considera que la DVD debida a la sobrecarga aguda de presión es la primera causa de muerte en los pacientes con TEP grave. La elevación brusca de las resistencias vasculares pulmonares produce la dilatación y DVD mediante el mecanismo de Frank-Starling. El aumento de la presión y el volumen del ventrículo derecho (**VD**) genera un aumento en la tensión de la pared y elongación de los miocitos, prolongando el tiempo de contracción del VD. La dilatación del VD da lugar a una desviación del tabique interventricular hacia el ventrículo izquierdo (**VI**) y puede llevar a una reducción del gasto cardiaco, contribuir a la hipotensión sistémica, a la inestabilidad hemodinámica e incluso al shock circulatorio y a la muerte (26,27).

Varios estudios han evaluado el significado pronóstico de la dilatación del VD identificada mediante angioTC de tórax en pacientes con TEP aguda sintomática (28,29). Una revisión sistemática analizó los datos de un total de 10 estudios (2.288 pacientes) prospectivos y retrospectivos, con en el objetivo de evaluar la utilidad pronóstica de la dilatación del VD determinada mediante angioTC de tórax en los pacientes con TEP aguda sintomática (30). Todos los estudios tenían un punto de corte del cociente VD/VI entre 0,9 y 1,5. En este análisis se observó que la dilatación del VD medida por el angioTC de tórax se asocia de forma significativa con la mortalidad por cualquier causa (OR 1,8; IC del 95%, 1,3-2,6), con la mortalidad por TEP (OR 7,4; IC del 95%, 1,4-39,5) y con las complicaciones relacionadas con la propia TEP (OR 2,4; IC del 95%, 1,2-4,7).

Estos resultados fueron similares a los del metanálisis de Meinel y colaboradores, donde se evidenció que la dilatación del VD medida por angioTC de tórax se asociaba a un riesgo 2,5 veces mayor de mortalidad por cualquier causa (OR 2,5; IC del 95%, 1,8-3,5) y 5 veces más riesgo de mortalidad por la propia TEP (OR 5,0; IC del 95%, 2,7-9,2) (31).

El estudio PROTECT (PROgnosTic valuE of CT study) fue un estudio prospectivo y multicéntrico que analizó el significado pronóstico de la dilatación del VD en la angioTC de tórax de 848 pacientes hemodinámicamente estables con TEP aguda sintomática. El estudio definió la dilatación del VD como un VD/VI >0,9 en el eje corto axial de las cámaras cardiacas. Los resultados de este estudio objetivaron una asociación no estadísticamente significativa (OR 1,29; IC del 95%, 0,75-2,24; p= 0,358) entre la dilatación del VD medida por angioTC de tórax y un curso clínico complicado en los primeros 30 días después del diagnóstico de la TEP (32).

Aunque sabemos que la ecocardiografía transtorácica (**ETT**) no se recomienda como prueba de imagen de rutina para el diagnóstico de la TEP, es útil para identificar, de una forma rápida y precisa, a pacientes normotensos con TEP y peor pronóstico a corto plazo.

Los criterios ecocardiográficos pronósticos más usados habitualmente en los pacientes con TEP incluyen: la dilatación del VD, aumento del cociente VD/VI, hipocinesia de la pared libre de VD, incremento de la velocidad del flujo de regurgitación tricuspídea, disminución de la excursión sistólica del anillo tricuspídeo (**TAPSE**), o combinaciones de los anteriores. Estos hallazgos han sido identificados como predictores independientes de complicaciones en pacientes con TEP aguda sintomática, pero su medición es operador dependiente, y los puntos de corte que definen mal pronóstico no han sido convenientemente estandarizados (33,34).

La ETT también proporciona información pronóstica en los pacientes con TEP aguda sintomática cuando se identifica un foramen oval permeable o la presencia de trombos en cavidades cardiacas derechas (**TCD**).

Los TCD pueden desarrollarse in situ o en asociación a enfermedad

cardiovascular como valvulopatías y fibrilación auricular, o pueden proceder de otras localizaciones, desde donde migran al corazón derecho (35,36). Aquellos provenientes del sistema venoso periférico que migran de forma accidental se denominan tipo A (conocidos como trombos en tránsito), y se caracterizan por ser extremadamente móviles debido a su morfología y son los que habitualmente se asocian a los episodios de TEP (37). Por el contrario, los trombos que se desarrollan en las cámaras cardiacas derechas se denominan tipo B (poco móviles y adheridos a la pared auricular o ventricular), mientras que el tipo C es muy infrecuente y son similares a los mixomas (38).

Los datos previamente publicados sugieren que los TCD son un hallazgo infrecuente (38,39). Aunque el uso extendido de la ETT para pronosticar a los pacientes con TEP ha incrementado la detección de TCD, su prevalencia sigue siendo baja (40), aproximadamente de un 4% (41). ICOPER fue un registro prospectivo y multicéntrico que incluyó 1.135 pacientes con TEP aguda sintomática a los que se realizó una ETT (41). De ellos, 42 (4%) pacientes presentaban TCD concomitante.

No se conoce el significado pronóstico de la coexistencia de TCD en los pacientes con TEP aguda sintomática y no hay evidencias suficientemente robustas sobre el mejor tratamiento de estos pacientes (38,40). Algunos estudios sugieren que la presencia de TCD en pacientes con TEP aguda sintomática se asocia a un riesgo aumentado de muerte a corto plazo. Un metanálisis publicado en 2002 analizó 177 casos con TEP y TCD y observó una mortalidad del 28,6% en aquellos pacientes que habían recibido terapia anticoagulante y hasta de un 100% en los que no recibieron tratamiento (42), mientras que Chartier y colaboradores analizaron 38 casos de pacientes con TEP y TCD y observaron una mortalidad por cualquier causa cercana al 45% (39). En ICOPER, los pacientes con TEP y TCD estaban hemodinámicamente más comprometidos (es decir, más frecuentemente con DVD, TAS <90 mmHg o FC >110 lpm) que aquellos con TEP sin TCD. Además, la mortalidad de los pacientes con TEP y TCD a los 14 días y a los 3 meses de seguimiento era significativamente mayor que la de los que no presentaban TCD (21% vs. 11%; p =0,032; y 29% vs. 16%, p =0,036, respectivamente) (41).

Aunque la Sociedad Europea de Cardiología (ESC) sugiere el uso de trombolisis en pacientes con TEP aguda sintomática y presencia de TCD (4), hasta la fecha no existen estudios que determinen qué pacientes podrían beneficiarse de un tratamiento más agresivo como la terapia de reperfusión.

Tabla 2. Pulmonary embolism severity index (PESI)

Variable	**Puntuación**
Edad	Años
Sexo masculino	+10
Historia de cáncer	+30
Historia de insuficiencia cardiaca	+10
Historia de enfermedad pulmonar crónica	+10
Frecuencia cardiaca ≥110 lpm	+20
Presión sistólica <100 mmHg	+30
Frecuencia respiratoria ≥30 rpm	+20
Temperatura <36ºC	+20
Estado mental alterado	+60
Saturación arterial de oxihemoglobina <90%	+20
La puntuación total para un paciente dado se obtiene sumando la edad del paciente en años y los puntos correspondientes a cada variable. La puntuación corresponde con las siguientes clases de riesgo: ≤65, clase I; 66-85, clase II; 86-105, clase III; 106-125, clase IV; y >125, clase V. Las clases I y II corresponden al riesgo bajo.	

Tabla 3. Escala PESI simplificada (PESIs)

Variable	**Puntuación**
Edad >80 años	1
Historia de cáncer	1
Historia de enfermedad cardiopulmonar crónica	1
Frecuencia cardiaca ≥110 lpm	1
Presión sistólica <100 mmHg	1
Saturación arterial de oxihemoglobina <90%	1
La puntuación total para un paciente dado se obtiene sumando los puntos. La puntuación corresponde con las siguientes clases de riesgo: 0, riesgo bajo; ≥ 1, riesgo alto.	

Tabla 4. Escala de riesgo de Ginebra

Variable	**Puntuación**
Historia de cáncer	2
Historia de insuficiencia cardiaca	1
TVP previa	1
TVP concomitante mediante ecografía	1
Presión sistólica <100 mmHg	1
PaO_2 <8kPa	1

TVP, trombosis venosa profunda.

La puntuación total para un paciente dado se obtiene sumando los puntos. La puntuación corresponde con las siguientes clases de riesgo: ≤2, riesgo bajo; ≥3, riesgo alto.

HIPÓTESIS

I. Hipótesis conceptual

La presencia de trombos en cavidades cardiacas derechas es un hallazgo infrecuente en pacientes con tromboembolia de pulmón aguda sintomática.

La presencia de trombos en cavidades cardiacas derechas empeora el pronóstico de los pacientes con tromboembolia pulmonar aguda sintomática.

El uso de tratamientos de reperfusión mejora el pronóstico de los pacientes con tromboembolia de pulmón y trombos en cavidades cardiacas derechas.

II. Hipótesis operativa

Se identifican trombos en cavidades cardiacas derechas en menos del 5% de los pacientes con tromboembolia de pulmón aguda sintomática.

La presencia de trombos en cavidades cardiacas derechas multiplica por dos el riesgo de complicaciones a corto plazo en pacientes con tromboembolia de pulmón.

El uso de tratamientos de reperfusión, comparados con la anticoagulación, reduce un 50% el riesgo de complicaciones a corto plazo en pacientes con tromboembolia de pulmón y trombos en cavidades cardiacas derechas.

OBJETIVOS

Podemos resumir nuestros objetivos en los siguientes puntos:

I. OBJETIVO PRINCIPAL

1. Evaluar el significado pronóstico de la presencia de trombos en cavidades cardiacas derechas de pacientes con TEP aguda sintomática.

II. OBJETIVOS SECUNDARIOS

1. Determinar la prevalencia de trombos en cavidades cardiacas derechas en pacientes con TEP aguda sintomática.

2. Identificar las variables predictoras de la presencia de trombos en cavidades cardiacas derechas en pacientes con TEP aguda sintomática.

3. Evaluar el efecto de los tratamientos de reperfusión (comparados con la anticoagulación) para pacientes con TEP aguda sintomática y trombos en cavidades cardiacas derechas.

RESULTADOS

I. RESUMEN DEL ARTÍCULO 1

Título: Trombos en cavidades cardiacas derechas en pacientes con tromboembolia pulmonar.

No se ha aclarado la prevalencia, las variables predictoras de TCD ni el significado pronóstico de los mismos en pacientes con TEP aguda sintomática.

En este estudio se incluyeron pacientes con TEP aguda sintomática del Registro Informatizado de la Enfermedad TromboEmbólica (**RIETE**), y se evaluó la prevalencia, las variables predictoras de TCD, y la asociación entre la presencia de TCD y la mortalidad por cualquier causa y por la propia TEP, las recurrencias trombóticas y el sangrado mayor en los primeros 30 días después del inicio del tratamiento de pacientes con TEP.

De los 12.441 pacientes con TEP que tenían una ecocardiografía basal realizada, el 2,6% (IC del 95% 2,3-2,9%) tenían TCD. Los factores predictores de TCD fueron: pacientes más jóvenes (edad <80 años), antecedentes de sangrado previo, insuficiencia cardíaca congestiva (**ICC**), cáncer, sincope, TAS <100 mmHg y satO_2 <90%.

Los pacientes con TEP y TCD tuvieron un riesgo significativamente mayor de mortalidad por cualquier causa (OR ajustado, 2,50; IC del 95%, 1,62-3,84; p <0,001) y de muerte por la propia TEP (OR ajustado 4,29; IC del 95%, 2,45-7,48; p <0,001) durante los primeros 30 días del diagnóstico de la TEP. La coexistencia de TEP y TCD se asoció a un riesgo significativamente mayor de recurrencia

durante el seguimiento (1,8% vs. 0,7%; p =0,04). El riesgo de sangrado mayor fue similar en pacientes con y sin TCD.

En pacientes con TEP aguda sintomática la presencia de TCD es infrecuente. Los pacientes con TEP y TCD tienen peor pronóstico que aquellos pacientes con TEP sin TCD.

Artículo 1

ORIGINAL ARTICLE
PULMONARY VASCULAR DISEASES

Right heart thrombi in pulmonary embolism

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ABSTRACT There is a lack of comprehensive data on the prevalence, predictors and prognostic significance of right heart thrombi (RHT) in pulmonary embolism.

In this study of patients with pulmonary embolism from the Registro Informatizado de la Enfermedad TromboEmbólica (RIETE) registry, we assessed the prevalence and predictors of RHT, and the association between the presence of RHT and the outcomes of all-cause mortality, pulmonary embolism-related mortality, recurrences, and major bleeding through 30 days after initiation of pulmonary embolism treatment.

Of 12 441 patients with pulmonary embolism and baseline echocardiographic data, 2.6% had RHT. The following increased the risk of RHT: younger age, previous bleeding, congestive heart failure, cancer, syncope, systolic blood pressure <100 mmHg, and arterial oxyhaemoglobin saturation <90%. Patients with RHT were significantly more likely to die from any cause (adjusted OR 2.50 (95% CI 1.62–3.84); p<0.001) and from pulmonary embolism (adjusted OR 4.29 (95% CI 2.45–7.48); p<0.001) during follow-up. RHT was associated with an increased risk of recurrence during follow-up (1.8% *versus* 0.7%; p=0.04). Major bleeding was similar in patients with and without RHT.

In patients presenting with pulmonary embolism, RHT is relatively infrequent. Patients with RHT had a worse outcome when compared with those without RHT.

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Right heart thrombus is an independent predictor of death in patients with acute pulmonary embolism http://ow.ly/y5i5302CDCS

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Artículo 1

Introduction

Pulmonary embolism is a potentially life-threatening cardiovascular condition [1]. Acute pulmonary embolism has a wide spectrum of clinical syndromes and varying clinical outcomes [2, 3]. Assessment of prognosis is of crucial importance for the therapeutic choices in patients with pulmonary embolism [4, 5].

It is commonly believed that right heart thrombi (RHT) are rare in patients with acute symptomatic pulmonary embolism [6, 7]. In these patients, the increased use of two-dimensional echocardiography for prognostic purposes has led to increased detection of RHT, and the true frequency of this complication is not well established. There is also limited documentation concerning the prognostic significance of concomitant RHT at the time of acute pulmonary embolism diagnosis [8]. Therapeutic options in these patients consist of anticoagulation, thrombolysis or surgical embolectomy, but the optimal management remains controversial.

The Registro Informatizado de la Enfermedad TromboEmbólica (RIETE) registry is an ongoing, multicentre, international, prospective registry of consecutive patients with symptomatic, objectively confirmed, acute venous thromboembolism (VTE) [9–11]. RIETE has sufficiently large sample size and study duration to compare the clinical characteristics and outcome of patients with RHT and of similarly treated patients without RHT. The objective of this study was thus three-fold: to estimate the prevalence of RHT; to identify the strongest predictors of RHT in pulmonary embolism patients; and to assess the association between RHT and short-term clinical outcomes.

Methods

Study design

This retrospective study used prospectively collected data from patients enrolled in the RIETE registry [1, 9]. All patients provided written or oral consent for participation in the registry in accordance with local ethics committee requirements.

Patients

At each participating site, RIETE investigators aimed to enroll consecutive patients that had acute symptomatic or asymptomatic VTE confirmed by objective testing that consisted of high probability ventilation-perfusion scintigraphy [12], positive contrast-enhanced, pulmonary embolism-protocol, helical chest computed tomography for pulmonary embolism [13], or lower limb venous compression ultrasonography positive for proximal deep vein thrombosis (DVT) [14]. Only patients diagnosed with acute symptomatic pulmonary embolism were eligible. The only exclusion criterion consisted of inability to complete transthoracic echocardiography testing.

Baseline variables

Patients enrolled in RIETE had data collected from around the time of pulmonary embolism diagnosis that included but was not limited to: age; sex; body weight; presence of coexisting conditions such as chronic heart or lung disease; recent (<30 days prior to pulmonary embolism) major bleeding; presence of risk factors for pulmonary embolism including active cancer (defined as newly diagnosed cancer or cancer undergoing treatment (*i.e.* surgery, chemotherapy, radiotherapy, hormonal or support therapy), recent immobility (defined as non-surgical patients assigned to bed rest with bathroom privileges for ⩾4 days in the 2 months prior to pulmonary embolism diagnosis), surgery (defined as those who had undergone major surgery in the 2 months prior to pulmonary embolism); clinical signs and symptoms on admission, including heart rate and systolic blood pressure; and laboratory results at hospital admission that included haemoglobin, platelet count and serum creatinine.

Study outcomes

This study used all-cause mortality through 30 days following the diagnosis of pulmonary embolism as the primary endpoint, and 30-day pulmonary embolism-related mortality, recurrent VTE, and major bleeding as secondary endpoints. The RIETE investigators used medical record review to assess vital status. For patients that died, further medical record review, and proxy interviews when necessary, assisted with determining date and cause of death. For deaths confirmed by autopsy or those following a clinically severe pulmonary embolism, either initially or shortly after an objectively confirmed recurrent event, in the absence of any alternative diagnosis, the investigators were instructed to judge death as due to fatal pulmonary embolism. Clinicians at RIETE enrolling sites managed patients with suspected recurrences according to their local practice. Typically, the RIETE investigators defined recurrent DVT as a new noncompressible vein segment, or an increase of the vein diameter by at least 4 mm compared with the last available measurement on venous ultrasonography [15]; recurrent pulmonary embolism as a new ventilation–perfusion mismatch on lung scan or a new intraluminal filling defect on spiral computed tomography of the chest [13]; and major bleeding episodes as those that required a transfusion of at least 2 units of blood, were retroperitoneal, spinal or intracranial, or were fatal [16].

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Artículo 1

Treatment and follow-up

Clinicians at RIETE-enrolling sites managed patients according to their local practice (*i.e.* no standardisation of treatment). In the RIETE registry, most patients received initial anticoagulation with intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin or fondaparinux, and overlap and long-term therapy with an oral anticoagulant. Clinicians administered thrombolytic treatment and/or inotropic support as deemed appropriate. In general, clinicians used thrombolytic treatment of acute pulmonary embolism in patients with cardiogenic shock (*e.g.* persistent systolic arterial pressure <90 mmHg in the setting of clinical signs of organ hypoperfusion (clouded sensorium, oliguria, cold and clammy skin or lactic acidosis)). In most patients with a contraindication to or a failure of anticoagulant treatment (*i.e.* VTE recurrence while on therapeutic doses of anticoagulation), clinicians used inferior vena cava filter therapy followed by anticoagulation if the contraindication resolved. RIETE recorded information related to patient outcomes through 3 months after the diagnosis of the acute pulmonary embolism, and this study analysed outcomes through 30 days after initiation of pulmonary embolism treatment.

Statistical analysis

We used Chi-squared or Fisher's exact tests to compare categorical data between groups. We used the Kolmogorov–Smirnov test to assess continuous data for a normal distribution. We used two-tailed unpaired t-tests to compare normally distributed continuous data between two groups, and we used the Mann–Whitney U-test for non-normally distributed continuous data comparisons.

We evaluated potential demographic and clinical risk factors for RHT in the entire cohort with the use of univariable logistic regression analysis. All variables with a univariable level of significance of <0.1 were included in a backward, stepwise multivariable logistic regression model.

To estimate the outcomes of time to death, Kaplan–Meier probabilities were computed [17], and differences between the groups were assessed with the log-rank test. Survival analyses censored for loss to follow-up (none) and end of study. The study used logistic regression to assess for an independent association between the presence of RHT at the time of presentation with pulmonary embolism and the outcome measures. For the manual backward stepwise multivariable logistic regression model, we assessed variables that had a significance level of $p<0.1$ in univariable analyses. The model retained those variables associated with the outcome at a significance level of $p<0.05$. Interaction terms with type of treatment (anticoagulation *versus* thrombolysis or surgery) and severity of pulmonary embolism (low-, intermediate- and high-risk pulmonary embolism, according to the European Society of Cardiology prognostic model) [5] were tested for significance at an α-level of 0.05. To test the robustness of the findings, the effects of excluding haemodynamically unstable patients (*i.e.* systolic blood pressure <90 mmHg), were assessed. Analyses were performed using SPSS, version 20 for the PC (SPSS, Inc. Chicago, IL, USA).

Results

We identified 30 254 patients with objectively confirmed symptomatic pulmonary embolism enrolled in RIETE during the time period of January 1, 2001, through December 15, 2015. The study excluded 17 813 patients because they did not have complete baseline echocardiographic data required for analyses (58.9%; 95% CI 58.3–59.4%). Patients who were ineligible were older and had more comorbid diseases (cancer, recent surgery, immobility and recent bleeding), but fewer signs of clinical severity (syncope, tachycardia and hypotension) compared with those that were eligible. A total of 12 441 patients (6718 women and 5723 men) were included in the present study (figure 1).

Overall, 325 patients (2.6%; 95% CI 2.3–2.9%) had RHT and 12 116 did not. Patients with RHT differed significantly from those without RHT in pre-existing medical conditions, and in relevant clinical, physiological and laboratory parameters. As shown in table 1, patients with RHT had a higher prevalence of chronic heart disease, cancer, immobilisation or recent major bleeding compared with those without RHT. Patients with RHT were more haemodynamically compromised than patients without RHT, with lower systolic blood pressure, higher heart rate and more frequent hypoxaemia and syncope (table 1). Patients with RHT also had a higher prevalence of renal insufficiency. With respect to similarities, age, prevalence of male sex, dyspnoea, chest pain and concomitant DVT were almost identical in patients with and without RHT, as was the frequency of chronic obstructive pulmonary disease, history of VTE and recent surgery. In the multivariable model, younger age (adjusted OR 1.01 per year; 95% CI 1.01–1.02), previous bleeding (adjusted OR 2.56; 95% CI 1.51–4.34), congestive heart failure (adjusted OR 2.06; 95% CI 1.51–2.81), cancer (adjusted OR 1.46; 95% CI 1.11–1.91), syncope (adjusted OR 1.83; 95% CI 1.42–2.36), systolic blood pressure <100 mmHg (adjusted OR 1.97; 95% CI 1.48–2.63) and arterial oxyhaemoglobin saturation <90% (adjusted OR 1.58; 95% CI 1.23–2.03) remained significantly associated with the presence of RHT. Treatment was significantly different between the two groups: 17.8% of patients with RHT received thrombolysis, compared with 4.9% of patients without RHT and 5.3% in the overall

Artículo 1

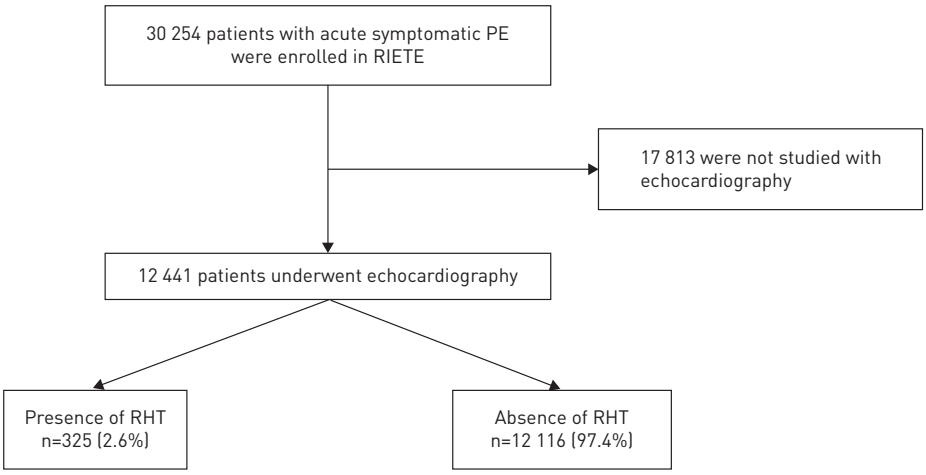

FIGURE 1 Patient flow diagram. PE: pulmonary embolism; RIETE: Registro Informatizado de la Enfermedad TromboEmbólica; RHT: right heart thrombi.

RIETE cohort. Embolectomy was performed in 3.7% of patients with RHT and in 0.9% of patients without RHT (table 1).

RHT and right ventricular function

Patients with RHT had double the frequency of right ventricular hypokinesis (54.3% *versus* 23.4%; p<0.001) and more often had elevated cardiac troponin (51.8% *versus* 36.3%; p<0.001) and BNP levels (87.5% *versus* 70.5%; p<0.01). Patients with RHT had significantly higher systolic pulmonary artery pressure (54.5±19.3 mmHg) than those without RHT (45.1±17.3 mmHg) (p<0.001). Tricuspid annular plane systolic excursion (17.5±5.8 mm *versus* 20.1±6.0 mm; p<0.001) was significantly lower among patients with RHT.

Outcome

Outcome data were available for all patients through the 30-day study follow-up (table 2). Overall, 382 (3.1%) out of 12 441 patients died (95% CI 2.8–3.4%). 122 (1.0%) out of 12 441 patients (95% CI 0.8–1.2%) died from pulmonary embolism, and 260 (2.1%) out of 12 441 patients (95% CI 1.8–2.4%) died from other causes. Other causes of death consisted of cancer (64 (0.5%) out of 12 441 patients), respiratory failure (42 (0.3%) of 12 441 patients), infection (24 (0.2%) out of 12 441 patients), major bleeding (22 (0.2%) out of 12 441 patients), congestive heart failure (18 (0.1%) out of 12 441 patients), miscellaneous diseases (58 (0.5%) out of 12 441 patients) and unknown (32 (0.3%) out of 12 441 patients). 28 deaths (8.6%) out of 325 patients (95% CI 5.8–12.2%) occurred in the group of patients entering the study with acute pulmonary embolism and RHT, whereas 354 deaths (2.9%) out of 12 116 patients (95% CI 2.6–3.2%) occurred in the group without RHT (absolute difference 5.7%, 95% CI 3.1–9.3%; p<0.001). Patients with acute pulmonary embolism and RHT had a significantly higher cumulative mortality than the patients with acute pulmonary embolism without RHT (p<0.001, log rank test) (figure 2). The multivariable model found that age (adjusted OR 1.03, 95% CI 1.02–1.04; p<0.001), cancer (adjusted OR 4.03, 95% CI 3.26–4.98; p<0.001), recent major bleeding (adjusted OR 1.73, 95% CI 1.03–2.88; p=0.04), recent immobility (adjusted OR 2.34, 95% CI 1.87–2.92; p<0.001), systolic blood pressure <100 mmHg (adjusted OR 2.24, 95% CI 1.71–2.93; p<0.001), heart rate ⩾110 beats·min^{-1} (adjusted OR 1.28, 95% CI 1.01–1.63; p=0.04) and RHT (adjusted OR 2.50, 95% CI 1.62–3.84; p<0.001) independently predicted 30-day all-cause mortality (table 3).

Pulmonary embolism-related mortality within 30 days of pulmonary embolism diagnosis occurred more frequently in patients with RHT (5.2% *versus* 0.9%; absolute difference 4.3%, 95% CI of the absolute difference 2.4–7.4%; p<0.001). Recurrent VTE within 30 days of pulmonary embolism diagnosis occurred in six patients (1.8%, 95% CI 0.7–4.0%) entering the study with RHT and in 87 patients (0.7%, 95% CI 0.6–0.9%) without RHT (absolute difference 1.1%, 95% CI of the absolute difference 0.1–3.2%; p=0.04) (table 2). 440 patients (3.5%, 95% CI 13.2–3.9%) suffered a major bleeding episode. 15 bleeds (15 (4.6%) out of 325 patients, 95% CI 2.6–7.5%) occurred in the group of patients entering the study with acute pulmonary embolism and RHT, whereas 425 bleeds (425 (3.5%) out of 12 116 patients, 95% CI 3.2–3.8%) occurred in the group without RHT (absolute difference 1.1%, 95% CI of the absolute difference −0.7–4.0%; p=0.36). Figure 3 shows a significant interaction between the type of treatment (anticoagulation *versus* thrombolysis or surgery), the severity of pulmonary embolism (low-, intermediate- and high-risk)

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Artículo 1

TABLE 1 Clinical characteristics of patients with or without right heart thrombi

	Presence of right heart thrombi	Absence of right heart thrombi	p-value
Patients n	325	12 116	
Clinical characteristics			
Age years	64.2±17.3	65.9±17.2	0.08
Age >80 years	57 (17.5)	2485 (20.5)	0.19
Male sex	149 (45.8)	5574 (46.0)	0.95
Weight kg	76.2±15.4	77.2±16.5	0.26
Risk factors for VTE			
History of VTE	54 (16.6)	1744 (14.4)	0.26
Cancer[#]	73 (22.5)	2064 (17.0)	0.01
Recent surgery[¶]	38 (11.7)	1286 (10.6)	0.53
Immobilisation for ⩾4 days[+]	81 (24.9)	2386 (19.7)	0.02
Comorbid diseases			
Chronic lung disease	54 (16.6)	1760 (14.5)	0.29
Chronic heart disease	60 (18.5)	1227 (10.1)	<0.001
Recent major bleeding	16 (4.9)	235 (1.9)	<0.001
Clinical symptoms and signs at presentation			
Syncope	98 (30.1)	2138 (17.6)	<0.001
Chest pain	153 (47.1)	5997 (49.5)	0.45
Dyspnoea	279 (85.8)	10 116 (83.5)	0.23
Heart rate ⩾110 beats·min^{-1}	108 (33.2)	2707 (22.3)	<0.001
Arterial oxyhaemoglobin saturation <90%	103 (31.7)	2499 (20.6)	<0.001
Systolic blood pressure <100 mmHg	72 (22.1)	1145 (3.5)	<0.001
Concomitant deep vein thrombosis	151 (46.5)	5396 (44.5)	0.49
Simplified PESI			
Low risk	93 (28.6)	4970 (41.0)	<0.001
High risk	232 (71.4)	7146 (59.0)	<0.001
Echocardiography and cardiac biomarkers			
RV hypokinesis (n=10 918)	157/289 (54.3)	2492/10 629 (23.4)	<0.001
RV/LV >1 (n=1671)	6/40 (15.0)	322/1631 (19.7)	0.46
Systolic pulmonary pressure mmHg	54.5±19.3	45.1±17.3	<0.001
TAPSE mm	17.5±5.8	20.1±6.0	<0.001
Elevated troponin (n=7419)	114/220 (51.8)	2611/7199 (36.3)	<0.001
BNP >100 pg·mL^{-1} (n=1555)	42/48 (87.5)	1063/1507 (70.5)	<0.01
Laboratory findings			
Abnormal creatinine levels (>2 mg·dL^{-1})	84 (25.8)	2266 (18.7)	<0.001
Haemoglobin g·dL^{-1}	13.3±8.7	13.2±3.3	0.64
Treatment used			
Unfractionated heparin	125 (38.5)	1714 (14.1)	<0.001
Low-molecular-weight heparin	212 (65.2)	10 577 (87.3)	<0.001
Thrombolysis	58 (17.8)	597 (4.9)	<0.001
Embolectomy	12 (3.7)	104 (0.9)	<0.001
Inferior vena cava filter	15 (4.6)	396 (3.3)	0.18

Data are presented as mean±SD, n (%) or n/N (%), unless otherwise stated. VTE: venous thromboembolism; PESI: Pulmonary Embolism Severity Index; RV: right ventricle; LV: left ventricle; TAPSE: tricuspid annular plane systolic excursion; BNP: brain natriuretic peptide. [#]: active or under treatment in the last year; [¶]: in the previous month; [+]: immobilised patients defined as non-surgical patients who had been immobilised (*i.e.* total bed rest with bathroom privileges) for ⩾4 days in the month prior to pulmonary embolism diagnosis.

and the prognostic effect of RHT as a forest plot. RHT significantly predicted 30-day all-cause mortality among those patients who received anticoagulant therapy (OR 3.24, 95% CI 2.05–5.13), but not among those patients who received thrombolysis or surgery (OR 0.92, 95% CI 0.30–2.82) (p<0.01 for interaction). Likewise, RHT significantly predicted 30-day all-cause mortality among low- (OR 6.71, 95% CI 2.55–17.66) and intermediate-risk patients (OR 2.62, 95% CI 1.56–4.40), but not among high-risk patients (OR 1.03, 95% CI 0.36–2.99) (p=0.02 for interaction).

Using the same model variables, RHT remained an independent predictor of all-cause mortality when hypotensive patients were excluded from the analysis (adjusted OR 3.31, 95% CI 2.09–5.24; p<0.001). After adjustment, RHT at the time of presentation was also independently significantly associated with

TABLE 2 30-day clinical events after diagnosis and treatment for patients with acute symptomatic pulmonary embolism

	All patients	Presence of right heart thrombi	Absence of right heart thrombi	p-value
Patients n	12441	325	12116	
Primary outcome				
All-cause death	382 (3.1)	28 (8.6)	354 (2.9)	<0.001
Pulmonary embolism-related death	122 (1.0)	17 (5.2)	105 (0.9)	<0.001
Secondary outcomes				
Recurrent pulmonary embolism	93 (0.7)	6 (1.8)	87 (0.7%)	0.04
Major bleeding	440 (3.5)	15 (4.6)	425 (3.5%)	0.36

Data are presented as n (%), unless otherwise stated.

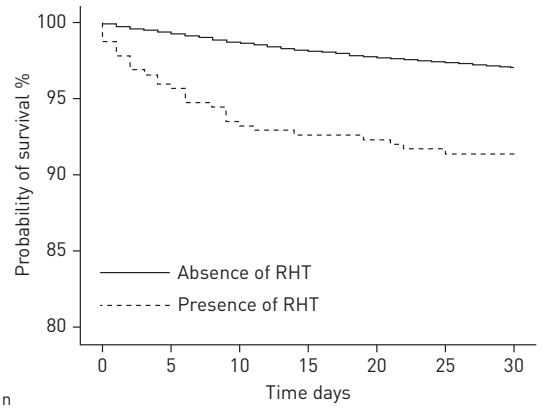
pulmonary embolism-related death (adjusted OR 7.71, 95% CI 4.34–13.69; p<0.001) and recurrent VTE within 30 days of pulmonary embolism diagnosis (adjusted OR 2.48, 95% CI 1.06–5.82; p=0.04).

Discussion

Uncertainty surrounding the prevalence and prognostic significance of RHT exists. The results of our study show that RHT affect approximately 3% of patients with an episode of acute symptomatic pulmonary embolism. Also, patients with RHT had a worse outcome when compared with those without RHT.

The prevalence of RHT in the study cohort confirms the current belief that this condition is uncommon [18]. The only large-scale population-based study in this field published up to now reported a prevalence of echocardiographically detected RHT in patients with pulmonary embolism of 3.8% [19]. For our prevalence estimates, we excluded patients who were not studied with echocardiography. Since potential risk factors for RHT (younger age, signs of clinical severity) were less frequent among patients who were ineligible compared to those that were eligible, we believe that our estimate of the prevalence of RHT should be viewed as the upper limit.

Prior evidence suggests that the risk of RHT is greatly increased among pulmonary embolism patients with heart failure and more haemodynamic compromise [19]. Heart failure showed a high predictive ability for RHT in our study. Though it has been postulated that only very large emboli arising from pelvic or proximal leg veins become lodged in the right heart [20], stasis in the dilated right heart due either to acute severe pulmonary embolism or pre-existing congestive heart failure, or both, seems to enhance the risk of RHT, regardless of whether it is due to *in situ* thrombosis or to entrapment of transiting thrombi. In our study, recent major bleeding was clearly associated with an increased risk of RHT. However, it should be noted that clinicians typically used suboptimal doses of anticoagulants in patients with previous episodes of major bleeding, contributing to the size of this increase in risk.



At risk n

Absence of RHT	12116	11963	11841	11762
Presence of RHT	325	303	299	297

FIGURE 2 Kaplan–Meier estimates of survival (primary end-point, all-cause mortality) in patients stratified by presence or absence of right heart thrombi (RHT).

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Artículo 1

TABLE 3 Factors associated with 30-day all-cause mortality in 12 441 patients with acute symptomatic pulmonary embolism

Risk factor	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age per year	1.03 (1.02–1.04)	<0.001	1.03 (1.02–1.04)	<0.001
Cancer#	4.03 (3.26–4.99)	<0.001	4.03 (3.26–4.98)	<0.001
Recent major bleeding	1.82 (1.09–3.04)	0.02	1.73 (1.03–2.88)	0.04
Congestive heart failure	1.28 (0.96–1.70)	0.09		
Immobilisation¶	2.25 (1.80–2.83)	<0.001	2.34 (1.87–2.92)	<0.001
Syncope	0.93 (0.71–1.23)	0.63		
Systolic blood pressure <100 mmHg	2.14 (1.62–2.83)	<0.001	2.24 (1.71–2.93)	<0.001
Heart rate ⩾110 beats·min^{-1}	1.23 (0.97–1.58)	0.09	1.28 (1.01–1.63)	0.04
Arterial oxyhaemoglobin saturation <90%	1.20 (0.94–1.52)	0.14		
Right heart thrombi	2.46 (1.60–3.80)	<0.001	2.50 (1.62–3.84)	<0.001

#: active or under treatment in the last year; ¶: immobilised patients defined as non-surgical patients who had been immobilised (*i.e.* total bed rest with bathroom privileges) for ⩾4 days in the month prior to pulmonary embolism diagnosis.

The Right Heart Thrombi European Registry was a prospective, international registry that reported the prognostic significance of RHT characteristics in patients with acute pulmonary embolism [8]. The main finding was that the clinical prognostic scores (*i.e.* simplified pulmonary embolism severity index [21] and shock index [22]) and the haemodynamic status at the time of pulmonary embolism diagnosis predicted mortality, while the RHT characteristics did not. In the subgroup of patients with intermediate-risk pulmonary embolism (*i.e.* right ventricular dysfunction), those with RHT had an increased mortality compared with those without RHT. We found that patients with RHT had a worse 30-day outcome when compared with those without RHT. Interestingly, the risk of death among low-risk patients with RHT was about seven-times higher than in patients without RHT. Also, in the subgroup of patients with intermediate-risk pulmonary embolism, those with RHT had a three-fold increased mortality compared with those without RHT. Our study's large sample size, the adjustment for potential confounders and the robustness of the findings provides strong evidence supporting the concept that RHT at the time of acute pulmonary embolism diagnosis is a predictor of all-cause death, pulmonary embolism-related death, and recurrent VTE, particularly in those without haemodynamic compromise.

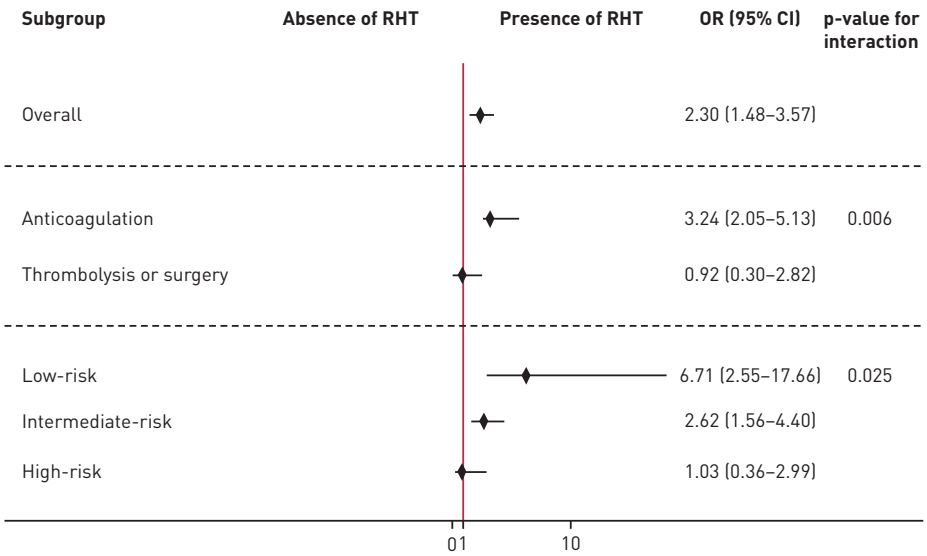

FIGURE 3 Prognostic significance of right heart thrombi (RHT) in the pre-specified subgroups.

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Artículo 1

Risk assessment in an individual patient should lead to tailoring of the intensity and type of treatment of acute symptomatic pulmonary embolism [23]. In this study, clinicians used thrombolysis or surgery more frequently in patients who had RHT, and this approach influenced the prognostic significance of clots in the right side of the heart. Among patients who received anticoagulation, the risk of death was about three-times high in those with RHT than in those without RHT. Obviously, changes in treatment, such as the routine use of thrombolysis or surgery, cannot be recommended on the basis of our findings in this cohort analysis.

What are the clinical implications of our findings for the future management of pulmonary embolism? First, physicians should increase their awareness of the potential for RHT in younger patients with pulmonary embolism who present with syncope, hypotension and/or hypoxaemia, particularly if there is a history of recent major bleeding, cancer or congestive heart failure. Second, for patients with RHT, research should focus on improving the initial treatment of pulmonary embolism in order to improve outcomes. Though randomised controlled trials would provide the strongest evidence regarding treatment efficacy and safety for RHT, there might be reasonable concern about excess complexity, expense, and time required to recruit study participants, as well as inadequate representativeness. Thus, well-designed observational studies should be carried out to examine and infer treatment effects.

RIETE is a prospective registry; the data reported are not from a prospective randomised controlled trial. As in most registries, neither diagnostic work-ups nor therapy were controlled. However, the strength of this report is the prospective collection of data from actual practice, from a very large number of pulmonary embolism patients based on diagnostic testing and clinical practices in a wide cross-section of institutions. Another drawback is the lack of clinical detail [24]. Although information on some potential confounders could not be adequately captured (*e.g.* intensity of anticoagulation), our study design and several sensitivity analyses have attempted to capture and reduce information and selection biases.

In conclusion, the results of this study of patients presenting with acute symptomatic pulmonary embolism suggest that RHT is relatively infrequent. Younger age, heart failure, cancer, recent bleeding, syncope, hypotension and hypoxaemia were associated with an increased risk of RHT. Since patients with concomitant RHT, compared with those without RHT, had worse prognosis, future diagnostic and therapeutic strategies should strive to minimise their consequences.

Acknowledgements

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Author contributions are as follows. Study concept and design: D. Barrios, V. Rosa-Salazar, D. Jiménez and M. Monreal; acquisition of data, analysis and interpretation of data, and statistical analysis: D. Barrios, V. Rosa-Salazar, D. Jiménez, R. Morillo, A. Muriel, J. del Toro, L. López-Jiménez, D. Farge-Bancel, R. Yusen and M. Monreal; drafting of the manuscript: D. Barrios, V. Rosa-Salazar, D. Jiménez, R. Morillo, R. Yusen and M. Monreal; critical revision of the manuscript for important intellectual content: D. Barrios, V. Rosa-Salazar, D. Jiménez, R. Morillo, A. Muriel, J. del Toro, L. López-Jiménez, D. Farge-Bancel, R. Yusen and M. Monreal; study supervision: D. Jiménez and M. Monreal. The corresponding author, D. Jiménez, had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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RESULTADOS

II. RESUMEN DEL ARTÍCULO 2

Título: Significado pronóstico de los trombos en cavidades cardiacas derechas en pacientes con tromboembolia pulmonar aguda sintomática: Revisión sistemática y metanálisis.

En los pacientes diagnosticados de TEP aguda sintomática, el significado pronóstico de la presencia de TCD concomitante es incierto.

Se realizó un metanálisis de estudios que incluyeron pacientes con TEP aguda, para analizar el significado pronóstico de los TCD detectados por ecocardiografía. El evento primario fue la mortalidad por cualquier causa a corto plazo, y el secundario la mortalidad por la TEP a corto plazo. Se realizaron búsquedas no restringidas de PubMed y Embase desde 1980 hasta el 31 de enero del 2016, y se usaron los términos "pulmonary embolism", " right heart thrombi" y "prognos*." Se usó un modelo de efectos aleatorios para estimar los resultados del estudio; el método de correlación de rango de Begg para evaluar el sesgo de publicación; y la prueba I^2 para evaluar la heterogeneidad.

Cumplieron criterios de inclusión seis de los 79 estudios potencialmente relevantes (15.220 pacientes). De los 593 pacientes con TCD detectados por ecocardiografía, 99 fallecieron (16,7%; IC del 95%, 13,8-19,9%), en comparación con 639 de 14.627 sin TCD (4,4%; IC del 95%, 4,0-4,7%). La presencia de TCD se asoció de forma estadísticamente significativa con la mortalidad por cualquier causa a corto plazo en todos los pacientes (OR 3,0; IC del 95%, 2,2-4,1; I^2 = 20%) y con la muerte relacionada con la propia TEP (tres cohortes, 12.955

pacientes; OR 4,8; IC del 95%, 2,0-11,3; I^2 =76%). Los resultados fueron consistentes para los estudios prospectivos (dos cohortes, 514 pacientes; OR 4,8; IC del 95%, 1,7-13,6; I^2 =56%) y retrospectivos (cuatro cohortes, 14.706 pacientes; OR 2,8; IC del 95%, 2,1-3,8; I^2 =0%).

En pacientes diagnosticados de TEP aguda sintomática, la presencia de TCD se asocia a un riesgo aumentado de muerte por cualquier causa y por la propia TEP en los primeros 30 días después del diagnóstico.

Artículo 2

[Original Research **Pulmonary Vascular Disease**]

CHEST

Prognostic Significance of Right Heart Thrombi in Patients With Acute Symptomatic Pulmonary Embolism

Systematic Review and Meta-analysis

Deisy Barrios, MD; Vladimir Rosa-Salazar, PhD; Raquel Morillo, MD; Rosa Nieto, MD; Sara Fernández, MD; José Luis Zamorano, PhD; Manuel Monreal, PhD; Adam Torbicki, PhD; Roger D. Yusen, MD; and David Jiménez, PhD

BACKGROUND: For patients diagnosed with acute pulmonary embolism (PE), the prognostic significance of concomitant right heart thrombi (RHT) lacks clarity.

METHODS: We performed a meta-analysis of studies that enrolled patients with acute PE to assess the prognostic value of echocardiography-detectable RHT for the primary outcome of short-term all-cause mortality and the secondary outcome of short-term PE-related mortality. Unrestricted searches were conducted of PubMed and Embase from 1980 through January 31, 2016, and used the terms "right heart thrombi," "pulmonary embolism," and "prognos.*" A random effects model was used to pool study results; Begg rank correlation method was used to evaluate for publication bias; and I^2 testing was used to assess for heterogeneity.

RESULTS: Six of 79 potentially relevant studies met the inclusion criteria (15,220 patients). Overall, 99 of 593 patients with echocardiography-detectable RHT died (16.7% [95% CI, 13.8-19.9]) compared with 639 of 14,627 without RHT (4.4% [95% CI, 4.0-4.7]). RHT had a significant association with short-term all-cause mortality in all patients (OR, 3.0 [95% CI, 2.2 to 4.1]; $I^2 = 20\%$) and with PE-related death (three cohorts, 12,955 patients; OR: 4.8 [95% CI, 2.0-11.3; $I^2 = 76\%$). Results were consistent for the prospective (two cohorts, 514 patients; OR, 4.8 [95% CI, 1.7-13.6]; $I^2 = 56\%$) and the retrospective (four cohorts, 14,706 patients; OR, 2.8 [95% CI, 2.1 to 3.8]; $I^2 = 0\%$) studies.

CONCLUSIONS: In patients diagnosed with acute PE, concomitant RHT were significantly associated with an increased risk of death within 30 days of PE diagnosis.

TRIAL REGISTRY: PROSPERO registry; No.: CRD42016033960; URL: https://www.crd.york.ac.uk/prospero/

CHEST 2017; 151(2):409-416

KEY WORDS: meta-analysis; mortality; prognosis; pulmonary embolism; right heart thrombi

ABBREVIATIONS: PE = pulmonary embolism; RHT = right heart thrombi

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Pulmonary embolism (PE) is a leading cause of death in the Western world.[1,2] Small studies have described the prevalence, natural history, and prognostic significance of right heart thrombi (RHT) in PE.[3-5] According to these studies, RHT can be detected echocardiographically in approximately 4% of patients with acute symptomatic PE.[6] Although the European Society of Cardiology guideline states that patients who have acute PE associated with RHT have a potentially life-threatening condition,[7] RHT pose an unclear risk of mortality.

A registry of patients with acute symptomatic PE supported the hypothesis that right-sided cardiac thrombi have a poor prognosis by showing that those with evidence of concomitant RHT had (compared with those without RHT) an increased risk of all-cause death over 3 months of follow-up.[8] The recent prospective, multicenter, international Right Heart Thrombi European Registry suggested an increased mortality risk for patients with RHT and right ventricular dysfunction.[9] However, other studies have not been able to show an association between concomitant RHT at the time of PE diagnosis and mortality rates.[10]

To clarify the prevalence and prognostic potential of concomitant RHT among patients with acute symptomatic PE and their usefulness for treatment decision-making, the present study aimed to systematically review the literature and perform an updated meta-analysis.

Materials and Methods

The authors used methods for this meta-analysis recommended in Meta- Analysis of Observational Studies in Epidemiology: A Proposal for Reporting.[11] The planned analysis was registered at the PROSPERO international prospective register of systematic reviews on February 4, 2016 (CRD42016033960).

Study Objectives

The study primarily aimed to determine an association between concomitant RHT and short-term (ie, through 30 days after the diagnosis of PE) all-cause mortality in patients with acute symptomatic PE. The study secondarily aimed to assess for an association between concomitant RHT and short-term PE-related death.

Data Sources and Searches

A computerized search of PubMed and Embase from 1980 through January 31, 2016, used the terms "pulmonary embolism," "right heart thrombi," and "prognos*" to identify eligible studies.[12,13] Full articles of all potentially appropriate abstracts were reviewed. Hand-searching of cited bibliographies and investigator files complemented the literature search.

Inclusion and Exclusion Criteria

Prespecified study inclusion criteria were prospective or retrospective studies with the following: (1) an objective diagnosis of PE; (2) echocardiography testing performed around the time of PE diagnosis; and (3) enrollment of consecutive patients (ie, an inception cohort or a retrospective identification of consecutive patients). Studies were included if they reported all-cause or PE-related mortality up to 30 days after PE diagnosis. For duplicate publications, the most recent was considered.

Study Selection

Two authors (D. B. and D. J.) independently assessed identified articles to determine study eligibility. Based on title and abstract review, the reviewers excluded nonrelevant studies. For relevant studies, the reviewers independently conducted data extraction by using a prepiloted, standardized form. Consensus or discussion with a third reviewer (R. M.) resolved eligibility and data extraction discrepancies or uncertainties.

Data Extraction and Quality Assessment

For each study, the authors abstracted data regarding study design (number of included patients, prospective or retrospective, and single-center or multicenter), patient characteristics (age, sex, and hemodynamic status at inclusion in the study), echocardiographic testing results (percentage of patients with RHT), and outcomes. Two authors (D. B. and D. J.) used the Quality in Prognosis Studies tool to independently assess the quality of the eligible studies.[14]

Data Synthesis and Analysis

For each study, the incidence of short-term all-cause and PE-related mortality was determined for the positive and negative RHT groups, and an OR and its 95% CI were calculated. ORs were pooled across studies by using a random effects model approach. Statistical heterogeneity between groups was measured by using Cochran Q statistic and the I^2 statistic of Higgins and Thompson.[15] The Begg rank correlation method assessed for publication bias. Separate analyses were planned for: (1) prospective studies; (2) retrospective studies; and (3) cohorts of hemodynamically stable patients. All analyses were conducted by using Review Manager 5.2 (The Cochrane Collaboration, Oxford, England) and MetaDisc version 1.4.[16]

Results

Description of Studies

Of the 79 articles screened, 13 seemed potentially eligible and underwent an in-depth review.[3,4,8-10,17-24] Eight of the 13 studies were deemed ineligible.[3,4,17-22] One of these studies was excluded because we were not able to obtain the necessary data from the investigators.[21] Hand-searching found one additional study[25]; six studies therefore met the eligibility criteria[8-10,23-25] (Fig 1). For one of these studies,[9] the numbers of patients who experienced an adverse outcome event were obtained by contacting the investigators. Overall, a total of six studies with 15,220 patients with acute PE

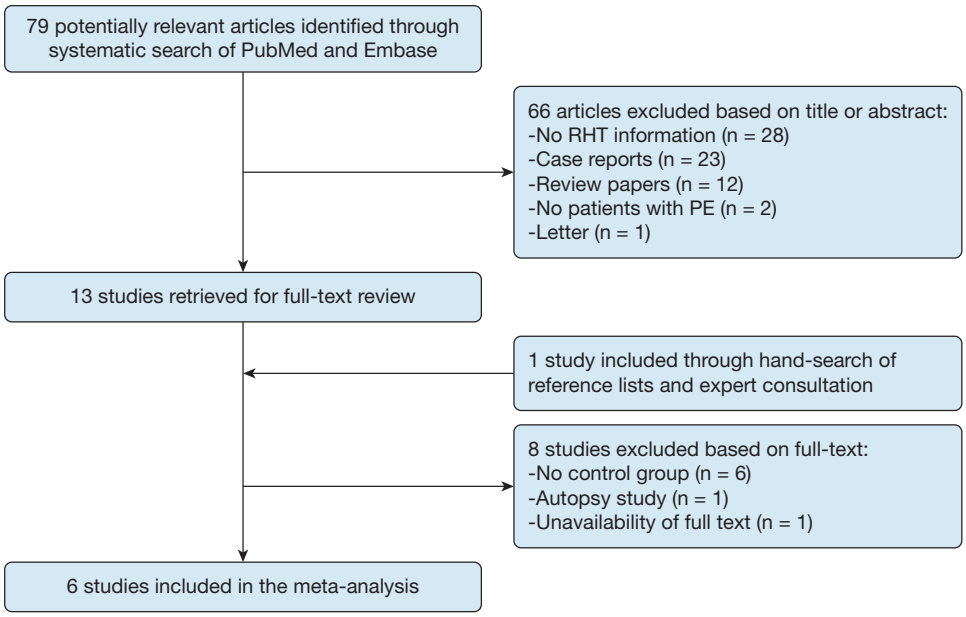


Figure 1 – *Flowchart of the study selection process. PE = pulmonary embolism; RHT = right heart thrombi.*

who underwent echocardiography testing were included in the analysis.

Two cohorts had a prospective design,[9,24] and four cohorts had a retrospective design.[8,10,23,25] Demographic features of study populations (age and sex) were similar across the studies, and all the included patients had an objective diagnosis of PE (Table 1). None of the studies included only hemodynamically stable patients. Time to study end point differed among the studies, varying from the in-hospital stay[10,23,24] up to 30 days.[9,25]

Quality Assessment of Included Studies

Regarding study quality assessment criteria (Table 2), the risk of selection bias was low in one study,[24] moderate in four studies,[8,9,23,25] and high in one study.[10] The risk of attrition bias (ie, the likelihood that the relationship between concomitant RHT and outcome is different for completing and noncompleting participants) was low in all the studies. Transthoracic echocardiography testing was performed in the six studies that adequately described methods for the assessment of concomitant RHT.[8-10,23-25] In one study, investigators also assessed the presence of RHT by using CT angiography.[23] Five studies[8,10,23-25] used all-case mortality as the primary outcome, whereas one study used PE-specific mortality.[9] In none of the studies did an independent blinded committee adjudicate the etiology of death. Most studies accounted for important potential confounders.[8,9,23-25] The use of appropriate statistical analyses in five studies[8,9,23-25] limited the potential for the incorporation of and presentation of invalid results, whereas one study did not perform any predictive statistics.[10]

End Points

For one of the studies,[9] investigators created a control (ie, patients without RHT) group from a cohort of independent patients, and thus the prevalence of RHT could not be calculated. Of the five cohorts with 14,806 participants that enrolled consecutive patients with acute PE, 455 (3.1% [95% CI, 2.8-3.4]) had echocardiography-detectable RHT, and 14,351 (96.9% [95% CI, 96.6-97.2]) did not. Overall, 99 of 593 patients with RHT assessed by echocardiography died (16.7% [95% CI, 13.8-19.9]) compared with 639 of 14,627 without RHT (4.4% [95% CI, 4.0-4.7]). Pooled results from the six cohorts showed that concomitant RHT was associated with threefold increased odds of short-term all-cause mortality (95% CI, 2.2 to 4.1; heterogeneity $\chi = 6.3$; $df = 5$; $P = .28$) (Fig 2A). The pooled estimate was dominated by the two larger studies,[8,25] which together provided approximately 90% of the total patients. Only one of the six cohorts[10] did not have statistically significant findings, although it showed the same trend.

There was no evidence of publication bias according to the Begg rank correlation method. The predictive value

Artículo 2

TABLE 1] Characteristics of the Included Studies

Author	Year	Study Design	Outcome Event	Concomitant RHT	Population, No.	Sex	Age, Mean ± SD, y	Follow-up	Study Results
Casazza et al[10]	1997	Retrospective	All-cause death	18%	Outpatients with massive PE, 130	62% female	66 ± 19	In-hospital	30% mortality rate for positive RHT group vs 24% for negative RHT group
Torbicki et al[8]	2003	Retrospective	All-cause death	3.9%	Outpatients and inpatients, 1,160	54% female	RHT positive: 63 ± 13 RHT negative: 63 ± 16	14 d	22% mortality rate for positive RHT group vs 10% for negative RHT group
Mollazadeh et al[24]	2009	Prospective	All-cause death	12%	Outpatients, 100	31% female	RHT positive: 59 ± 18 RHT negative: 52 ± 19	In-hospital	Crude all-cause mortality rate was fivefold (95% CI, 3.0-10.0) greater in patients with concomitant RHT
Kukla et al[23]	2015	Retrospective	All-cause death	5.1%	Outpatients, 975	59% female	66 ± 15	In-hospital	Adjusted all-cause mortality rate was 2.4-fold (95% CI, 1.1-5.0) greater in patients with concomitant RHT
Koc et al[9]	2016	Prospective	All-cause and PE-related death	NC[a]	Stable and unstable patients, 414	RHT positive: 50% female RHT negative: 56%	RHT positive: 62 ± 19 RHT negative: 64 ± 18	30 d	Propensity score adjusted all-cause mortality rate was 2.7-fold (95% CI, 1.7-5.6) greater in patients with concomitant RHT
Barrios et al[25]	2016	Retrospective	All-cause and PE-related death	2.6%	Outpatients and inpatients, 12,441	54% female	66 ± 17	30 d	Adjusted all-cause mortality rate was 2.5-fold (95% CI, 1.6-3.8) greater in patients with concomitant RHT

PE = pulmonary embolism; RHT = right heart thrombi.
[a]Because the investigators created a control (ie, patients without RHT) group from a cohort of independent patients, the prevalence of RHT could not be calculated (NC).

TABLE 2] Quality Assessment of Studies Included in the Systematic Review

Study	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting
Casazza et al[10]	High bias	Low bias	Low bias	Moderate bias	High bias	High bias
Torbicki et al[8]	Moderate bias	Low bias	Low bias	Low bias	Low bias	Low bias
Mollazadeh et al[24]	Low bias	Low bias	Low bias	Low bias	Low bias	Low bias
Kukla et al[23]	Moderate bias	Low bias	Low bias	Low bias	Low bias	Low bias
Koc et al[9]	Moderate bias	Low bias	Low bias	Low bias	Low bias	Low bias
Barrios et al[25]	Moderate bias	Low bias	Low bias	Low bias	Low bias	Low bias

of concomitant RHT with respect to death was confirmed when the analysis was limited to two studies (514 patients) that used a prospective design (OR, 4.8 [95% CI, 1.7-13.6), with evidence for moderate heterogeneity ($I^2 = 56\%$) (Fig 2B). The retrospective (OR, 2.8 [95% CI, 2.1-3.8]; heterogeneity $\chi = 3.0$; $df = 3$; $P = .39$; $I^2 = 0\%$) studies showed similar results (Fig 2C).

The pooled estimated negative predictive value for concomitant RHT was 95.6% (95% CI, 95.3-95.9), and the positive predictive value was 16.7% (95% CI, 13.8-20.0). The meta-analysis showed the following: (1) a slight increase in the rate of echocardiography-detectable concomitant RHT in patients who died, compared with the rate of RHT in patients who survived (positive likelihood ratio: 3.93 [95% CI, 3.21-4.82]); and (2) a slight decrease in the rate of negative echocardiography assessments for concomitant RHT in patients who died, compared with the rate of negative echocardiography assessments for RHT in patients who survived (negative likelihood ratio: 0.90 [95% CI, 0.87-0.92]) during the short-term follow-up.

Three studies (12,955 patients) reported on deaths resulting from PE. Overall, 187 events were observed: 49 in 475 patients with RHT (10.3% [95% CI, 7.7-13.4]) and 138 in 12,480 without RHT (1.1% [95% CI, 0.9 to 1.3]).[9,24,25] Concomitant RHT was associated with 4.8-fold increased odds of short-term PE-related mortality (95% CI, 2.0 to 11.3; heterogeneity $\chi = 8.3$; $df = 2$; $P = .02$) (Fig 3).

Two studies (11,834 patients) reported on deaths in normotensive patients with PE. Overall, 395 events were observed: 42 in 390 patients with RHT (10.8% [95% CI, 7.9-14.3]) and 353 in 11,839 without RHT (3.0% [95% CI, 2.7-3.3]).[9,25] Concomitant RHT was associated with 1.8-fold increased odds of short-term mortality (95% CI, 0.5 to 6.1; heterogeneity $\chi = 11.2$; $df = 1$; $P < .001$). Concomitant RHT was associated with 2.3-fold increased odds of short-term PE-related mortality (95% CI, 0.2 to 31.7; heterogeneity $\chi = 35.7$; $df = 1$; $P < .001$).

Discussion

In this meta-analysis of six cohorts that included 15,220 patients with acute symptomatic PE, patients with concomitant echocardiography-detectable RHT had a threefold increased risk of short-term death compared with patients without RHT. This outcome is physiologically plausible because thrombus burden has been shown to predict a nonbenign course in patients with acute symptomatic PE.[26]

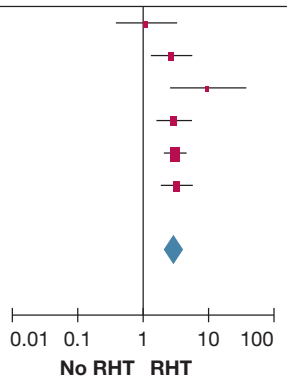
In patients with acute symptomatic PE, studies have reported prevalences of coexisting RHT that range from 2.6% to 18%.[10,25] However, these studies may be confounded by selection and detection bias. The prevalence of echocardiography-detectable coexisting RHT in this meta-analysis (3.1%) was similar to that in two previous registries that included > 13,500 patients[8,25] and confirms that RHT is an uncommon finding in patients with PE.

For patients with acute symptomatic PE, hemodynamic instability (ie, sustained hypotension, shock) is associated with increased short-term mortality.[27] For normotensive patients with PE, clinical variables, blood tests, and imaging studies may assist with identification of patients into intermediate- to high-risk categories.[28]

A

Study or Subgroup	RHT Events	RHT Total	No RHT Events	No RHT Total	Weight	OR M-H-Random-95% CI	Year
Casazza et al[10]	5	23	21	107	7.0%	1.14 (0.38-3.42)	1997
Torbicki et al[8]	10	45	106	1,115	14.4%	2.72 (1.31-5.65)	2003
Mollazadeh et al[24]	6	12	8	88	4.8%	10.00 (2.61-38.38)	2009
Kukla et al[23]	16	50	125	925	18.5%	3.01 (1.61-5.62)	2015
Barrios et al[25]	28	325	354	12,116	33.8%	3.13 (2.10-4.68)	2016
Koc et al[9]	34	138	25	276	21.5%	3.28 (1.87-5.77)	2016
Total (95% CI)		**593**		**14,627**	**100.0%**	**3.03 (2.24-4.11)**	
Total events	99		639				

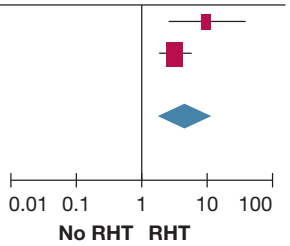
Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 6.28$, $df = 5$ ($P = .28$); $I^2 = 20\%$
Test for overall effect: $z = 7.13$ ($P < .00001$)



B

Study or Subgroup	RHT Events	RHT Total	No RHT Events	No RHT Total	Weight	OR M-H-Random-95% CI	Year
Mollazadeh et al[24]	6	12	8	88	34.5%	10.00 (2.61-38.38)	2009
Koc et al[9]	34	138	25	276	65.5%	3.28 (1.87-5.77)	2016
Total (95% CI)		**150**		**364**	**100.0%**	**4.82 (1.70-13.65)**	
Total events	40		33				

Heterogeneity: $\tau^2 = 0.35$; $\chi^2 = 2.25$, $df = 1$ ($P = .13$); $I^2 = 56\%$
Test for overall effect: $z = 2.96$ ($P = .003$)



C

Study or Subgroup	RHT Events	RHT Total	No RHT Events	No RHT Total	Weight	OR M-H-Random-95% CI	Year
Casazza et al[10]	5	23	21	107	7.2%	1.14 (0.38-3.42)	1997
Torbicki et al[8]	10	45	106	1,115	16.3%	2.72 (1.31-5.65)	2003
Kukla et al[23]	16	50	125	925	22.4%	3.01 (1.61-5.62)	2015
Barrios et al[25]	28	325	354	12,116	54.0%	3.13 (2.10-4.68)	2016
Total (95% CI)		**443**		**14,263**	**100.0%**	**2.82 (2.10-3.79)**	
Total events	59		606				

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.98$, $df = 3$ ($P = .39$); $I^2 = 0\%$
Test for overall effect: $z = 6.88$ ($P < .00001$)

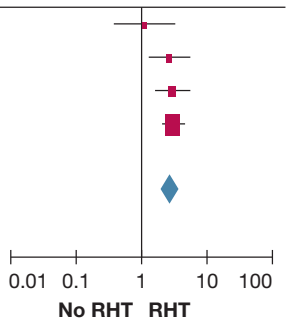


Figure 2 – *A-C, ORs of short-term all-cause mortality based on the presence or absence of concomitant RHT in patients with acute PE. A, Random effects meta-analysis of six cohorts. B, Prospective subset of PE cohorts. C, Retrospective subset of PE cohorts; M-H = Mantel-Haenszel. See Figure 1 legend for expansion of other abbreviations.*

Among them, coexisting RHT has been associated with worse outcomes in PE.[23] In fact, this meta-analysis confirms that RHT is associated with short-term death in patients with acute symptomatic PE. Nonetheless, our results do not support the use of coexisting RHT for the identification of low-risk patients for outpatient management because of the following factors: (1) the pooled estimated negative predictive value for concomitant RHT was not extreme (83%); (2) clinical prediction rules have demonstrated an excellent accuracy for the identification of patients with PE at low risk of short-term complications[29]; and (3) coexisting RHT in normotensive patients with PE did not lead to a higher all-cause mortality.

This study found that concomitant RHT has a low positive predictive value for death during short-term follow-up of 16.7%. This finding is similar to those obtained with cardiac biomarkers and echocardiographic signs of right ventricular dysfunction.[30] Whether RHT testing could improve the positive predictive value of echocardiography and cardiac biomarkers for death is

Study or Subgroup	RHT Events	RHT Total	No RHT Events	No RHT Total	Weight	OR M-H, Random, 95% CI
Barrios et al[25]	17	325	105	12,116	39.8%	6.31 (3.74-10.67)
Koc et al[9]	26	138	25	276	38.3%	2.33 (1.29-4.21)
Mollazadeh et al[24]	6	12	8	88	21.9%	10.00 (2.61-38.38)
Total (95% CI)		**475**		**12,480**	**100.0%**	**4.77 (2.01-11.28)**
Total events	49		138			

Heterogeneity: $\tau^2 = 0.41$; $\chi^2 = 8.29$, $df = 2$ ($P = .02$); $I^2 = 76\%$
Test for overall effect: $z = 3.55$ ($P = .0004$)

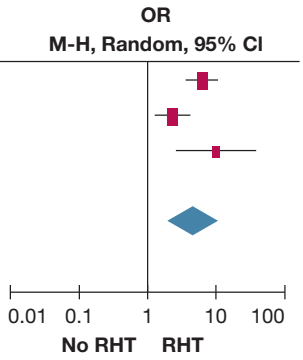


Figure 3 – *ORs of short-term PE-related death based on the presence or absence of concomitant RHT in patients with acute PE: random-effects meta-analysis of 3 cohorts (with results on the secondary outcome). See Figure 1 and 2 legends for expansion of other abbreviations.*

currently unknown. Future studies might address the potential survival benefit associated with the use of advanced therapy in these high-risk patients.

What are the implications of these findings? First, because the prevalence of RHT among PE patients is low, and the association between RHT and mortality is not strong and might be (at least in part) linked to the patient's hemodynamic status, systematic screening for RHT that includes routine echocardiography testing is not warranted and should be restricted to patients with PE who have positive clinical prognostic scores (ie, Pulmonary Embolism Severity Index, simplified Pulmonary Embolism Severity Index).[7] Second, the data to support the best treatment approach in patients with acute PE and coexisting RHT are limited. Future studies are required to determine the clinical benefits of more aggressive treatments in patients with acute PE and concomitant RHT. Meanwhile, the best management for these patients requires a multidisciplinary approach: different specialists can determine the pros and cons of using advanced therapy rather than anticoagulation therapy alone.

This meta-analysis has limitations. Although the large total sample size, the proportion of patients with echocardiography-detectable RHT, and the death rate all allowed for reasonable estimates of risk, we did not have sufficient information that would allow us to adjust for confounding variables. Meta-analyses of individual patient data could have potentially allowed for such adjustments. However, the varied settings and patient characteristics improved the generalizability of the study results. Limitations of each of the included studies may have introduced significant biases into this meta-analysis's estimates of the prognostic value of concomitant RHT. Nonetheless, our main analysis showed no evidence of heterogeneity between the outcomes of the incorporated studies.

Conclusions

This systematic review showed that concomitant RHT had an association with increased risk of mortality in patients with acute symptomatic PE.

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Author contributions: D. J. had full access to all the data in the study and had final responsibility for the decision to submit for publication. D. B., V. R.-S., R. M., A. T., R. D. Y., and D. J. were responsible for the study concept and design; D. B., V. R.-S., R. M., R. N., S. F., J. L. Z., M. M., A. T., R. D. Y., and D. J. were responsible for acquisition of data, analysis and interpretation of data, and statistical analysis; D. B., M. M., R. D. Y., and D. J. were responsible for drafting of the manuscript; D. B., V. R.-S., R. M., R. N., S. F., J. L. Z., M. M., A. T., R. D. Y., and D. J. were responsible for critical revision of the manuscript for important intellectual content; and D. B. and D. J. were responsible for study supervision.

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III. RESUMEN DEL ARTÍCULO 3

Título: Tratamiento de los trombos en cavidades cardiacas derechas en pacientes con TEP aguda sintomática.

Las guías de práctica clínica no ofrecen recomendaciones basadas en la evidencia sobre el tratamiento de los pacientes con TEP aguda sintomática y TCD concomitante.

Este estudio incluyó pacientes con TEP aguda sintomática y TCD que fueron incluidos en el RIETE. Evaluamos la eficacia del tratamiento de reperfusión (trombolisis sistémica, trombolisis dirigida por catéter o embolectomía quirúrgica) vs. tratamiento anticoagulante para las variables de resultados de mortalidad por cualquier causa, mortalidad por la propia TEP, ETEV recurrente y sangrado mayor en los primeros 30 días de tratamiento de la TEP. Utilizamos un análisis de propensión para estimar el efecto del tratamiento de reperfusión, teniendo en cuenta las variables que predijeron que los pacientes recibieran dicho tratamiento.

De los 325 pacientes con TEP y TCD, 255 (78%; IC del 95%, 74-83%) recibieron anticoagulación y 70 (22%; IC del 95%, 17-26%) recibieron tratamiento de reperfusión. Los resultados de este estudio indican que el tratamiento de reperfusión, comparado con la anticoagulación, no se asocia a una reducción estadísticamente significativa de la mortalidad por cualquier causa (6,2% vs. 14%, p =0,15) o de mortalidad por la propia TEP (4,7% vs. 7,8%; p =0,47). De los pacientes que recibieron tratamiento de reperfusión, un 6,2% experimentó

una recurrencia trombótica durante el seguimiento, en comparación con un 0% de los que recibieron anticoagulación (p =0,049). No hubo diferencias estadísticamente significativas en la incidencia de episodios hemorrágicos mayores entre los 2 grupos de tratamiento (3,1% vs. 3,1%, p =1,00).

En pacientes con TEP y TCD, no hubo diferencias significativas en las tasas de mortalidad y sangrado entre el tratamiento de reperfusión y el tratamiento anticoagulante. La tasa de recurrencias trombóticas fue significativamente mayor en el grupo de pacientes que recibieron reperfusión, en comparación con el grupo que recibió anticoagulación.

La presencia aislada de trombos en cavidades derechas no justifica la escalada de tratamiento en pacientes con TEP aguda sintomática.

Artículo 3

CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Treatment of Right Heart Thrombi Associated with Acute Pulmonary Embolism

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ABSTRACT

BACKGROUND: Evidence-based recommendations do not adequately address the treatment of right heart thrombi in patients who present with acute symptomatic pulmonary embolism.

METHODS: This study included patients who had acute pulmonary embolism associated with right heart thrombi and participated in the Registro Informatizado de la Enfermedad TromboEmbólica registry. We assessed the effectiveness of anticoagulation versus reperfusion treatment for the outcomes of all-cause mortality, pulmonary embolism−related mortality, recurrent venous thromboembolism, and major bleeding rates through 30 days after initiation of pulmonary embolism treatment. We used propensity score matching to adjust for the likelihood of receiving reperfusion treatment.

RESULTS: Of 325 patients with pulmonary embolism and right heart thrombi, 255 (78%; 95% confidence interval, 74-83) received anticoagulation and 70 (22%; 95% confidence interval, 17-26) also received reperfusion treatment. Propensity score−matched pairs analyses did not detect a statistically lower risk of all-cause death (6.2% vs 14%, $P = .15$) or pulmonary embolism−related mortality (4.7% vs 7.8%; $P = .47$) for reperfusion compared with anticoagulation. Of the patients who received reperfusion treatment, 6.2% had a recurrence during the study follow-up period, compared with 0% of those who received anticoagulation ($P = .049$). The incidence of major bleeding events was not statistically different between the 2 treatment groups (3.1% vs 3.1%; $P = 1.00$).

CONCLUSIONS: In patients with pulmonary embolism and right heart thrombi, no significant difference was found between reperfusion therapy and anticoagulant therapy for mortality and bleeding. The risk of recurrences was significantly higher for reperfusion therapy compared with anticoagulation. Right heart thrombi may not warrant riskier interventions than standard anticoagulation.

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KEYWORDS: Anticoagulation; Pulmonary embolism; Right heart thrombi; Thrombolysis; Treatment

See related Editorial, p501.

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Conflict of Interest: None.

Authorship: All authors had access to the data and played a role in writing this manuscript.

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Pulmonary embolism ranks high among the causes of cardiovascular mortality.[1,2] Hemodynamic decompensation after acute pulmonary embolism most strongly predicts pulmonary embolism—related poor outcome.[3] Alternatively, patients who do not have hypotension and evidence of right ventricular dysfunction have a low short-term mortality rate. Although coexisting right heart thrombi do not commonly occur in patients who have acute symptomatic pulmonary embolism, studies have validated right heart thrombi as a predictor of poor outcome.[4-6]

Management options for patients who have pulmonary embolism associated with right heart thrombi include anticoagulation, systemic or catheter-directed thrombolysis, and surgical embolectomy.[7] Although the European Society of Cardiology guidelines suggest the use of thrombolysis for patients with acute symptomatic pulmonary embolism and coexisting right heart thrombi,[8] studies have not clearly determined which patients with pulmonary embolism and right heart thrombi would benefit from reperfusion treatment. In the absence of randomized clinical trials that assess the effects of reperfusion therapy plus anticoagulation versus anticoagulation alone for right heart thrombi associated with pulmonary embolism, investigators may use observational studies to examine and infer treatment effects. Although retrospective observational studies may suffer from various types of bias, propensity scores may reduce the impact of any imbalance in pretreatment patient characteristics and may address concerns about confounding.

Given the lack of data supporting the efficacy and safety of reperfusion therapy in patients with acute pulmonary embolism and right heart thrombi, we conducted this study of data collected for the Registro Informatizado de la Enfermedad TromboEmbólica (RIETE) Registry.[9] The study compared outcomes during the first month after treatment for an acute symptomatic pulmonary embolism in patients who had coexisting right heart thrombi for those who receive reperfusion treatment (ie, thrombolysis, surgery) with a propensity-matched cohort of those who did not.

CLINICAL SIGNIFICANCE

- The optimal management of right heart thrombi in patients who present with acute symptomatic pulmonary embolism lacks clarity.
- Right heart thrombi may not warrant riskier interventions than standard anticoagulation.
- Our findings provide a rationale for further trials to assess the efficacy and safety of reperfusion therapy for right heart thrombi associated with pulmonary embolism.

MATERIALS AND METHODS

Study Design

Previous publications have shown the design, methods, and main results of the large international contemporary RIETE registry.[10-13] Eligibility for this study consisted of objectively diagnosed acute symptomatic pulmonary embolism, coexisting right heart thrombi, and treatment with reperfusion therapy followed by anticoagulation or anticoagulation alone. We used Registry enrollment dates of January 1, 2001, to December 15, 2015. Pulmonary embolism confirmation by objective testing consisted of high-probability ventilation-perfusion scintigraphy[14] or positive contrast-enhanced, pulmonary embolism protocol, helical chest computed tomography for pulmonary embolism.[15] Right heart thrombi were diagnosed with the use of echocardiographic examination. Reperfusion treatment included administration of (systemic or catheter-directed) thrombolysis or cardiac surgery around the time of pulmonary embolism diagnosis because of coexisting right heart thrombi. All patients provided written or oral consent for participation in the Registry in accordance with local ethics committee requirements.

Covariates of Interest

Patients enrolled in RIETE had data collected from around the time of pulmonary embolism diagnosis that included but was not limited to age; gender; body weight; presence of coexisting conditions such as chronic heart or lung disease; recent (<30 days before pulmonary embolism) major bleeding; presence of risk factors for pulmonary embolism including active cancer (defined as newly diagnosed cancer or cancer undergoing treatment [ie, surgery, chemotherapy, radiotherapy, hormonal, or support therapy]), recent immobility (defined as nonsurgical patients assigned to bed rest with bathroom privileges for ≥4 days in the 2 months before pulmonary embolism diagnosis), surgery (defined as those who had undergone major surgery in the 2 months before pulmonary embolism); clinical signs and symptoms on admission, including heart rate and systolic blood pressure; and laboratory results at hospital admission that included hemoglobin, platelet count, and serum creatinine.

Outcome Measures

We identified all-cause mortality through 30 days after the diagnosis of pulmonary embolism as the primary end point, and 30-day pulmonary embolism—related mortality, recurrent venous thromboembolism, and major bleeding as secondary end points. The RIETE investigators used medical record review to assess vital status. For patients who died, further medical record review, and proxy interviews when necessary, assisted with determining date and cause of death. For deaths confirmed by autopsy or those after a clinically severe pulmonary embolism, initially or shortly after an objectively confirmed recurrent event, in the absence of any alternative diagnosis, the investigators were instructed to judge death as due to fatal pulmonary

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embolism. The RIETE investigators defined recurrent deep vein thrombosis as a new noncompressible vein segment or an increase of the vein diameter by at least 4 mm compared with the last available measurement on venous ultrasonography[16]; recurrent pulmonary embolism as a new ventilation–perfusion mismatch on lung scan or a new intraluminal filling defect on spiral computed tomography of the chest[15]; and major bleeding episodes as those that required a transfusion of at least 2 units of blood, were retroperitoneal, spinal or intracranial, or were fatal.[17]

Statistical Analysis

We used chi-square or Fisher exact tests to compare categoric data between groups. We used the Shapiro-Wilk test to assess continuous data for a normal distribution. We used 2-tailed unpaired *t* tests to compare normally distributed continuous data between 2 unpaired groups, and we used the Mann-Whitney *U* test for non-normally distributed continuous data comparisons. We used multivariate adjustment for the simplified Pulmonary Embolism Severity Index[18] and recent bleeding to see whether reperfusion treatment was an independent significant predictor of all-cause mortality in the entire sample (n = 325).

Because clinicians did not randomly allocate reperfusion therapy, the patients who received reperfusion treatment likely systematically differed from patients who did not with respect to baseline characteristics, clinical course, clinical examination and test findings, and comorbid conditions. We used a propensity score adjustment to compare treatment effects for patients with similar predicted probabilities of receiving reperfusion therapy.[19] We used logistic regression to estimate propensity scores. We modeled the log odds of the probability that a patient received reperfusion therapy by using baseline demographic and clinical variables ("Covariates of Interest" shows the definitions) that were previously shown to be associated with mortality or treatment selection. These variables included the simplified Pulmonary Embolism Severity Index (age >80 years, history of cancer, history of chronic cardiopulmonary disease, heart rate ≥110 beats/min, systolic blood pressure <100 mm Hg, and oxyhemoglobin saturation <90%), recent bleeding, immobilization, and concomitant deep vein thrombosis.

After generation of the propensity scores, we sought to estimate the reduction in 30-day overall mortality due to the reperfusion treatment by using a greedy matched-paired analysis that has a 1:1 matching algorithm and does not allow for replacements. We randomly selected a patient in the reperfusion therapy group and then matched that patient with the nearest patient in the anticoagulant group within a fixed caliper width of 0.15 (0.25 of the standard deviation of the logit of the propensity score).[20] To assess the success of the matching procedure, we measured standardized differences (measured in percentage points) in observed confounders between the matched groups.[21] We estimated the reperfusion therapy effect using generalized estimating equation methods to incorporate the matched-pairs design and adjusted for those covariates that remained unbalanced after matching.[22] We used psmatch2 for the propensity score analyses, and we used Stata version 14.1 (StataCorp LP, College Station, Tex) for Windows for all other analyses.

RESULTS

During the 15-year study period, we identified 325 patients (2.6%; 95% confidence interval [CI], 2.3-2.9) who had objectively confirmed symptomatic pulmonary embolism and coexisting right heart thrombi (**Figure 1**). Of these, 255 (78%; 95% CI, 74-83) received anticoagulation alone and 70 (22%; 95% CI, 17-26) received anticoagulation plus reperfusion treatment (systemic thrombolysis, 58 [17.9%; 95% CI, 13.8-22.5]; surgery, 12 [3.7%; 95% CI, 1.9-6.4]).

Patients who received reperfusion therapy differed significantly from those who received anticoagulation in preexisting medical conditions and in relevant clinical, physiologic, and laboratory parameters. As shown in **Table 1**, patients who received reperfusion therapy were older and had a higher prevalence of high-risk simplified Pulmonary Embolism Severity Index, immobilization, and concomitant deep vein thrombosis compared with those who received anticoagulation alone. Patients who received reperfusion treatment also were more hemodynamically compromised than patients who received anticoagulation alone, with lower systolic blood pressure, higher heart rate, and more frequent hypoxemia, syncope, and right ventricle hypokinesis (**Table 1**). However, the 2 treatment groups had similar proportions of male gender, congestive heart failure, history of venous thromboembolism, cancer, surgery, and recent bleeding.

Outcome

Outcome data were available for all patients through the 30-day study follow-up (**Table 2**). Of the 28 of 325 patients who died (8.6%; 95% CI, 5.8-12.2), 17 (17/325 patients; 5.2%; 95% CI, 3.1-8.2) died of pulmonary embolism and

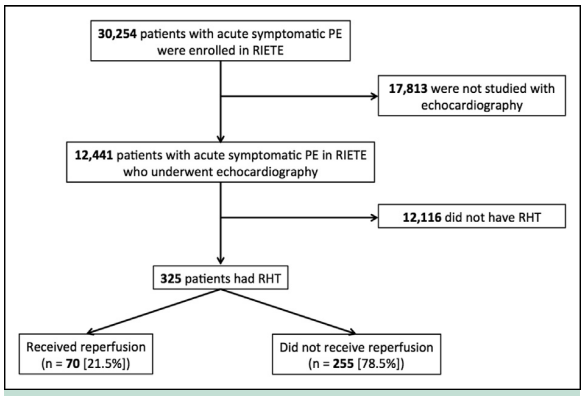

Figure 1 Patient eligibility flow diagram. PE = pulmonary embolism; RHT = right heart thrombi; RIETE = Registro Informatizado de la Enfermedad TromboEmbólica.

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Artículo 3

Table 1 Clinical Characteristics of Patients Who Received Reperfusion or Anticoagulant Therapy

	Received Reperfusion Therapy N = 70	Did Not Receive Reperfusion Therapy N = 255	*P* Value
Clinical characteristics			
Age, y (mean ± SD)	58.8 ± 17.1	65.7 ± 17.1	<.01
Age >80 y, n (%)	5 (7.14%)	52 (20.4%)	.01
Male gender, n (%)	33 (47.1%)	116 (45.5%)	.81
Weight, kg (mean ± SD)	77.4 ± 1.8	75.9 ± 1.0	.38
Risk factors for venous thromboembolism			
History of venous thromboembolism, n (%)	11 (15.7%)	43 (16.8%)	.82
Cancer, n (%)*	12 (17.1%)	61 (23.9%)	.23
Recent surgery, n (%)†	9 (12.7%)	29 (11.3%)	.73
Immobilization for ≥4 d, n (%)‡	26 (37.1%)	55 (21.6%)	<.01
Comorbid diseases			
Chronic lung disease, n (%)	17 (24.3%)	37 (14.5%)	.05
Chronic heart disease, n (%)	14 (20%)	46 (18.0%)	.71
Recent major bleeding, n (%)	2 (2.9%)	14 (5.5%)	.29
Clinical symptoms and signs at presentation			
Syncope, n (%)	37 (53.6%)	61 (24.6%)	<.001
Chest pain, n (%)	42 (60%)	111 (44.6%)	.02
Dyspnea	63 (90%)	216 (85.4%)	.32
Heart rate ≥110 beats/min, n (%)	48 (68.6%)	60 (23.5%)	<.001
Arterial oxyhemoglobin saturation (SaO2) <90%, n (%)	35 (50%)	68 (26.7%)	<.001
Systolic blood pressure <100 mm Hg, n (%)	35 (50%)	68 (26.7%)	<.001
Concomitant deep vein thrombosis, n (%)	41 (58.6%)	110 (43.1%)	.02
Simplified pulmonary embolism severity index			
Low risk, n (%)	12 (17.1%)	81 (31.8%)	.02
High risk, n (%)	58 (82.9%)	7146 (68.2%)	.02
Echocardiography and cardiac biomarkers			
Right ventricle hypokinesis, n (%)	53 (79.1%)	104 (46.8%)	<.001
Tricuspid annular plane systolic excursion, mm (mean ± SD)	18.2 ± 7.6	17.3 ± 5.3	.55
Elevated troponin, n (%) (220)	34/58 (58.6%)	80/162 (49.4%)	.23
Brain natriuretic peptide >100 pg/mL, n (%) (48)	8/9 (88.9%)	34/39 (87.2%)	.89
Laboratory findings			
Abnormal creatinine levels (>2 mg/dL), n (%)	22 (31.4%)	62 (25.6%)	.33
Hemoglobin, g/dL (mean ± SD)	12.9 ± 1.8	13.5 ± 9.8	.62

SD = standard deviation.
*Active or under treatment in the last year.
†In the previous month.
‡Immobilized patients defined as nonsurgical patients who had been immobilized (ie, total bed rest with bathroom privileges) for ≥4 days in the month before pulmonary embolism diagnosis.

Table 2 Thirty-Day Clinical Events After Diagnosis and Treatment of Acute Symptomatic Pulmonary Embolism and Coexisting Right Heart Thrombi

	All Patients N = 325	Received Reperfusion Therapy N = 70	Did Not Receive Reperfusion Therapy N = 255	*P* Value
Primary outcome, n (%)				
All-cause death	28 (8.6%)	4 (5.7%)	24 (9.4%)	.33
PE-related death	17 (5.2%)	3 (4.3%)	14 (5.5%)	.69
Secondary outcomes, n (%)				
Recurrent PE	6 (1.8%)	4 (5.7%)	2 (0.8)	<.01
Major bleeding	15 (4.6%)	3 (4.3%)	12 (4.7%)	.88

PE = pulmonary embolism.

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Table 3 Reperfusion Therapy as Determinant of Outcome in 325 Patients Who Had Acute Symptomatic Pulmonary Embolism and Right Heart Thrombi

Event	Unadjusted OR (95% CI)	*P* Value	Adjusted OR* (95% CI)	*P* Value
All-cause mortality	0.58 (0.19-1.74)	.33	0.34 (0.10-1.11)	.08
PE-related mortality	0.77 (0.21-2.76)	.69	0.48 (0.12-1.92)	.30
Recurrent venous thromboembolism	7.67 (1.37-42.77)	.02	8.20 (1.35-49.61)	.02
Major bleeding	0.90 (0.24-3.30)	.88	0.70 (0.17-2.80)	.62

CI = confidence interval; OR = odds ratio; PE = pulmonary embolism.
*Multivariate adjustment for the simplified Pulmonary Embolism Severity Index[18] and recent bleeding.

11 (11/325 patients; 3.4%; 95% CI, 1.7-6.0) died of other causes.

Four deaths (4/70 patients; 5.7%; 95% CI, 1.6-14.0) occurred in the reperfusion therapy group, whereas 24 deaths (24/255 patients; 9.4%; 95% CI, 6.1-13.7) occurred in the anticoagulation group (absolute difference [AD], 3.7%; 95% CI of the AD, −5.9 to 9.6; $P = .33$). After adjustment by the simplified Pulmonary Embolism Severity Index and recent major bleeding, a multivariable showed a nonsignificant trend toward lower risk of all-cause death for reperfusion treatment compared with sole anticoagulant treatment (odds ratio [OR], 0.34; 95% CI, 0.10-1.11; $P = .08$) (Table 3).

Although pulmonary embolism—related mortality within 30 days of pulmonary embolism diagnosis occurred more frequently in patients who received anticoagulation (5.5% vs 4.3%; AD, 1.2%; 95% CI of the AD, −7.7 to 6.1; $P = .69$), reperfusion therapy did not independently predict 30-day pulmonary embolism—related mortality in a multivariable model (Table 3).

Fatal and nonfatal recurrent venous thromboembolism within 30 days of pulmonary embolism diagnosis occurred in 4 patients (5.7%; 95% CI, 1.6-14.0) who received reperfusion therapy and in 2 patients (0.8%; 95% CI, 0.1-2.8) who received sole anticoagulation therapy (AD, 4.9%; 95% CI of the AD, 0.4-14.0; $P < .01$) (Table 2).

Overall, 15 of the 325 patients (4.6%; 95% CI, 2.6-7.5) had a major bleeding episode. Three bleeds (3/70 patients; 4.3%; 95% CI, 0.9-12.0) occurred in the group of patients receiving reperfusion therapy, whereas 12 bleeds (12/255 patients; 4.7%; 95% CI, 2.4-8.1) occurred in the group who received anticoagulation (AD 0.4%; 95% CI of the AD, −8.4 to 5.2; $P = .88$).

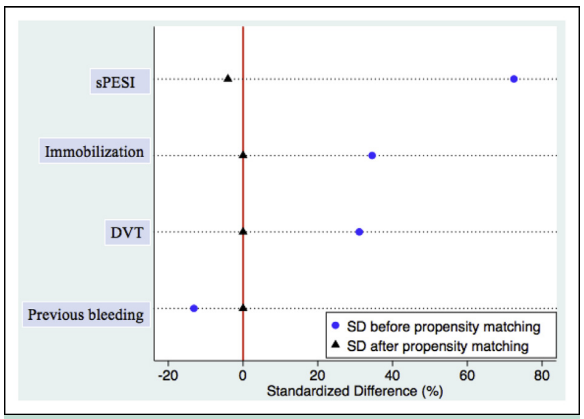

Figure 2 Covariable balance for selected variables before (*circles*) and after (*triangles*) matching, contrasting characteristics of patients undergoing reperfusion therapy or sole anticoagulant therapy. Values on the horizontal axis represent the percent standardized difference. DVT = deep vein thrombosis; SD = standardized difference; sPESI = simplified Pulmonary Embolism Severity Index.

Propensity Score—Matched Cohorts

The matching of patients presenting with acute pulmonary embolism and right heart thrombi yielded 64 patients treated with reperfusion procedures and 64 patients treated with anticoagulation. This model showed good to excellent discrimination with an area under the curve of 0.71. The standardized differences of less than 10% for all matched variables supported the assumption of balance between treatment groups in observed confounders (Figure 2).

Reperfusion therapy did not have a significantly lower mortality than nonreperfusion treatment in the matched cohort of patients with pulmonary embolism and right heart thrombi (6.2% vs 14.1%; risk difference, 7.8%; 95% CI, −4.2 to 20.0; $P = .15$) (Table 4). Reperfusion therapy did not have a significantly different risk of pulmonary embolism—related mortality in comparison with nonreperfusion therapy (4.7% vs 7.8%; risk difference, 3.1%; 95% CI, −7.4 to 13.9; $P = .47$). Of the patients who received reperfusion treatment, 6.2% had a venous thromboembolism recurrence during the study follow-up period in comparison with 0% of those who solely received anticoagulation ($P = .049$). The 2 treatment groups had the same proportion of patients who had a major bleeding event (3.1% vs 3.1%; $P = 1.00$) (Table 4).

DISCUSSION

In this study of treatment propensity-matched cohorts of patients who had acute symptomatic pulmonary embolism and coexisting right heart thrombi, we found no difference in short-term survival and major bleeding between the group that had reperfusion therapy and the group that received

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Table 4 Adjusted Clinical Outcomes for Propensity-Matched Cohorts

30-Day Outcome	Reperfusion n/Total n (%)	No Reperfusion n/Total n (%)	OR (95% CI)	*P* Value
Death	4/64 (6.2%)	9/64 (14.1%)	0.40 (0.11-1.40)	.15
PE-related death	3/64 (4.6%)	5/64 (7.8%)	0.58 (0.13-2.55)	.47
Recurrent venous thromboembolism	4/64 (6.2%)	0/64 (0%)	-	.049
Major bleeding	2/64 (3.1%)	2/64 (3.1%)	1.00 (0.13-7.38)	1.00

CI = confidence interval; OR = odds ratio; PE = pulmonary embolism.

only anticoagulant therapy. However, reperfusion therapy was associated with a higher risk of recurrent venous thromboembolism than sole anticoagulation therapy.

Limited and conflicting data, all from nonrandomized studies, support reperfusion therapy over anticoagulation in patients who have acute pulmonary embolism and coexisting right heart thrombi. For 119 patients with mobile right heart thrombi, the prospective multicenter European Cooperative Study on the clinical significance of right heart thrombi found that short-term mortality was excessive (64%) in patients who received anticoagulation alone, compared with patients who received thrombolysis (40%) or surgery (27%).[23] In contrast, patients who enrolled in the International Cooperative Pulmonary Embolism Registry with acute pulmonary embolism and coexisting right heart thrombi did not show differences in survival among the heparin, thrombolytic, and surgical treatment groups (23.5%, 20.8%, and 25.0%, respectively).[5] Our study did not demonstrate a significantly lower mortality associated with reperfusion therapy compared with anticoagulation alone. The absence of a detectable survival benefit of the reperfusion therapy may reflect an undersized study population and the limited power of the study to detect a difference in outcomes between the groups. However, by assuming that reperfusion might have conferred a benefit in a larger study population, it seems reasonable to conclude that this benefit would have been relatively small.

Our study found a higher risk of recurrent venous thromboembolism associated with reperfusion therapy in comparison with sole anticoagulation. A previous trial that assessed the efficacy and safety of thrombolytic therapy in patients with acute deep vein thrombosis found that 9 patients (9%; 95% CI, 4.2-16.4) who received systemic thrombolysis experienced subsequent symptomatic pulmonary embolism, whereas no recurrent pulmonary embolism occurred in patients who received only conventional anticoagulant therapy.[24] In a retrospective study that used hospital discharge data, patients who received thrombolytics had a lower case fatality rate if they also received an inferior vena cava filter.[25] It should be noted that these findings represent nonrandomized data that may have been subject to bias; whether or not an inferior vena cava filter enhances safety for patients undergoing thrombolysis is not clear.

By putting our findings into context with other published studies, the data suggest that anticoagulation alone might be adequate treatment for most patients with pulmonary embolism and coexisting right heart thrombi. Therefore, reperfusion therapies might be reserved for patients who have acute symptomatic pulmonary embolism and associated hypotension or shock, irrespective of the presence or absence of coexisting right heart thrombi. Because patients with acute pulmonary embolism and coexisting right heart thrombi have a worse outcome when compared with those without right heart thrombi,[26] a Pulmonary Embolism Response Team might assist with rapid mobilization of the necessary resources to provide the most appropriate care.[27]

Study Limitations

This study of the large RIETE Registry has several limitations. The retrospective analysis of observational data may lack some clinical details that may be important determinants of patient selection and outcomes. Confounding may have affected the results of this observational study. We used propensity score matching to make the patient groups comparable according to the measured confounders, and we successfully eliminated the observed differences. However, residual confounding still may have occurred. The relatively small sample size of patients who had pulmonary embolism associated with right heart thrombi and the fairly low event rates resulted in wide CIs and a decreased ability to detect a significant association between treatment strategy and outcomes.

CONCLUSIONS

The results of this study of patients presenting with acute symptomatic pulmonary embolism and coexisting right heart thrombi suggest that there is no significant difference in mortality and major bleeding outcomes between reperfusion therapy and anticoagulant therapy. In addition, the risk of recurrent venous thromboembolism may be significantly higher for reperfusion therapy in comparison with sole anticoagulation. Well-designed studies should be carried out to further assess the efficacy and safety of reperfusion therapy for right heart thrombi associated with pulmonary embolism.

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Artículo 3

APPENDIX

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RIETE = Registro Informatizado de la Enfermedad TromboEmbólica.

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DISCUSIÓN

La TEP es una enfermedad frecuente y potencialmente mortal (43). Constituye la tercera causa de muerte cardiovascular. Su espectro clínico y pronóstico es amplio, y resulta fundamental una estratificación adecuada del riesgo para la elección del mejor tratamiento (anticoagulación, reperfusión, otros) (44).

Aunque no se conoce exactamente su prevalencia, parece que la presencia de TCD es infrecuente en los pacientes con TEP aguda sintomática. Torbicki y colaboradores evaluaron 1.113 pacientes con TEP a los que se había realizado una ecocardiografía y observaron una frecuencia de TCD del 3,8%. Nuestro estudio demuestra que se identifican TCD en un 2,6% de los pacientes con un episodio de TEP aguda sintomática. Algunos estudios previos han descrito prevalencias más elevadas de TCD en pacientes con TEP, que van desde el 7 al 18% (39,45,46). Sin embargo, estos datos provienen de serie de casos y estudios con un tamaño muestral inferior al nuestro.

Existen estudios que sugieren que el riesgo de TCD aumenta en pacientes con TEP asociada a insuficiencia cardiaca e inestabilidad hemodinámica (41,47). Aunque se ha descrito que los TCD pueden ser trombos migrados provenientes de la pelvis o de las venas proximales de los miembros inferiores, la estasis sanguínea resultante de la dilatación de las cavidades cardiacas derechas secundaria a la TEP aguda grave o secundaria a la ICC preexistente, o ambas, parece aumentar el riesgo de TCD (47). También hemos encontrado que el antecedente de sangrado mayor reciente aumenta el riesgo de TCD, posiblemente porque en estos pacientes se utilizan dosis subóptimas de anticoagulantes o incluso no son anticoagulados.

Koc y colaboradores publicaron los resultados de un registro europeo de pacientes con trombos en cavidades cardiacas derechas, que fueron comparados con un grupo control de pacientes con TEP sin TCD (mediante un análisis de propensión) (40). Observaron que el estado hemodinámico y las escalas clínicas pronósticas (i.e., la escala del shock [48] y la escala PESIs [12])

en el momento del diagnóstico de la TEP son predictores de la mortalidad a corto plazo, mientras que la presencia y características de los TCD no lo son. En el grupo de pacientes con TEP de riesgo intermedio (i.e., con DVD), la presencia de TCD se asoció a una mortalidad aumentada. En nuestro estudio encontramos que los pacientes con TEP y TCD tuvieron peor pronóstico a 30 días que los pacientes con TEP sin TCD. Así mismo, los pacientes con TEP de riesgo intermedio y TCD tenían tres veces mayor riesgo de morir en comparación con aquellos sin TCD. Es importante señalar que nuestro estudio cuenta con la mayor muestra de pacientes con TEP y TCD publicada hasta la fecha, y que el ajuste realizado para todos los posibles factores confusores y la robustez de los resultados proporcionan una fuerte evidencia que apoya la premisa de que los TCD en el momento de diagnóstico de la TEP son un predictor de mortalidad por cualquier causa, por la propia TEP y de la ETEV recurrente.

Los resultados de nuestro metanálisis indican que la presencia de TCD multiplica el riesgo de mortalidad a corto plazo de los pacientes con TEP aguda sintomática. Aun así, la tasa de mortalidad de los pacientes con TCD (16,7%) es similar a la de los pacientes con elevación de biomarcadores cardiacos o con signos ecocardiográficos de DVD (49). Se desconoce si la combinación de todos estos factores predictivos permitiría identificar un subgrupo de pacientes con TEP que se podrían beneficiar de tratamientos avanzados para su enfermedad.

Las alternativas de tratamiento para pacientes con TEP asociada a TCD incluyen la anticoagulación, la trombolisis sistémica o dirigida por catéter y la embolectomía quirúrgica (50). Aunque la Sociedad Europea de Cardiología sugiere el uso de la fibrinolisis para pacientes con TEP y TCD, no hay evidencias robustas sobre el beneficio de este tratamiento para estos pacientes. De hecho, no existen ensayos clínicos aleatorizados que evalúen los efectos de la terapia de reperfusión y la anticoagulación versus la anticoagulación sola para los pacientes con TCD asociado a la TEP. En el registro europeo de pacientes con TEP y TCD, los investigadores encontraron que la mortalidad de los pacientes que recibieron anticoagulación sola (64%) fue mayor que la de los pacientes que recibieron trombolisis (40%) o cirugía (27%) (38). Por el contrario, los pacientes con TEP aguda sintomática y TCD incluidos en el registro ICOPER no mostraban

diferencias en la supervivencia según recibieran tratamiento con heparina, fibrinolisis o cirugía (23,5%; 20,8% y 25,0%, respectivamente) (41).

Utilizando los datos recogidos en el RIETE evaluamos la eficacia del tratamiento de reperfusión, comparado con el tratamiento anticoagulante, sobre la mortalidad por cualquier causa, mortalidad por la propia TEP, la ETEV recurrente y el sangrado mayor en los primeros 30 días después del inicio del tratamiento para la TEP asociada a TCD (49). De los 325 pacientes con TEP y TCD, el análisis de propensión no demostró diferencias estadísticamente significativas en la mortalidad por cualquier causa (6,2% vs. 14%, p =0,15) o en la mortalidad por la propia TEP (4,7% vs. 7,8%, p =0,47) para las dos formas de tratamiento (reperfusión vs. anticoagulación). Estos hallazgos pueden deberse al tamaño muestral y a una potencia insuficiente del estudio para encontrar diferencias entre ambos grupos.

Sin embargo, aunque un estudio con mayor tamaño muestral demostrara una diferencia estadísticamente significativa a favor del tratamiento de reperfusión, este beneficio sería pequeño. Nuestro estudio tampoco encontró diferencias significativas en la tasa de episodios hemorrágicos entre los dos grupos de tratamiento (3,1% vs. 3,1%, p =1,00). No obstante, observamos un riesgo aumentado de recurrencias trombóticas en los pacientes que recibieron tratamiento de reperfusión comparados con los que recibieron anticoagulación sola (6,2% vs. 0%, p =0,049). El estudio de Schweizer y colaboradores, que evaluó la eficacia y seguridad del tratamiento trombolítico en pacientes con TVP, confirmó que un 9% de los pacientes que recibieron tratamiento de reperfusión experimentaron una recurrencia trombótica en forma de TEP, comparado con un 0% de los pacientes que recibieron anticoagulación sola (51). Existen datos de un estudio retrospectivo que objetiva menos eventos trombóticos fatales en aquellos pacientes que recibieron tratamiento de reperfusión a los que se les había insertado un filtro de vena cava inferior (**FVCI**) (52). Dados los sesgos de este tipo de estudios (retrospectivos, no aleatorizados) no se pueden hacer recomendaciones firmes sobre la indicación de FVCI en pacientes con TEP y TCD que van a ser sometidos a fibrinolisis.

Si bien es cierto que nuestro estudio puede tener varias limitaciones por no tratarse de un ensayo clínico controlado y aleatorizado, el gran número de pacientes incluidos en RIETE, el uso de un análisis de propensión, los distintos análisis de sensibilidad y el ajuste por posibles factores confusores aumentan la robustez de nuestros resultados.

Al poner nuestros hallazgos en el contexto de otros estudios publicados, los datos sugieren que la anticoagulación sola podría ser un tratamiento adecuado para la mayoría de los pacientes con TEP y TCD, y que los tratamientos de reperfusión deberían reservarse para pacientes con TEP aguda sintomática e hipotensión o shock asociados, independientemente de la presencia o ausencia de TCD.

CONCLUSIONES

En los pacientes con TEP aguda sintomática, la presencia de trombos en cavidades cardiacas derechas es infrecuente.

La edad joven, la insuficiencia cardiaca, el cáncer, los antecedentes de sangrado reciente, el síncope, la hipotensión y la hipoxemia se asocian de manera independiente con la presencia de trombos en cavidades cardiacas derechas de pacientes con TEP aguda sintomática.

Los pacientes con TEP aguda sintomática y trombos en cavidades cardiacas derechas tienen una mortalidad a corto plazo mayor que los pacientes con TEP que no presentan trombos en cavidades cardiacas derechas.

De manera general, los pacientes con TEP aguda sintomática y trombos en cavidades cardiacas derechas deben recibir el mismo tratamiento que aquellos con TEP sin trombos en cavidades cardiacas derechas. De manera aislada, la presencia de trombos en cavidades cardiacas derechas *per se* no justifica el uso de tratamientos de reperfusión

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ANEXO

Se presenta en este apartado un artículo, pendiente de publicación, pero que no forma parte del cuerpo de la tesis. Sin embargo, representa una gran aportación sobre la terapia de reperfusión en pacientes con TEP y TCD.

Association Between Reperfusion Therapy and Outcomes in Patients with Acute Pulmonary Embolism and Right Heart Thrombi

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Background

Right heart thrombi (RHT), representing clots in-transit, may be detected in <4% of patients with PE,[1] and are associated with worse outcomes.[1, 2] Given the limited existing evidence, guidelines do not provide detailed recommendations for management of PE patients with RHT.[3, 4] It is plausible that reperfusion strategies (thrombolytic therapy to help dissolve the RHT and emboli, or percutaneous or surgical thrombectomy to reduce the thromboembolic burden) reduce the adverse outcomes. In turn, such therapies carry risks, including increased bleeding. Using the data from RIETE (Registro Informatizado Enfermedad TromboEmbolica), a prospective international registry of patients with venous thromboembolism, we sought to compare the outcomes of patients with PE and coexisting RHT, with or without reperfusion therapy.

Methods

The design and methodology of RIETE have been previously described.[5] Institutional review board approval and informed consent were obtained at participating sites. We included patients with PE from 0/3/2001-09/2019 and determined the use of reperfusion therapies within 3 days from echocardiographic identification of RHT. The main outcomes were 30-day PE-related mortality (autopsy-confirmed, or death within 10 days from PE, in the absence of an alternative cause), all-cause mortality, major bleeding (events that were overt and required ≥ 2 units of blood, or retroperitoneal, spinal or intracranial, or fatal), and recurrent PE.

In the primary analysis, 1:1 propensity score matching was used. We matched each patient receiving reperfusion therapy with the nearest patient not

receiving reperfusion, within a caliper width of 0.2-times the standard deviation of the log odds of the propensity score. The score was derived from a group of variables thought to influence the use of reperfusion therapies and outcomes (including vital signs, age, history of heart failure and cancer).

As confirmatory analyses, we included all patients with RHT in multivariable logistic regression, assessing the association between reperfusion therapies and outcomes. Analyses were conducted with Stata Version 16.1. A 2-sided P-value <0.05 was considered significant.

Results

Among 42,620 patients with PE, 443 (1.0%) had RHT, of whom 102 received reperfusion therapy (thrombolytic therapy in 74, percutaneous or surgical thrombectomy in 28). After propensity-score matching, patient characteristics were comparable (Table).

During 30-day follow-up, 40 (9.0%) patients died, including 24 (5.4%) from PE. In the propensity-matched cohort (82 pairs), use of reperfusion therapy was not associated with significantly reduced odds of 30-day PE-related mortality (odds ratio [OR]: 0.65, 95% confidence interval [CI]: 0.20-2.16, P=0.48) or all-cause mortality (OR: 0.86, 95% CI: 0.30-2.43, P=0.78). The rate of major bleeding was comparable (OR: 1.00, 95% CI: 0.25-3.92, P=0.999). Six patients receiving reperfusion therapy and 0 controls had recurrent PE (risk difference: 0.08, 95% CI: 0.02-0.14). Findings were similar in multivariable logistic regression analyses (Figure).

Discussion

In this study, we failed to find a significantly reduced odds of PE-related mortality with reperfusion attempt, mainly through thrombolytic therapy. Despite reporting the largest series of patients with RHT from a multinational registry, *type II error* is possible, similar to a prior investigation,[6]. Considering the hypothesis-generating increase in recurrent PEs, it might be prudent to avoid routine use of thrombolytic therapy in hemodynamically-stable PE patients with RHT. Nevertheless, these patients have an increased risk of adverse outcomes and alternative strategies, including surgical, or percutaneous thrombectomy require further investigations. Despite reporting the largest patient series with PE and RHT, small numbers made it unfeasible to assess the clinical subgroups. Given the rarity of this condition, it is unlikely that a large trial becomes available.

In conclusion, in patients with PE and RHT, use of reperfusion therapy was not associated with significantly lower PE-related mortality. Additional studies are required to identify effective treatments for this high-risk clinical subgroup.

Disclosures

Dr. Bikdeli reports that he is a consulting expert (on behalf of the plaintiff) for litigation related to a specific type of inferior vena cava filters. The current study is the idea of the investigators and has not been performed at the request of a third party. We express our gratitude to Sanofi Spain for supporting this Registry with an unrestricted educational grant. We also express our gratitude to Bayer Pharma AG for prior support to this Registry. Bayer Pharma AG's support was limited to the part of RIETE outside Spain. The funders had no role in the study design, statistical analyses, or submission of the results for publication.

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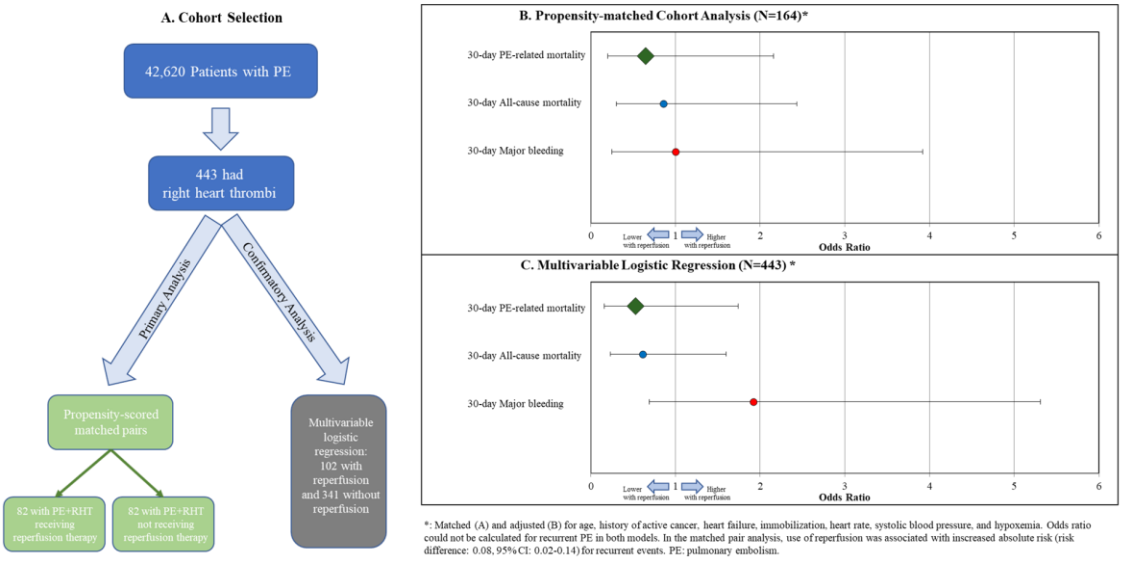
Table. Baseline Characteristics of Patients with Pulmonary Embolism and Right Heart Thrombi

	Before Propensity-Score Matching			After Propensity Score Matching		
	Reperfusion Therapy* N= 102	No Reperfusion Therapy* N=341	P-value	Reperfusion Therapy* N=82	No Reperfusion Therapy* N=82	P-value
Demographics						
Age (years, mean ± SD)	58.8 (17.5)	64.4 (17.2)	0.003	59.1	58.9	0.94
Co-morbidities						
Heart failure (%)	17.6	15.0	0.51	14.6	15.9	0.83
Active cancer (%)	14.7	22.3	0.10	14.6	13.4	0.82
Immobilization (%)	38.2	24.3	0.006	35.3	31.7	0.62
Vital Signs						
Heart rate	112.7	96.3	<0.001	108.4	108.7	0.94
Systolic blood pressure	101.9	121.5	<0.001	107.8	107.3	0.91
Oxygen saturation <90%	46.0	22.9	<0.001	39.0	40.2	0.87

*: In the first 3 days, SD: standard deviation.

Figure. Outcomes with or without Reperfusion: Propensity-matched Cohort (A), and Multivariable Logistic Regression Among All Participants (B)

Figure. Cohort Selection (A) and Outcomes with or without Reperfusion: Propensity-matched Cohort (B), and Multivariable Logistic Regression Among All Participants (C)



*: Matched (A) and adjusted (B) for age, history of active cancer, heart failure, immobilization, heart rate, systolic blood pressure, and hypoxemia. Odds ratio could not be calculated for recurrent PE in both models. In the matched pair analysis, use of reperfusion was associated with increased absolute risk (risk difference: 0.08, 95% CI: 0.02-0.14) for recurrent events. PE: pulmonary embolism.

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