Universitat Autònoma de Barcelona

Enfermedad tromboembólica venosa en situaciones especiales: cáncer y obesidad mórbida

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Enfermedad tromboembólica venosa en situaciones especiales: cáncer y obesidad mórbida

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LISTADO DE ABREVIATURAS

ACOD	Anticoagulante oral de acción directa
angioTC	Angiografía por tomografía computerizada
ASH	*American Society of Hematology*
AVK	Antagonistas de la vitamina K
CFR	*Case-fatality rate*
EP	Embolia pulmonar
ETV	Enfermedad tromboembólica venosa
FA	Fibrilación auricular
FC	Frecuencia cardíaca
FG	Filtrado glomerular
h	hora
HBPM	Heparina de bajo peso molecular
HNF	Heparina no fraccionada
IAM	Infarto agudo de miocardio
IMC	Índice de masa corporal
kg	kilogramo
mg	miligramo
min	minuto
mL	mililitro
RM	Resonancia magnética
OR	*Odds ratio*
RIETE	Registro Informatizado de Enfermedad Tromboembólica
RM	Resonancia magnética

RR	Riesgo relativo
SPECT	*single photon emission computed tomography*
TAS	tensión arterial sistémica
TC	Tomografía computerizada
PESI	*pulmonary embolism score index*
sPESI	*simplified pulmonary embolism score index*
TC	Tomografía computerizada
TVP	Trombosis venosa profunda
UE	Unión Europea
VIH	Virus de la inmunodeficiencia humana

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RESUMEN

La presente tesis doctoral se basa en 2 artículos que evalúan la evolución clínica durante los primeros 3 meses de anticoagulación en dos situaciones especiales del tratamiento de la enfermedad tromboembólica venosa (ETV): el paciente con cáncer en quien se detecta una embolia pulmonar (EP) incidental y el paciente con obesidad mórbida.

Estos dos estudios han mostrado que durante los primeros 3 meses de anticoagulación la mortalidad de estos pacientes es muy inferior a la habitual en el resto de pacientes.

Los pacientes con cáncer y EP incidental presentan una tasa similar de recurrencias sintomáticas de ETV, así como de hemorragias graves, en comparación con los pacientes con EP sospechada clínicamente y confirmada. Sin embargo, presentan una menor mortalidad, tanto por cualquier motivo como por EP y en relación a la neoplasia subyacente.

Los pacientes con ETV y obesidad mórbida (definida por un IMC > 40kg/m^2), también presentan una tasa de recurrencias sintomáticas de ETV y hemorragias graves similar a la del paciente con peso normal (IMC 18.5-24.9 kg/m^2). Sin embargo, en este grupo de pacientes se observó una disminución de un tercio de la mortalidad, independientemente de la presencia de cáncer, en comparación con los pacientes con peso normal. Esta menor mortalidad en el paciente con obesidad ya ha sido descrita previamente en la literatura, lo que se ha descrito como la “paradoja de la obesidad”.

El curso más favorable, en términos de mortalidad, que se ha podido observar en estos dos grupos de pacientes, hace necesario plantear la realización de nuevos estudios con diseño aleatorizado, para comprobar si se pueden beneficiar de un tratamiento anticoagulante de menor intensidad o duración, con el objetivo de mejorar el balance riesgo/beneficio durante la anticoagulación.

ABSTRACT

This doctoral thesis is based on 2 articles that evaluated the natural history of the disease during the first 3 months of anticoagulation in two special situations of venous thromboembolism (VTE): the patient with cancer and incidentally found pulmonary embolism (PE), and the patients with morbid obesity.

The two studies revealed that the mortality rates during the first 3 months of anticoagulation are much lower in patients with these special situations than in the remaining patients with VTE.

Patients with cancer and incidental PE had a similar rate of symptomatic recurrences of VTE or major bleeding than those with clinically uspected and confirmed PE. However, these patients have much lower mortality rate, both from any cause, PE or due to the underlying malignancy.

Patients with VTE and morbid obesity, (defined by a BMI > 40kg / m2), also had a rate of symptomatic recurrences of VTE or major bleeding similar to those in patients with normal weight (BMI 18.5-24.9 kg / m2). Again, this group of patients also hada one-third decrease in mortality, irrespectively of the presence of cancer, compared to patients with normal weight. This lower mortality in obese patients has already been previously described in the literature, which has been described as the “obesity paradox”.

The lower mortality rate that has been observed in these two subgroups of patients warrants new studies necessary to confirm whether or not they could benefit from a lower intensity or a shorter duration of anticoagulant therapy , with the aim of improving the balance risk / benefit during anticoagulation.

1. INTRODUCCIÓN

1.1. DEFINICIÓN DE ETV

La ETV consiste en un conjunto de enfermedades que se caracterizan por la formación de trombos en la circulación venosa. La forma de presentación más habitual es como TVP en extremidades o EP, siendo habitualmente la EP una complicación de una TVP previa (sobre todo en miembros inferiores)(1). Sin embargo, la trombosis puede producirse en cualquier territorio venoso, dando lugar a diferentes presentaciones clínicas: trombosis esplácnicas (portal, esplénica, mesentérica...), trombosis de vena cava, trombosis de senos venosos cerebrales, trombosis de venas pulmonares... Aunque el pilar del tratamiento de todas ellas es la anticoagulación, cada una de las entidades presenta unas particularidades específicas.

1.2. EPIDEMIOLOGÍA DE LA ETV

La ETV es la 3º causa de enfermedad vascular en nuestro entorno, por detrás de la cardiopatía isquémica y el ictus(2). Estudios epidemiológicos a nivel europeo evidencian que la incidencia anual de EP es de 39-115 casos por cada 100 000 personas y para la TVP de 53-162 casos por cada 100 000 personas(1). Otros estudios muestran que la incidencia de ETV aumenta con la edad, siendo 8 veces más frecuente en pacientes de más de 80 años respecto a pacientes de entre 50-60 años(3). Paralelamente, en los últimos años, diversos estudios muestran un aumento de los casos de ETV. Todo ello representa un elevado impacto en términos de morbi-mortalidad para la población, así como un importante gasto económico(1)(4). Un estudio reciente muestra que en Europa, la ETV genera unos gastos totales, directos e indirectos, de unos 8.5 billones de euros(5).

En términos de mortalidad, un estudio en el año 2004 realizado en 6 países de la UE, con una población total de más de 450 millones de personas, mostró una mortalidad por ETV de más de 370000 pacientes(6). Asimismo, cuando analizamos de manera separada la mortalidad atribuible a la ETV a los 30 días, dependiendo de la forma de presentación, ésta es de un 2-3% en los pacientes con EP estable hemodinámicamente, de un 9-10% si la EP se presenta con inestabilidad hemodinámica, e inferior a un 0.5% si se presenta en forma de TVP aislada (7)(8)(9).

1.3. TRATAMIENTO DE LA ETV NO ASOCIADA A CÁNCER

En términos generales, el pilar del tratamiento de los pacientes con ETV es la anticoagulación, diferenciándose 3 fases bien definidas: tratamiento de la fase aguda, tratamiento a largo plazo y tratamiento extendido.

El **tratamiento de la fase aguda** comprende los primeros 7-10 días de tratamiento, excepto si se usa rivaroxaban que se considera los primeros 21 días. En esta fase, según las últimas guías de práctica clínica, el tratamiento de elección para los pacientes que debutan con estabilidad hemodinámica y que presentan un bajo riesgo de deterioro clínico y hemodinámico son los ACOD(1,10). Para los pacientes con EP de alto riesgo y que por tanto se presentan con inestabilidad hemodinámica, el tratamiento anticoagulante de elección son las HBPM(1) después de la realización de alguna de las terapias de reperfusión. Los dos ACOD disponibles para esta fase son rivaroxaban y apixaban. Una alternativa a los ACOD son las HBPM por vía subcutánea y en los casos con antecedente o sospecha de trombocitopenia inducida por heparina el fondaparinux (ver dosificación de HBPM y fondaparinux en tabla 1). La heparina no fraccionada se ha asociado a una mayor tasa de hemorragias respecto la HBPM y se reserva para casos muy seleccionados de pacientes con EP de alto riesgo o de riesgo intermedio-alto con riesgo elevado de inestabilización hemodinámica(1,10,11).

El **tratamiento a largo plazo** se extiende hasta un mínimo de 3 meses. En esta fase nos decantamos por la anticoagulación oral, siendo el tratamiento de elección cualquiera de los 4 ACOD que actualmente disponemos: dabigatrán, rivaroxaban, apixaban y edoxaban. Una alternativa a los ACOD serán los AVK, o en su defecto las HBPM o fondaparinux(1,10,11). Cabe recordar que, en la actualidad, el tratamiento con ACOD de la ETV en España está excluido de la financiación por parte del Sistema Nacional de Salud, con la consiguiente problemática que este hecho causa en la prescripción.

El **tratamiento extendido** se inicia a partir de los 3 meses de tratamiento anticoagulante. En este punto, se deberá realizar una evaluación periódica del riesgo de recurrencia de la ETV y del riesgo de hemorragia, y así decidir la óptima duración del tratamiento. Una valoración individualizada de los factores predisponentes de recurrencia la ETV (ver apartado 3) y del riesgo de sangrado, será de capital importancia. En esta fase el tratamiento de elección continuará siendo los ACOD, y en aquellos casos en que no sea posible, nos decantaremos por los AVK o, en un segundo término, por las HBPM o el fondaparinux(1,10,11).

1.3.1. Dosificación de la HBPM para el tratamiento de la ETV

Según ficha técnica y los diferentes ensayos clínicos, las HBPM se prescriben según el peso del paciente(1,10–12). Se debe tener en cuenta que cada HBPM tiene una dosificación diferente (ver tabla 1) y que la presencia de insuficiencia renal obliga a valorar la reducción de la dosis (por ejemplo, en el caso de la enoxaparina se deberá disminuir a 1mg/kg/día si el FG < 30mL/min/1.73m2).

Mientras que en los pacientes con peso normal existe evidencia de la dosificación más adecuada de la HBPM, ésto no sucede en los pacientes con pesos extremos, ya sea por bajo peso o por obesidad, debido a que, de manera sistemática, son excluidos de los ensayos clínicos.

Tabla 1. Dosificación de HBPM y fondaparinux para el tratamiento de la ETV

Tipo de fámaco	**Dosificación**
Clexane® (enoxaparina) o enoxaparina biosimilar	1.5mg/kg/24h o 1mg/kg/12h
Hibor® (bemiparina)	115UI/kg/24h
Innohep® (tinzaparina)	175UI/kg/24h
Arixtra® (fondaparinux)	Peso <50kg: 5mg/24h Peso 50-100kg: 7.5mg/24h Peso >100kg: 10mg/24h

1.4. ABORDAJE DE LA ETV EN SITUACIONES ESPECIALES

En la ETV existen situaciones clínicas poco habituales, conocidas como situaciones especiales, en las cuales prácticamente no existen ensayos clínicos y por tanto la evidencia científica es escasa. En estos escenarios, el mejor abordaje terapéutico no ha sido demostrado y habitualmente debemos recurrir a estudios observacionales, como los registros de práctica clínica en vida real.

Algunas de las situaciones especiales más frecuentes en la práctica clínica habitual son la insuficiencia renal grave con FG < 30mL/min, la trombocitopenia con menos de 50000 plaquetas por mL, la coagulopatía definida como la alteración del tiempo de protrombina y/o tiempo de tromboplastina parcial, el antecedente reciente de

hemorragia o cirugía, el cáncer diseminado, el bajo peso, la obesidad mórbida o el embarazo.

Para la presente tesis doctoral, dentro de estas situaciones especiales, hemos escogido el paciente con cáncer diagnosticado de una EP incidental y el paciente con obesidad mórbida, dado que son dos situaciones clínicas relativamente habituales en la práctica clínica, pero en cambio no disponemos de suficiente evidencia sobre cuál es el tratamiento más adecuado.

1.4.1 ETV ASOCIADA A CÁNCER

1.4.1.1. Epidemiología de la ETV asociada a cáncer

En los últimos años, a diferencia de la estabilidad en los nuevos diagnósticos de ETV en los pacientes sin cáncer, existe un claro aumento en la incidencia y prevalencia de la ETV asociada a cáncer(13). Ello está en relación al aumento del diagnóstico del cáncer, el aumento de la supervivencia de los pacientes con cáncer en fases avanzadas y a la mejoría del diagnóstico de la ETV(14). El cáncer constituye uno de los factores de riesgo más importantes para desarrollar un primer evento de ETV, así como para presentar una recurrencia tras suspender la anticoagulación(1)(15)(16)(17). El 20% de los pacientes con ETV tiene cáncer, estimándose que el éste supone un aumento del riesgo de desarrollar una trombosis venosa de entre 4 a 6.5 veces respecto al paciente sin cáncer(18)(19), siendo el riesgo más elevado en los 3 primeros meses después del diagnóstico del cáncer(18). En relación a la mortalidad, la ETV es la tercera causa de muerte en el paciente con cáncer, después de la propia enfermedad neoplásica y las infecciones, y la aparición de una ETV se asocia con un aumento del riesgo de muerte del triple respecto al paciente sin ETV(19). Sin embargo, el aumento del riesgo trombótico y hemorrágico no es igual en todos los pacientes, dependiendo de los factores clásicos relacionados con el paciente y, en gran medida, determinados por el tipo de cáncer y el tratamiento oncoespecífico (18)(20). En este caso, las neoplasias que se asocian a mayor riesgo de trombosis son la de pulmón, páncreas y gástrica, y las que se asocian a una mayor tasa de hemorragias durante la anticoagulación son las de colon, vejiga urinaria y la de próstata(20)(18). Asimismo, los pacientes con cáncer bajo tratamiento anticoagulante tienen de 2 a 6 veces mayor riesgo de tener una complicación hemorrágica que los pacientes sin cáncer(17)(21). Además, la aparición de ETV en un paciente con cáncer se asocia a un importante

impacto sobre la calidad de vida del paciente por diferentes motivos, como la incomodidad del tratamiento anticoagulante (en la mayor parte de los casos con HBPM por vía subcutánea), la aparición de hematomas y otras complicaciones hemorrágicas, la ansiedad al riesgo de recurrencia después de suspender la anticoagulación, entre otros (22).

1.4.1.2.Tratamiento de la ETV asociada a cáncer

En la actualidad, el tratamiento habitual de la ETV asociada a cáncer sigue siendo la HBPM tanto en la fase aguda como a largo plazo (ver Tabla 1). Los estudios que han comparado el tratamiento con HBPM respecto AVK han demostrado que la HBPM es más eficaz y al menos tan segura como los AVK (10)(23)(17)(24). No obstante, en algunas situaciones clínicas podremos decantarnos por la anticoagulación oral, preferiblemente con un ACOD, por su mejor perfil de seguridad con relación a las hemorragias que los AVK. No obstante, los ensayos clínicos publicados con edoxaban y rivaroxaban en comparación con HBPM han mostrado que debemos tener especial precaución con el uso de los ACOD en los pacientes con neoplasias localizadas en el tracto digestivo superior y genitourinario, al asociarse en estos casos a mayor tasa de hemorragias que con el uso de HBPM(24,25). Recientemente, se ha publicado un ensayo clínico en el que se compara apixaban con HBPM, mostrando que el primero no es inferior en cuanto al riesgo de hemorragias, sin un aumento del riesgo de hemorragia, constituyendo una buena alternativa al tratamiento clásico con HBPM(19)(26). Por otro lado, en los pacientes con tratamiento oncoespecífico activo, previo al inicio del tratamiento con ACOD deberemos de comprobar si existen potenciales interacciones(1).

1.4.1.3. Evolución de la ETV asociada a cáncer y duración de la anticoagulación.

La evolución de la ETV asociada a cáncer es muy compleja y difícil de predecir, dado que en ella están implicados numerosos factores, algunos de los cuales son modificables y otros no. En este sentido, tanto el riesgo de recurrencia de la ETV como el riesgo de hemorragia durante la anticoagulación es multifactorial, en función de factores intrínsecos al paciente, características de la neoplasia (básicamente según el tipo de neoplasia y tratamiento oncoespecífico) y factores transitorios a los que se vea sometido el paciente(27)(19).

Los factores de riesgo relacionados con el paciente y los transitorios que pueden subyacer van a ser comunes a los pacientes sin cáncer, por lo que los factores diferenciales respecto a los de la ETV no asociada a cáncer van a ser aquellos propiamente relacionados con la neoplasia, incluyendo el tratamiento oncoespecífico. Un estudio observacional donde se compararon las tasas de recurrencias y hemorragias durante la anticoagulación de pacientes con cáncer de mama, colorrectal, pulmón y mama, evidenció que en los dos primeras casos tuvieron una tasa de recurrencias y hemorragias similares, la neoplasia de pulmón un mayor riesgo de recurrencias, y la de próstata un balance favorable a un mayor riesgo de hemorragia(20). Asimismo, será necesario evaluar concienzudamente el tratamiento oncoespecífico que está realizando el paciente, puesto que algunos fármacos se relacionan con un aumento del riesgo de progresión o recurrencia de la trombosis y otros con un aumento del riesgo de hemorragia. En los últimos años, se ha comprobado que la biología molecular del cáncer también puede tener un cierto efecto sobre el riesgo de que el paciente presente una trombosis venosa, en esta línea la mutación del gen ALK(28) y del gen ROS(29) en los pacientes con cáncer de pulmón, aumenta el riesgo de presentar un primer evento de ETV. Por este motivo, para la toma de decisiones más adecuada en relación de la anticoagulación, así como la óptima duración de la misma, se deberán tener en cuenta todos estos factores anteriormente mencionados.

En los pacientes con cáncer activo deberemos mantener el tratamiento anticoagulante durante al menos 6 meses, y posteriormente individualizar cada caso, y valorar el balance riesgo recurrencia / riesgo hemorragia, ya que, como ya se ha mencionado, se trata de un grupo de paciente muy heterogéneo(1,10). Para ello será necesario, además de valorar el tipo y localización del cáncer, evaluar el estado de éste (remisión completa, remisión completa o parcial, enfermedad estable, progresión enfermedad) y el estadio (sin o con metástasis, cáncer irresecable…), así como el tratamiento oncoespecífico(1,10,23). En aquellos casos en los que el riesgo de recurrencia exceda el riesgo de sangrado mantendremos la anticoagulación, mientras que si el riesgo de hemorragia es superior al de tener un nuevo evento tromboembólico, nos decantaremos por la suspensión. Existe escasa evidencia en la literatura de la evolución clínica a partir de los 6 meses de anticoagulación, aunque hay evidencia que a partir de este período el riesgo de recurrencia de la ETV es inferior, sim embargo éste permanecerá siendo significativo en un grupo numeroso de los pacientes(1,10,23)(17). En los pacientes curados o en remisión completa el riesgo es bajo, por lo que se deberá valorar la suspensión de la anticoagulación(1,10,23).

1.4.1.4. Pronóstico de la ETV asociada a cáncer

El pronóstico del paciente con cáncer viene dado por diversos factores, como los relacionados con el propio paciente, aunque en gran medida dependerá de la neoplasia subyacente y el tratamiento oncoespecífico, así como con la evolución clínica que presente. Pese a que diversos ensayos clínicos y estudios observacionales muestran que la mortalidad por EP del paciente con cáncer es de entre un 1 a un 7% al 1 % a los 3 mesess, hay una sólida evidencia que el diagnóstico de ETV en un paciente con cáncer tienen un impacto negativo en términos de morbimortalidad (27,30). De tal manera que, la aparición de una trombosis venosa en un paciente con cáncer se asocia a un aumento independiente de la mortalidad de entre 2 a 3 veces respecto al paciente sin cáncer(27)(30).

En términos de morbilidad, además de la incomodidad del tratamiento anticoagulante, que en la mayor parte de los casos será por vía subcutánea, y el impacto que tendrá este hecho en la calidad de vida del paciente, destaca el aumento del riesgo de tener un evento hemorrágico durante el tratamiento anticoagulante, el cual es mayor en pacientes con cáncer que sin él (18,20)(21). El impacto en calidad de vida del paciente ocurre tanto si es una hemorragia grave como si es clínicamente relevante (21). Asimismo, la aparición de una hemorragia puede tener un impacto negativo en el curso del tratamiento anticoagulante y oncoespecífico, ya que puede hacer que sea necesario cambiar tanto la estrategia de la anticoagulación como la del tratamiento del propio cáncer(21).

1.4.1.5. EP incidental

Se define EP incidental la EP que se diagnostica como hallazgo inesperado al realizar una prueba de imagen, generalmente una TC, por cualquier otro motivo que no sea la sospecha de una EP y siempre en ausencia de TVP(1). En la actualidad, a los pacientes con cáncer se les realiza con frecuencia TC de control para valorar la extensión de la neoplasia, la respuesta al tratamiento oncoespecífico o para el cribado de enfermedad metastásica. Este hecho hace que se diagnostiquen con mayor frecuencia EP incidentales. La prevalencia de una EP incidental en el pacientes con cáncer activo varía entre el 1.1% y el 5%(31–33).

En el paciente con cáncer, debido a limitaciones presentes en el momento del diagnóstico, como presencia de metástasis pulmonares, pleurales o derrame pleural, toxicidad cardíaca o pulmonar por la quimioterapia o radioterapia, comorbilidades,

desacondicionamiento físico, etc, la clínica de una EP se puede ver enmascarada, aumentando la probabilidad de que una EP no sea sospechada(34,35).

Será necesario realizar una correcta anamnesis y exploración física ya que en alrededor de un 20-30% existirá algún signo o síntoma de EP, mientras que en el resto el paciente estará totalmente asintomático, lo que se conoce como una EP incidental verdadera o *truly incidental pulmonary embolism* (36). Desde hace unos años existe un aumento creciente del diagnóstico de EP incidental, debido al aumento en la incidencia de cáncer, aumento de la supervivencia de pacientes con cáncer metastásico, y la mejoría de la sensibilidad las pruebas diagnósticas(34)(37).

En la actualidad, aunque las guías de práctica clínica aconsejan tratar a estos pacientes de la misma manera que los que tienen una EP sintomática(1,10), la mejor estrategia de tratamiento de este grupo de pacientes sigue siendo desconocida(23), ya que estas recomendaciones se basan en estudios retrospectivos con diferencias no significativas en las tasas de recurrencias, hemorragias y mortalidad respecto los pacientes con EP clínicamente sospechada. Además, la mayor parte de estos estudios son series cortas y por lo tanto con una escasa potencia para encontrar diferencias entre el grupo de pacientes con EP incidental y con una EP clínicamente sospechada(38–41). Todo lo antes expuesto, junto a que habitualmente estos pacientes presentan un riesgo hemorrágico aumentado, hace que sea necesaria la búsqueda de la mejor estrategia terapéutica.

En los últimos años han aparecido algunas publicaciones que muestran que el diagnóstico de una ETV incidental, se relaciona con una tasa de recurrencias y hemorragias similares a la EP sintomático, aunque con una menor mortalidad(42)(40). Un metaanálisis en el que se que incluían 11 cohortes de pacientes con EP incidental y cáncer encontró un elevado riesgo de recurrencia de la EP, especialmente después de suspender la anticoagulación. Sin embargo, este estudio sólo realizaba un seguimiento de 6 meses y no se informaba con detalle del tratamiento anticoagulante, del tipo de episodio de EP recurrente ni del tipo de hemorragias durante la anticoagulación(43). Posteriormente, se estudiaron los 715 pacientes con EP incidental y cáncer del registro RIETE (hasta la fecha), observándose que la tasa de hemorragias graves durante el tratamiento anticoagulante era 3 veces mayor que la tasa de recurrencias de la EP, y que la tasa de hemorragia fatal era 4 veces mayor que la tasa de EP fatal. No obstante, tras suspender la anticoagulación, la tasa de hemorragias graves era inferior a la tasa de EP recurrente, sin encontrarse diferencias

en la tasa de mortalidad por EP o sangrado. No se pudieron identificar factores de riesgo independientes de recurrencia durante la anticoagulación(44).

Recientemente, en un estudio observacional prospectivo que incluía a 695 pacientes diagnosticados de EP incidental seguidos durante 12 meses, sin grupo control, se observó una tasa de recurrencias de ETV acumulada de un 6%, una tasa acumulada de hemorragias graves de un 5.7% y una mortalidad por cualquier causa durante el seguimiento de un 43%. La incidencia de recurrencia de ETV a los 12 meses fue de un 6.4% en aquellos pacientes con EP subsegmentaria, en comparación con un los que presentaban una EP más proximal que era de un 6%. Se concluyó que el riesgo de recurrencia de ETV no era menospreciable pese a la anticoagulación, sin observarse que la localización de la EP tuviera una influencia significativa(42)(42)(42)(42)(42).
Asimismo, un estudio comparó los 331 pacientes con ETV incidental respecto los 679 pacientes con una ETV sintomática incluidos en el estudio HOKUSAI VTE cancer, que fueron randomizados a recibir edoxaban o dalteparina. El objetivo primario fue la variable combinada de presentar un primer evento de ETV recurrente o hemorragia grave, y los secundarios fueron las recurrencias de ETV, las hemorragias graves o la mortalidad. En los pacientes con ETV incidental el objetivo primario ocurrió en un 12.7% de los pacientes, frente a un 13.8% en los pacientes con una ETV sintomática. Respecto a los objetivos secundarios, en la ETV incidental se observó una hemorragia grave en un 6.6% de los pacientes y una recurrencia de la ETV en un 7.9%, mientras que en la ETV sintomática la tasa de hemorragias graves y recurrencias de la ETV fue de un 4.9% y de un 10.9% de los pacientes. La mortalidad fue similar en ambos grupos. El estudio concluyó que los resultados fueron sustancialmente altos en ambos grupos, y por tanto apoyarían a las recomendaciones de la guías de práctica clínica de tratar a los pacientes de ambos grupos de manera similar con anticoagulación(45).
Otro estudio retrospectivo de 200 pacientes, examinó la influencia en términos de mortalidad del diagnóstico de una TVP incidental en el paciente que había sido diagnosticado de EP incidental, durante los 3 primeros meses. Se observó que la presencia de una TVP incidental concomitante no tuvo incidencia en la mortalidad. En el análisis multivariante, el bajo peso y la presencia de metástasis se asociaron con un aumento de la mortalidad(46).

1.4.2. ETV EN EL PACIENTE CON OBESIDAD MÓRBIDA

Según la OMS, se define como sobrepeso al paciente con IMC ≥ 25kg/m2, obesidad con IMA ≥30kg/m2 y obesidad mórbida si tienen un IMC ≥ 40kg/m^2(47). La obesidad

mórbida constituye un claro factor de riesgo para diversas patologías respecto al paciente no obseso, sobre todo enfermedades cardiovasculares, aunque también se ha demostrado que tiene un mayor riesgo de padecer ETV y de su recurrencia tras suspender la anticoagulación, debido a la disminución de la movilidad y al aumento de presión intraabdominal sobre las venas femorales(48)(49).

Aunque la relación causal entre ETV y obesidad está ampliamente descrita, la mejor estrategia terapéutica de este grupo de pacientes con respecto a la anticoagulación no ha sido bien definida. Este hecho es en parte a que es un grupo de pacientes que, de manera sistemática, queda excluido de los ensayos clínicos de ETV y anticoagulación. Aunque conocemos que en el paciente diagnosticado de ETV el bajo peso constituye un factor de riesgo independiente de hemorragia grave y de mortalidad(50), no existen estudios prospectivos en los que se evalúe el riesgo de recurrencia y hemorragia, así como la mortalidad del paciente con obesidad mórbida con respecto al paciente no obeso(51,52).

Existe escasa evidencia sobre la relación entre obesidad y mortalidad, a la vez que contradictorios.

Un estudio consistente en un análisis combinado de 20 estudios prospectivos que incluían 9564 pacientes con obesidad extrema observó que estos pacientes tenían una mayor mortalidad, siendo la mayor parte del exceso de mortalidad por cardiopatía, cáncer y diabetes(53).

En cambio, otros estudios encontraron que un IMC elevado se asociaba a una mayor supervivencia. El primer artículo que recogía este hecho fue publicado en 2005 y se analizaron los datos de 7767 pacientes con insuficiencia cardíaca categorizados según el IMC basal: bajo peso (IMC <18.5), peso saludable (IMC 18.5-24.9), sobrepeso (IMC 25.0-29.9) y obesidad (IMC ≥30.0). Se realizó un seguimiento medio de 37 meses. Los resultados evidenciaron una relación inversamente proporcional entre las tasas brutas de mortalidad por todas las causas y los pacientes de las dos categorías de IMC más altos. Después del análisis multivariable, los pacientes con sobrepeso y obesidad tenían una menor mortalidad (OR 0.88; 0.80-0.96) y (OR 0.81; 0.72-0.92) respectivamente, en comparación con los pacientes en un peso saludable. Por el contrario, los pacientes con bajo peso e insuficiencia cardíaca estable tenían un mayor riesgo de muerte (OR 1.21; 0.95-1.53). Dicho estudio fue el origen de la expresión “paradoja de la obesidad”(54).

Posteriormente, una revisión describió que los pacientes con obesidad que presentaban determinadas enfermedades crónicas como enfermedad renal crónica, insuficiencia cardíaca crónica, enfermedad pulmonar obstructiva crónica, cáncer, SIDA, artritis reumatoide y los ancianos, presentaban una progresión más lenta de dichas enfermedades crónicas, lo que se asociaba a una disminución significativa de la mortalidad a corto plazo(55).

En otro trabajo se investigó la asociación del IMC con la mortalidad a largo plazo en pacientes con enfermedad coronaria conocida o sospechada, mediante un estudio de cohortes retrospectivo de 5.950 pacientes. Los pacientes se clasificaron en peso insuficiente, normal, sobrepeso y obesidad, según la clasificación de la OMS, y se realizó un tiempo medio de seguimiento de 6 ± 2,6 años. Los pacientes con sobrepeso y obesidad tuvieron una mortalidad significativamente menor que pacientes con un IMC normal (OR 0.65; 0.6-0.7 para sobrepeso) y (OR 0.61, 0.5-0.7 para pacientes obesos). El estudio concluye que el IMC está inversamente relacionado con la mortalidad a largo plazo en pacientes con enfermedad arterial coronaria conocida o sospechada. De este modo, se consideró que un IMC más bajo constituía un predictor independiente de mortalidad a largo plazo(56).

Otro estudio analizó 32.605 pacientes con cirrosis hepática, de los cuales 29701 no eran obsesos y 2904 pacientes presentaban obesidad. Se observó una mortalidad bruta menor en los pacientes cirróticos obesos respecto de los no obesos (2.7% respecto 3.5%). Por contra, la estancia media y los costes derivados del ingreso hospitalario fueron mayores en los pacientes cirróticos con obesidad. En la regresión logística multivariante, la obesidad se asoció con una menor mortalidad hospitalaria (OR = 0.73, 055-0.95)(57).

En otro grupo de pacientes con patología cerebrovascular subyacente, también se ha observado la presencia de la “paradoja de la obesidad”(58).

Con respecto a la evidencia disponible de la asociación entre ETV y obesidad, existe una escasa evidencia científica.

Los dos primeros trabajos en los que se evaluó la evolución clínica del paciente con ETV según el peso fueron dos publicaciones realizadas a partir del Registro RIETE. En el primer estudio se evaluó la evolución clínica según 3 categorías de peso (<50 kg, 50-100 kg, >100 kg). Se observó que los pacientes con un peso < 50 kg presentaban más complicaciones hemorrágicas respecto a los de peso 50-100 kg (OR 2.2; 1.2-4), pero en cambio no se observó ninguna diferencia significativa en el grupo de >100 kg

respecto al grupo de 50-100 kg(59). En el segundo artículo, se evaluó la mortalidad durante los 3 primeros meses de anticoagulación según el IMC (<18.5, 18.5-24.9, 25-30 y >30), evidenciándose menos de la mitad de mortalidad en el grupo de pacientes con obesidad (OR 0.5; 0.4-0.6), lo que supuso la primera evidencia en la literatura de la “paradoja de la obesidad” en pacientes con ETV(60).

Posteriormente, un artículo evaluó la asociación entre obesidad y TVP, clasificando los pacientes según el IMC: normal (<25), sobrepeso (25-29.9), obesidad grado I (30-34.9), obesidad grado II (35-39.9) y obesidad grado III (≥ 40). Se incluyeron 662 pacientes con TVP, de los cuales el 28% tenían sobrepeso y el 49% eran obesos. La TVP recurrente fue mayor en los pacientes con obesidad grado I (p <0,01), mientras que las tasas de mortalidad fueron mayores en los grupos de pacientes no obesos (p = 0,001). El cáncer, la diabetes mellitus y la afectación de la vena femoral común fueron predictores de mortalidad, mientras que el IMC ≥ 30 fue un predictor de supervivencia. Los modelos de regresión de Cox mostraron que, después de ajustar por edad, sexo, embolia pulmonar y duración del tratamiento con warfarina, los pacientes con IMC ≥ 40 tuvieron una mayor supervivencia(52).

Finalmente, un estudio valoró la relación entre obesidad y embolia pulmonar mediante el análisis de un registro de hospitales de corta estancia de Estados Unidos. De un total de 17979200 pacientes obesos, 203500 pacientes (1,1%) fueron diagnosticados de EP, en comparación con 2034100 (0,6%) de 346.049.800 pacientes no obesos (RR 2,03). El RR de EP fue mayor entre los pacientes obesos de 11 a 20 años (RR = 5,80) y fue mayor en las mujeres obesas (RR = 2,08) que en los hombres obesos (RR = 1,74). La mortalidad fue del 4,3% en pacientes obesos con embolia pulmonar en comparación con el 9,5% en pacientes no obesos (RR = 0,45). La mortalidad en pacientes con embolia pulmonar fue menor en pacientes obesos que en pacientes no obesos, con mayores efectos en mujeres, pacientes mayores y pacientes estables(51).

1.4.3 Tratamiento personalizado con HBPM de la ETV en los pacientes con EP incidental y en la obesidad mórbida

Las diferentes guías de práctica clínica, en base a los ensayos clínicos disponibles, recomiendan tratar de una manera muy similar a todos los pacientes con ETV(1,10–12).

En este sentido, con relación al tratamiento anticoagulante con HBPM, se recomienda prescribir la dosis según el peso corporal en todas las situaciones clínicas, no teniendo

en cuenta otros importantes factores como el tipo de evento tromboembólico, las características propias de cada paciente, y los tratamientos concomitantes. Por este motivo, se hace necesario evaluar cada paciente con el objetivo de prescribir el tratamiento anticoagulante de la manera más individualizada posible.

En el paciente con EP incidental con cáncer, aunque las guías clínicas actuales recomiendan la misma estrategia anticoagulante que en los pacientes con EP sintomática, ésta recomendación no está basada en ensayos clínicos ni en estudios observacionales de calidad(1,12,23). Asimismo, el hecho de que la presentación clínica suele ser menos grave que en el paciente con EP sintomática hace pensar que el abordaje terapéutico más adecuado no debería ser el mismo en los dos escenarios clínicos.

Respecto a el tratamiento de la ETV en el paciente con obesidad mórbida, nos encontramos de nuevo en un escenario con escasa evidencia científica, en las que la mayor parte de guías de práctica clínica aconsejan prescribir la HBPM ajustada al peso del paciente, sin límite de dosis de ésta(1,10,11). De hecho, esto ocurre también en los pacientes con bajo peso(1,10,11). Mientras que se conoce que el bajo peso es un factor de riesgo independiente de hemorragia y de mortalidad, la evidencia disponible en el paciente con obesidad mórbida es más limitada, por la falta de ensayos clínicos y de grandes cohortes específicas.

1.5. REGISTRO RIETE (Registro informatizado de enfermedad tromboembólica)

El Registro RIETE es un registro prospectivo internacional de pacientes consecutivos diagnosticados de ETV, diseñado para recopilar y analizar datos sobre patrones de tratamiento y resultados en pacientes con ETV aguda. Se inició en España en 2001 y 6 años después se tradujo la base de datos al inglés, con el objetivo de ampliar el Registro a otros países. A diferencia de los ensayos controlados aleatorios, no existe una intervención experimental impuesta: el tratamiento lo determinan únicamente los médicos. Por lo tanto, proporciona datos sobre pacientes con ETV en una situación de práctica clínica real con una población de pacientes no seleccionada. Los datos de RIETE generan hipótesis y proporcionan retroalimentación de situaciones clínicas del mundo real. Hasta ahora, nos ha permitido conocer la historia natural de la ETV en pacientes con contraindicaciones relativas o absolutas a la terapia anticoagulante, y la de pacientes que de manera sistemática son excluidos de los ensayos clínicos

randomizados(61)(62). A fecha de Junio de 2021, el Registro RIETE cuenta con 237 centros de 28 países, y con 98.545 pacientes incluidos.

2. JUSTIFICACIÓN

La ETV es la tercera causa de muerte vascular y además se asocia a una elevada morbilidad y a unos elevados costes económicos, tal y como se ha explicado anteriormente.

En los pacientes con cáncer, la ETV se asocia a una elevada morbilidad e impacto en la calidad de vida del paciente y además puede afectar negativamente en la evolución clínica de la propia neoplasia. En términos de mortalidad, la ETV es la tercera causa de muerte en el paciente con cáncer y el desarrollo de ETV se asocia de manera independiente a un aumento por 3 del riesgo de muerte respecto al paciente con cáncer sin ETV. Asimismo, el aumento del riesgo de recurrencias de la ETV y de hemorragia durante la anticoagulación hace que el abordaje terapéutico de estos pacientes sea especialmente complejo.

En la ETV existe un importante número de situaciones en las que existe una escasa evidencia científica del abordaje más adecuado, escenarios conocidos como situaciones especiales. En estas circunstancias, habitualmente las tomas de decisiones están basadas en estudios observacionales de baja calidad o en consejos de expertos. Dos de estas situaciones son la ETV en el paciente con obesidad mórbida y la EP incidental en el paciente con cáncer.

Por todo ello, surge el interés por conocer con mayor profundidad y detalle cuál es la evolución natural de estos subgrupos de pacientes y cuál debería ser el abordaje terapéutico más adecuado, precisando estudios con mayor grado de evidencia científica que los que disponemos hasta la fecha, para así poder mejorar la atención de estos pacientes.

El Registro RIETE dispone de las mayores cohortes de pacientes con EP incidental y cáncer, así como de ETV en el paciente con obesidad mórbida de la literatura. Por este motivo, tenemos a nuestro alcance una situación favorable para poder analizar estos dos grupos de pacientes y así poder avanzar hacia una estrategia terapéutica lo más personalizada posible, hasta que dispongamos de algún ensayo clínico específico.

Se definió como paciente con EP incidental con cáncer aquellos pacientes en los que se diagnosticaba una EP como hallazgo al realizar una prueba de imagen por otra causa, sin presentar ningún síntoma respiratorio. Por otro lado, se definió obesidad mórbida según los criterios de la OMS, definidos como aquellos con un IMC ≥ 40kg/m^2.

3. HIPÓTESIS

1. Los pacientes con EP incidental y cáncer presentan una evolución clínica diferente de la de los pacientes con cáncer y EP sintomática durante la anticoagulación.

2. Los pacientes con obesidad mórbida que son diagnosticados de ETV, presentan una evolución clínica diferente durante a la anticoagulación, respecto a los pacientes con peso normal.

4. OBJETIVOS

Objetivo principal

1. Evaluar la tasa de recurrencias sintomáticas de ETV (TVP o EP), hemorragias y mortalidad durante la anticoagulación en los pacientes con cáncer y EP incidental respecto de los pacientes con cáncer y EP sintomática, así como la de los pacientes con ETV y obesidad mórbida respecto de los pacientes con ETV y peso normal.

Objetivos secundarios

1. Análisis descriptivo de las características clínicas y tratamiento en la cohorte del Registro RIETE de pacientes con cáncer diagnosticados de EP incidental.

2. Análisis descriptivo de las características clínicas y tratamiento en la cohorte del Registro RIETE de los pacientes con obesidad mórbida diagnosticados de ETV.

5. ARTÍCULOS CON RESOLUCIÓN FAVORABLE DE LA COMISIÓN ACADÉMICA DEL PROGRAMA DE DOCTORADO EN MEDICINA

5.1. **Artículo 2:** Morbid Obesity and Mortality in Patients With VTE: Findings From Real-Life Clinical Practice.

Giorgi-Pierfranceschi M, López-Núñez JJ, Monreal M, Cattabiani C, Lodigiani C, Di Micco P, Bikdeli B, Braester A, Soler S, Dentali F; RIETE researchers. Morbid Obesity and Mortality in Patients With VTE: Findings From Real-Life Clinical Practice. Chest. 2020 Jun;157(6):1617-1625. doi: 10.1016/j.chest.2019.12.040. Epub 2020 Jan 29. Erratum in: Chest. 2021 Mar;159(3):1310. PMID: 32004553

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CHEST

Morbid Obesity and Mortality in Patients With VTE

Findings From Real-Life Clinical Practice

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BACKGROUND: The influence of morbid obesity on mortality in patients receiving anticoagulant therapy for VTE has not been consistently evaluated.

METHODS: Data from the RIETE (Registro Informatizado Enfermedad TromboEmbólica) registry were used to compare the mortality risk during anticoagulation in patients with VTE and morbid obesity (BMI ≥ 40 kg/m^2) vs those with normal weight (BMI, 18.5-24.9 kg/m^2). Patients with or without active cancer were analyzed separately.

RESULTS: By September 2018, there were 1,642 patients with VTE and morbid obesity and 14,848 with normal weight in RIETE. Of these, 245 (5.5%) and 1,397 (11.6%), respectively, had cancer. Median duration of anticoagulant therapy was longer in the morbidly obese patients, with cancer (185 vs 114 days) or without cancer (203 vs 177 days). Among cancer patients, 44 (18.0%) morbidly obese and 1,377 (32.8%) patients with normal weight died during anticoagulation. Among those without cancer, 44 (3.1%) morbidly obese died and 601 (5.6%) with normal weight died. On bivariate analysis, morbid obesity was associated with a lower mortality rate, both in patients with cancer (hazard ratio, 0.34; 95% CI, 0.25-0.45) and in those without cancer (hazard ratio, 0.43; 95% CI, 0.32-0.58). Multivariable analysis confirmed a lower hazard of death in morbidly obese patients with cancer (hazard ratio, 0.68; 95% CI, 0.50-0.94) and without cancer (hazard ratio, 0.67; 95% CI, 0.49-0.96). The risk for VTE recurrences or major bleeding did not differ in patients with or without morbid obesity.

CONCLUSIONS: In patients with VTE, the risk for death during anticoagulation was about one-third lower in morbidly obese patients than in those with normal weight, independently of the presence of cancer.

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KEY WORDS: morbid obesity; mortality; VTE

ABBREVIATIONS: DOAC = direct oral anticoagulant; HR = hazard ratio; LMWH = low-molecular-weight heparin; PE = pulmonary embolism

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According to the World Health Organization, obesity is defined as excessive fat accumulation that may impair health. BMI is an index of weight-for-height that is conventionally used to classify overweight and obesity. For adults, the World Health Organization defines overweight and obesity as having a BMI $\geq$ 25 kg/m^2 and $\geq$ 30 kg/m^2, respectively. Morbid obesity (class III obesity or extreme obesity) is a serious health condition that can interfere with basic physical functions and is defined as BMI $\geq$ 40 kg/m^2.[1] The global prevalence of obesity is rapidly expanding, with marked prevalence in industrial societies, and alarming figures in developing countries.[2]

Obese people are at an increased risk for VTE compared with individuals of normal weight,[3,4] most likely due to impaired mobility and increased pressure in the intraabdominal and femoral veins.[5] However, the relation between BMI and mortality is controversial. Although obesity is often associated with an increased risk for cardiovascular diseases and death in the general population,[6-9] a number of studies in patients with cardiovascular and noncardiovascular diseases found an inverse correlation between increasing BMI and death.[10-14] This phenomenon has been defined as the "obesity paradox" and is still not well understood. Little is known about the influence (if any) of morbid obesity on clinical outcomes during the course of anticoagulant therapy in patients with acute VTE.[15,16]

We used the data from the RIETE (Registro Informatizado Enfermedad TromboEmbólica) registry[17] to compare outcomes during the course of anticoagulation in morbidly obese patients with acute VTE vs in those with normal weight (BMI, 18.5-24.9 kg/m^2).

Materials and Methods

RIETE is an ongoing, multicenter registry of consecutive patients with objectively confirmed, acute VTE.[18] It started in Spain in 2001, and after 6 years, it expanded to other countries. Currently, RIETE includes 254 collaborating centers in 27 countries.

Patients

Consecutive patients with symptomatic, acute DVT or pulmonary embolism (PE) confirmed by results of objective tests (compression ultrasonography or contrast venography for DVT; helical CT scan, ventilation-perfusion lung scintigraphy, or angiography for PE) were enrolled in RIETE. The rationale and methodology of RIETE have been published elsewhere.[17] Patients were excluded if they were currently participating in a therapeutic clinical trial with a blinded therapy. All patients (or their relatives) provided written or oral informed consent for participation in the registry, in accordance with local ethics committee requirements.

For the current study, we selected patients with morbid obesity (BMI $\geq$ 40 kg/m^2) and those with normal weight (BMI, 18.5-24.9 kg/m^2). Patients were separately analyzed according to the presence or absence of active cancer (defined as newly diagnosed cancer or cancer that is being treated [surgery, chemotherapy, radiotherapy, support therapy, or combined treatments]).

Outcomes

The major outcome was the occurrence of death during the course of anticoagulant therapy. Secondary outcomes were VTE recurrences and major bleeding. Fatal PE, in the absence of autopsy, was defined as any death appearing within 10 days of a symptomatic, objectively confirmed PE event, in the absence of any alternative cause of death. Major bleeding was defined as any overt bleed requiring a transfusion of two or more units of blood, or if it was retroperitoneal, spinal, intracranial, or fatal. Fatal bleeding was defined as any death occurring within 10 days of a major bleeding episode, in the absence of an alternative cause of death.

Baseline Variables

The following parameters were recorded when the qualifying episode of VTE was diagnosed: sex, age, weight, and height; presence of coexisting conditions such as chronic heart or lung disease; concomitant therapies; recent (< 30 days prior to VTE diagnosis) major bleeding; recent immobility (ie, total bed rest with bathroom privileges for $\geq$ 4 days in the 2-month period prior to VTE diagnosis), recent surgery (in the 2 months prior to VTE), active cancer, hormonal therapy, pregnancy, puerperium, prior VTE, and recent travel. Laboratory data were also recorded at baseline, including whole blood cell counts and serum creatinine levels.

Treatment and Follow-up

Patients were managed according to the clinical practice of each participating hospital (ie, there was no standardization of therapy). The drug, dose, and duration of anticoagulant therapy were recorded. The decision regarding the type and duration of therapy was left to the attending physicians. Patients were followed up in the outpatient clinic (or by telephone interview in patients who could not attend the clinic for a visit). During each visit, any signs or symptoms suggesting VTE recurrences or major bleeding were noted. Each episode of suspected recurrent VTE was investigated by using repeat compression ultrasonography, lung scan, helical CT scan, or pulmonary angiography, as appropriate.

Statistical Analysis

All data are reported as mean $\pm$ SDs. Differences in mean values between groups were assessed by using the Student t test analysis. Categorical variables were compared by using the χ^2 test or Fisher exact test when appropriate. Associations between BMI and mortality were assessed by using the multivariable Cox proportional hazards regression model, in which age, sex, risk factors for VTE, prior VTE, recent major bleeding, creatinine clearance levels, anemia, abnormal platelet count, type and duration of treatment, and clinical presentation of VTE at baseline (PE vs DVT alone) were adjusted as confounding factors. Hazard ratios (HRs) and corresponding 95% CIs were calculated. Given the obvious association between active cancer and weight, we separately analyzed patients with active cancer and those without. Statistical analyses were conducted by using SPSS for Windows Release 12.5 (IBM SPSS Statistics, IBM Corporation).

TABLE 1] Clinical Characteristics of the Patients, According to Their BMI at Baseline

Characteristic	With Cancer		Without Cancer	
	BMI ≥ 40.0 kg/m²	BMI 18.5-24.9 kg/m²	BMI ≥ 40.0 kg/m²	BMI 18.5-24.9 kg/m²
No. of patients	245	4,198	1,397	10,650
Clinical characteristics				
Male sex	55 (22%)[a]	2,382 (57%)	404 (29%)[a]	4,837 (45%)
Age, y	64 ± 12[a]	67 ± 14	59 ± 16[a]	61 ± 22
Weight, kg	111 ± 17[a]	62 ± 8.2	116 ± 21[a]	63 ± 8.8
VTE characteristics				
Symptomatic PE at baseline	127 (52%)	1,972 (47%)	884 (63%)[a]	5,243 (49%)
Risk factors for VTE				
Surgery	22 (9.0%)[b]	593 (14%)	143 (10%)	1,108 (10%)
Immobility	46 (19%)	819 (20%)	322 (23%)	2,644 (25%)
Estrogen intake	23 (9.4%)[a]	152 (3.6%)	79 (5.7%)[a]	1,188 (11%)
Pregnancy/puerperium	1 (0.41%)	4 (0.10%)	17 (1.2%)[a]	306 (2.9%)
Metastatic cancer	89 (36%)[a]	2,057 (49%)	0	0
Lung cancer	22 (9.0%)[a]	765 (18%)	0	0
Colorectal cancer	23 (9.4%)	568 (14%)	0	0
Breast cancer	65 (27%)[a]	421 (10%)	0	0
Prostate cancer	8 (3.3%)[b]	308 (7.3%)	0	0
Hematologic	24 (9.8%)	331 (7.9%)	0	0
Bladder	5 (2.0%)[b]	231 (5.5%)	0	0
Gastric	3 (1.2%)[c]	227 (5.4%)	0	0
Pancreas	1 (0.41%)[a]	227 (5.4%)	0	0
CNS	9 (3.7%)	128 (3.0%)	0	0
Others	85 (35%)[a]	992 (24%)	0	0
None of the above (unprovoked)	0	0	857 (61%)[a]	5,760 (54%)
Previous VTE	32 (13%)	493 (12%)	242 (17%)[a]	1,481 (14%)
Underlying diseases				
Chronic lung disease	41 (17%)[b]	497 (12%)	235 (17%)[a]	1,095 (10%)
Chronic heart failure	18 (7.3%)	228 (5.4%)	124 (8.9%)[c]	721 (6.8%)
Arterial hypertension (n = 11,128)	121 (65%)[a]	1,101 (38%)	639 (62%)[a]	2,392 (34%)
Diabetes (n = 11,128)	57 (31%)[a]	400 (14%)	272 (26%)[a]	667 (9.5%)
Laboratory tests				
Renal function, N	179	2,812	978	6,326
CrCl levels, mL/min	68 ± 29[c]	74 ± 29	74 ± 29[b]	77 ± 31
CrCl levels > 60 mL/min	99 (55%)[a]	1,923 (68%)	672 (69%)	4,381 (69%)
CrCl levels 30-60 mL/min	62 (35%)[c]	687 (24%)	229 (23%)	1,476 (23%)
CrCl levels < 30 mL/min	18 (10%)	202 (7.2%)	77 (7.9%)	469 (7.4%)
Anemia	121 (49%)[a]	2,673 (64%)	340 (24%)[a]	3,324 (31%)
Abnormal platelet count	20 (8.2%)[b]	556 (13%)	50 (3.6%)[a]	618 (5.8%)

Data are presented as mean ± SD unless otherwise indicated. CrCl = creatinine clearance; PE = pulmonary embolism.
Differences between patients with normal weight vs the morbidly obese: [a]$P < .001$, [b]$P < .05$, [c]$P < .01$.

Results

From March 2001 to September 2018, a total of 75,452 patients with VTE were enrolled in RIETE. Of these, 1,642 (2.2%) had morbid obesity, and 14,848 (20%) were of normal weight. Overall, 245 patients with morbid obesity (14.9%) and 4,198 with normal weight (28.3%) had active cancer. Compared with those with normal weight, patients with morbid obesity (with or without

cancer) were more likely: to be women; younger; to have chronic lung or heart disease, diabetes, or hypertension; or to initially present as PE (compared with DVT). However, they were less likely to have anemia or abnormal platelet count at baseline (Table 1). Among patients with cancer, those with morbid obesity were less likely to have metastases or to have lung, prostate, bladder, pancreatic, or gastric cancer, than those with normal weight; they were more likely to have breast cancer, however.

The duration of anticoagulant therapy was longer in obese patients than in those with normal weight, both among patients with cancer (median, 185 vs 114 days; respectively; $P < .001$) or without cancer (median, 203 vs 177 days; $P < .001$). For initial therapy, patients with morbid obesity (with or without cancer) were less likely to receive low-molecular-weight heparin (LMWH) and more likely to receive unfractionated heparin than those with normal weight (Table 2). Among patients initially receiving LMWH, morbidly obese patients received lower mean daily doses per weight than those with normal weight (140 ± 43 IU/kg per day vs 179 ± 45 IU/kg per day in patients with cancer; 152 ± 42 IU/kg per day vs 183 ± 45 IU/kg per day in those without cancer). For long-term therapy, patients with morbid obesity were more likely to switch to vitamin K antagonists than those with normal weight, regardless of the presence or absence of cancer. Again, morbidly obese patients treated with long-term LMWH received lower daily doses per weight than those with normal weight.

During the course of anticoagulation, 2,066 patients died (fatal PE, n = 164; fatal bleeding, n = 104), 491 presented with VTE recurrences, and 512 had major bleeding. As to be expected, patients with cancer (with or without morbid obesity) had higher rates of VTE recurrences, major bleeding, or death than those without cancer (Table 3). However, cancer patients with morbid obesity had a much lower mortality rate (HR, 0.34; 95% CI, 0.25-0.45), a similar rate of VTE recurrences (HR, 0.62; 95% CI, 0.34-1.05), and a lower rate of major bleeding (HR, 0.54; 95% CI, 0.28-0.96) than those with normal weight. Non-cancer patients with morbid obesity also had a lower mortality rate (HR, 0.43; 95% CI, 0.32-0.58) and a similar rate of VTE recurrences (HR, 0.79; 95% CI, 0.53-1.15) or major bleeding (HR, 0.82;

TABLE 2] Treatment Strategies, According to BMI at Baseline and the Presence or Absence of Cancer

	With Cancer		Without Cancer	
Characteristic	BMI ≥ 40.0 kg/m^2	BMI 18.5-24.9 kg/m^2	BMI ≥ 40.0 kg/m^2	BMI 18.5-24.9 kg/m^2
No. of patients	245	4,198	1,397	10,650
Duration of therapy, d				
Mean days	309 ± 352[a]	191 ± 301	346 ± 467[a]	268 ± 388
Median days (IQR)	185 (103-367)[a]	114 (65-210)	203 (119-374)[a]	177 (101-271)
Initial therapy				
LMWH	208 (85%)[b]	3,767 (90%)	1,109 (79%)[a]	8,970 (84%)
LMWH mean dose, IU/kg/d	140 ± 43[a]	179 ± 45	152 ± 42[a]	183 ± 45
LMWH dose < 175 IU/kg/d	158 (77%)[a]	1,416 (38%)	721 (65%)[a]	3,000 (34%)
LMWH dose < 150 IU/kg/d	102 (50%)[a]	763 (20%)	440 (40%)[a]	1,678 (19%)
Unfractionated heparin	28 (11%)[c]	243 (5.8%)	162 (12%)[a]	706 (6.6%)
Pentasaccaride	4 (1.6%)	79 (1.9%)	46 (3.3%)	293 (2.8%)
Direct oral anticoagulants	2 (0.82%)	40 (0.95%)	29 (2.1%)[c]	396 (3.7%)
Thrombolytics	2 (0.82%)	24 (0.57%)	37 (2.6%)[b]	176 (1.7%)
Long-term therapy				
Vitamin K antagonists	96 (39%)[a]	1,006 (24%)	1,048 (75%)[a]	7,013 (66%)
LMWH	125 (51%)[a]	2,663 (63%)	198 (14%)[a]	2,172 (20%)
LMWH mean dose, IU/kg/d	127 ± 40[a]	162 ± 47	123 ± 44[a]	155 ± 52
LMWH dose < 150 IU/kg/d	84 (67%)[a]	924 (35%)	134 (68%)[a]	927 (43%)
Direct oral anticoagulants	9 (3.7%)	112 (2.7%)	113 (8.1%)[b]	1,072 (10%)

Data are presented as mean ± SD unless otherwise indicated. IQR = interquartile range; LMWH = low-molecular-weight heparin.
Differences between patients with normal weight vs the morbidly obese: [a]$P < .001$, [b]$P < .05$, [c]$P < .01$.

TABLE 3] Clinical Outcomes During Anticoagulant Therapy, According to BMI at Baseline and Presence or Absence of Cancer: Univariable Analyses

Variable	BMI ≥ 40.0 kg/m^2		BMI 18.5-24.9 kg/m^2		
	No.	N per 100 Patient-Years	No.	N per 100 Patient-Years	Hazard Ratio (95% CI)
Patients with cancer	245		4,198		
Recurrent PE	8	4.00 (1.86-7.60)	105	4.90 (4.03-5.90)	0.82 (0.37-1.61)
Recurrent DVT	5	2.50 (0.92-5.54)	127	5.99 (5.02-7.11)	0.42 (0.15-0.94)
Recurrent VTE	13	6.74 (3.75-11.2)	226	10.9 (9.54-12.4)	0.62 (0.34-1.05)
Major bleeding	11	5.37 (2.82-9.33)	214	9.91 (8.65-11.3)	0.54 (0.28-0.96)
Death	44	21.2 (15.6-28.2)	1,377	62.9 (59.6-66.2)	0.34 (0.25-0.45)
Causes of death					
PE	0	…	88	4.02 (3.24-4.93)	…
Initial PE	0	…	64	2.92 (2.27-3.71)	…
Recurrent PE	0	…	24	1.10 (0.72-1.61)	…
Respiratory insufficiency	2	0.96 (0.16-3.19)	70	3.20 (2.51-4.01)	0.30 (0.05-1.03)
Sudden, unexpected	0	…	9	0.41 (0.20-0.75)	…
Bleeding	2	0.96 (0.16-3.19)	59	2.69 (2.07-3.45)	0.40 (0.10-1.06)
Disseminated malignancy	31	14.9 (10.3-21.0)	803	36.7 (34.2-39.4)	0.41 (0.28-0.57)
Infection	1	0.48 (0.02-2.38)	58	2.65 (2.03-3.40)	0.18 (0.01-0.93)
Multiorganic failure	3	1.45 (0.37-3.94)	40	1.83 (1.32-2.46)	0.79 (0.19-2.27)
Patients without cancer	1,397		10,650		
Recurrent PE	14	1.08 (0.61-1.76)	94	1.22 (0.99-1.49)	0.88 (0.49-1.52)
Recurrent DVT	16	1.23 (0.73-1.96)	130	1.70 (1.42-2.01)	0.72 (0.42-1.19)
Recurrent VTE	30	2.34 (1.61-3.30)	222	2.94 (2.57-3.35)	0.79 (0.53-1.15)
Major bleeding	35	2.69 (1.90-3.70)	252	3.28 (2.89-3.70)	0.82 (0.57-1.15)
Death	44	3.34 (2.46-4.44)	601	7.69 (7.09-8.32)	0.43 (0.32-0.58)
Causes of death					
PE	7	0.53 (0.23-1.05)	69	0.88 (0.69-1.11)	0.60 (0.25-1.25)
Initial PE	6	0.46 (0.18-0.95)	55	0.70 (0.54-0.91)	0.65 (0.25-1.43)
Recurrent PE	1	0.08 (0.00-0.37)	14	0.18 (0.10-0.29)	0.42 (0.02-2.38)
Sudden, unexpected	2	0.15 (0.03-0.50)	29	0.37 (0.25-0.53)	0.41 (0.07-1.45)
Respiratory insufficiency	6	0.46 (0.18-0.95)	63	0.81 (0.62-1.02)	0.56 (0.22-1.23)
Bleeding	3	0.23 (0.06-0.62)	40	0.51 (0.37-0.69)	0.44 (0.11-1.28)
Infection	6	0.46 (0.18-0.95)	80	1.02 (0.82-1.27)	0.44 (0.18-0.96)
Multiorganic failure	7	0.53 (0.23-1.05)	35	0.45 (0.32-0.62)	1.19 (0.49-2.56)

See Table 1 legend for expansion of abbreviation.

0.57-1.15) than those with normal weight. Moreover, morbidly obese patients with cancer (HR, 0.18; 95% CI, 0.01-0.93) or without cancer (HR, 0.44; 95% CI, 0.18-0.96) had a lower mortality rate due to infection, and those with cancer also had a lower mortality rate due to disseminated malignancy (HR, 0.41; 95% CI, 0.28-0.57).

On multivariable analysis, both patients with cancer and non-cancer patients who were morbidly obese had a lower risk of death than the corresponding categories of normal weight patients (HR, 0.68 [95% CI, 0.50-0.94] and 0.67 [95% CI, 0.49-0.96], respectively). However, the risks for VTE recurrences (HR, 1.03 [95% CI, 0.52-2.01] and 1.01 [95% CI, 0.64-1.58]) or major bleeding (HR, 0.99 [95% CI, 0.51-1.93] and 1.03 [95% CI, 0.67-1.58]) were similar in cancer and in non-cancer patients (Table 4).

Discussion

Morbid obesity is associated with an increased mortality rate in the general population.[2,3] In a pooled analysis of

TABLE 4] Multivariable Analyses for All-Cause Mortality, VTE Recurrences, and Major Bleeding in Patients With or Without Cancer

Variable	VTE Recurrences	Major Bleeding	Death
Patients without cancer			
Age > 65 y	…	1.70 (1.20-2.41)[a]	5.25 (3.71-7.42)[b]
BMI ≥ 40.0 kg/m²	1.01 (0.64-1.58)	1.03 (0.67-1.58)	0.67 (0.49-0.96)[c]
Chronic heart failure	…	1.50 (1.03-2.18)[c]	1.32 (1.06-1.65)[c]
Chronic lung disease	…	…	…
Recent major bleeding	…	…	…
Anemia	…	2.07 (1.55-2.78)[b]	1.40 (1.15-1.70)[b]
Abnormal platelet count	…	1.89 (1.23-2.90)[a]	1.47 (1.10-1.97)[a]
Transient risk factors	…	-	1.70 (1.40-2.08)[b]
Symptomatic PE	…	1.47 (1.09-1.99)[c]	1.62 (1.32-2.00)[b]
CrCl levels 30-60 mL/min	…	1.42 (1.02-1.99)[c]	1.82 (1.44-2.30)[b]
CrCl levels < 30 mL/min	…	2.03 (1.34-3.07)[b]	3.49 (2.70-4.51)[b]
LMWH and then VKAs	0.76 (0.55-1.06)	0.55 (0.41-0.74)[b]	0.56 (0.45-0.69)[b]
Duration of therapy > 90 d	0.41 (0.24-0.69)[b]	0.24 (0.17-0.34)[b]	0.00 (0.00-7,319)
Patients with cancer			
Age > 65 y	0.40 (0.28-0.59)[b]	…	1.12 (0.98-1.29)
BMI ≥ 40.0 kg/m²	1.03 (0.52-2.01)	0.99 (0.51-1.93)	0.68 (0.50-0.94)[c]
Chronic lung disease	…	…	1.17 (0.98-1.39)[c]
Recent major bleeding	…	2.42 (1.37-4.27)[a]	…
Anemia	…	1.61 (1.09-2.38)[c]	1.22 (1.05-1.41)[a]
Abnormal platelet count	…	1.60 (1.05-2.42)[c]	1.38 (1.16-1.65)[b]
Initial presentation as PE	…	…	1.24 (1.09-1.41)[a]
CrCl levels 30-60 mL/min	…	1.50 (1.03-2.20)[c]	…
CrCl levels <30 mL/min	…	2.51 (1.51-4.17)[b]	1.90 (1.51-2.40)[b]
Metastatic cancer	1.73 (1.20-2.50)[a]	0.91 (0.64-1.30)	2.70 (2.30-3.17)[b]
Breast cancer	Reference	Reference	Reference
Lung cancer	3.04 (1.41-6.56)[a]	…	2.01 (1.44-2.81)[b]
Colorectal cancer	…	2.90 (1.20-6.99)[c]	1.48 (1.03-2.13)[c]
Prostatic cancer	…	2.61 (0.95-7.15)	1.15 (0.74-1.79)
Hematologic cancer	2.77 (1.13-6.82)[c]	…	…
Bladder cancer	4.32 (1.71-10.87)[a]	2.80 (1.05-7.46)[c]	1.68 (1.12-2.52)[c]
Gastric cancer	2.56 (0.95-6.85)	3.42 (1.28-9.14)[c]	2.09 (1.39-3.13)[b]
Pancreatic cancer	2.75 (1.08-7.02)[c]	…	2.28 (1.57-3.32)[b]
Cerebral cancer	…	5.54 (1.89-16.23)[a]	3.52 (2.15-5.78)[b]
Other cancers	2.11 (1.00-4.46)[c]	2.31 (1.01-5.24)[c]	1.53 (1.10-2.12)[c]
LMWH only	0.91 (0.63-1.32)	0.70 (0.50-0.98)[c]	0.90 (0.78-1.05)
Duration of therapy > 90 d	0.38 (0.25-0.58)[b]	0.08 (0.05-0.13)[b]	0.00 (0.00-14,360)

Data are presented as hazard ratios and 95% CIs. VKAs = vitamin K antagonists. See Table 1 and 2 legends for expansion of other abbreviations. Differences between patients with normal weight vs the morbidly obese: [a]$P < .01$, [b]$P < .001$, [c]$P < .05$.

20 prospective studies that included 9,564 extremely obese individuals, those with morbid obesity had a higher mortality rate, and most of the excess deaths were associated to heart diseases, cancer, and diabetes.[9] Conversely, a number of studies have found that a high BMI was associated with a better survival in patients with chronic diseases such as heart failure, coronary artery disease, liver cirrhosis, renal insufficiency, cerebrovascular disease, or atrial fibrillation, thus originating the expression "obesity paradox."[10-14] Our findings, obtained from a large cohort of patients with VTE, show that those with morbid obesity (one in every

50 patients with VTE) also were at a lower risk of dying than those with normal weight. This was consistently found in patients with or without cancer. Findings were robust after adjusting for potentially confounding variables. The lower risk for death in the morbidly obese was uniformly found for most causes of death (PE, bleeding, sudden death, respiratory insufficiency, infection, or disseminated cancer), although in many of them it did not reach statistically significant differences, most likely due to the sample size.

The mortality rate in the current study seemed to be not negligible in normal weight patients, potentially influencing our results. However, the mortality rate in the whole population seems in line with other observational studies,[19] reinforcing the validity reliability of our findings.

A previous study based on RIETE assessed the influence of weight on short-term (15 days) outcomes and found a lower mortality rate in patients weighing > 100 kg than in those weighing 50 to 100 kg (0.7% vs 3.0%, respectively).[20] However, the study sample was limited (there were only 294 patients weighing > 100 kg), and the results were not confirmed on multivariable analysis. In a subsequent study also using RIETE, the mortality rate was lower in 2,752 patients with VTE and a BMI > 30 kg/m^2 than in those with normal BMI (18.5-24.9 kg/m^2), thus suggesting for the first time the existence of an obesity paradox also in patients with VTE.[21] In the current study, to better assess the influence of BMI in this setting, we only considered patients with morbid obesity, and we provided separate analyses of patients according to the presence or absence of cancer. Certainly, morbidly obese patients in our cohort were younger (by 2 years) than those with normal weight. However, they were also more likely to have comorbidities such as chronic lung or heart disease, diabetes, and hypertension, or to initially present with PE. Of note, the HRs comparing the mortality rates in patients with cancer and in non-cancer patients after adjusting for a number of potential confounder patients were similar. Our results have several potential explanations, including the possible existence of a metabolically healthy obese phenotype and the role of regional body fat distribution and ectopic fat accumulation, concepts that emphasize the remarkable heterogeneity of obesity.[22]

The current study has some limitations. First, these results should be treated with caution considering the limitations of observational studies to infer causality. Weight measure was not centralized, and small differences in data collection among the participating centers are likely. Furthermore, in RIETE, information on weight is collected only at the time of enrollment, and we could not exclude the possibility that patients in different groups may have lost or gained weight during the study. However, because the mean follow-up is relatively short, it is unlikely that these variations have profoundly affected our analyses.

In RIETE, creatinine clearance was evaluated with the Cockcroft-Gault equation, and we are aware that this equation relies on total weight and potentially overestimating the glomerular filtration rate in obese patients.[23] Thus, presence of renal failure may be underestimated in this group of patients.

Morbidly obese patients underwent anticoagulation for a longer period than normal weight patients. The former group was probably perceived as high risk for VTE recurrence. Indeed, despite younger age than those with normal weight, these patients were more likely to have a number of different comorbidities. Furthermore, some observational studies and a meta-analysis suggest obesity itself could be a risk factor for VTE.[3] However, differences in the duration of anticoagulation did not seem to influence our findings because only the anticoagulation period was considered in the analysis.

Finally, a not negligible proportion of morbid obese patients were treated with direct oral anticoagulants (DOACs), and expert consensus suggests that DOACs should not be used in these patients[24] because the clinical data in this setting are limited. In addition, the available pharmacokinetic/pharmacodynamic evidence suggests that decreased drug exposures, reduced peak concentrations, and shorter half-lives may occur, potentially increasing risk of underdosing in this population. However, recent secondary analyses of large randomized controlled trials suggest that the efficacy and safety profile of DOACs was similar across BMI categories.[25]

Conclusions

In a large cohort of patients experiencing acute VTE, the risk for death during anticoagulation in morbidly obese patients was about one-third lower than in those with normal weight, independently of the presence of cancer. These findings support the existence of a survival advantage of morbid obesity in this setting. Further prospective studies should be properly designed to assess potential mechanisms explaining these results.

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5.2. Artículo 1: *Clinical characteristics and 3-month outcomes in cancer patients with incidental versus clinically-suspected and confirmed pulmonary embolism.*

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Original article

Clinical characteristics and 3-month outcomes in cancer patients with incidental *versus* clinically-suspected and confirmed pulmonary embolism

Marisa Peris, Juan J. López-Nuñez, Ana Maestre, David Jimenez, Alfonso Muriel, Behnood Bikdeli, Ido Weinberg, Cihan Ay, Lucia Mazzolai, Alicia Lorenzo, Manuel Monreal,

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Clinical characteristics and 3-month outcomes in cancer patients with incidental vs. clinically-suspected and confirmed pulmonary embolism.

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And the RIETE Investigators*
**A full list of the RIETE investigators is given in the appendix*

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Abstract

Background Current guidelines suggest treating cancer patients with incidental pulmonary embolism (PE) similar to those with clinically-suspected and confirmed PE. However, the natural history of these presentations has not been thoroughly compared.

Methods We used the data from the RIETE registry to compare the 3-month outcomes in patients with active cancer and incidental PE vs. those with clinically-suspected and confirmed PE. The primary outcome was 90-day all-cause mortality. Secondary outcomes were PE-related mortality, symptomatic PE recurrences and major bleeding.

Results From July 2012 to January 2019, 1,004 cancer patients with incidental PE and 2,274 with clinically-suspected and confirmed PE were enrolled. Most patients (95% vs. 90%) received low-molecular-weight heparin therapy. During the first 90 days, 613 patients died, including 42 from PE. Patients with incidental PE had a lower all-cause mortality rate than those with suspected and confirmed PE (12% vs. 22%; odds ratio [OR]: 0·47; 95%CI: 0·38-0·59). Results were consistent for PE-related mortality (0·3% vs. 1·7%; OR: 0·17; 95% CI: 0·05-0·56). Multivariable analysis confirmed that patients with incidental PE were at lower risk to die (adjusted OR: 0·46; 95%CI: 0·36-0·58). Overall, 29 patients (0·9%) developed symptomatic PE recurrences, and 128 (3·9%) had major bleeding. There were no significant differences in PE recurrences (OR: 0·59; 95%CI: 0·24-1·45) or major bleeding (OR: 0·88; 95%CI: 0·60-1·31).

Conclusions Cancer patients with incidental PE had a lower mortality rate compared to those with clinically-suspected and confirmed PE. Further studies are required to validate these findings, and to explore optimal management strategies in these patients.

Introduction

Patients with cancer frequently undergo chest computed tomography (CT) scans to assess the extent of the malignancy, the response to cancer therapy, or to screen for metastases. These tests may lead to identification of incidental cases with pulmonary embolism (PE). Further, presence of baseline cardiopulmonary limitations in cancer patients (including pulmonary metastases, pleural or pericardial effusion, chemotherapy-induced or radiation-associated cardiomyopathy, co-morbidities, as well as general deconditioning) may mask the development of PE, increasing the possibility that a PE diagnosis is unsuspected, but rather, incidental. With widespread use of CT testing in cancer patients, the detection of incidental PE has become increasingly common.[1,2] The prevalence of incidental PE in the population of patients with active cancer is reported to range between 1.1%-5.0%.[3-5] Several guidelines recommend using the same treatment strategy for patients with incidental PE as for those with clinically-suspected and confirmed PE.[6-8] These recommendations, however, are based mainly on retrospective studies that have reported no significant differences in the rates of recurrent venous thromboembolism (VTE), major bleeding, and mortality in patients with incidental vs. clinically suspected PE. However, most of these studies were small, were under-powered to detect differences on important outcomes, and did not focus on case fatality rates (i.e., PE-related mortality).[9-12]

The RIETE (Registro Informatizado de Enfermedad TromboEmbólica) Registry is an ongoing, multicenter, international registry of consecutive patients with objectively confirmed acute VTE (ClinicalTrials.gov identifier: NCT02832245).[13]

Data from this registry have been used to evaluate outcomes after acute VTE, such as the frequency of recurrent VTE, bleeding and mortality, and risk factors for these outcomes in cancer-associated VTE.[14-18] The goal of the current study is to compare the clinical characteristics and 3-month outcomes of cancer patients with incidental PE versus those with clinically-suspected and confirmed PE.

Patients and Methods

Data source

Details about the methodology of RIETE have been discussed elsewhere.[11] In brief, RIETE is a multicenter prospective registry of consecutive patients with objectively-confirmed acute deep vein thrombosis (DVT) or PE with 205 collaborating centers from 27 countries. The protocol for enrolling patients into RIETE has been approved by the ethics committees at the participating sites. All patients provided written or oral consent for participation in the registry, in accordance with local ethics committee requirements. Physicians participating in the RIETE registry made all efforts to enroll consecutive patients.

Inclusion criteria

Incidental PE was defined as PE detected on a CT-scan ordered for reasons other than a clinical suspicion of PE.[19] Patients with incidental PE have been incorporated into RIETE since July 2012. Thus, for this study we only included patients who were enrolled in RIETE from July 2012 to January 2019 and grouped them in two groups of incidental PE versus suspected and confirmed PE. For this study, we only included patients in both groups who were

diagnosed by contrast-enhanced computed tomography, to make the comparisons between the two groups more consistent. Active cancer was defined as newly (<3 months before) diagnosed cancer, metastatic cancer, or cancer that was being treated (i.e. surgery, chemotherapy, radiotherapy, support therapy, or combined therapies). CT-scan findings were classified as centrally located thrombi (defined as a central or lobar thrombus location) and more peripherally located thrombi (defined as a segmental or sub-segmental thrombus location), according to the site reports.

Nomenclature

We used the term *incidental* because this is the terminology endorsed by the International Society of Thrombosis and Haemostasis.[19] Patients with *suspected and confirmed* PE were those investigated specifically for PE based on signs and symptoms. Chart reviews of patients with incidentally diagnosed PE suggest that some of them are in fact symptomatic, with symptoms possibly attributed to the underlying cancer or other factors, rather than to PE before the PE diagnosis was made.[18] Thus, we made a priori plans to divide patients with incidental PE into symptomatic vs. asymptomatic incidental PE in supplemental analyses.

Main comparisons and outcomes

We compared the clinical characteristics, treatment and 3-month outcomes of cancer patients with incidental PE vs. those with suspected PE. The primary outcome was all-cause mortality within the first 90 days. Secondary outcomes were fatal PE, symptomatic PE recurrences and major bleeding. Fatal PE, in

the absence of autopsy, was defined as any death appearing within 10 days after symptomatic PE diagnosis (either the index PE or recurrent PE), in the absence of any alternative cause of death. Each episode of clinically suspected recurrent PE was investigated by repeat helical-CT scan. Bleeding complications were classified as 'major' if they were overt and required a transfusion of two units of blood or more, or were retroperitoneal, spinal, intracranial, intraocular, intrapericardial or when they were fatal. Fatal bleeding was defined as any death occurring within 10 days of a major bleeding episode, in the absence of an alternative cause of death.

Baseline variables

The following parameters were routinely recorded in RIETE: demographics, history of chronic heart or lung disease, cancer sites and stage, other risk factors for VTE, laboratory data, treatment received upon VTE diagnosis (drugs, doses and duration) and the clinical outcome during the course of anticoagulant therapy. RIETE, by design, includes follow-up for all (100%) patients for at least 90 days or until death. Immobilized patients were defined as non-surgical patients who had been immobilized (i.e., total bed rest with bathroom privileges) for ≥4 days in the 2-month period prior to VTE diagnosis. Surgical patients were defined as those who underwent a major surgical intervention in the 2 months prior to VTE. Recent bleeding was defined as a major bleeding episode less than 30 days prior to VTE.

Treatment and follow-up

Patients were managed according to the clinical practice of each participating hospital (i.e., there was no standardization of treatment). All patients were followed-up for at least 3 months, or until death if it occurred earlier. During each visit, any signs or symptoms suggesting symptomatic VTE recurrences or bleeding events were noted. The outcomes were classified as reported by the clinical enrolling site. However, if staff at the RIETE coordinating center were concerned about background variables (e.g. inconceivable values), the site investigators were contacted for clarifications. For uncertain or ambiguous outcome values, the events were reviewed by a central adjudicating committee (less than 10% of events).

Statistical analysis

We reported continuous data as mean and standard error of the mean (or median with interquartile range if not normally distributed), and categorical data as frequency counts with percentages. We used Student's t test and X^2 test (or Fisher's exact test where appropriate) to compare continuous or categorical variables. Then, a multivariable analysis was carried out through a logistic regression model to identify the predictors for all-cause death within the first 3 months. Covariates entering in the model were selected by a significance level of $p < 0.10$ on univariable analysis, or by a well–known association reported in the literature. SPSS software (version 20, SPSS Inc. Chicago, Illinois) was used for the statistical management of the data, and a two-sided $p < 0.05$ was considered to be statistically significant.

Results

From July 2012 to January 2019, 3,324 patients with active cancer and PE were enrolled in RIETE. Of these, 1,020 (31%) had incidental PE and 2,304 (69%) had clinically-suspected and confirmed PE. Most patients in both subgroups (1,004 and 2,274, respectively) received anticoagulant therapy, and were included into the current analysis.

Baseline characteristics

Patients with incidental PE were more likely to be men (odds ratio [OR]: 1.25; 95%CI: 1.08-1.45), and slightly younger than those with suspected and confirmed PE (Table I). Only 58 patients (5.6%) with incidental PE complained of respiratory symptoms, and very few had tachycardia, tachypnea, hypotension, hypoxemia or atrial fibrillation at baseline. In contrast, nearly all patients with suspected and confirmed PE had a constellation of such symptoms and signs. At baseline, patients with incidental PE were less likely to have chronic lung or heart disease, recent surgery, leukocytosis, renal insufficiency, abnormal prothrombin time or abnormal fibrinogen levels than those with clinically-suspected PE, but were more likely to have anemia. The anatomical burden of larger branches on CT-scan was relatively similar. Among patients who had echocardiographic data available, those with incidental PE had lower pulmonary artery pressure levels or evidence of right ventricle dysfunction. Finally, patients with incidental PE were more likely to have metastases (OR: 1.98; 95%CI: 1.69-2.33), or to have colorectal, pancreatic, gastric cancer or melanoma than those with suspected PE, and less likely to have breast, prostatic, hematologic malignancies or primary brain tumors than those with clinically-suspected PE (Table II).

Treatment

Median duration of anticoagulant therapy was similar in both subgroups (162 vs. 146 days; p=0.844), as shown in Table III. The majority of patients (95% vs. 90%) were initially treated with low-molecular-weight heparin (LMWH), but those with incidental PE received lower daily doses (161±43 vs. 174±42 IU/kg/day; p <0.001) than those with clinically-suspected PE. No patient with incidental PE received thrombolytic therapy, as compared to 33 patients (1.5%) with suspected and confirmed PE. For long-term therapy, most patients in both subgroups kept receiving LMWH (90% vs. 69%), again with lower doses per body weight in those with incidental PE (151±41 vs. 158±42 IU/kg/day; p <0.001). A lower proportion of patients with incidental PE switched to vitamin K antagonists (4.7% vs. 17%; p <0.001).

Outcomes

During the first 3 months of therapy, 613 patients (19%) died (fatal PE 42, fatal bleeding 20), 29 (0.9%) developed recurrent symptomatic PE, 39 (1.2%) had DVT and 128 (3.9%) had major bleeding. Patients with incidental PE had a lower mortality rate than those with suspected and confirmed PE (12% vs. 22%; OR: 0.47; 95%CI: 0.38-0.59), as shown in Table IV. Results were consistent for PE-related mortality (0.3% vs. 1.7%; OR: 0.17; 95%CI: 0.05-0.56) (Figure 1). There were 29 symptomatic PE recurrences and 39 subsequent DVTs, with no statistically significant differences between subgroups in the rates of PE recurrences (OR: 0.59; 95%CI: 0.24-1.45), symptomatic DVT (OR: 0.78; 95%CI: 0.38-1.60) or major bleeding (OR: 0.88; 95%CI: 0.60-1.31). There were

138 major bleeding events, with no significant difference between the two subgroups (OR: 0.88; 95%CI: 0.60-1.31).

When separately considering patients with incidental PE according to the presence or absence of respiratory symptoms, those with truly asymptomatic PE had a lower mortality rate than those with respiratory symptoms (11% vs. 26%; OR: 0.35; 95%CI: 0.19-0.66), as shown in Table V. They also had a lower mortality rate due to disseminated malignancy (8.0% vs. 17%; OR: 0.42; 95%CI: 0.21-0.90).

On multivariable analysis, after adjusting for patient's age and gender, additional risk factors for VTE, systolic blood pressure levels and heart rate at baseline, anemia, renal function, presence of metastases, site of cancer and treatment for cancer, patients with incidental PE had nearly half the risk for all-cause mortality than those with suspected PE (hazard ratio: 0.46; 95%CI: 0.36-0.58), as shown in Table VI.

Discussion

Our findings, obtained from a large series of consecutive patients with active cancer and PE, reveal that nearly a third of PEs were incidental. In our cohort, patients with incidental PE were more likely to have metastases than those with symptomatic PE and less likely to have chronic lung or heart disease, renal insufficiency or abnormal coagulation tests at baseline. There were only slight differences in the treatment of PE, though 1.5% of patients with symptomatic PE and no one with incidental PE received thrombolytics. During the first 3

months of therapy, there were no significant differences in the rates of symptomatic PE recurrences or major bleeding, but the mortality rate was half in patients with incidental PE than in those with suspected PE. Among patients with incidental PE, those without any respiratory symptoms also had a lower mortality rate than those with symptoms. Patients with incidental PE had a significantly lower mortality due to PE, but also due to respiratory failure and even to disseminated malignancy, than those with symptomatic PE. The results were consistent after adjusting for a number of potential confounders.

The lower rate of all-cause mortality in patients with incidental PE is clinically relevant and deserves further discussion. First, the lower rate of fatal PE in patients with incidental PE could have been expected. Second, we should acknowledge that the lower mortality rate due to disseminated malignancy was unexpected, since patients with incidental PE were more likely to have metastases and less likely to have less aggressive cancers (i.e., breast or prostate) than those with suspected PE. Interestingly, the mortality rate was lower in patients with truly asymptomatic PE than in those with respiratory symptoms, as already found in another study on 283 patients with cancer and unsuspected PE.[11] On multivariable analysis, we tried to adjust for a number of variables, but patients with cancer may have additional confounders that were not considered in this analysis. For instance, in RIETE there is no information on the duration or the intensity of chemo- and radiotherapy.

The non-significant differences in the rates of PE recurrences or major bleeding also found in other studies led to suggest that patients with incidental PE should be treated as those with suspected PE.[6-8,21] However, in patients with incidental

PE in our cohort the rate of major bleeding was 6-fold higher than the rate of symptomatic PE recurrences (36 vs. 6 events), as already reported earlier.[22] In patients with clinically suspected PE the rate of major bleeding was “only” 4-fold higher than the rate of recurrent PE (92 vs. 23 events), and the PE-related mortality was particularly high during the first few days. Further studies are needed to identify which cancer patients with incidental PE are at increased risk for bleeding, and could benefit from reduced doses of LMWH (or maybe of shorter durations of therapy). We hypothesize that a less aggressive therapy could perhaps have been associated with a lower rate of major bleeding and only a mild increase in PE recurrences.

The present study has several limitations. First, RIETE is an observational study (not a randomized trial). Second, treatment was not standardized across sites and unmeasured biases are likely present. However, our results reflect practices from several centers, with widespread clinical and geographical diversity..Third, the use of CT scan in patients with incidental PE is variable and could have resulted in selection bias. Patients receiving chemotherapy, those with metastases and those with colorectal, stomach or pancreatic cancers are more likely to undergo regular CT-scans. In contrast, patients in palliative care, and those without metastases or with breast, prostatic or brain tumors are less likely to be scanned. Finally, variability in the treating physicians’ index of suspicion for PE may have influenced whether patients with cancer were referred for radiologic studies to rule out PE, even in the presence of symptoms. Thus, patients who were included in the incidental PE subgroup were separately analyzed in a supplemental Table according to the presence or

absence of respiratory symptoms. And those with truly asymptomatic PE had an even lower mortality rate.

In conclusion, cancer patients with incidental PE who were treated with anticoagulation had a more benign clinical course, including lower rates of PE-related mortality and lower rates of all-cause mortality, compared with patients with clinically suspected and confirmed PE. Further studies are needed to explore optimal treatment strategies in cancer patients with incidental PE.

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APPENDIX
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Table I. Clinical characteristics at baseline (and CT-scan findings) in patients with incidental vs. suspected PE.

	Incidental PE	Suspected PE	Odds ratio (95% CI)
Patients, N	***1,004***	***2,274***	
Clinical characteristics,			
Male gender	584 (58%)	1,197 (53%)	1.25 (1.08-1.45)
Age (mean years±SD)	67±11	68±13	p <0.001
Body weight (mean kg±SD)	72±13	74±15	p <0.0001
Additional risk factors for VTE,			
Surgery	110 (11%)	379 (17%)	0.62 (0.49-0.77)
Immobility ≥4 days	137 (14%)	354 (16%)	0.86 (0.69-1.06)
Prior VTE	66 (6.6%)	246 (11%)	0.58 (0.44-0.77)
Underlying conditions,			
Chronic lung disease	106 (11%)	394 (17%)	0.56 (0.45-0.71)
Chronic heart disease	32 (3.2%)	162 (7.1%)	0.43 (0.29-0.63)
Recent (<30 days) major bleeding	40 (4.0%)	75 (3.3%)	1.22 (0.82-1.80)
PE symptoms/signs at baseline,			
Dyspnea	46 (5.1%)	1,834 (82%)	0.01 (0.01-0.02)
Chest pain	11 (1.2%)	786 (36%)	0.02 (0.01-0.04)
Syncope	5 (0.55%)	281 (13%)	0.04 (0.02-0.09)
Hemoptysis	4 (0.44%)	91 (4.2%)	0.10 (0.04-0.28)
SBP levels <100 mm Hg	51 (5.4%)	236 (10%)	0.49 (0.36-0.67)
Heart rate >100 bpm	116 (13%)	826 (37%)	0.24 (0.20-0.30)
Respiratory rate >20 pm (N=1,665)	43 (8.4%)	523 (46%)	0.11 (0.08-0.15)
Sat O_2 levels <90% (N=1,367)	11 (4.9%)	325 (29%)	0.13 (0.07-0.24)
Atrial fibrillation	17 (1.7%)	124 (5.5%)	0.30 (0.18-0.50)
Largest arteries involved on CT-scan,			
Segmental or subsegmental	363 (36%)	781 (34%)	1.08 (0.93-1.26)
Pulmonary or lobar	444 (44%)	847 (37%)	1.34 (1.15-1.55)
Not reported	197 (20%)	646 (28%)	0.62 (0.51-0.74)
Transthoracic echocardiogram (n=744),			
Mean PAP levels (mm Hg±SD)	36±11	45±16	p <0.0001
Right ventricle dysfuction	4 (3.8%)	117 (18%)	0.17 (0.06-0.48)
Laboratory data,			
Anemia	628 (63%)	1,288 (57%)	1.28 (1.10-1.49)
Leukocyte count >11,000/µL	202 (20%)	754 (33%)	0.51 (0.42-0.61)
Platelet count <100,000/µL	39 (3.9%)	122 (5.4%)	0.71 (0.49-1.03)
CrCl levels <60 mL/min	236 (23%)	686 (30%)	0.71 (0.60-0.84)
Abnormal prothrombin time (N=2,473)	205 (43%)	591 (50%)	0.74 (0.60-0.92)
Abnormal fibrinogen levels (N=1,667)	236 (23%)	686 (30%)	0.71 (0.60-0.84)

Abbreviations: PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism; SBP, systolic blood pressure; bpm, beats per minute; CrCl, creatinine clearance; PAP, pulmonary artery **pressure; CI, confidence intervals.**

Table II. Cancer characteristics

	Incidental PE	Suspected PE	Odds ratio (95% CI)
Patients, N	***1,004***	***2,274***	
Time from cancer diagnosis			
Median months (IQR)	5 (2-22)	6 (1-26)	p=NS
<3 months	398 (40%)	1,046 (46%)	0.77 (0.66-0.90)
>12 months	314 (31%)	739 (32%)	0.95 (0.81-1.11)
Metastases			
Yes	708 (71%)	1,243 (55%)	1.98 (1.69-2.33)
Sites of cancer,			
Lung	203 (20%)	503 (22%)	0.89 (0.74-1.07)
Colorectal	230 (23%)	304 (13%)	1.93 (1.59-2.33)
Breast	82 (8.2%)	311 (14%)	0.56 (0.43-0.72)
Prostate	36 (3.6%)	182 (8.0%)	0.43 (0.30-0.62)
Pancreas	69 (6.9%)	104 (4.6%)	1.54 (1.13-2.11)
Stomach	68 (6.8%)	69 (3.0%)	2.32 (1.65-3.27)
Hematologic	25 (2.5%)	106 (4.7%)	0.52 (0.34-0.81)
Bladder	34 (3.4%)	83 (3.6%)	0.93 (0.62-1.39)
Ovary	31 (3.1%)	82 (3.6%)	0.85 (0.56-1.30)
Uterine	27 (2.7%)	81 (3.6%)	0.75 (0.48-1.16)
Central nervous system	17 (1.7%)	87 (3.8%)	0.43 (0.26-0.73)
Kidney	40 (4.0%)	65 (2.9%)	1.41 (0.94-2.11)
Carcinoma of unknown origin	24 (2.4%)	34 (1.5%)	1.61 (0.95-2.74)
Orofarinx	18 (1.8%)	36 (1.6%)	1.13 (0.64-2.01)
Melanoma	29 (2.9%)	20 (0.9%)	3.35 (1.89-5.95)
Biliary tract	11 (1.1%)	38 (1.7%)	0.65 (0.33-1.28)
Esophagic	15 (1.5%)	21 (0.9%)	1.63 (0.84-3.17)
Liver	6 (0.60%)	28 (1.2%)	0.48 (0.20-1.17)
Other	39 (3.9%)	117 (5.1%)	0.75 (0.51-1.08)
Therapy for cancer,			
Chemotherapy	549 (58%)	939 (46%)	1.60 (1.37-1.87)
Radiotherapy	116 (13%)	307 (16%)	0.78 (0.62-0.98)
Chemo- and radiotherapy	92 (10%)	199 (10%)	0.98 (0.76-1.27)
Hormonal therapy	65 (7.1%)	298 (16%)	0.42 (0.31-0.55)
None of the above	356 (37%)	803 (39%)	0.93 (0.79-1.09)

Abbreviations: PE, pulmonary embolism; IQR, inter-quartile ratio; CI, confidence intervals.

Table III. Treatment strategies.

	Incidental PE	Suspected PE	Odds ratio (95% CI)
Patients, N	***1,004***	***2,274***	
Duration of anticoagulation,			
Mean days (±SD)	246±289	244±336	p=0.844
Median days (IQR)	162 (95-290)	146 (69-291)	
Initial therapy,			
Unfractionated heparin	14 (1.4%)	124 (5.5%)	0.25 (0.14-0.43)
Low-molecular-weight heparin	954 (95%)	2,050 (90%)	2.08 (1.52-2.86)
Mean LMWH dose (IU/kg/day)	161±43	174±42	p <0.001
LMWH <100 IU/kg/day	80 (8.4%)	135 (6.6%)	1.30 (0.97-1.73)
Fondaparinux	6 (0.60%)	28 (1.2%)	0.48 (0.20-1.17)
DOACs	3 (0.30%)	24 (1.1%)	0.28 (0.08-0.94)
Thrombolytics	0	33 (1.5%)	-
Inferior vena cava filter	43 (4.3%)	110 (4.8%)	0.88 (0.61-1.26)
Long-term therapy,			
LMWH	902 (90%)	1,567 (69%)	3.99 (3.19-4.99)
Mean LMWH dose (IU/kg/day)	151±41	158±42	p <0.001
LMWH <100 IU/kg/day	78 (8.7%)	130 (8.3%)	1.05 (0.78-1.40)
Vitamin K antagonists	47 (4.7%)	395 (17%)	0.23 (0.17-0.32)
DOACs	14 (1.4%)	106 (4.7%)	0.29 (0.16-0.51)
Fondaparinux	6 (0.60%)	30 (1.3%)	0.45 (0.19-1.08)

Abbreviations: PE, pulmonary embolism; SD, standard deviation; IQR, inter-quartile ratio; LMWH, low-molecular-weight heparin; IU, international units; DOACs, direct oral anticoagulants; CI, confidence intervals.

Table IV. Clinical outcomes at 90 days.

	Incidental PE	Suspected PE	Odds ratio (95% CI)
Patients, N	***1,004***	***2,274***	
Symptomatic PE	6 (0.6%)	23 (1.0%)	0.59 (0.24-1.45)
Deep vein thrombosis	10 (1.0%)	29 (1.3%)	0.78 (0.38-1.60)
Major bleeding	36 (3.6%)	92 (4.0%)	0.88 (0.60-1.31)
Sites of major bleeding,			
Gastrointestinal	16 (1.6%)	37 (1.6%)	0.98 (0.54-1.77)
Intracranial	4 (0.4%)	13 (0.6%)	0.70 (0.20-2.05)
Death	117 (12%)	496 (22%)	0.47 (0.38-0.59)
Causes of death,			
Pulmonary embolism	3 (0.3%)	39 (1.7%)	0.17 (0.05-0.56)
Initial PE	0	36 (1.6%)	-
Recurrent PE	3 (0.3%)	3 (0.1%)	2.27 (0.46-11.3)
Respiratory failure	2 (0.2%)	24 (1.1%)	0.19 (0.04-0.79)
Sudden, unexpected	2 (0.2%)	5 (0.2%)	0.91 (0.18-4.68)
Bleeding	3 (0.3%)	17 (0.7%)	0.40 (0.12-1.36)
Disseminated cancer	86 (8.6%)	309 (14%)	0.60 (0.46-0.77)
Infection	9 (0.9%)	17 (0.7%)	1.20 (0.53-2.70)
Multiorganic failure	3 (0.3%)	13 (0.6%)	0.52 (0.15-1.83)
Heart insufficiency	0	8 (0.4%)	-
Ischemic stroke	1 (0.1%)	4 (0.2%)	0.57 (0.06-5.07)
Other/unknown	8 (0.8%)	60 (2.6%)	0.30 (0.13-0.60)

Abbreviations: PE, pulmonary embolism; CI, confidence intervals.

Table V. Clinical outcomes at 90 days in patients with incidental and asymptomatic PE, those with incidental but symptomatic PE and those with suspected PE.

	Incidental PE		Suspected PE
	Without symptoms	With respiratory symptoms	
Patients, N	***946***	***58***	***2,274***
Symptomatic PE	6 (0.63%)	0	23 (1.0%)
Deep vein thrombosis	8 (0.85%)	2 (3.4%)	29 (1.3%)
Major bleeding	30 (3.2%)	6 (10%)*	92 (4.0%)
Sites of major bleeding,			
Gastrointestinal	14 (1.5%)	2 (3.4%)	37 (1.6%)
Intracranial	4 (0.42%)	0	13 (0.57%)
Death	102 (11%)‡	15 (26%)	496 (22%)
Causes of death,			
Pulmonary embolism	3 (0.32%)‡	0	39 (1.7%)
Initial PE	0	0	36 (1.6%)
Recurrent PE	3 (0.32%)	0	3 (0.13%)
Respiratory failure	1 (0.11%)†	1 (1.7%)	24 (1.1%)
Sudden, unexpected	2 (0.21%)	0	5 (0.22%)
Bleeding	2 (0.21%)	1 (1.7%)	17 (0.75%)
Disseminated cancer	76 (8.0%)‡	10 (17%)	309 (14%)
Infection	7 (0.74%)	2 (3.4%)	17 (0.75%)
Multiorganic failure	3 (0.32%)	0	13 (0.57%)
Heart failure	0	0	8 (0.35%)
Ischemic stroke	1 (0.11%)	0	4 (0.18%)
Other/unknown	7 (0.74%)‡	1 (1.7%)	60 (2.6%)

Comparisons between patients with suspected PE (reference subgroup) vs. the other subgroups: *p <0.05; †p <0.01; ‡p <0.001.

Abbreviations: PE, pulmonary embolism; CI, confidence intervals.

Table VI. Bivariate- and multivariable analysis for all-cause death at 90 days.

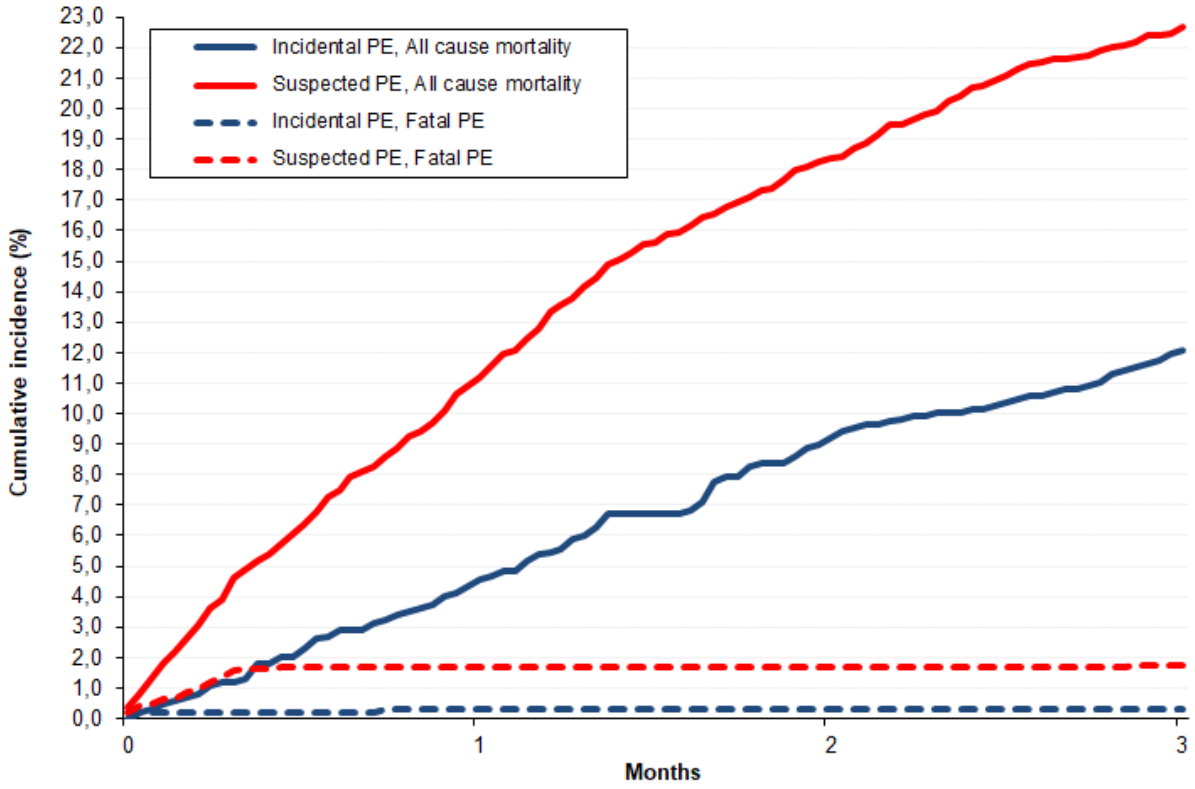
	Bivariate	Multivariable
Incidental PE,		
Yes	0.49 (0.40-0.60)‡	0.46 (0.36-0.58)‡
Clinical characteristics,		
Body weight ≥70 Kg.	0.63 (0.53-0.73)‡	0.74 (0.61-0.90)†
Recent surgery	0.42 (0.30-0.58)‡	0.39 (0.27-0.57)‡
Recent immobility ≥4 days	1.94 (1.61-2.34)‡	1.46 (1.18-1.79)‡
Chronic lung disease	1.28 (1.04-1.57)*	0.93 (0.73-1.18)
PE signs at baseline,		
SBP levels <100 mm Hg	1.71 (1.35-2.15)‡	1.53 (1.18-1.98)†
Heart rate >100 bpm	1.85 (1.58-2.18)‡	1.51 (1.26-1.82)‡
Laboratory data,		
Anemia	1.66 (1.40-1.97)‡	1.68 (1.38-2.05)‡
Leukocyte count >11,000/µL	2.23 (1.90-2.62)‡	1.71 (1.43-2.06)‡
CrCl levels <30 mL/min	2.28 (1.61-3.24)‡	1.75 (1.18-2.61)†
Metastases		
Yes	3.51 (2.86-4.32)‡	3.39 (2.63-4.37)‡
Sites of cancer,		
Lung	Ref.	Ref.
Colorectal	0.32 (0.23-0.43)‡	0.40 (0.28-0.58)‡
Breast	0.31 (0.22-0.45)‡	0.49 (0.32-0.77)†
Prostate	0.38 (0.25-0.58)‡	0.46 (0.27-0.76)†
Pancreas	1.79 (1.36-2.35)‡	1.97 (1.44-2.68)‡
Hematologic	0.43 (0.26-0.72)†	0.53 (0.29-0.97)*
Bladder	0.45 (0.27-0.76)†	0.66 (0.37-1.17)
Ovary	0.61 (0.38-0.97)*	0.70 (0.41-1.19)
Uterine	0.51 (0.30-0.86)*	0.71 (0.40-1.26)
Orofarinx	0.25 (0.09-0.68)†	0.41 (0.13-1.31)
Biliary tract	1.78 (1.12-2.82)*	1.39 (0.85-2.30)
Liver	1.95 (1.17-3.24)*	2.13 (1.21-3.73)†
Therapy for cancer,		
Chemotherapy	0.75 (0.62-0.90)†	0.78 (0.63-0.96)*
Radiotherapy	0.80 (0.61-1.05)	0.93 (0.69-1.26)
Hormonal therapy	0.43 (0.30-0.60)‡	0.81 (0.54-1.22)

Variables entering in the multivariable analysis: patient's age, gender, chronic heart or lung disease, additional risk factors for VTE, systolic blood pressure levels and heart rate at baseline, anemia, renal function, presence of metastases, site of cancer and treatment for cancer.

*p <0.05; †p <0.01; ‡p <0.001.

Abbreviations: PE, pulmonary embolism; SBP, systolic blood pressure; bpm, beats per minute; CrCl, creatinine clearance; Ref., reference.

Figure 1. Cumulative mortality rates during the first 90 days of anticoagulant therapy in patients with incidental vs. suspected PE.



Days		2	10	30	60	90
All-cause death	**Incidental PE**	3 (0.3%)	13 (1.3%)	45 (4.5%)	90 (9.2%)	117 (12%)
	Suspected PE	30 (1.3%)	111 (4.9%)	250 (11%)	405 (18%)	496 (23%)
Fatal PE	**Incidental PE**	2 (0.2%)	2 (0.2%)	3 (0.3%)	3 (0.3%)	3 (0.3%)
	Suspected PE	11 (0.5%)	36 (1.6%)	38 (1.7%)	38 (1.7%)	39 (1.8%)

Abbreviations : PE, pulmonary embolism.

6. RESUMEN GLOBAL DE LOS RESULTADOS

En el primero de los artículos, se comparan los 1648 pacientes del Registro RIETE con obesidad mórbida, definida por un IMC ≥40 kg/m2, que presentaron una ETV, respecto los 14848 pacientes del Registro que fueron diagnosticados de ETV pero que presentaban un peso normal al diagnóstico, definido como un IMC de 18.5-24.9 kg/m2. Los pacientes fueron incluidos entre marzo de 2001 y septiembre de 2018. De estos pacientes, 245 (14.9%) de los que tenían obesidad mórbida y 4198 (28.3%) de los que tenían un peso normal, presentaban un cáncer activo en el momento del diagnóstico de la ETV.

Los pacientes con obesidad mórbida eran predominantemente mujeres y más jóvenes, en mayor proporción tenían patología cardiorrespiratoria, diabetes o hipertensión arterial, y la ETV se presentaba más frecuentemente en forma de EP. Respecto a los pacientes con cáncer, los que además tenían obesidad mórbida tenían menos cáncer metastásico y menor proporción de cáncer de pulmón, próstata, vejiga, páncreas o estómago; en cambio los pacientes con peso normal tenían una mayor proporción de cáncer de mama.

La duración de la anticoagulación fue mayor en los pacientes obesos, independientemente de si tenían cáncer o no. En relación con el tratamiento de la fase aguda, los pacientes con obesidad mórbida recibieron con menor probabilidad HBPM, pero más frecuentemente HNF. De los pacientes que recibieron HBPM en la fase aguda de la ETV, aquellos con obesidad mórbida recibieron una dosis media diaria por peso inferior a los pacientes con peso normal: en los pacientes con cáncer 140 ± 43UI/kg/día vs 179 ± 45UI/kg/día y en los pacientes sin cáncer 152 ± 42UI/kg/día vs 183 ± 45UI/kg/día. En el tratamiento anticoagulante a largo plazo, los pacientes con obesidad mórbida cambiaron a AVK en una mayor proporción, independientemente de que tuvieran cáncer o no. Nuevamente, los pacientes con obesidad mórbida recibieron una dosis media diaria por peso inferior que los pacientes con peso normal.

Durante el curso de la anticoagulación murieron 2066 pacientes (164 de EP fatal y 104 de hemorragia fatal), 491 presentaron una recurrencia de la ETV y 512 tuvieron una hemorragia grave. Globalmente, los pacientes con cáncer presentaron más recurrencias de ETV, más hemorragias graves y mayor mortalidad que los pacientes sin cáncer. No obstante, los pacientes con cáncer y obesidad mórbida presentaron menor mortalidad (OR 0.34; 0.25-0.45), una tasa similar de recurrencias (OR 0.62;

0.34-1.05) y menos hemorragias graves (0.34; 0.28-0.96), que los pacientes con cáncer y peso normal. Los pacientes con obesidad mórbida sin cáncer presentaron menor mortalidad (OR 0.43; 0.32-0.57), y una tasa similar de recurrencias (OR 0.79; 0.53-1.15) y de hemorragias graves (OR 0.82; 0.28-0.96), que los pacientes con peso normal. Los pacientes con obesidad mórbida, con o sin cáncer, tuvieron una mortalidad inferior por infecciones (OR 0.18; 0.01-0.93 y OR 0.44; 0.18-0.96, respectivamente), y los pacientes con cáncer una menor mortalidad por la diseminación de la neoplasia (OR 0.41; 0.28-0.57).

En el análisis multivariante, los pacientes con obesidad mórbida, con o sin cáncer, tuvieron una menor mortalidad que los pacientes con peso normal (OR 0.68, 0.50-0.94 y OR 0.67, 0.49-0.96). No obstante, el riesgo de recurrencia de la ETV y de hemorragia graves fue similar en los pacientes con y sin cáncer.

En el segundo de los artículos, se compara la cohorte de 2274 pacientes del registro RIETE, incluidos entre julio del 2012 y enero 2019, con EP sospechada clínicamente y confirmada respecto a los 946 pacientes del registro con EP incidental. Los pacientes con EP incidental no referían ningún síntoma respiratorio atribuible a la EP, por lo que todos ellos presentaban una EP incidental verdadera o *truly incidental pulmonary embolism.* Se definió cáncer activo como aquel cáncer de recién diagnostico (<3 meses antes), cáncer metastásico o cáncer que estaba siendo tratado (cirugía, quimioterapia, radioterapia, tratamiendo de sporte o tratamientos combinados).

En este artículo se comparan la tasa de recurrencias de ETV, hemorragias y mortalidad durante los primeros 3 meses de la anticoagulación. El objetivo primario fue la mortalidad por cualquier causa a los 90 días y los objetivos secundarios la mortalidad por EP, las recurrencias sintomáticas de EP y las hemorragias graves.

En cuanto a las características basales, los pacientes con EP incidental eran mayoritariamente hombres y ligeramente más jóvenes que los pacientes con EP sospechada clínicamente y confirmada. La mayor parte de pacientes con EP sospechada clínicamente y confirmada tenían taquicardia, taquipnea, hipotensión, hipoxemia o fibrilación auricular, en contraposición a los pacientes con EP incidental en el que sólo lo presentaban algunos pacientes. En relación con las comorbilidades y factores predisponentes, los pacientes con EP incidental tenían menos patología cardiorrespiratoria previa, menos cirugía previa o inmovilidad, leucocitosis, insuficiencia renal, alteración del tipo de protrombina o menos niveles anómalos de

fibrinógeno, que los pacientes con EP sospechada clínicamente y confirmada. En cuanto a la afectación de arterias pulmonares proximales, ésta fue similar en los dos grupos de pacientes. Respecto a la alteración ecocardiográfica, en los pacientes con EP incidental se detectó una menor presión en la arteria pulmonar y una menor disfunción del ventrículo derecho. Finalmente, los pacientes con EP incidental presentaron mayor probabilidad de afectación metastásica y tenían en mayor proporción una neoplasia primaria colorrectal, de páncreas, gástrica o melanoma, pero en menor proporción mama, próstata, neoplasia de origen hematológico o primaria cerebral, en comparación con los pacientes con EP sospechada clínicamente y confirmada.

La duración media del tratamiento anticoagulante fue similar en los dos grupos. La HBPM fue el tratamiento más habitual en la fase aguda, sin embargo, los pacientes con EP incidental fueron tratados con dosis diarias más bajas (160±43 vs 172±42 UI/kg/día; p<0.001). Ningún paciente con EP incidental recibió tratamiento trombolítico, en cambio éste se indicó en 33 pacientes (1.5%) con EP sospechada clínicamente y confirmada. En referencia al tratamiento a largo plazo, el más habitual en los dos grupos de pacientes fue la HBPM, sobre todo en los pacientes con EP incidental (90% vs 69%), aunque nuevamente los pacientes con EP incidental recibieron menos dosis diaria de HBPM (150±41 vs 158±42UI/kg/día; p<0.001). En comparación con los pacientes con EP sospechada clínicamente y confirmada, los pacientes con EP incidental recibieron en menos proporción tratamiento con AVK (4.5% vs 17%; p<0.001).

Durante los primeros 3 meses de tratamiento anticoagulante los pacientes con EP incidental tuvieron una menor mortalidad global (11% vs 22%, OR 0.43) y por EP fatal (0.3% vs 1.7%, OR 0.18). No hubo diferencias entre los dos grupos en cuanto a recurrencias sintomáticas de la ETV (EP o TVP) ni en las hemorragias graves.

En el análisis multivariable, después de ajustar por edad, sexo, factores de riesgo de ETV, TAS y FC al diagnóstico, anemia, función renal, presencia de metástasis, origen primario de la neoplasia y tratamiento de ésta, se observa que los pacientes con EP incidental presentan prácticamente la mitad de mortalidad por cualquier causa que los pacientes con EP sospechada clínicamente y confirmada (OR 0.43; 0.34-0.56). Se realizó un análisis de propensión que replicó los mismos resultados que los anteriores (OR 0.50; 0.40-0.64). El análisis por subgrupos reveló una mayor influencia de la EP incidental en los hombres (OR 0.33; 0.23-0.47) respecto a las mujeres (OR 0.65; 0.43-

0.99), en pacientes con ≤ 75 años (OR 0.36; 0.26-0.51) respecto a los pacientes con ≥ 75 años (OR 0.62; 0.38-1.00) y en paciente sin metástasis (OR 0.38; 0.28-0.51) respecto a los pacientes con metástasis (OR 0.92; 0.50-1.72).

7. RESUMEN GLOBAL DE LA DISCUSIÓN

En la actualidad, en el tratamiento de la ETV existe un gran número de situaciones en las que no disponemos de suficiente evidencia científica sobre cuál debería ser el tratamiento óptimo, con la consiguiente incertidumbre y riesgo que ello conlleva. Dos de estas situaciones son el paciente con EP inicidental y cáncer, y el paciente con obesidad mórbida.

La primera situación especial que abordamos es la del paciente con obesidad mórbida y ETV. En el segundo artículo se describe la cohorte de pacientes con obesidad mórbida del Registro RIETE, formada por 1642 pacientes con IMC ≥ 40 kg/m^2, y se compara con los 18848 pacientes con IMC normal (IMC 18.5-24.9 kg/m^2). La obesidad constituye uno de los factores predisponentes clásicos de ETV, debido a la disminución de la movilidad y al aumento de la presión intraabdominal y de las venas femorales(49). Se trata de un tema clínicamente relevante, por ser una población en aumento debido al actual estilo de vida(47), a que la obesidad mórbida supone un aumento de la mortalidad en la población general(49,63), y a que es una población infrarrepresentada en los estudios de ETV(48,49).

Hasta la fecha existen estudios contradictorios sobre con la mortalidad en el paciente con obesidad mórbida. Nuestro estudio, compuesto por una de las muestras más grandes de la literatura de pacientes con obesidad mórbida con ETV, evidenció una menor mortalidad respecto los pacientes con peso normal, independientemente de si tenían cáncer o no, y después de ajustar por las variables de confusión. El menor riesgo de muerte en el paciente con obesidad mórbida se objetivó en la mayoría de las causas: EP, hemorragia, muerte súbita, insuficiencia respiratoria, infección o cáncer diseminado, aunque la diferencia fue sólo significativa en la muerte por infección. La mortalidad observada en los pacientes con peso normal fue similar a la observada en otros estudios observacionales(64), lo que refuerza la validez de nuestros resultados.
En el presente estudio sólo se consideraron los pacientes con obesidad mórbida según el IMC y se realizó un análisis por separado de acuerdo con si tenían cáncer o no. Los pacientes con obesidad mórbida de nuestra cohorte eran de media 2 años más jóvenes respecto a los que tienen un IMC normal, aunque tenían más comorbilidades como patología cardiorrespiratoria, diabetes o hipertensión, como era esperable. Asimismo, la ETV se presentaba más frecuentemente en forma de EP en el grupo de obesidad mórbida.

Los pacientes con obesidad mórbida recibieron anticoagulación durante más tiempo respecto a los no obesos, probablemente por la percepción de que estos pacientes tenían un mayor riesgo de recurrencia de la ETV. De hecho, como ya se ha comentado anteriormente, algunos estudios sugieren que la obesidad es un factor predisponente de mayor riesgo de recurrencia de la ETV(49). No obstante, esta diferencia en la duración del tratamiento anticoagulante no parece tener influencia en nuestros hallazgos, dado que sólo se ha analizado el período en el que los pacientes estaban bajo anticoagulación.

En relación con la anticoagulación con HBPM, resulta controvertida la dosis más adecuada en el paciente con obesidad. En el caso de la enoxaparina, aunque la actual ficha técnica en España recoge que los pacientes deben recibir la dosis correspondiente sin limitar o capar la dosis máxima de la misma, en otros países (p. ej Canadá) la ficha técnica indica que se debe de capar la dosis máxima a 18000 UI/día, del mismo modo que también lo aconseja la última edición de la guía de práctica clínica de la ASH(12). Por este motivo, recientemente hemos analizado los pacientes del Registro RIETE con un peso > 100 kg y se ha comparado como variable resultado primario la variable combinada de recurrencias de ETV, hemorragia grave o muerte, en función de si habían recibido una dosis de HBPM capada a 18000 UI/día (N=454) o si ésta no se había capado (N=2392). El análisis multivariante mostró que los pacientes obesos que habían recibida una dosis de HBPM capada presentaban una tasa inferior de la variable resultado combinada respecto a los que no se había capado la HBPM (OR 0.16; IC del 95%, 0.04 a 0.68) (65).

Una proporción no despreciable de pacientes (>2%) recibieron tratamiento con un ACOD. El tratamiento anticoagulante con ACOD en el paciente con obesidad mórbida es controvertido, en base a que no está aconsejado en algunos consensos de expertos de año 2016 en aquellos pacientes con peso > 120 kg (66), aunque recientemente dos análisis secundarios de dos ensayos clínicos randomizados sobre pacientes con FA sugiere que los ACOD son eficaces y seguros en este perfil de paciente (67,68).

La gran heterogeneidad de los pacientes con obesidad mórbida podría justificar que la evolución natural de estos pacientes sea muy diferente entre sí. Esta heterogeneidad podría explicar que, a un subgrupo de pacientes, la propia obesidad les confiera una protección y por tanto una mejor evolución clínica. Existen varias teorías que intentan justificar porque un subgrupo de pacientes con obesidad presenta una mejor

evolución, como la existencia de un fenotipo metabólico sano, la “paradoja de la obesidad”, o el papel protector de la distribución del tejido adiposo con formación ectópica del mismo(69).

Nuestro estudio presenta algunas limitaciones, como que se trata de un estudio observacional, lo que no permite inferir sus datos, que la recogida del peso no está centralizada y que sólo se recoge el peso en el momento de la inclusión del paciente. Sin embargo, el seguimiento relativamente corto de la cohorte hace que dicha variación del peso sea poco significativa. Además, en el registro RIETE el filtrado glomerular se evalúa según la fórmula de Cockcroft-Gault, la cual se basa en el peso total y tiende a sobreestimarlo en el paciente obeso.

En relación con el abordaje del paciente con cáncer, previo a los dos artículos de la presente tesis publicamos un artículo sobre este tema, en el que realizamos una revisión de la literatura basada sobre todo en los artículos publicados gracias al Registro RIETE, con el objetivo de ofrecer el tratamiento anticoagulante más personalizada para cada situación clínica del paciente con ETV asociada a cáncer. En el momento de la realización de este artículo, en el registro RIETE había 10962 pacientes con cáncer incluidos. En este artículo se tratan diversos escenarios de interés en la práctica clínica y con un escaso grado de evidencia, de tal manera que detectamos que una de las principales necesidades era mejorar el abordaje de la EP incidental(70).

Las actuales guías de práctica clínica sugieren tratar los pacientes con EP incidental de la misma manera que los que presentan una EP sintomática(10), en el caso de que los defectos de perfusión afecten a las arterias segmentarios o a las más proximales(1).

Nuestro segundo estudio incluye la serie más grande publicada hasta la fecha en pacientes con cáncer diagnosticado de EP incidental. Además, se incorpora un grupo comparativo del mismo Registro RIETE, con pacientes que presentan una EP sospechada clínicamente y confirmada con métodos objetivos, lo que no está presente en la mayor parte de estudios publicados hasta la fecha. Asimismo, los pacientes con EP incidental de nuestro estudio no presentan ningún signo ni síntoma respiratorio, lo que denominamos EP incidental verdadera o *truly incidental pulmonary embolism*. En nuestra cohorte, los pacientes con EP incidental tenían más frecuentemente metástasis que los pacientes con EP sospechada clínicamente y confirmada, y menos

frecuencia de patología cardiorrespiratoria, insuficiencia renal o alteración de la coagulación en la analítica basal. Entre los dos grupos, sólo había alguna pequeña diferencia en el tratamiento anticoagulante, en cambio ningún paciente con EP incidental recibió tratamiento trombolítico. En los 3 primeros meses de seguimiento no hubo diferencias en la tasa de recurrencias ni en la de hemorragias. Sin embargo, los pacientes con EP incidental tuvieron una menor mortalidad por EP, así como también en relación con la insuficiencia respiratoria y a la neoplasia metastásica. Estos resultados se mantuvieron después de ajustarse por todos los potenciales confusores.

El resultado más remarcable de este artículo fue la menor tasa de mortalidad en los pacientes con EP incidental. Esta menor tasa de mortalidad por EP era esperable, en base a que se trata de un cuadro clínico de menor gravedad. Sin embargo, es más sorprendente el hecho de que también presenten una menor mortalidad debido a la propia neoplasia. Una posible explicación es que es más habitual presentar metástasis por neoplasias menos agresivas (como mama o próstata), las cuales tienen menor mortalidad que otros tipos de cáncer (como pulmón o páncreas).

El hecho de que los pacientes con EP incidental tengan una tasa de recurrencias de EP sintomática y de hemorragias similar al de los pacientes con EP sintomática ya estaba descrito previamente en la literatura, y por este motivo las guías de práctica clínica aconsejan tratar a estos pacientes del mismo modo(1,23,42,45). Se necesitan más estudios para intentar identificar qué pacientes con EP incidental tienen mayor riesgo de sangrado y si se pudieran beneficiar de una menor intensidad en el tratamiento anticoagulante. Son necesarios ensayos clínicos randomizados para definir cuál sería el mejor abordaje terapéutico de este grupo de pacientes.

Posteriormente a nuestro artículo, se ha publicado un estudio retrospectivo unicéntrico, realizado a partir de un registro de pacientes con cáncer en el que 15689 pacientes se habían sometido a un TC con contraste de control, encontraron 174 pacientes con una EP incidental y 13197 sin EP, lo que suponía una incidencia de un 1.3%. Ningún paciente falleció de EP. Después de ajustar por el cáncer y características de la ETV, se observó que la mortalidad fue superior en el grupo de la EP incidental (OR 2.26; 1.53–3.33). El cáncer metastásico y haber recibido un tratamiento oncoespecífico curativo, fueron factores pronósticos de mortalidad, mientras que la presencia de una EP central y una TVP proximal residual no mostraron asociación(71).

En el estudio más reciente publicado, se compararon los pacientes con ETV incidental respecto a los pacientes con ETV sintomática durante los primeros 3 meses de anticoagulación, procedentes de un registro de pacientes diagnosticados de ETV. Se incluyeron 131 pacientes con una ETV incidental (con un 52% de los pacientes sin cáncer) y 1931 pacientes con una ETV sintomática. La mortalidad en los pacientes con ETV incidental y sintomática fue similar, siendo además la tasa de recurrencias similar en ambos grupos, por lo que se recomienda anticoagular a los pacientes con ETV incidental de ambos grupos, independientemente de la presencia de cáncer(72).

El presente estudio presenta varias limitaciones. El Registro RIETE es un estudio observacional, los tratamientos no se estandarizaron entre los diferentes centros, y el uso de TC en los pacientes con EP incidental es variable y pudo haberse realizado un sesgo de selección. De tal manera que, en los pacientes en tratamiento quimioterápico, o con cáncer metastásico colorrectal, gástrico o pancreático, es más probable que se les realice un TC; mientras que, a los pacientes en cuidados paliativos, o aquellos sin metástasis o con cáncer primario de mama, próstata o cerebral, es menos probable que reciban un TC durante el seguimiento. Otras limitaciones son que la causa de la muerte es la referenciada por el investigador de cada centro y que las diferencias entre la sospecha clínica de EP entre los diferentes centros pudieron haber influenciado en si a los pacientes se les indicaba o no una TC (incluso en presencia de síntomas). Otra limitación de nuestro estudio es que en el Registro RIETE no disponemos de información sobre el tipo de quimioterapia o la duración de los tratamientos oncoespecíficos.

8. CONCLUSIONES

1. Los pacientes con cáncer diagnosticados de EP incidental presentan una similar tasa de recurrencias sintomáticas y de hemorragias graves durante los primeros 3 meses de anticoagulación, en comparación con los pacientes con EP sospechada clínicamente y confirmada.
2. Los pacientes con cáncer diagnosticados de EP incidental presentan un curso clínico más benigno, con una tasa de mortalidad por cualquier causa inferior y por EP durante los primeros 3 meses de anticoagulación, en comparación con los pacientes con EP sospechada clínicamente y confirmada.
3. Los pacientes con obesidad mórbida diagnosticados de ETV presentan una tasa de recurrencias y hemorragias graves similar durante los primeros 3 meses de anticoagulación, en comparación con los pacientes con peso normal diagnosticados de ETV.
4. Los pacientes con obesidad mórbida diagnosticados de ETV presentan una menor tasa de mortalidad durante los primeros 3 meses de anticoagulación, en comparación con los pacientes con peso normal diagnosticados de ETV.

9. LÍNEAS DE FUTURO

La presente tesis doctoral nos permite avanzar en el conocimiento de estos 2 grupos de pacientes con ETV, de los que disponemos de una escasa evidencia científica. Sin embargo, seguiremos trabajando para mejorar el abordaje de los pacientes con EP incidental y cáncer, y con los pacientes con obesidad mórbida y ETV.

En relación con los pacientes con EP incidental y cáncer, en el registro RIETE disponemos de la cohorte más grande de la literatura, la cual va creciendo año tras año. En un futuro, realizaremos un estudio comparativo según la dosis de HBPM que han recibido, para ver si aquellos que recibieron menor dosis de HBPM o un tratamiento más corto tuvieron un mejor perfil de tasa de recurrencias/tasa de hemorragias y de mortalidad, en base a la evolución clínica que hemos observado en el primer artículo de la presente tesis doctoral. Como hemos podido comprobar, este grupo de pacientes presentan un curso de la enfermedad más benigno, asociado a una menor mortalidad durante los 3 primeros meses de anticoagulación. Asimismo, cuando la cohorte aumente de tamaño, analizaremos cual es la evolución clínica durante los primeros 6 meses de anticoagulación, y cuál es la tasa de recurrencias, hemorragias y mortalidad después de suspender la misma.

Respecto a los pacientes con obesidad mórbida diagnosticados de ETV, también disponemos de la mayor cohorte conocida, lo que nos ha permitido comprobar que presentan una menor mortalidad durante al menos los primeros 3 meses de anticoagulación, y que parece que capar las dosis de HBPM a 18000 UI/día ofrece un mejor perfil de seguridad sin un aumento de las recurrencias de ETV. En un futuro, analizaremos que ocurre en términos de recurrencias de la ETV, hemorragias y mortalidad después de suspender la anticoagulación.

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11. ANEXO

11.1. Artículo 1: Management of venous thromboembolism in patients with cancer.

López-Núñez JJ, Trujillo-Santos J, Monreal M. Management of venous thromboembolism in patients with cancer. J Thromb Haemost. 2018 Dec;16(12):2391-2396. doi: 10.1111/jth.14305.

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REVIEW ARTICLE

Management of venous thromboembolism in patients with cancer

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Summary. Current guidelines for anticoagulant therapy do not so far suggest any form of differentiated approach to cancer patients with venous thromboembolism (VTE). This review article provides an overview of the published literature in cancer patients with VTE, mostly using data from the RIETE registry. Our findings provide some insights into what factors may be used to guide physicians in adapting recommended anticoagulant regimens to the individual patient, as oncologists are increasingly doing with cancer treatments. For instance, patients presenting with deep vein thrombosis (DVT) alone might benefit from curtailing treatment intensity as anticoagulant therapy progresses. The site of cancer also needs to be considered. In patients with incidental PE or splanchnic vein thrombosis, we should be more cautious before prescribing anticoagulant therapy. The optimal duration of anticoagulant therapy is unknown.

Keywords: anticoagulant therapy; bleeding; cancer; death; recurrences; venous thromboembolism.

Introduction

Venous thromboembolism (VTE) is a frequent complication and a major cause of death in patients with cancer [1,2]. Large population-based studies and disease registry surveys have revealed that around 20% of patients with VTE have active cancer [3–5]. In these patients, VTE is not only associated with shortened survival, but it also has an impact on quality of life because of chronic residual symptoms and anxiety caused by fear of recurrence [6]. However, there is also evidence that bleeding to death is a major complication for some cancer patients receiving anticoagulants to manage their VTE.

Based on randomized clinical trials and meta-analyses [7–11], current guidelines of antithrombotic therapy recommend that cancer patients with VTE receive initial therapy with low-molecular-weight heparin (LMWH), fondaparinux or unfractionated heparin, followed by long-term therapy with LMWH rather than vitamin K antagonists (VKAs) [1,12–15]. The use of LMWH during the first 3 months has been established by clinical trials with a high level of evidence, but there is no consensus regarding the optimal duration of anticoagulation beyond the third month. In the absence of data, the decision regarding the termination or continuation of anticoagulant therapy beyond the first 3 months is largely based on individual evaluation of the benefit : risk ratio. However, most randomized clinical trials were underpowered to assess fatal VTE or fatal bleeding, and a substantial proportion of patients were excluded because of a high risk of bleeding or terminal stages of the malignancy. Consequently, real-world data reporting has become increasingly relevant.

Large administrative databases, primarily from healthcare insurance claims, are impressive in terms of the quantity of data, but have limitations in terms of the accuracy, consistency and completeness of coding and reporting [16]. Even if prescribed-medication data are sometimes available, association with clinical outcomes is missing. The RIETE (Registro Informatizado Enfermedad Trombo Embólica) registry provides real-world estimates using the natural history of patients with symptomatic, objectively proven deep vein thrombosis (DVT) or pulmonary embolism (PE) [17]. This review article provides an overview of the published literature in cancer patients with VTE, mostly using data from RIETE.

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Rationale, design and methodology of the RIETE registry

RIETE is an ongoing, prospective multicenter observational study of patients with acute VTE. The registry was originally started in Spain in 2001 with the goal of gathering a large sample of patients with VTE, with specific attention given to those excluded from randomized trials of anticoagulant therapy. The aim was to understand their common presentation, management pattern and outcomes, as well as factors associated with better or worse patient outcomes. The hope was also to use the hypothesis-generating findings to help design new randomized clinical studies. The platform was translated into English from 2006 and the network expanded to other participating centers. RIETE is registered at Clinicaltrials.gov (NCT: 02832245). Detailed information about participating centers is also available at the registry website: https://www.riete.org/.

At each participating site, patients are screened by the site investigators and checked for eligibility. All patients had objectively confirmed acute symptomatic or asymptomatic VTE. More recently, RIETE also started to enroll patients with superficial vein thrombosis, splanchnic vein thrombosis, retinal vein thrombosis and cerebral vein thrombosis. At each participating center, every attempt is made to enroll consecutive patients and RIETE investigators are committed, by contract agreement, to enroll consecutive patients. Periodic audits of the sites have confirmed consecutiveness. No duplicate entries are permitted and patients who are enrolled in blinded treatment trials are ineligible.

The number of variables has been progressively increasing over the years. Recently, depending on the events, ancillary tests, therapies and follow-up duration, each patient may be represented by up to 1000 variables filled out. Data quality is electronically monitored on a weekly basis. In the case of identification of several inconsistencies from any enrolling center, a full audit of all the data from that center is performed. In addition, trained staff make periodic visits to participating centers and compare the information in a randomly selected sample of patients entered by the site investigators.

Case-fatality rates of VTE recurrences and major bleeding

The advantages of anticoagulant therapy must be weighed against the risk of adverse events, primarily bleeding. Moreover, when weighing the risks and benefits of anticoagulation in an individual cancer patient, in addition to considering the absolute risk of VTE recurrences and major bleeding, the consequences associated with each of these outcomes need to be considered. In this sense, the case-fatality rate (CFR) of recurrent VTE and major bleeding, defined as the proportion of patients who died as a consequence of these conditions, could provide useful information to balance the risks and benefits of anticoagulant therapy.

A systematic study of 13 prospective cohort studies and 56 randomized trials assessed the CFR of recurrent VTE and major bleeding during anticoagulation and recurrent VTE after anticoagulation [18]. The authors found that the CFRs of recurrent VTE and major bleeding were similar during the initial period of VTE treatment (3 or 6 months), but the CFR of recurrent VTE decreased after completion of the initial period of anticoagulation. However, most of the patients in that review did not have cancer and estimates came from heterogeneous trial and cohort populations.

To provide reliable estimates of the CFR of recurrent VTE and major bleeding in cancer patients with VTE in real-life clinical practice, we studied 9112 patients receiving anticoagulation for a mean of 7.8 ± 0.6 months [19]. Among 4498 patients initially presenting with PE, 185 developed VTE recurrences (46 died of PE) and 186 had major bleeding (42 died of bleeding). Among 4614 cancer patients initially presenting with DVT, there were 217 VTE recurrences (20 died of PE) and 51 major bleeds (51 died of bleeding). Thus, although cancer patients with PE more likely had a recurrence as PE, those presenting with DVT most likely had a recurrence as DVT. Interestingly, the highest incidence of both VTE recurrences and major bleeding was observed in the first weeks of therapy and progressively decreased afterwards. Our data also confirmed that although initially similar, the CFR of recurrent VTE progressively decreased during anticoagulation, whereas the CFR of major bleeding barely varied over time. The CFR of major bleeding exceeded the CFR of recurrent VTE after the first month of therapy, leading to a higher cumulative mortality from this cause.

Fatal PE and fatal bleeding in cancer patients with VTE

In January 2006, 14 391 patients with VTE were enrolled in RIETE, of whom 2945 (20%) had active cancer [20]. In patients with cancer, the rate of fatal PE during the first 3 months was 2.6% and fatal bleeding was 1.0%. These frequencies were much higher than in VTE patients without cancer (1.4% and 0.3%, respectively). Some years later we assessed the time-course and clinical characteristics of cancer patients with VTE who died of PE or bleeding [21]. There were 10 962 patients (5740 with PE, 5222 with DVT alone), and during the 12-month follow-up, 239 (2.17%) died of PE and 170 (1.55%) had fatal bleeding. After disseminated cancer, PE was the second most frequent cause of death, followed by respiratory insufficiency, infection and then bleeding. Thus, fatal PE was the most common cause of preventable death, accounting for 5.4% of deaths (239 of 4406 deaths), and bleeding accounted for 3.9% (171 deaths). Interestingly, one in every 10 patients with fatal PE (11%) or fatal bleeding (8.2%) was under 50 years old, and one in every four (24% and 29%, respectively) did not

have metastases (Table 1). This is important because it is particularly critical that fatalities in cancer patients with relatively good prognosis are avoided. Interestingly, 44% of the fatal PEs and 36% of the fatal bleeds developed shortly after surgery or immobilization (and thus could have been prevented).

Fatal PE occurred early after the initial event and mostly during the first month of anticoagulant therapy, before reaching close to maximum at 3 months, after which very few cases occurred [21]. In contrast, cases of fatal bleeding occurred throughout the 12 months, with just less than half of cases within the first month of treatment. As it could be expected, most cases of fatal PE and fatal bleeding occurred while on anticoagulant therapy but a higher proportion (1/11) of fatal bleeds than fatal PEs (1/25) occurred after discontinuing anticoagulation.

For patients initially presenting with PE, subsequent PE was the most prominent cause of death and three times more common than bleeding, whereas in patients with DVT alone at baseline, bleeding was as common as infection as a cause of death and over three times more common than PE [21]. The lower risk of dying from PE in patients initially presenting with DVT can be attributed to the fact that DVT patients most likely recurred as DVT. The daily doses of LMWH therapy did not appear to account for differences in outcomes between patients presenting with DVT alone or with PE, and the rate of fatal bleeding was similar over time [21]. Thus, our data suggest that a key factor in determining the intensity and duration of anticoagulant therapy should be the initial presentation of VTE.

The influence of cancer site on outcome

A number of variables (including advanced cancer stage, concomitant therapies and co-morbidities) may have an influence on outcomes during anticoagulation for VTE [3,5]. However, the influence of the cancer site on outcome has not been consistently studied yet. In another study by our group, we compared the rates of VTE recurrences and major bleeding during anticoagulant therapy in patients with breast ($n = 938$), prostate ($n = 629$), colorectal ($n = 1189$) or lung ($n = 1191$) cancer [22]. Of these, 55% had metastases (42%, 36%, 53% and 72%, respectively). During the course of anticoagulant therapy (mean duration, 139 days), the rate of VTE recurrences was similar to the rate of major bleeding in patients with breast (5.6 vs. 4.1 events per 100 patient-years) or colorectal cancer (10 vs. 12 per 100 patient-years). In contrast, in patients with prostate cancer the rate of VTE recurrences was half the rate of major bleeding (6.9 vs. 13 events per 100 patient-years), whereas in those with lung cancer, the rate of VTE recurrences was over 2-fold higher than the rate of major bleeding (27 vs. 11 per 100 patient-years).

For patients with breast, prostate or colorectal cancer, the rate of VTE recurrences was half that of major bleeds during the first month of therapy. Also, patients with lung cancer suffered a 2-fold higher rate of VTE recurrences than major bleeds, both during and beyond the first 30 days of therapy. Thus, our findings revealed that the rate of VTE recurrences and major bleeding during anticoagulation largely varies according to the location of cancer. These findings suggest the development of cancer-specific anticoagulant strategies is an area for further research.

Incidental PE

Current guidelines on antithrombotic therapy suggest treating patients with incidentally found PE similarly to patients with symptomatic PE [1]. Van der Hulle *et al.* evaluated the outcome in 926 cancer patients with incidental PE from 11 cohorts, and found a high risk of symptomatic PE events during follow-up, particularly when left untreated [23]. However, the follow-up period was limited to only 6 months, and there was no information on the quality of anticoagulation, the consequences of PE, the frequency and severity of bleeding events or the outcomes after discontinuing anticoagulant therapy. In another RIETE study on 715 cancer patients with incidental PE [24], patients were followed-up for a mean of 235 days during anticoagulation, and then 117 days after discontinuing anticoagulation. The rate of major bleeding during therapy was 3-fold higher than the rate of symptomatic PE (10.1 vs. 3.17 events per 100 patient-years, respectively), and the rate of fatal bleeding was 4-fold

Table 1 Clinical characteristics of cancer patients with VTE who died of PE or bleeding

	All patients	Fatal PE	Fatal bleeding
Patients, *N*	10 962	239	171
Age < 50 years	1090 (9.9%)	25 (11%)	14 (8.2%)
With metastases	5652 (52%)	195 (76%)	122 (71%)
Recent surgery	1690 (15%)	17 (7.1%)	13 (7.6%)
Recent immobility ≥ 4 days	2064 (19%)	88 (37%)	49 (29%)
Initial presentation as PE	5740 (52%)	213 (89%)	82 (48%)
Diagnosis of cancer < 3 months before	4086 (37%)	84 (35%)	65 (38%)
Time from VTE (mean days ± SD)		17 ± 38	118 ± 223
On anticoagulant therapy		228 (96%)	150 (88%)

VTE, venous thromboembolism; PE, pulmonary embolism; SD, standard deviation.

higher than the rate of fatal PE (2.66 vs. 0.66 deaths per 100 patient-years). After discontinuing anticoagulant therapy, the rate of major bleeding was lower than the rate of symptomatic PE (3.00 vs. 8.37 events per 100 patient-years), but there were no differences in the rate of fatal events (one death each). Unfortunately, we were unable to identify independent predictors for symptomatic PE during follow-up.

Splanchnic vein thrombosis

The role of anticoagulant therapy in patients with splanchnic vein thrombosis (SVT) is uncertain, given the absence of randomized trials and the increased risk of bleeding in patients who often also have liver cirrhosis or cancer. Current guidelines recommend the use of anticoagulant therapy in patients with symptomatic SVT and suggest no anticoagulation in those with incidental SVT [1], but supporting evidence for these recommendations is limited by the small size of the studies.

Of 604 patients recruited in a large international cohort of patients with SVT, 136 (22.5%) had solid cancer [25]. Anticoagulation was administered to 465 (77%) patients (mean, 13.9 months) and the incidence rates during anticoagulation in the whole cohort were 3.9 per 100 patient-years for major bleeding and 5.6 for thrombotic events. After treatment discontinuation, rates were 1.0 per 100 patient-years and 10.5, respectively. We recently reported our experience of 521 patients with SVT (45% had cancer) [26]. Many of them were at increased risk of bleeding, because of liver cirrhosis, gastroduodenal ulcer, esophageal varices, cancer, renal insufficiency, thrombocytopenia or anemia. The majority of patients in our cohort (93%) did receive anticoagulation, often at therapeutic doses and for over 6 months in up to 50% of cases. During the course of anticoagulation, the mortality associated with major bleeding outweighed the mortality associated with VTE recurrences, particularly during the first month. Interestingly, patients with incidental SVT had a 2-fold higher risk of symptomatic VTE recurrences than and a similar risk of major bleeding to those with symptomatic SVT. Hence, the risk/benefit ratio of anticoagulant therapy in patients with SVT should be better evaluated in future studies.

Anticoagulant therapy in real-life practice

A number of studies and registries conducted from around the world report suboptimal adherence to guideline-recommended anticoagulant therapy even during the acute treatment period [27]. Reasons for this poor performance are unknown. In another RIETE study on 6345 cancer patients with VTE, 66% received long-term LMWH therapy and 24% switched to vitamin K antagonists (VKA) [28]. Compared with those receiving VKA, patients on long-term LMWH therapy were younger, less likely to have renal insufficiency and more likely to have anemia or metastases.

Clinical trials on cancer patients with VTE found that, compared to treatment with VKAs, 3–6 months of LMWH (dalteparin at 200 U kg^{-1} day^{-1} for 1 month followed by 150 U kg^{-1} day^{-1}, enoxaparin at 1.5 mg kg^{-1} day^{-1}, or tinzaparin at 175 IU kg^{-1} day^{-1}) was associated with fewer VTE recurrences [7–10]. However, the ideal doses of LMWH have not been thoroughly studied. We compared the outcomes during the first 3 months in cancer patients receiving long-term therapy with < 150 vs. ≥ 150 IU kg^{-1} day^{-1} of LMWH [29]. We found that one in every two patients received lower daily doses of LMWH than those used in the randomized trials, with large variations from patient to patient, probably reflecting the absence of firm recommendations on this issue. In all, 1472 patients (46%) received < 150 IU kg^{-1} day^{-1} (mean, 112 ± 28) and 1750 received ≥ 150 IU kg^{-1} day^{-1} (mean, 184 ± 32). On propensity score analysis, patients receiving < 150 IU kg^{-1} day^{-1} had more DVT recurrences and fewer major bleeds than those treated with ≥ 150 IU kg^{-1} day^{-1}, but also had fewer fatal PEs. This is an unexpected finding, which might not be explained by these patients probably being sicker, because any difference in their baseline characteristics is likely to have disappeared after propensity score matching.

Optimal duration of anticoagulant therapy

The optimal duration of anticoagulation in cancer patients with VTE is unknown. In the literature, no studies have yet consistently assessed the efficacy and safety of anticoagulant therapy beyond the first 6 months. In the absence of data, the decision regarding the termination or continuation of anticoagulant therapy beyond the first 3 or 6 months is largely based on individual evaluation of the benefit : risk ratio and patients' preferences. The comparative risk of fatal PE (after anticoagulant withdrawal) or bleeding (as a result of continued anticoagulant therapy) needs to be determined. Meanwhile, published cohort studies and registries conducted from around the world have uniformly reported suboptimal adherence to guideline-recommended therapy [30–33].

Direct oral anticoagulants (DOACs)

The Hokusai VTE-cancer trial compared the efficacy and safety of edoxaban for 6–12 months vs. dalteparin in 1046 cancer patients with VTE [34]. During the course of anticoagulation, patients receiving edoxaban had a lower rate of DVT recurrences (hazard ratio [HR], 0.56; 95% CI, 0.32–0.97), a similar rate of PE recurrences (HR, 1.0; 95% CI, 0.59–1.69), a higher rate of major bleeding (HR, 1.77; 95% CI, 1.03–3.04) and a non-significantly higher rate of non-major but clinically relevant bleeding (HR,

Table 2 Reasons for a personalized approach to VTE in patients with cancer

Initial VTE presentation	Fatal PE recurrences more frequent in patients initially presenting with PE than in those with DVT alone
Site of cancer	More VTE recurrences than major bleeds in lung cancer
	More major bleeds than recurrences in prostatic cancer
	Similar rates in breast or colorectal cancer
	Non-reported data for other cancer sites
Site of VTE	In incidental PE, more major bleeds than symptomatic PE recurrences
Duration of therapy	No available data
LMWH doses	Only one study comparing < 150 vs. ≥ 150 IU kg^{-1} day^{-1}

VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; IU, international units.

1.38; 95% CI, 0.98–1.94). Similar findings (fewer VTE recurrences and more major bleeds) were found in a trial that compared rivaroxaban for 6 months vs. dalteparin, although the study was not sufficiently powered to allow definitive conclusions [35]. Most bleeding events in patients with DOACs in both trials occurred in the gastrointestinal tract and in patients with gastrointestinal cancers. There also is some real-world experience on the use of DOACs in cancer patients with VTE. In the Mayo Thrombophilia Clinic DOACs registry, there were no differences in the rates of VTE recurrences or major bleeding in patients receiving rivaroxaban or enoxaparin for 3–12 months [36].

Limitations of RIETE

Our studies have a number of potential limitations, which need to be addressed. First, RIETE is an observational registry and our findings are hypothesis generating. There is no external adjudication of the events, which are reported by the treating physicians. The dosing and regimen of prescribed drugs can vary according to country, center, underlying diseases and site of cancer. Finally, a variety of practitioners entered data into the registry, which may lend itself to potential inaccuracies in the data being reported.

Conclusions

Current guidelines for anticoagulant therapy do not so far suggest any form of differentiated approach to cancer patients with VTE. Our findings provide some insights into what factors may be used to guide physicians in adapting recommended anticoagulant regimens to the individual patient, as oncologists are increasingly doing with cancer treatments (Table 2). For instance, patients presenting with DVT alone might benefit from curtailing treatment intensity as anticoagulant therapy progresses. The site of cancer also needs to be considered, because the rate of VTE recurrences during therapy was half the rate of major bleeding in patients with prostate cancer, and over 2-fold higher in those with lung cancer. In patients with incidental PE or splanchnic vein thrombosis, we should be more cautious before prescribing anticoagulant therapy. The optimal duration of anticoagulant therapy is unknown.

Disclosure of Conflict of Interests

M. Monreal reports grants from Sanofi and Bayer, outside the submitted work.

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11. **Artículo 2:** Comparing low-molecular-weight heparin dosing for treatment of venous thromboembolism in patients with obesity (RIETE registry).

Mirza R, Nieuwlaat R, López-Núñez JJ, Barba R, Agarwal A, Font C, Ciammaichella M, Grandone E, Ikesaka R, Crowther M, Monreal M; RIETE Investigators. Comparing low-molecular-weight heparin dosing for treatment of venous thromboembolism in patients with obesity (RIETE registry). Blood Adv. 2020 Jun 9;4(11):2460-2467. doi: 10.1182/bloodadvances.2019001373.

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REGULAR ARTICLE

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Comparing low-molecular-weight heparin dosing for treatment of venous thromboembolism in patients with obesity (RIETE registry)

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Key Points

- This is the first study to compare clinical outcomes of treatment dosing strategies for LMWH in patients with obesity.
- Dosing of LMWH by body weight in patients with obesity may lead to increased rates of the composite of bleeding, VTE recurrence, and death.

Because of the absence of comparative evidence, current guidelines and product monographs diverge in the dosing of low-molecular-weight heparin (LMWH) for obese patients with venous thromboembolism (VTE). We used the RIETE registry to compare the primary composite outcomes (VTE recurrence, major bleeding, or death) in patients with VTE who weighed >100 kg during LMWH therapy with capped doses of LMWH (18 000 IU/d) vs uncapped doses (>18 000 IU/d). Multivariable logistic regression analysis was used to account for possible confounders. A total of 2846 patients who weighed >100 kg were included: 454 (16%) received capped doses of LMWH, and the remaining 2392 received uncapped doses. Mean (standard deviation) LMWH treatment duration was 14.8 (20.6) and 14.3 (32.3) days, respectively. Thirty-one patients (1.9%) had VTE recurrences, 38 (1.3%) had bleeding episodes, 65 (2.3%) died, and 122 (4.3%) had at least 1 of the composite outcomes. Unadjusted outcome rates revealed that capped dosing was associated with a decrease in the composite outcome (rate ratio, 0.22; 95% confidence interval [CI], 0.04-0.75). Multivariable analysis confirmed that patients who received capped doses had significantly lower rates of the composite outcome (odds ratio, 0.16; 95% CI, 0.04-0.68) while receiving LMWH. These retrospective observational data suggest that capped dosing of LMWH is an acceptable alternative to uncapped dosing based on body weight, given the significantly lower composite event rate of VTE recurrence, major bleeding, and all-cause death.

Introduction

Obesity is a growing epidemic affecting up to 11% of adults worldwide and 38% of Americans.[1] Obese people are at an increased risk of venous thromboembolism (VTE), compared with individuals of normal weight.[2] Putative mechanisms include stasis secondary to decreased mobility and compression of intra-abdominal and femoral vessels,[3] inflammation secondary to adipokines,[4] and endothelial damage secondary to associated metabolic diseases, including diabetes and hypertension.[5] With predictable pharmacokinetics and near 100% bioavailability, low-molecular-weight heparins (LMWHs) have been routinely used in the initial treatment of VTE, before transition to an oral agent.[6-8] However, the most appropriate LMWH dosing in patients with obesity remains unclear.

LMWHs are hydrophilic and therefore largely remain in the intravascular compartment. In obese individuals with disproportionately more adipose tissue, there is a concern about overdose and bleeding

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when treatment with standard dosing by actual body weight is applied.[7] The alternative strategy, capping at a maximum dose regardless of actual body weight, may cause an underdose.[9] There are no rigorous trials or observational studies comparing therapeutic LMWH dosing strategies in obese patients with VTE that examine clinical end points.[10] The Canadian drug product monographs recommend capped dosing, given that LMWH preferentially distributes to plasma[11-13]; however, practice patterns and the 2018 American Society of Hematology guidelines conditionally recommend uncapped LMWH doses[14] because of concerns about underdosing and the danger of treatment failure. The 2018 American Society of Hematology guidelines conditionally recommend capped LMWH based on evidence of very low certainty.[14] The evidence is based on a meta-analysis of 5 studies, none of which directly compared dosing strategies, revealing no difference in benefit or harm between indirect comparison of dosing strategies. Concerns about underdosing and the serious consequences of therapeutic failure are cited as justification for the recommendation.

Methods

Database

The RIETE (Registro Informatizado Enfermedad TromboEmbólica) database is an ongoing, multinational, observational registry of consecutive patients with objectively confirmed, acute VTE (registered at www.clinicaltrials.gov as #NCT02832245). The database was founded in Spain in 2001 and has expanded to >15 countries since then. The rationale and methodology of RIETE has been published.[15] Patients are excluded if they are currently participating in a therapeutic clinical trial with a blinded therapy. All patients (or their relatives) provide written or oral consent for participation in the registry, in accordance with local ethics committee requirements.

Population

The study population included patients registered in the RIETE registry who met 4 criteria: age ≥18 years; diagnosis of acute, objectively confirmed deep vein thrombosis (DVT) or pulmonary embolism (PE); obesity; and initial therapy with LMWH for any treatment duration. Our concern in specifying a minimum for treatment duration was the risk of excluding patients who experienced adverse events and therefore had LMWH discontinued. Obesity was defined as body weight >100 kg, a value used by other studies[10] as a pragmatic proxy, because height and body mass index (BMI) are not always recorded in clinical practice. For individual patients, the longest treatment phase on LMWH following the qualifying VTE was chosen for analysis. Patients treated with thrombolytics were excluded from analysis.

Exposure groups

We compared capped dosing (chosen as a dose of 18 000 IU/d, the typical suggested capped dose for LMWH) to noncapped LMWH dosing (any dose equivalent to >18 000 IU/d). Only patients treated with enoxaparin, dalteparin, or tinzaparin were included, given that the recommended capped dose is 18000 IU for all 3 drugs in the Canadian product monographs.[11-13]

Baseline variables

The following parameters were collected when the qualifying episode of VTE was diagnosed: sex, age, body weight, and, in most cases, height; risk factors for VTE: recent immobility (ie, total bed rest with bathroom privileges for ≥4 days in the 2-month period before VTE diagnosis), recent surgery (in the 2 months before VTE), active cancer (defined as newly diagnosed cancer, metastatic cancer, or cancer that was receiving treatment), hormonal therapy, pregnancy, recent birth prior VTE, and recent travel; and presence of coexisting conditions: chronic heart or lung disease, concomitant therapies, recent (<30 days before enrollment in RIETE) major bleeding, and laboratory data (also at baseline), including complete blood counts and serum creatinine levels.

Treatment and follow-up

Patients were treated according to the clinical practice of each participating hospital (ie, there was no standardized therapy). The drug, dose, and duration of therapy were recorded. The decision on the type and duration of anticoagulant therapy was left to the attending physicians. Patients were followed up in the outpatient clinic (or by telephone interview if they could not visit the clinic). During each visit, any signs or symptoms suggesting VTE recurrences or major bleeding were noted.

Outcome definitions

The primary outcome was the composite of recurrent VTE, major bleeding, or all-cause death attributable to LMWH treatment. The secondary outcome was the composite outcome at 15 days, whether the patient had transitioned from LMWH to another anticoagulant or not.

Major bleeding was defined as overt bleeding requiring a transfusion of 2 or more units of blood or retroperitoneal, spinal, intracranial, or fatal bleeding episodes. Bleeding was attributed to LMWH therapy when it occurred during LMWH treatment or within 3 days of discontinuation of LMWH. Our decision to include up to 3 days after discontinuation was based on 3 factors: (1) there may be a delay in the diagnosis of bleeding; (2) the half-life of LMWH is increased when the glomerular filtration rate is reduced; (3) doses in this population are at and above the upper limits of the studied doses and therefore may be associated with altered kinetics and dynamics.

Each episode of suspected recurrent VTE was investigated by repeat compression ultrasonography, lung scan, computed tomographic pulmonary angiography or pulmonary angiography, as chosen by the treating physician. Most outcomes were classified as reported by the clinical centers; there was no central adjudication of outcome events. VTE recurrences were attributed to LMWH if they occurred while the patient was receiving therapy or during or within 7 days of discontinuation of treatment. Attributing clots within 7 days of discontinuation encompasses cases in which there is delayed diagnosis.

Similarly, deaths were considered attributable to LMWH therapy if they occurred during therapy or within 7 days of treatment discontinuation.

Statistical analysis

All calculations were performed with SPSS Statistics (IBM). Differences in patient and treatment variables were assessed with the χ^2 test for categorical variables; the independent Student *t* test for normally distributed, continuous variables; and the Mann-Whitney *U* test for continuous variables without normal distribution.

Table 1. Patient demographics and treatment variables

	Capped dose	Uncapped dose	*P*
Patients, n	454	2392	
Male sex, n (%)	309 (68)	1641 (69)	.826
Age, mean ± SD, y	56.8 ± 15.8	54.8 ± 15	.011
Body weight, mean ± SD, kg	106.9 ± 8.6	111.3 ± 13.5	<.001
Body height (n = 2010), mean ± SD, cm	173 ± 9.9	173 ± 10	<.987
Body mass index (n = 2010), mean ± SD	36 ± 5.1	38 ± 6.1	<.001
Body mass index >30 (n = 2010), n (%)	320 (93)	1581 (95)	.241
VTE risk factor, n (%)			
Recent immobility ≥4 d	74 (16)	430 (18)	.421
Recent surgery	42 (9.3)	255 (11)	.403
Active cancer	83 (18)	279 (12)	<.001
Metastatic cancer	31 (6.8)	105 (4.4)	.571
Estrogen use	26 (5.7)	115 (4.8)	.409
Pregnancy or postpartum	2 (0.44)	18 (0.75)	.758
None of the above (unprovoked)	272 (60)	1,462 (61)	.637
Prior VTE	88 (19)	386 (16)	.099
Underlying disease, n (%)			
Major bleeding in the past month	5 (1.1)	16 (0.67)	.363
Chronic lung disease	54 (12)	295 (12)	.876
Chronic heart failure	21 (4.6)	119 (5.0)	.814
Anemia	102 (22)	505 (21)	.532
Platelet count $<100 \times 10^9$/μL	8 (1.8)	34 (1.4)	.528
Creatinine clearance level <60 mL/min	22 (4.8)	96 (4.0)	.440
Creatinine clearance level <30 mL/min	2 (0.44)	10 (0.42)	>.99
Initial VTE presentation, n (%)			
Deep vein thrombosis	252 (56)	989 (30)	<.001
Upper limb DVT	20 (4.4)	62 (2.6)	.045
Lower limb proximal DVT	191 (42)	746 (31)	<.001
Lower limb distal DVT	37 (8.1)	124 (5.2)	.015
Pulmonary embolism, n (%)	124 (27)	949 (40)	<.001
DVT and PE, n (%)	78 (17)	504 (21)	.068

SD, standard deviation.

Unadjusted rates of the primary and secondary outcomes were calculated during LMWH therapy. Binary multivariable logistic regression was used to calculate adjusted odds ratios [ORs] for the association of treatment (capped vs uncapped) with the primary composite outcome during LMWH therapy and also at 15 days from initiation of therapy (regardless of transition to another agent) as a secondary outcome. Potential confounders were entered into the multivariable model based on associations from the literature.[16,17] Variables were kept in the model if they were associated with the outcome ($P < .1$). The following variables were entered as potential confounders: age, sex, history of chronic heart or lung disease, recent immobility, cancer, metastatic cancer, recent major bleeding, anemia, thrombocytopenia, renal insufficiency, initial presentation of VTE, type of LMWH used for initial therapy, concomitant therapy with antiplatelets, and long-term therapy with vitamin K antagonists. We planned to compare the effect of dosing strategy in patients with and without metastatic cancer. Of the variables included, 3 had missing data: concomitant antiplatelets (208 missing values) and platelet and hemoglobin count (3 missing values for both counts). The missing data were imputed by the mode value.

Results

A total of 2846 patients weighing >100 kg were included: 454 (16%) received capped doses (18 000 IU/d), and the remaining 2392 received uncapped doses (mean, 20 865 IU/d). Mean treatment duration was 14.8 ± 20.6 and 14.3 ± 32.3 days, respectively. Patients were followed up for a median of 300 days and a mean of 501 days, respectively. Patients who received capped doses were slightly older (56.8 ± 15.8 and 54.8 ± 15.0 years, respectively), weighed less (106.9 ± 8.6 and 111.3 ± 13.5 kg), and were more likely to have active cancer and to initially present with DVT (vs PE) than those receiving uncapped doses (Table 1). In addition, patients who received capped doses of LMWH were more likely to be prescribed tinzaparin or dalteparin, but less likely to receive

Table 2. Details of therapy

	Capped dose	Uncapped dose	P
Patients, n	454	2392	
Initial therapy			
Enoxaparin, n (%)	127 (28)	2186 (91)	<.001
Tinzaparin, n (%)	249 (55)	72 (3.0)	<.001
Dalteparin, n (%)	78 (17)	134 (5.6)	<.001
Mean ± SD, d	14.8 ± 20.6	14.3 ± 32.3	.735
Median (IQR), d	11 (8-14)	10 (8-13)	.001
Treatment dose			
Mean LMWH dose, IU/kg per d	169 ± 12	189 ± 17	.001
LMWH dose >18 000 IU/kg per d, n (%)	0 (0)	2392 (100)	—
Mean dose ± SD per d, n	18 000 ± 0	20 865 ± 2102	.001
Long-term therapy, n (%)			
LMWH	110 (24)	393 (16)	<.001
Vitamin K antagonists	317 (70)	1776 (74)	.064
Direct oral anticoagulants	25 (5.5)	191 (8.0)	.081
Fondaparinux	1 (0.22)	6 (0.25)	>.99
Concomitant therapy, n (%)			
Antiplatelets	32 (7.0)	259 (11)	.014
Corticosteroids	27 (5.9)	116 (4.8)	.348

IQR, interquartile range.

enoxaparin, and were also less likely to have concomitant therapy with antiplatelets (Table 2). For long-term therapy, most patients switched to vitamin K antagonists (70% vs 74%), but a higher proportion of those with capped doses (24% vs 16%) continued to receive LMWH for long-term therapy. The breakdown of weights between groups is reported in Table 3.

Forty-nine total events were attributable to LMWH therapy, according to the prespecified rule of counting events if they occurred within 3 or 7 days of discontinuation (Table 4). Two events were counted in the capped-dose group: 2 PEs (0.44%) and 1 death attributable to PE (0.22%). There were no bleeding events. (Only the first event in a single individual was counted toward the composite, therefore

Table 3. Unadjusted outcome rates (uncapped vs capped dosing) at 15 days in patients initiated on LMWH and transitioned to other agents

	Capped dose	Uncapped dose	OR (95% CI)	P
Patients, n	454	2392		
15-d outcome, n (%)				
Recurrent PE	2 (0.44)	5 (0.21)	2.11 (0.41-10.9)	.310
Recurrent DVT	0 (0)	4 (0.17)	—	>.99
Recurrent VTE	2 (0.44)	9 (0.38)	1.17 (0.25-5.44)	.691
Major bleeding	0 (0)	26 (1.1)	—	.026
Gastrointestinal	0 (0)	6 (0.25)	—	.598
Hematoma	0 (0)	5 (0.21)	—	>.99
Intracranial	0 (0)	4 (0.17)	—	>.99
Recurrent VTE or major bleeding	2 (0.44)	35 (1.5)	0.30 (0.07-1.24)	.109
Death	1 (0.22)	21 (0.88)	0.25 (0.03-1.86)	.237
Cause of death, n (%)				
Pulmonary embolism	1 (0.22)	9 (0.38)	0.58 (0.07-4.62)	>.99
Sudden, unexpected	0 (0)	2 (0.08)	—	>.99
Bleeding	0 (0)	1 (0.04)	—	>.99
Disseminated cancer	0 (0)	3 (0.13)	—	>.99
Ischemic stroke	0 (0)	2 (0.08)	—	>.99
Composite outcome	2 (0.44)	2 (2.2)	0.20 (0.05-0.82)	.008

Table 4. Unadjusted clinical outcomes during initial therapy with LMWH

	Capped dose		Uncapped dose		
	n	Events per 100 patient-years	n	Events per 100 patient-years	Rate ratio (95% CI)
Patients, n	454		2392		
Duration of therapy, d					
Mean ± SD	15 ± 21		14 ± 32		0.650
Median (IQR)	11 (8-14)		10 (8-13)		0.001
Event					
Recurrent PE	2	10.9 (1.82-35.9)	3	3.21 (0.828.73)	3.39 (0.40-22.8)
Recurrent DVT	0	—	3	3.21 (0.828.74)	—
Recurrent VTE	2	10.9 (1.82-35.9)	6	6.43 (2.61-13.4)	1.69 (0.24-8.00)
Major bleeding	0	—	24	25.7 (16.837.7)	—
Gastrointestinal	0	—	5	5.35 (1.9611.8)	—
Hematoma	0	—	4	4.28 (1.3810.3)	—
Intracranial	0	—	4	4.28 (1.3810.3)	—
Recurrent VTE or major bleeding	2	11.0 (1.82-35.9)	30	32.2 (22.145.4)	0.34 (0.05-1.20)
Death	1	5.43 (0.27-26.8)	21	22.5 (14.333.8)	0.24 (0.01-1.30)
Cause of death					
Pulmonary embolism	1	5.43 (0.27-26.8)	9	9.63 (4.7017.7)	0.56 (0.03-3.43)
Sudden, unexpected	0	—	2	2.14 (0.397.06)	—
Respiratory failure	0	—	0	—	—
Bleeding	0	—	2	2.14 (0.397.06)	—
Disseminated cancer	0	—	4	4.28 (1.3810.3)	—
Composite outcome	2	10.9 (1.82-35.9)	47	50.5 (37.966.6)	0.22 (0.04-0.75)

the sum of individual events do not match the total.) In the uncapped dose group, there were 47 events: 3 PEs (0.13%), 3 DVTs (0.13%), 24 major bleeding incidents (1%), and 21 deaths (0.88%).

During the first 15 days of anticoagulant therapy (including events not attributable to LMWH by our rule), 11 patients (0.39%) developed VTE recurrences (7 recurrent PE, 4 recurrent DVT), 26 (0.91%) had major bleeding, 22 (0.77%) died (10 died of PE, 1 of bleeding), and 54 (1.9%) had at least 1 of the composite outcomes (Table 5).

We prespecified that patients with metastatic cancer would have a higher risk of death, thrombosis, and bleeding. However, we did not have sufficient power to test statistically for interaction of dosing strategy with metastatic cancer. The composite outcomes of the capped vs uncapped strategy in metastatic cancer at 15 days were 0 vs 11 events (0% vs 10.4%; $P = .051$). Table 6 includes detailed outcomes for this subgroup.

Multivariable binary logistic regression revealed that patients receiving capped doses of LMWH were at a lower risk for composite outcomes, both during LMWH therapy (OR, 0.16; 95% confidence interval [CI], 0.04-0.68) and at 15 days (OR, 0.17; 95% CI, 0.04-0.71; Table 7). This effect was mainly due to a trend toward lower rates of unadjusted major bleeding: no episodes in the capped-dose group vs 24 in the uncapped-dose group (Figure 1).

Discussion

The optimal dose of LMWH therapy for obese patients with acute VTE is guided by limited pharmacokinetic data with no substantiating clinical data. To our knowledge, there are no data in the literature that compare rates of clinical events in obese patients with VTE treated with capped vs uncapped doses. Ours is the first study to compare these 2 therapeutic LMWH dosing strategies on the basis of patient-important clinical outcomes.

Our data, obtained from RIETE, a large registry of patients with VTE, reveal that 1 in every 6 patients (19%) weighing >100 kg was prescribed capped doses of LMWH, whereas the remainder received

Table 5. Multivariable analyses for the composite outcome at 15 days in patients first treated with LMWH and during therapy with LMWH

	15 d, OR (95% CI)	During LMWH therapy, OR (95% CI)
No. of events	54	49
Total sample, n	2846	2843
Capped doses of LMWH	0.17 (0.04-0.71)*	0.16 (0.04-0.68)*
Male sex	0.61 (0.35-1.04)	0.59 (0.33-1.06)
Body weight <106 kg	—	2.55 (1.35-4.81)†
Active cancer	2.52 (1.30-4.87)†	—
Anemia	1.95 (1.10-3.44)*	—
Creatinine clearance level <60 mmol/L	1.97 (0.82-4.73)	—
PE as initial VTE presentation	—	—
Corticosteroids	—	3.06 (1.45-6.47)†

Outcomes at 15 days includes patients who first received LMWH and transitioned to other agents. Outcomes during LMWH therapy include only outcomes attributable to LMWH as described in "Methods." ORs marked with a dash did not reach $P < .1$ in univariable analyses and therefore were not included in multivariable analyses.
*$P < .05$; †$P < .01$.

Table 6. Unadjusted outcome rates (uncapped vs capped dosing) in patients with metastatic cancer

	Capped dose	Uncapped dose	OR (95% CI)	P
Patients, n	31	105		
15-d outcome, n (%)				
Recurrent PE	0 (0)	0 (0)	—	—
Recurrent DVT	0 (0)	2 (1.9)	—	>.99
Recurrent VTE	0 (0)	2 (1.9)	—	>.99
Major bleeding	0 (0)	2 (1.9)	—	>.99
Retroperitoneal	0 (0)	1 (0.95)	—	>.99
Menorrhagia	0 (0)	1 (0.95)	—	>.99
Death	0 (0)	7 (6.7)	—	.351
Cause of death				
Pulmonary embolism	0 (0)	2 (1.9)	—	>.99
Sudden, unexpected	0 (0)	1 (0.95)	—	>.99
Ischemic stroke	0 (0)	1 (0.95)	—	>.99
Neoplasia	0 (0)	3 (2.9)	—	>.99
Composite outcome	0 (0)	11 (10.4)	—	.051

an uncapped dose. The concern regarding uncapped doses is the subtherapeutic anticoagulant effect resulting in otherwise avoidable thromboembolisms.[9] In our study, 1.5% of patients experienced major bleeding and 1.2% had a VTE when exposed to uncapped dosing, compared with 0.22% and 0.66%, respectively, of those receiving a capped dose at 90 days after therapy initiation (results are not statistically significant for all individual comparisons). After adjustment for multiple potential confounders, patients with obesity who were receiving capped doses were at a lower risk of having the composite outcome of VTE recurrences, major bleeding, or all-cause death at 15 and 90 days.

This study has several significant limitations, broadly categorized as risk of significant bias and problems relating to the analysis. First, data were derived from the RIETE registry, which is a large, prospective case series of patients with VTE and may be subject to selection bias. Second, there were several prognostic differences at baseline between the 2 groups: patients receiving capped doses were significantly more likely to have active and metastatic cancer, to weigh less, and to have DVT (vs PE) and were significantly less likely to have received concomitant antiplatelet therapy. Despite our attempt to control for these potential confounders in multivariable analysis, residual confounding may partially explain the difference in outcomes between capped and uncapped dosing. Moreover, some baseline differences point toward confounding by indication: for example, those who received capped doses typically weighed less and were more likely to receive enoxaparin than those who received capped doses (91% vs 28%). Further, dosing regimens were different for tinzaparin 175 μg/kg per day vs dalteparin 200 IU/kg per day vs enoxaparin 1 mg (~100 IU/kg) twice daily or 1.5 mg daily. A maximum unit threshold that is the same across each drug and dose strategy means that the weights at which a dose should be defined as capped vs not capped can vary, as would the pharmacologic effects. Third, outcome events were not adjudicated centrally. As physicians were aware of treatment allocation, it is possible that their knowledge of dosage influenced their reporting of clinical events. In terms of the multivariable analysis, there was a relatively low number of events, especially in the capped-dose group, which may have led to overfitting in multivariable analysis. In addition, the mean actual dose difference between the 2 groups was small (18 000 vs 20 865 IU/d). Finally, our composite analysis assumed that an episode of VTE, a major bleeding episode, and all-cause death had equal value. Higher doses could cause both more bleeding and decreased VTE, reducing the value of this composite end point.

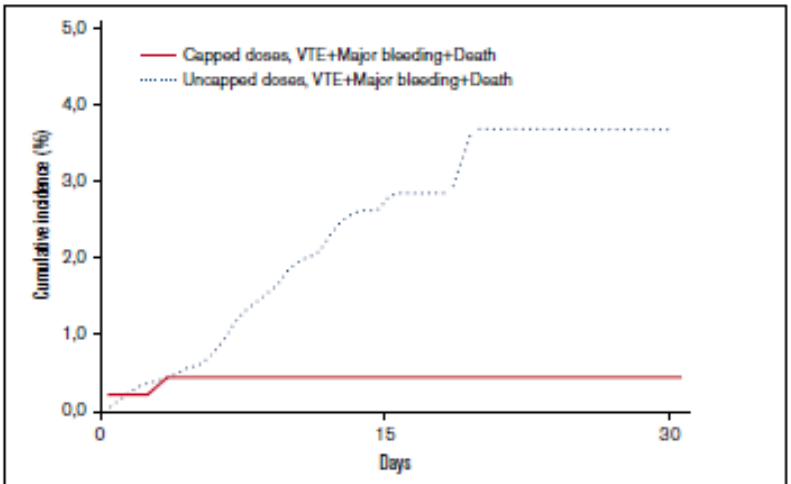
Given the higher percentage of patients with active and metastatic cancer in the capped-dose group and the lower unadjusted event rates in the group, it seems improbable that capped dosing is harmful in either subgroup.

Our results are potentially valuable, however, as they suggest that capped dosing may have a role in obese patients with VTE who are at high risk for bleeding. Indeed, our findings are consistent with

Table 7. Use of capped vs uncapped LMWH doses according to body weight

	Capped dose	Uncapped dose	P
Patients, n	454	2392	
100-110 kg	364 (80)	1.526 (64)	<.001
111-120 kg	68 (14)	479 (20)	.002
121-130 kg	20 (4.4)	205 (8.6)	.002
131-140 kg	4 (0.88)	89 (3.7)	<.001
141-150 kg	1 (0.22)	56 (2.3)	<.001
151-160 kg	1 (0.22)	16 (0.67)	.501
161-170 kg	1 (0.22)	10 (0.42)	>.99
171-180 kg	0 (0)	3 (0.13)	>.99
181-190 kg	0 (0)	5 (0.21)	>.99
191-200 kg	0 (0)	0 (0)	0
201-210 kg	0 (0)	2 (0.08)	>.99
211-220 kg	0 (0)	1 (0.04)	>.99

Unless otherwise indicated, values are n (%).



Days		15	30
At risk (Composite outcome)	*Capped doses*	280	67
	Uncapped doses	1,445	288
Composite outcome	*Capped doses*	2 (0.44%)	2 (0.44%)
	Uncapped doses	44 (2.94%)	46 (3.69%)

Figure 1. Cumulative rates of composite outcome (VTE, major bleeding, or death) during the first 30 days of LMWH therapy (uncapped vs capped dosing).

a meta-analysis of the bariatric surgery literature suggesting higher rates of bleeding episodes, without reduction in rates of VTE, using weight-adjusted heparin prophylaxis dosing.[18] We emphasize that our findings are at high risk of bias and should not change current practice, but should spur further investigation in the form of an appropriately powered randomized controlled trial.

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Authorship

Contribution: R.M. conceived and coordinated the study, designed the study, conducted the initial analysis, and wrote the initial draft; R.N. played a central role in formulating the question, conducting statistical analyses, and editing the manuscript. J.J.L.-N., R.B., A.A., C.F., R.I., and E.G. contributed significantly to the interpretation of the findings and the writing of the manuscript, in addition to contributing to the database itself; M.C. helped recruit experts to choose and interpret the outcomes and made major contributions to the text, leading to substantial revisions; and M.M. provided the data, recruited a team that assisted throughout the study, and assisted at each stage of the process.

Conflict-of-interest disclosure: R.I. has participated on an advisory board once with both Apsen Pharmacare and LEOPharma. M.C. is receiving or has received monetary compensation from Bayer, Pfizer, CSL Behring, Servier Canada, Diagnostica Stago, Asahi Kasei, and Alnylam. The remaining authors declare no competing financial interests.

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