UNIVERSITAT DE BARCELONA

Evaluación de factores de riesgo de retrombosis y sangrado en pacientes con enfermedad tromboembólica venosa

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EVALUACIÓN DE FACTORES DE RIESGO DE RETROMBOSIS Y SANGRADO EN PACIENTES CON ENFERMEDAD TROMBOEMBÓLICA VENOSA.

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Listado de abreviaturas

ACODs: Anticoagulantes orales de acción directa

AINEs: Antinflamatorios no esteroideos

Angio-TAC: Angiografía por tomografía computarizada

AT: Antitrombina

AVK: Antagonistas de la vitamina K

ClCr: Clearence de creatinina

COMMAND-VTE: Contemporary management and outcomes in patients with venous thromboembolism

ESC: European Society of Cardiology

ETV: Enfermedad Tromboembólica Venosa

FDPs : Productos de degradación del fibrinógeno

FT: Factor tisular

FVC: Filtro de vena cava

HBPM: Heparina de bajo peso molecular

HNF: Heparina no fraccionada

IMC: Índice de Masa Corporal

ISTH: International Society of Thrombosis and Haemostasis

NIH: National Institutes of Health

RIETE: Registro Informatizado de Pacientes con Enfermedad TromboEmbólica

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

Sc: Subcutánea

TEP: Tromboembolia pulmonar

TFI: Inhibidor del factor tisular

t-PA: Activador tisular del plasminógeno

TM: Trombomodulina

TVP: Trombosis venosa profunda

UCI: Unidad de cuidados intensivos

u-PA: Activador del plasminógeno tipo uroquinasa

vo: Vía oral

vWf : Factor de von Willebrand

Tesis en formato de compendio de publicaciones

La tesis consta de 7 objetivos y 5 artículos (4 artículos originales y 1 carta al editor). El artículo 1 corresponde al primer, segundo y tercer objetivo; el artículo 2 corresponde al cuarto objetivo, el artículo 3 corresponde al quinto objetivo; el artículo 4 corresponde al sexto objetivo y el artículo 5 corresponde al séptimo objetivo.

- **Artículo 1: Cristina Gabara,** Jesus Aibar, Yuji Nishimoto, Yugo Yamashita, Paolo Prandoni, Geoffrey D Barnes, Behnood Bikdeli, David Jiménez, Pablo Demelo-Rodríguez, Mª Luisa Peris1, Son Truong Nguyen, Manuel Monreal and the RIETE Investigators. *Clinical outcomes after discontinuing anticoagulant therapy in patients with first unprovoked venous thromboembolism*. Journal of Thrombosis and Haemosthasis. 2024; 22 (8):2234-2246.
  doi: 10.1016/j.jtha.2024.05.007. Epub 2024 May 16. PMID: 38762019.
  Factor de impacto: 5,5. Cuartil: Q1.

- **Artículo 2:** Prandoni P, **Gabara C**, Bilora F, Aibar J, Pesavento R, Villalobos A, Campello E, Miguel PL, Tormene D, Monreal M; RIETE Investigators. *Age over 75 does not increase the risk of recurrent venous thromboembolism: Findings from the RIETE registry*. Thrombosis Research. 2023; 222: 16-19.
  doi: 10.1016/j.thromres.2022.12.005. Epub 2022 Dec 17. PMID: 36549192.
  Factor de impacto: 3,7. Cuartil: Q1.

- **Artículo 3: Gabara C**, Montoya-Rodes M, López N, Zamora-Martínez C, Ortiz M, Morancho A, Moisés J, Osorio J, Coloma E, Font C, Jiménez S, Zarco F, Burrel M, Bermúdez P, Barrufet M, Aibar J. *Inferior Vena Cava Filters: Adherence to Clinical Practice Guidelines Recommendations, Retrieval Rates, and Filter Complications in a Tertiary Hospital.* Angiology. 2023; 20: 33197231190184.
  doi: 10.1177/00033197231190184. Epub ahead of print. PMID: 37470426**.**
  Factor de impacto: 2,6. Cuartil: Q2.

- **Artículo 4:** Nestor López, Carles Zamora-Martinez, Marc Montoya-Rodes, **Cristina Gabara**, María Ortiz, Jesús Aibar. *Comparison of inferior vena cava filter use and outcomes between cancer and non-cancer patients in a tertiary hospital*. Thrombosis Reserch. 2024; 236:136-143.
  doi: 10.1016/j.thromres.2024.02.020. Epub 2024 Feb 28. PMID: 38447420.
  Factor de impacto: 3,7. Cuartil: Q1.

- **Artículo 5:** Muñoz-Rivas N, Aibar J, **Gabara-Xancó C**, Trueba-Vicente Á, Urbelz-Pérez A, Gómez-Del Olmo V, Demelo-Rodríguez P, Rivera-Gallego A, Bosch-Nicolau P, Perez-Pinar M, Rios-Prego M, Madridano-Cobo O, Ramos-Alonso L, Alonso-Carrillo J, Francisco-Albelsa I, Martí-Saez E, Maestre-Peiró A, Méndez-Bailón M, Hernández-Rivas JÁ, Torres-Macho J; PROTHROMCOVID Trial Investigators. *Efficacy and Safety of Tinzaparin in Prophylactic, Intermediate and Therapeutic Doses in Non-Critically Ill Patients Hospitalized with COVID-19: The PROTHROMCOVID Randomized Controlled Trial*. Journal of Clinical Medicine. 2022; 11 (19): 5632.
  doi: 10.3390/jcm11195632. PMID: 36233500; PMCID: PMC9571371.
  Factor de impacto: 3,0. Cuartil: Q1.

1. INTRODUCCIÓN

1.1 Fisiología de la hemostasia (1–4)

La hemostasia es el equilibrio por el cual la sangre permanece en estado fluido mientras se encuentra en el compartimento intravascular y pasa a estado sólido al producirse una solución de continuidad en el mismo. Este equilibrio incluye los mecanismos anticoagulantes que suceden al romperse un vaso sanguíneo, la coagulación y la disolución del coágulo. Para simplificar su estudio, este proceso se divide en hemostasia primaria, hemostasia secundaria, regulación antitrombótica y fibrinolisis, pero hay que tener en cuenta que estas fases no son independientes, sino que se producen de manera prácticamente simultánea.

En el endotelio sano se producen óxido nítrico y prostaciclina, sustancias vasodilatadoras que inhiben a las plaquetas y las mantienen en reposo. Al romperse el endotelio se produce, en primer lugar, una vasoconstricción, para evitar una mayor pérdida de sangre. A su vez, al romperse, el endotelio deja expuesta la superficie colágena y libera, por un lado, factor de von Willebrand (vWF), que es necesario para que las plaquetas se activen y adhieran y, por otro lado, factor tisular (FT), que será importante para iniciar la coagulación. Al activarse, las plaquetas se adhieren al endotelio y se agregan entre sí, formando el coágulo primario. Este primer coágulo es lábil, pero es importante porque las membranas plaquetarias sirven para que se recluten y activen ahí los factores de la coagulación y se inicie la fase de hemostasia secundaria, que consiste en la generación de un coágulo más estable (coágulo secundario) gracias a la formación de una malla de fibrina.

Los factores de la coagulación, que se encuentran en el plasma en forma de zimógenos, se activan mediante hidrólisis, lo que los convierte en proteasas de serina que, a su vez, activan a otros factores. En el modelo celular de la coagulación, a diferencia de lo que se pensaba anteriormente, ya no se considera que estos factores se activan en cascada, sino que se acepta que las reacciones se dan de forma simultánea y sobre membranas celulares: primero sobre la membrana endotelial y luego sobre la membrana plaquetaria.

El FT activa al factor VII en presencia de fosfolípidos aniónicos y calcio. Luego, el FT y el factor VII activado (VIIa) activan a los factores IX y X. El factor Xa unido al cofactor Va,

generan cantidades pequeñas o microdosis de trombina (factor IIa) que dará lugar a: i) una mayor activación plaquetaria y, por consiguiente, a una mayor superficie para la activación de los factores de coagulación; ii) una amplificación del proceso al activar a los factores V, XI y XIII de la coagulación y iii) una activación del factor VIII al separarlo del vWF con el que viaja unido en el plasma *(Figura 1).* El factor IXa junto con el cofactor VIIIa, activan al factor X para que, así, el Xa y su cofactor Va, generen ahora sí dosis mucho mayores o macrodosis de trombina.

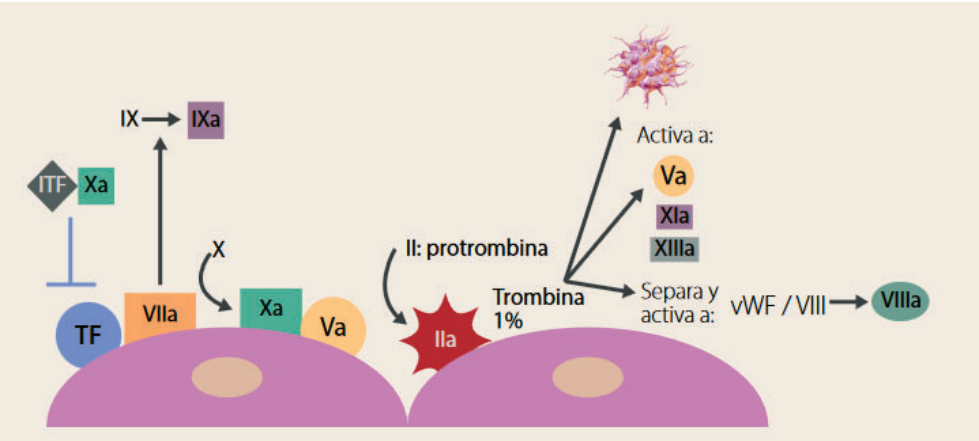

Figura 1: Esquema del inicio de la coagulación y producción de microdosis de trombina. Extraído de: González-Villalva A, et al. Fisiología de la hemostasia y su alteración por la coagulopatía en COVID-19. Rev Fac Med. 2020 (1).

Además de su papel como agonista plaquetario y activador de factores de la coagulación, la trombina incide también sobre el fibrinógeno, dando lugar a la formación de polímeros de fibrina que formarán, inicialmente, un coágulo frágil, que se estabilizará posteriormente a través de enlaces cruzados por acción del factor XIIIa (*Figura 2*). En la fase de regulación antitrombótica, el endotelio sano juega un papel fundamental, dado que es el encargado de sintetizar las proteínas de regulación antitrombótica: el inhibidor del factor tisular (TFI), la trombomodulina (TM) y la antitrombina (AT). El TFI se une con el factor Xa y juntos inhiben al FT, con lo que pueden prevenir la formación inicial de trombina. Por otro lado, la trombina, al unirse a la TM, favorece la activación de la proteína C, que, junto con su cofactor, la proteína S, hidrolizan a los factores de la coagulación V y VIII, con lo que se limita la formación del coágulo. Por último, la AT inhibe directamente a la trombina *(Figura 2).*

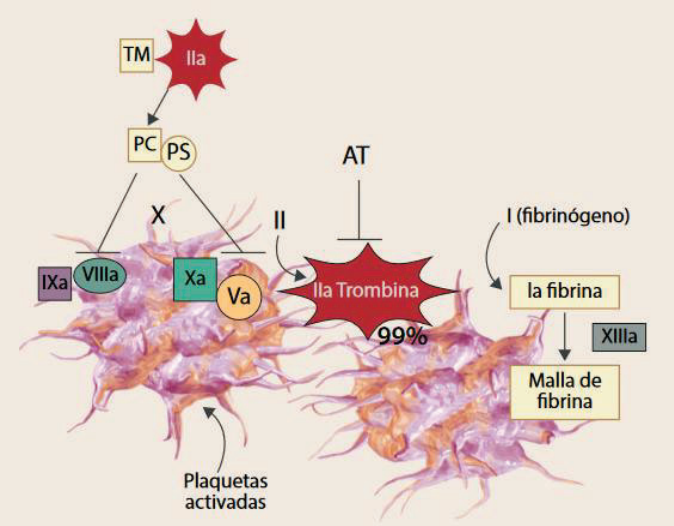

Figura 2: Esquema de la propagación de la coagulación y regulación antitrombótica. Extraído de: González-Villalva A, et al. Fisiología de la hemostasia y su alteración por la coagulopatía en COVID-19. Rev Fac Med. 2020 (1)**.**

La fibrinolisis es el proceso de disolución del coágulo. Los depósitos de fibrina se degradan por acción de la plasmina, una enzima que surge a partir del plasminógeno por el activador tisular de plasminógeno (t-PA) y por la urokinasa (u-PA). Esta enzima hidroliza tanto a los polímeros del fibrinógeno, dando lugar a los productos de degradación del fibrinógeno (FDPs), como a la fibrina estable, dando lugar a los dímeros-D. Para regular este proceso, existen mecanismos anti-fibrinolíticos: por un lado, el inhibidor del activador de plasmina 1 (PAI-1) bloquea al t-PA o al u-PA y, por el otro, la α2-antiplasmina que inhibe a la plasmina *(Figura 3).*

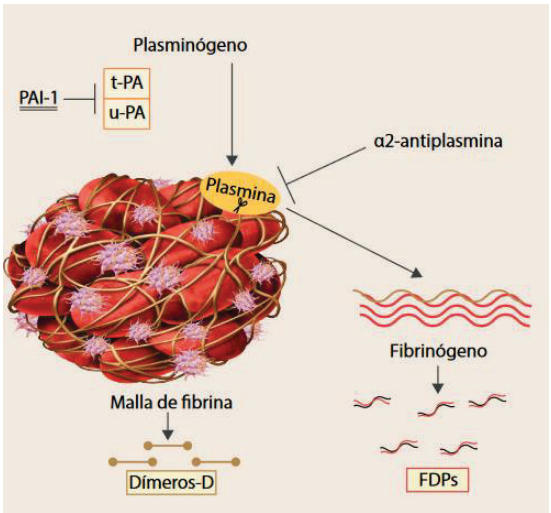

Figura 3: Esquema de la Fibrinolisis. Extraído de: González-Villalva A, et al. Fisiología de la hemostasia y su alteración por la coagulopatía en COVID-19. Rev Fac Med. 2020 (1)**.**

Cuando se produce un desequilibrio en este complejo sistema hemostático, es cuando aparecen las complicaciones trombóticas o hemorrágicas.

1.2 Epidemiología de la Enfermedad Tromboembólica Venosa

La enfermedad tromboembólica venosa (ETV) incluye dos manifestaciones clínicas: la trombosis venosa profunda (TVP) y la tromboembolia pulmonar (TEP). Pese a tratarse de una enfermedad que a menudo se presenta con sintomatología inespecífica (o incluso de forma asintomática) y que en ocasiones no se diagnostica, es frecuente, con una incidencia anual global de 115-269/100.000 habitantes (5). En cuanto a las formas de presentación, la TVP aislada es más frecuente (53-162/100.000 habitantes) que la TEP asociada o no a TVP (39-115/100.000 habitantes) (6). A su vez, es una enfermedad con una importante morbimortalidad asociada, siendo la tercera causa de muerte vascular tras el ictus y el infarto agudo de miocardio (7).

1.3 Fisiopatología de la Enfermedad Tromboembólica Venosa

Clásicamente, se han implicado tres factores en la formación del trombo (Triada de Virchow): una alteración en el flujo sanguíneo (estasis venoso), un daño vascular endotelial y alteraciones en la constitución de la sangre (hipercoagulabilidad hereditaria o adquirida) (8). Habitualmente la trombosis se origina en áreas con disminución del flujo sanguíneo (como las válvulas o senos venosos), donde se produce un depósito de fibrina que activa de forma local la coagulación y la agregación plaquetaria, dando lugar a la formación y propagación del trombo (9). En las fases iniciales, el trombo no está íntimamente adherido al endotelio vascular, por lo que puede desprenderse y viajar a través del sistema venoso hasta la aurícula derecha y, de allí, a las arterias pulmonares originando una TEP (10).

1.4 Formas clínicas de presentación de la Enfermedad Tromboembólica Venosa

Como se ha comentado previamente, la ETV puede tener diferentes manifestaciones clínicas. La TVP se define como la oclusión parcial o total de una vena del sistema venoso profundo. Aunque la localización más habitual son las venas de las extremidades inferiores, esta entidad puede afectar a cualquier localización: extremidades superiores, territorio esplácnico, venas suprahepáticas, ováricas, renales

o senos venosos cerebrales (11). Las TVP de extremidades inferiores se clasifican, según su localización, en proximales (venas ilíacas, femoral común, femoral superficial, femoral profunda y poplítea) y distales (venas tibiales, peroneas, gemelares y pedias). De la misma manera, las TVP de extremidades superiores se clasifican también en proximales (vena yugular, subclavia, axilar y braquial) y distales (venas radial y cubital). Esta clasificación será importante no solo para guiar la duración del tratamiento anticoagulante sino porque tiene implicaciones pronósticas, dado que las TVP proximales tienen un mayor riesgo de desprendimiento y, por tanto, de dar lugar a una TEP, que las distales aisladas (11).

La TEP se produce por la obstrucción de las arterias pulmonares. El 90% provienen de una TVP de extremidades inferiores y un 5-10% de TVP de extremidades superiores u otras localizaciones. Según su localización, podemos clasificarla también como proximal (si hay afectación de ramas arteriales pulmonares principales y/o lobares) o distal (si afecta a arterias segmentarias y subsegmentarias). Se trata de una complicación grave, con una mortalidad en torno al 30% sin tratamiento; y con una mortalidad mucho mayor que la TVP aislada (12,13).

1.5 Factores de riesgo de la Enfermedad Tromboembólica Venosa

Se han descrito múltiples factores que pueden inducir, de forma transitoria o persistente, estasis, daño vascular endotelial o hipercoagulabilidad y, por tanto, aumentar el riesgo de trombosis. En la *Tabla 1* (14) se resumen los principales factores de riesgo de ETV clasificados según su mecanismo etiopatogénico.

Tabla 1: Factores de riesgo de ETV.

Estasis venosa	Lesión endoletial vascular	Hipercoagulabilidad
Hospitalización	Catéter venoso central	Factores genéticos
		Factor V de Leiden
		Mutación del gen de la Protrombina 20210G→A
		Déficit de antitrombina
		Déficit de Proteína C y S
Inmovilidad	Cirugía, especialmente ortopédica	Síndrome antifosfolípido
Paresia o parálisis	Traumatismos o fracturas	Cáncer activo
Viaje de > 4 horas	Sepsis	Embarazo y postparto
		Terapia estrogénica
		Edad avanzada
		Obesidad
		Enfermedades autoinmunes o inflamatorias crónicas

Abreviaciones: ETV, enfermedad tromboembólica venosa. Adaptado de: Di Nisio M, et al. Deep vein thrombosis and pulmonary embolism. Lancet. 2016 (14).

En los últimos años se ha postulado que no todos los factores de riesgo identificados contribuyen de igual forma al desarrollo de ETV y que, de hecho, el riesgo de ETV incrementa con el número de factores predisponentes asociados (10). En este sentido, en base a estudios de grandes cohortes publicados, las Guías de la *European Society of Cardiology* (ESC) de 2019 realizadas con la colaboración de la *European Respiratory Society,* clasifican los factores de riesgo de ETV en 3 grupos en función de su grado de asociación: factores de riesgo débiles (definidos como aquellos con odds ratio < 2), moderados (definidos como odds ratio 2-9) y fuertes (definidos como odds ratio > 9) (6). En la *Tabla 2* se estratifican los factores de riesgo en función de si son débiles, moderados o fuertes (15).

En función de la existencia o no, de estos factores predisponentes, la ETV se clasifica en provocada por un factor de riesgo transitorio, provocada por un factor de riesgo permanente, o no provocada, representando éste último grupo un 50% de los casos (14). Esta clasificación, como se describe más adelante, será relevante a la hora de decidir la duración del tratamiento anticoagulante.

Tabla 2: Estratificación de los factores de riesgo de ETV.

Factores de riesgo débiles	Factores de riesgo moderado	Factores de riesgo fuertes
Reposo en cama >3 días	Cirugía artroscópica de rodilla	Fractura de miembros inferiores
Viaje prolongado	Enfermedad autoinmune	Daño medular
Factores de riesgo cardiovasculares	Transfusiones/Agentes estimulantes de colonias	Cirugía de cadera o rodilla
Edad	Catéteres venosos	Hospitalización los 3 meses previos
Cirugía menor	Cardiopatía o neumopatía	Traumatismo mayor
Embarazo/Puerperio	Terapia hormonal	Trombofília *Mutación homocigota del factor V de Leiden, Mutación homocigota del gen de la protrombina, Déficit de antitrombina o Trombofília combinada*
Varices	Infecciones	Síndrome antifosfolípido
	Enfermedad inflamatoria intestinal	Trombosis previa
	Cáncer/Quimioterapia	
	Ictus que condicione paresia/parálisis	
	Trombosis venosa superficial	

Abreviaciones: ETV, enfermedad tromboembólica venosa. Adaptado de: Pastori D, Cormaci VM et al. A Comprehensive Review of Risk Factors for Venous Thromboembolism: From Epidemiology to Pathophysiology. Int J Mol Sci. 2023 (15).

1.6 Diagnóstico de la Enfermedad Tromboembólica Venosa

El diagnóstico de la ETV, basado en los signos y síntomas, no es totalmente fiable debido a la baja especificidad de las manifestaciones clínicas. De hecho, se ha descrito que sólo en un 25% de los pacientes con síntomas compatibles con TVP y un 5% de los pacientes con sospecha clínica de TEP se confirma el diagnóstico (16).

En este contexto se han diseñado diferentes aproximaciones diagnósticas para pacientes con sospecha de ETV. La más aceptada y extendida es la que se basa en la

aplicación secuencial de escalas de probabilidad clínica pretest que combinan síntomas, signos y factores de riesgo, el análisis del dímero-D y una prueba de imagen (ecografía doppler en caso de las TVP de extremidades, angiografía por tomografía computarizada (Angio-TAC) en TVP de otras localizaciones y Angio-TAC/Gammagrafía de ventilación/perfusión en caso de la TEP).

En el caso de la TVP, la escala de probabilidad clínica pretest más utilizada y validada es la escala modificada de Wells (*Tabla 3*), que clasifica a los pacientes con sospecha clínica en pacientes con probabilidad baja o alta (score de 2 niveles) (17).

Tabla 3: Escala de Wells modificada para TVP.

Características clínicas	Valor
Cáncer activo (paciente con quimioterapia en los 6 meses previos o tratamiento paliativo)	+1
Parálisis, paresia o inmovilización con yeso de una extremidad	+1
Encamamiento reciente ≥ 3días o cirugía mayor en las últimas 12 semanas	+1
Dolor a la presión a lo largo de la distribución del sistema venoso profundo	+1
Tumefacción de toda la extremidad	+1
Aumento del perímetro >3cm respecto a la extremidad asintomática (medido 10cm por debajo de la tuberosidad tibial)	+1
Edema en la extremidad afectada	+1
Venas colaterales superficiales (no varicosas)	+1
Antecedente de TVP previa documentada	+1
Diagnóstico alternativo al menos tan probable como TVP	-2
Probabilidad	
TVP probable	**≥2**
TVP improbable	**≤1**

Abreviaciones: TVP, trombosis venosa profunda. Adaptada de: L. Mazzolai, V. Aboyans, et al. Diagnosis and management of acute deep vein thrombosis: a joint consensus document from the european Society of Cardiology working groups of aorta and peripheral vascular diseases and pulmonary circulation and right ventricular function. Eur. Heart J. 2018 (17).

En el caso de la TEP, las escalas más aceptadas son la Escala de Wells (18) y la Escala de Ginebra modificadas (19) (*Tabla 4*), que también clasifican a los pacientes con sospecha clínica en pacientes con probabilidad baja o alta (score de 2 niveles).

Tabla 4: Escala de Wells y de Ginebra modificadas para TEP.

Escala de Wells modificada	
Características clínicas	Valor
Antecedente de TEP o TVP	+1
Cirugía o inmovilización las últimas 4 semanas	+1
Cáncer	+1
Hemoptisis	+1
Frecuencia cardíaca>100lpm	+1
Signos clínicos de TVP	+1
Diagnóstico alternativo menos probable que TEP	+1
Probabilidad	
TEP probable	**≥2**
TEP improbable	**0-1**
Escala de Wells y de Ginebra modificada	
Edad≥65 años	+1
Antecedente de TEP o TVP	+1
Cirugía o fractura el último mes	+1
Cáncer activo	+1
Dolor unilateral de extremidad inferior	+1
Hemoptisis	
Frecuencia cardíaca	
75-94lpm	+1
≥95lpm	+2
Dolor a la palpación o edema unilateral de la extremidad inferior	+1
Probabilidad	
TEP probable	**≥3**
TEP improbable	**0-2**

Abreviaciones: TVP, trombosis venosa profunda; TEP: tromboembolia pulmonar, lpm: latidos por minuto. Adaptada de: Righini M, Robert.H, et al. Diagnosis of acute pulmonary embolism. Haemostaseologie. 2018 (16).

En la *Figura 4* y *Figura 5* se resume el algoritmo diagnóstico de la TVP y la TEP aguda sintomática respectivamente. En primer lugar, se deberá realizar la evaluación de la probabilidad clínica mediante una escala pretest. En caso de que se trate de una TVP o TEP probable, deberá realizarse directamente una prueba de imagen. En caso de TVP o TEP improbable, deberá realizarse la determinación del dímero-D: en caso de ser negativo se descarta la TVP o TEP, y en caso de ser positivo deberá realizarse una prueba de imagen para confirmar o descartar el diagnóstico.

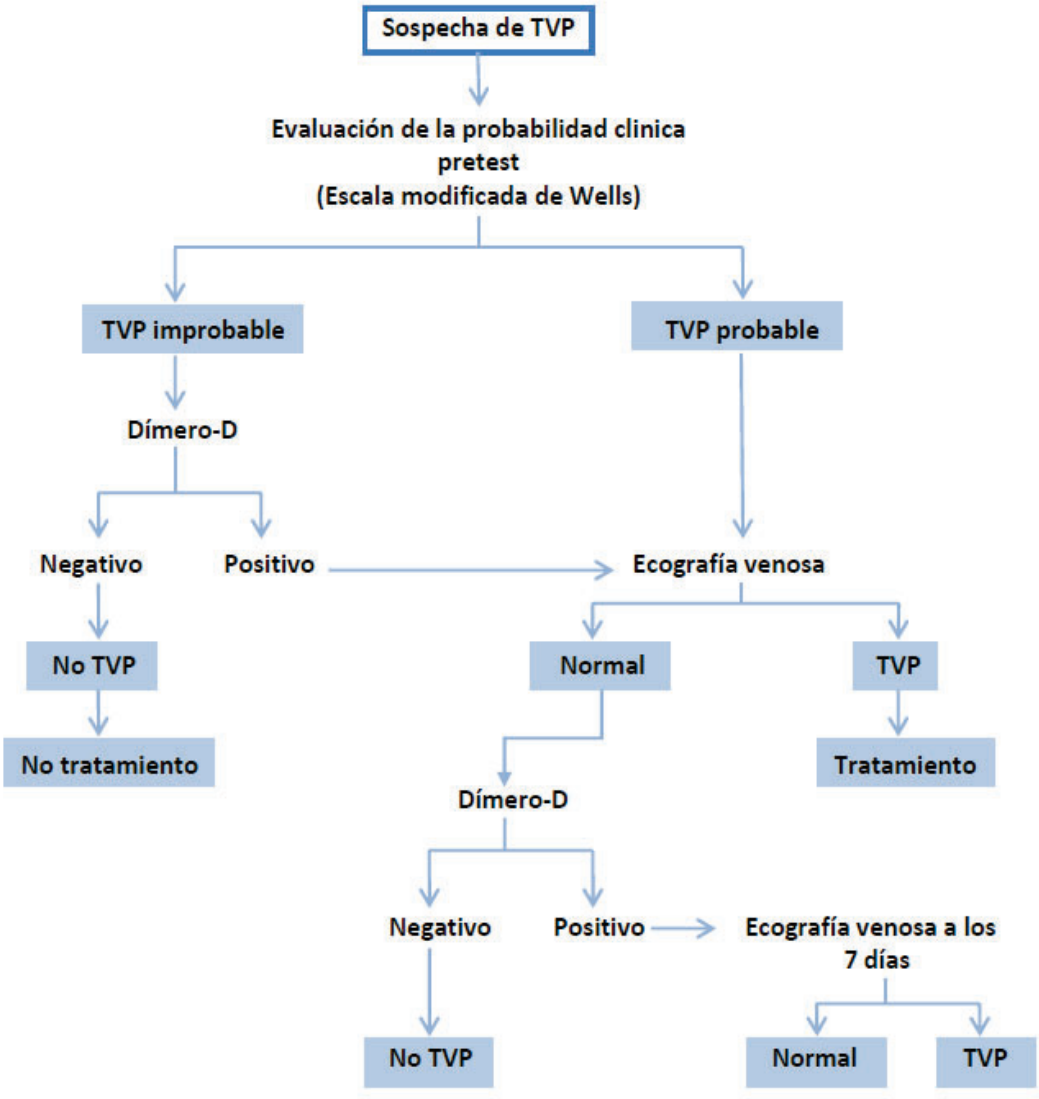

Figura 4: Algoritmo diagnóstico de la TVP aguda sintomática. Adaptado de: Mazzolai. L, Ageno. W, Alatri. A, et al. Second concensus document on diagnosis and management of acute deep vein thrombosis . Eur J Prev Cardiol. 2022 (17).

* Dímero-D anormal >500 ng/mL (ajustado por edad en > 50 años: Positivo si dímero-D > Edad en años x10).

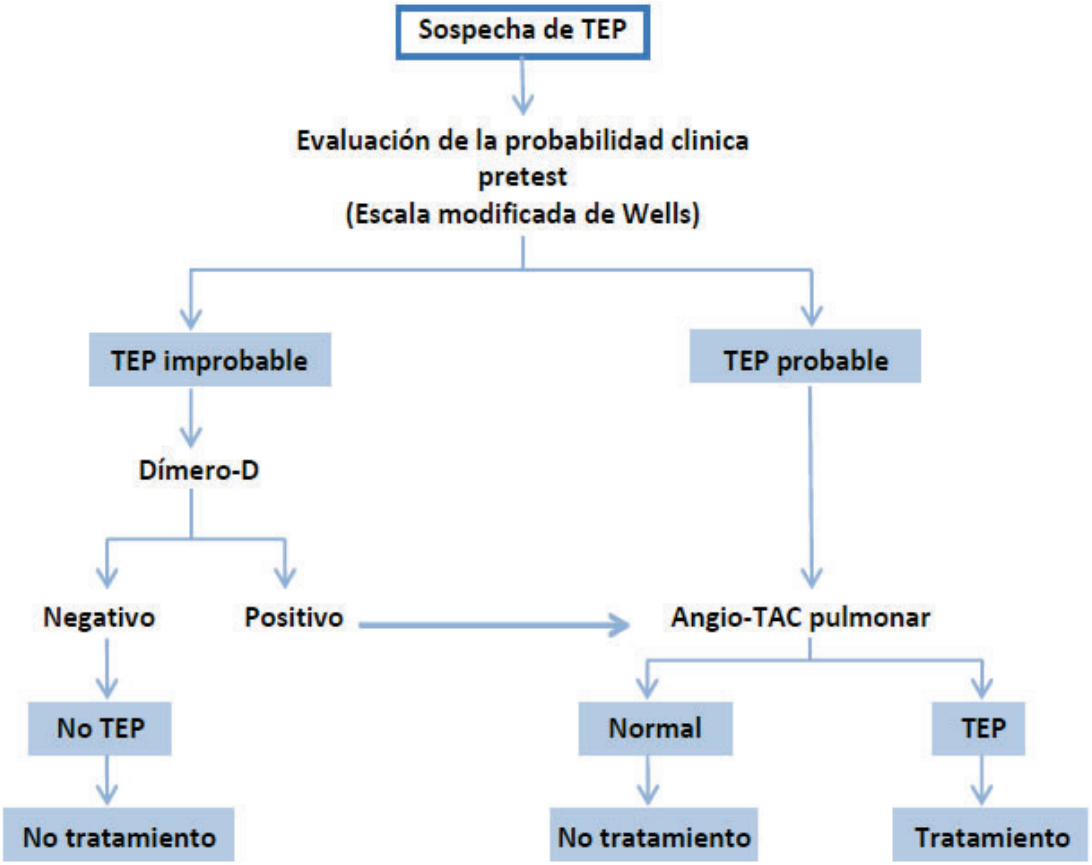

Figura 5: Algoritmo diagnóstico de la TEP aguda sintomática. Adaptado de: Di Nissio. M, Van Es. N, et al. Deep vein thrombosis and pulmonary embolism. Lancet. 2016 (14).

* Dímero-D anormal >500 ng/mL (ajustado por edad en > 50 años: Positivo si dímero-D > Edad en años x10).

1.7 Tratamiento anticoagulante en la Enfermedad Tromboembólica Venosa

El tratamiento anticoagulante es el tratamiento más importante en pacientes con ETV. Está indicado para los pacientes con TVP proximal o TEP de riesgo bajo, intermedio-bajo o intermedio-alto siempre y cuando no haya una contraindicación absoluta para ello (sangrado activo, coagulopatía y cirugía o traumatismo mayor reciente). En los pacientes con TVP distal aislada, se puede optar por un manejo sintomático con seguimiento clínico estrecho, siempre y cuando el paciente no presente factores de riesgo de progresión de la TVP (neoplasia activa, trombofilia o enfermedad inflamatoria activa, inmovilización...). En los pacientes con TEP de riesgo alto el tratamiento de elección es la fibrinolisis sistémica. La trombectomía mecánica se reserva para pacientes con TEP de riesgo intermedio-alto o alto que tengan una contraindicación para la fibrinolisis.

El tratamiento anticoagulante se compone de tres *fases (Figura 6)*: la fase aguda o inicial, la fase a largo plazo y la fase de tratamiento extendido o ampliado en aquellos casos en que se considere indicado. El objetivo del tratamiento en la fase aguda (0-21 días) es evitar la progresión del trombo y prevenir las complicaciones precoces (TEP, muerte,...) y tardías (ETV recurrente, síndrome post-trombótico e hipertensión pulmonar tromboembólica crónica…). El objetivo del tratamiento en la fase a largo plazo (hasta los 3-6 meses) es evitar o reducir las recurrencias secundarias a la reactivación del trombo inicial. Por último, el objetivo del tratamiento extendido, ampliado o indefinido en el tiempo es evitar las recurrencias una vez finalizado el tratamiento a largo plazo, es decir, realizar una prevención secundaria de la ETV.

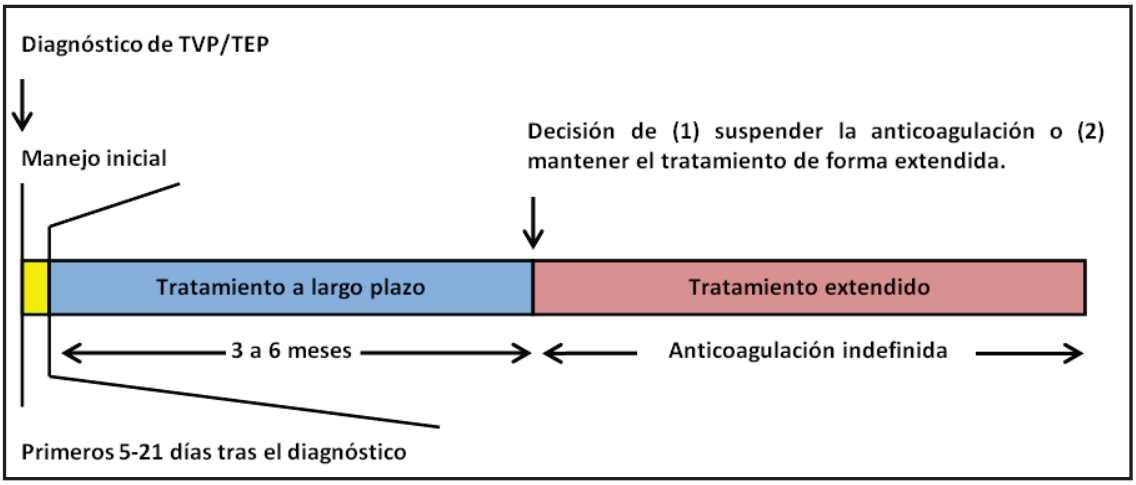

Figura 6: Fases del tratamiento anticoagulante. Adaptado de: Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. Blood Adv. 2020 (20).

Actualmente existen múltiples opciones terapéuticas. Si el paciente está hospitalizado, como tratamiento en fase inicial se suele utilizar heparina no fraccionada (HNF) o heparina de bajo peso molecular (HBPM) por presentar una semivida de eliminación menor que el resto de opciones terapéuticas, lo que facilitará el manejo en el caso de presentar complicaciones hemorrágicas o en el caso de precisar procedimientos diagnósticos o terapéuticos invasivos. Diversos estudios han demostrado que el manejo óptimo de la HNF es difícil de conseguir en la práctica clínica habitual (21,22) y que, además, ésta tiene un riesgo de hasta 8-10 veces mayor que las HBPM de presentar trombocitopenia inducida por heparina (23,24) por lo que su uso ha

quedado actualmente bastante restringido. Puede ser de elección en pacientes con alto riesgo hemorrágico (como pacientes de unidades de cuidados intensivos (UCI)) por su vida media corta y su posibilidad de reversibilidad completa con sulfato de Protamina, y en poblaciones especiales como pesos extremos o insuficiencia renal grave (aclaramiento de creatinina ≤ 30mL/min) (22). En el resto de pacientes, las HBPM serán el tratamiento inicial de elección. Respecto a qué tipo de HBPM es más recomendable, es importante remarcar que, aunque las diferentes HBPM se consideran entidades farmacológicas distintas (por su peso molecular, relación de efecto anti Xa/IIa...) los estudios clínicos no han demostrado una efectividad superior de una HBPM sobre la otra de forma significativa, por lo que el uso de una u otra HBPM dependerá de la disponibilidad del centro. El Fondaparinux también se puede emplear como agente parenteral para el tratamiento inicial de pacientes hospitalizados a los cuales posteriormente se les iniciará antagonistas de la vitamina K (AVK) o anticoagulantes orales de acción directa (ACODs). En el caso de pacientes ambulatorios, puede utilizarse como tratamiento inicial la HBPM o los ACODs (Apixabán o Rivaroxabán) a las dosis recomendadas para esta fase *(Figura 5).*

Para el tratamiento a largo plazo, disponemos de HBPM, AVK o ACODs. Los AVK son anticoagulantes eficaces pero tienen múltiples inconvenientes: en primer lugar, presentan variabilidad de acción anticoagulante tanto a nivel interindividual (por polimorfismos genéticos responsables del 50-60% de la variabilidad de las dosis necesarias) (25) como intraindividual, por su interacción con los alimentos y con múltiples fármacos (26); y, en segundo lugar, requieren de controles periódicos de INR. Además, si se plantea el uso de AVK, el tratamiento parenteral con HBPM, Fondaparinux o HNF debe mantenerse al menos durante 5 días previamente y hasta que se alcance un INR ≥2 (27).

Dentro de los ACODs, tenemos actualmente comercializados 4 fármacos: Apixabán Rivaroxabán y Edoxabán, que son inhibidores del Factor X, y Dabigatrán, que es un inhibidor del Factor II (Trombina). Estos fármacos han demostrado ser al menos tan eficaces como el tratamiento convencional con AVK (28–31) en pacientes con ETV y tienen la ventaja de que no requieren monitorización, su efecto no se modifica con la dieta y apenas tienen interacciones farmacológicas. Su vida media es mayor que la de

la HNF y las HBPM y pueden acumularse en pacientes con insuficiencia renal grave (ClCr <30mL/min) o insuficiencia hepática Child Pugh B o C. Dabigatrán dispone de antídoto comercializado (Idarucizumab) (32) y el resto de ACODs pueden revertirse mediante Andexanet Alfa (33). Comparaciones indirectas entre los diferentes ACODs han mostrado reducciones estadísticamente similares en el riesgo de muerte relacionada con ETV y en el riesgo de recurrencia (34). Respecto a los sangrados mayores, parece que Apixabán tienen un perfil mejor de seguridad respecto a los demás ACODs (34), sobre todo en cuanto a sangrados digestivos y urológicos. Si optamos por Dabigatrán o Edoxaban, se deben iniciar tras tratamiento con HNF, Fondaparinux o HBPM durante 5-10 días. En el caso de Rivaroxabán y Apixabán, tal y como se ha comentado, se pueden emplear para el tratamiento agudo desde el inicio sin tratamiento parenteral previo. Actualmente, en nuestro medio, para esta indicación está financiado por el sistema nacional de salud únicamente el Dabigatrán.

Por último, como tratamiento extendido podemos utilizar fármacos AVK o ACODs. Dento de los ACODs, Apixabán y Rivaroxabán se pueden utilizar con dosis reducidas (Apixabán 2,5mg/12 horas, Rivaroxabán 10mg/24h) a partir de los 6 primeros meses, dado que han demostrado una buena eficacia en cuanto a recurrencias trombóticas sin aumentar el riesgo de sangrado respecto a placebo y aspirina, respectivamente (35,36).

En la *Figura 7* se resumen las posibilidades de tratamiento anticoagulante para la ETV.

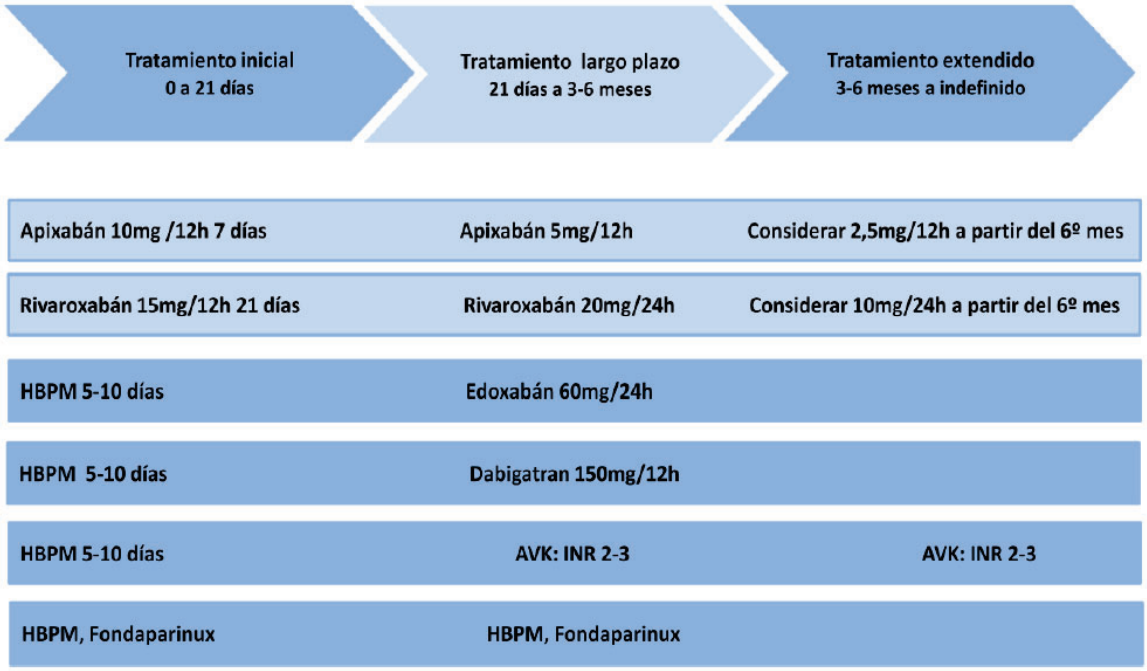

Figura 7. Opciones de tratamiento anticoagulante para pacientes con ETV. Abreviaciones: HBPM, heparina de bajo peso molecular; AVK: antagonistas de la vitamina K. Adaptado de: Streiff. M, Agnelli. G, et al. Guidance for the treatment of deep vein thrombosis and pulmonary embolism. J Thromb Thrombolysis. 2016 (37).

Un factor clave en la decisión de mantener o suspender el tratamiento anticoagulante más allá de los 3-6 meses es el riesgo de recurrencia trombótica y el riesgo de sangrado de cada paciente.

Tras la suspensión del tratamiento anticoagulante, el riesgo de recurrencia a lo largo de los años, tras un primer episodio, es de alrededor de un 25%, siendo mayor los primeros 6-12 meses con un descenso progresivo posterior. Este riesgo es más del doble en pacientes con ETV no provocada respecto a aquellos con ETV provocada por un factor de riesgo reversible. Dentro de estos, la tasa de recurrencia es mayor en pacientes médicos que en pacientes quirúrgicos (38). Cuando el factor de riesgo reversible es una intervención quirúrgica el riesgo de recurrencia tras la finalización del tratamiento anticoagulante es bajo (1% al año, 3% a los 5 años). En el caso de que el factor de riesgo de ETV no sea quirúrgico (inmovilización, tratamiento hormonal, embarazo, traumatismo menor sin cirugía…) el riesgo de recurrencias sigue siendo bajo, pero es mayor que en el paciente quirúrgico (5% al año y 15% a los 5 años) (39). En el caso de la ETV no provocada, la tasa de recurrencia es del 10% al año, del 25% a los 5 años y del 36% a los 10 años (40), lo que sugiere que, probablemente, estos

pacientes puedan beneficiarse de una terapia anticoagulante de mayor duración que los pacientes con ETV provocadas por un factor de riesgo transitorio. Por último, si el factor de riesgo es una neoplasia, la tasa de recurrencia puede ser superior al 20% el primer año (41). Por contra, el riesgo de sangrado mayor en los pacientes que mantienen la anticoagulación más allá de los 3-6 meses es del 1-3% anual, ascendiendo hasta el 5% en ancianos, y con una incidencia acumulada a los 5 años de 6,3% (40). Además, estos sangrados tienen una tasa de mortalidad del 15% (6), lo que supone unos ratios de mortalidad entre 2 y 3 veces más elevados en pacientes con sangrado mayor que en pacientes con recurrencia de ETV (40,42,43).

Con estos datos, las guías clínicas actuales recomiendan 3 meses de tratamiento anticoagulante en pacientes con ETV distal, entre 3-6 meses de tratamiento en pacientes con una ETV provocada por un factor de riesgo reversible y mantener el tratamiento anticoagulante mientras el cáncer esté activo en pacientes con ETV asociada a cáncer o en pacientes con una ETV provocada por un factor de riesgo persistente. En el caso de los pacientes con un primer episodio de ETV proximal no provocada, las guías clínicas recomiendan mantener al menos 3-6 meses de tratamiento anticoagulante y valorar mantener el tratamiento de forma indefinida en función del riesgo de recurrencia, el riesgo de sangrado y las preferencias del paciente (6,20,44); lo que supone un reto en la práctica clínica habitual. De forma general, se recomienda mantener el tratamiento anticoagulante de forma indefinida en pacientes con alto riesgo de recurrencia y riesgo bajo de sangrado, sin haberse establecido de forma clara en la literatura qué pacientes están incluidos en este grupo.

1.8 Valoración del riesgo de recurrencia trombótica

Además de la etiología de la trombosis, varios factores de riesgo se han asociado de forma independiente a un mayor riesgo de recurrencia en la literatura: la localización proximal de la ETV, el antecedente personal de ETV, el sexo masculino (en caso de ETV no provocada), niveles de dímero-D elevado tras finalizar el tratamiento anticoagulante (en caso de ETV no provocada), la presencia de anticuerpos antifosfolipídicos, la trombofilia hereditaria, la presencia de trombosis residual tras una TVP y los pacientes de raza blanca o negra vs los asiáticos, pero todos ellos con

odds ratios inferiores a 2 (45). Un factor controvertido es la edad avanzada: tal y como se ha descrito previamente, la edad avanzada se ha asociado en múltiples estudios con un mayor riesgo de ETV, pero su papel en la recurrencia no está claro dada la ausencia de evidencia.

Una asociación que sí que parece clara en la literatura es que la forma inicial de presentación de la ETV está relacionada con la forma de presentación de la recurrencia, de tal modo que los pacientes con TEP tienen más riesgo de recurrir en forma de TEP y los pacientes con TVP más riesgo de recurrir en forma de TVP. Esta asociación, además de una importancia clínica, conlleva una importancia pronóstica, dado que los pacientes con recurrencia en forma de TEP tienen una mortalidad mayor que los pacientes con recurrencia en forma de TVP aislada (6,44,45).

Hasta la fecha, se han desarrollado varios *scores,* que incluyen datos clínicos, para la valoración del riesgo de recurrencia tras un primer episodio de ETV (HERDOO2 score, Vienna score, DASH score and VTE-PREDICT score (46–50)) pero 2 de ellos no tienen validación externa (HERDOO2 y DASH score) y ninguno de ellos se utiliza de forma rutinaria en la práctica clínica por su baja aplicabilidad. El HERDOO2 score es el único que de forma explícita da información de en qué grupo de pacientes se tendría que suspender el tratamiento anticoagulante (mujeres de "bajo riesgo") pero tiene dos limitaciones: no ha sido capaz de estratificar el riesgo en hombres y, además, a las mujeres que han presentado una ETV bajo tratamiento estrogénico las considera como mujeres con un evento no provocado, cuando sabemos que el riesgo de recurrencia es menor (siempre que se suspenda el tratamiento hormonal) en mujeres con una ETV asociada a estrógenos que en mujeres con una ETV no provocada. El Vienna score propone valorar la suspensión del tratamiento anticoagulante en función del riesgo de recurrencia de cada paciente a los 12 y 60 meses; y el DASH score propone suspenderlo en pacientes con una puntuación ≤ 1 punto dado que son pacientes con un riesgo de recurrencia inferior al 5% anual en su cohorte. Por último, el VTE-PREDICT score tiene la peculiaridad de que por primera vez se incluyen ambos, el riesgo de recurrencia y el riesgo de sangrado de cada paciente a los 5 años, y valora eventos tanto provocados como no provocados. En la *Tabla 5* se resumen las características principales de cada uno de ellos.

Otro aspecto importante es que, pese a que, como se ha comentado, la gravedad de la recurrencia es mayor en pacientes con TEP que con TVP, ninguno de los scores propuestos hasta la fecha valora de forma independiente el riesgo de recurrencia en forma de TEP y TVP.

Tabla 5: Características de los scores de riesgo de recurrencia tras la suspensión del tratamiento anticoagulante.

	HERDOO2 score (2008)	Vienna score (2010)	DASH score (2012)	VTE-PREDICT score (2023)
Criterios de inclusión	Primer episodio de ETV no provocada No recurrencias trombóticas durante el tratamiento	Primer episodio de ETV no provocada	Primer episodio de ETV no provocada	Primer episodio de ETV
Criterios de exclusion	Deficiencia de AT, Proteina C o S Presencia de AL ETV distal	Deficiencia de AT, Proteina C o S Presencia de AL Homozigosis para el Factor V de Leiden o Mutación del gen de la Protrombina Trombofília combinada Cáncer activo	Deficiencia de AT Presencia de anticuerpos antifosfolipídicos ETV distal	Cáncer activo
Predictores de riesgo incluídos	Sexo femenino Dímero-D >250 µg/L Edad≥65 años Síndrome post-trombótico IMC ≥30kg/m2	Sexo Niveles de dímero-D (µg/L) Localización de la ETV	Sexo masculino (+1) Dímero-D alto (+2) Edad<50 años (+1) Tratamiento hormonal (-2)	Sexo femenino Edad IMC Tensión arterial sistólica TEP ETV provocada por cirugía, traumatismo, inmovilización ETV por terapia estrogénica Antecedente de cáncer Antecedente de ETV Antecedente de sangrado Ictus Valores de hemoglobina Uso de AINEs Tratamiento extendido
Categorización del riesgo	Bajo riesgo: Mujeres con ningun o 1 factor de riesgo.	Ratios de recurrencia a los 12 y 60 meses.	Bajo riesgo: DASH score≤1 punto.	Riesgo a los 5 años de recurrencia y sangrado.
Validación externa	No	Sí	No	Sí

Abreviaciones: AINEs, antinflamatoriso no esteroides; AL, anticoagulante lúpico; AT, antitrombina; ETV, enfermedad tromboembólica venosa; IMC, índice de masa corporal; TEP, tromboembolismo pulmonar. Producción propia.

1.9 Valoración del riesgo de sangrado en pacientes con ETV

Para la valoración del riesgo de sangrado bajo tratamiento anticoagulante, las guías del 2016 de la American College of Chest Physicians estratificaron a los pacientes en bajo riesgo de sangrado (0,8% de riesgo anual de sangrado mayor), moderado riesgo (1,6% de riesgo anual de sangrado mayor) y alto riesgo de sangrado (≥6,5% de riesgo anual de sangrado mayor) en función de los factores de riesgo expuestos en la *Tabla 6* (51).

Tabla 6: Factores de riesgo para sangrado bajo tratamiento anticoagulante.

Factor de Riesgo
Edad > 65 años
Edad > 75 años
Hemorragias previas
Cáncer
Cáncer metastásico
Insuficiencia renal
Insuficiencia hepática
Trombocitopenia
Ictus previo
Diabetes
Anemia
Antiagregantes plaquetarios
Mal control del tratamiento anticoagulante
Capacidad funcional reducida y comorbilidad
Cirugía reciente
Caídas frecuentes
Abuso de alcohol
AINEs
Riesgo hemorrágico
Riesgo hemorrágico bajo: Ningún factor de riesgo
Riesgo hemorrágico moderado: 1 factor de riesgo
Riesgo hemorrágico alto: 2 o más factores de riesgo

Abreviaciones: AINEs: antinflamatorios no esteroideos. Adaptado de: Kearon. C, Akl. E, et al. Antithrombotis therapy for VTE disease. CHEST. 2016 (51).

Sin embargo, hay que tener en cuenta que tanto estos factores enumerados en la *Tabla 6* como otros scores de sangrado propuestos (The RIETE (52), VTE-BLEED (53)) no han sido validados en la práctica clínica para pacientes con ETV no provocada en los que se mantiene la anticoagulación más allá de los 3-6 meses y se deben aplicar con precaución (54,55).

Otro aspecto relevante es que, una vez suspendido el tratamiento anticoagulante, el riesgo de sangrado mayor de los pacientes no es cero, sino que persiste, habiéndose descrito tasas en torno al 1% a los 5 años (56). Este hecho añade otra dimensión a la dicotomía de mantener o suspender el tratamiento anticoagulante, indicando que no hay que valorar únicamente el riesgo de sangrado derivado del tratamiento anticoagulante, sino el aumento de riesgo que otorga el mantener este tratamiento a cada paciente.

1.10 Papel del Filtro de vena Cava Inferior en pacientes con Enfermedad Tromboembólica

Como hemos visto, el tratamiento anticoagulante es un pilar fundamental del tratamiento de la ETV, pero está contraindicado en pacientes con un sangrado activo. En estas situaciones, deberemos valorar otras opciones de tratamiento que intenten minimizar el riesgo de complicaciones derivadas de la progresión de la ETV no tratada.

En este sentido, los filtros de vena cava inferior (FVC) se utilizan para reducir el riesgo de TEP en pacientes con TVP o TEP que tienen una contraindicación absoluta para la anticoagulación (57). A pesar de la falta de datos sobre su beneficio en términos de mortalidad, estos dispositivos se han convertido en una parte importante del tratamiento de la ETV (58–60). Actualmente, la mayoría de las guías de práctica clínica recomiendan la colocación de un FVC con indicación absoluta en pacientes con ETV aguda (de menos de 1 mes) y contraindicación para la anticoagulación (pacientes con sangrado gastrointestinal activo, ictus hemorrágico agudo, presencia de lesiones cerebrales, trastornos de la coagulación, etc.). Sin embargo, existe una disparidad de opiniones con respecto a las indicaciones relativas como el tratamiento de la TVP ilio-femoral, los pacientes con trombo flotante o reserva cardiopulmonar deficiente y las indicaciones profilácticas como los pacientes expuestos a cirugía bariátrica o cirugía

traumatológica (51,61–65). Esta falta de consenso es probablemente la responsable, en parte, de las indicaciones heterogéneas de la colocación de FVC a nivel de los centros hospitalarios y hace que, incluso, en ocasiones, se coloquen FVC sin una clara indicación; hecho relevante dado que estos dispositivos no están exentos de complicaciones.

Está descrito que sólo un tercio de los FVC que se colocan se retiran (66), y esto se ha asociado a altas tasas de complicaciones a largo plazo como migración del filtro (10-25%), perforación (22-93%), trombosis del filtro (3,5- 50%) y TVP (5-18%) en estos pacientes. La mayoría de estas complicaciones aparecen en pacientes cuyos filtros no se han retirado pasados 30 días después de la colocación, por lo que las recomendaciones actuales son de: i) colocación de filtros removibles o recuperables, ii) iniciar lo antes posible el tratamiento anticoagulante (siempre y cuando no haya contraindicación) y iii) intentar la retirada como máximo a los 30-60 días (64–70).

Un subgrupo de pacientes que merecen especial atención, y sobre los que hay muy escasa literatura, son los pacientes con cáncer. Estos pacientes tienen un riesgo de ETV entre cuatro y siete veces más alto que la población general (71), pero además tienen también un riesgo aumentado de sangrado derivado del propio tumor y del tratamiento quimioterápico, por lo que son pacientes en los que no es infrecuente que haya que recurrir a tratamientos “alternativos” a la anticoagulación tras un episodio de ETV por contraindicación a la misma.

Hasta la fecha, las características clínicas, del paciente y del filtro, asociadas con la no retirada y las complicaciones no se han descrito de forma adecuada.

1.11 Tromboprofilaxis en pacientes médicos hospitalizados

Como hemos visto, son múltiples los factores de riesgo para desarrollar ETV, siendo el ingreso hospitalario uno de los más importantes por ser el causante de un porcentaje elevado (en torno al 25%) de los eventos tromboembólicos (72). En este sentido, sabemos que la tromboprofilaxis en los pacientes hospitalizados disminuye el riesgo de ETV, lo que se traduce en una disminución del riesgo de muerte por dicha causa. De hecho, la realización de una correcta tromboprofilaxis evita 1 de cada 10 muertes

hospitalarias, siendo la ETV la principal causa prevenible de muerte en este medio (72). Por este motivo, es importante identificar qué pacientes presentan un alto riesgo de ETV durante el ingreso y, por tanto, se beneficiarían del uso de tromboprofilaxis.

Se han reportado diferentes factores de riesgo de ETV en pacientes hospitalizados. Los más importantes son las enfermedades médicas agudas, la cirugía, el cáncer, el tratamiento del cáncer, los traumatismos, la inmovilización, la presencia de catéteres venosos centrales, los antecedentes de ETV previa, la edad avanzada y la obesidad. En este sentido, y con el objetivo de estandarizar la indicación de tromboprofilaxis en el paciente médico hospitalizado, se han desarrollado diferentes escalas o scores que ayudarán en la toma de decisiones, siendo las más utilizadas la escala de Padua (73) (*Tabla 7*) y el Improve Risk score (74) (*Tabla 8*). En estudios comparativos, la escala de Padua fue la que mejor predijo los episodios de ETV a los 90 días entre los pacientes clasificados de alto riesgo. Es una escala validada para estratificar el riesgo de ETV en el paciente médico hospitalizado, pero no se ha validado en poblaciones especiales como pacientes de UCI. Los pacientes con una puntuación mayor o igual a 4 en la escala de Padua, o una puntuación mayor o igual a 2 en el Improve Risk score, tienen indicación de tromboprofilaxis farmacológica siempre y cuando no haya contraindicación a la misma. Por este motivo, antes de instaurar la tromboprofilaxis farmacológica, y al mismo tiempo que evaluamos el riesgo trombótico, se debe valorar el riesgo de sangrado del paciente. En este sentido la escala Improve-Bleeding (75) (*Tabla 9*) ayuda a identificar a los pacientes hospitalizados con enfermedades agudas y con mayor riesgo de sangrado.

Tabla 7: Escala de Padua.

Características clínicas	Score
Cáncer activo[1]	+3
Antecedente de ETEV (excluyendo trombosis superficial)	+3
Movilidad reducida[2]	+3
Estado protrombótico conocido[3]	+3
Traumatismo o cirugía reciente (en el último mes)	+2
Edad avanzada (>70 años)	+1
Insuficiencia cardiaca y/o respiratoria	+1
Infección aguda y/o enfermedad reumatológica	+1
Obesidad (IMC>30)	+1
Tratamiento hormonal	+1
Puntuación: **≥ 4 puntos: riesgo alto**	

[1] Pacientes con metástasis locales o a distancia y/o que se haga realizado quimioterapia o radioterapia los 6 meses previos.

[2] Reposo en cama con privilegio de ir al baño (ya sea por la limitación del paciente o por orden del médico) durante al menos 3 días.

[3] Déficit de antitrombina, proteína C o S, factor V de Leiden, mutación del gen de la protrombina G20210A y síndrome antifosfolípido.

Abreviaciones: IMC, Índice de Masa Corporal. Adaptado de: Barbar. S, Noventa. F, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. JTH. 2010 (73).

Tabla 8: Improve risk score.

Características clínicas	Score
ETV previa	+3
Trombofilia[1]	+2
Parálisis de miembros inferiores	+2
Cáncer activo	+2
Inmovilización ≥ 7 días[2]	+1
Ingreso en UCI/Unidad Coronaria	+1
Edad mayor de 60 años	+1
Puntuación:	
0-1: riesgo bajo (ETV sintomática <1%)	
2-3: riesgo mdoerado (ETV sintomática 1-1.5%)	
≥ 4: riesgo alto (ETV sintomática >4%)	

[1] Déficit de antritrombina, resistencia a la proteína C activada, déficits de proteína C y S, mutación gen de la protrombina G20210A, Factor V Leiden, síndrome antifosfolipídico.
[2] Incluye los días previos al ingreso hospitalario más los días de ingreso hospitalario.

Abreviaciones: UCI/UCC, Unidad de Cuidados Intensivos o Unidad Coronaria. Adaptado de: Spyropoulus. A, Anderson. F, et al. Predictive and Associative Models to Identify Hospitalized Medical Patients at risk for VTE. CHEST. 2011 (74).

Tabla 9: Escala Improve-Bleeding.

Características clínicas	Score
Úlcera gastrointestinal activa	+4,5
Hemorragia en los tres meses previos	+4
Recuento plaquetario < 50 x 10^9/L	+4
Edad ≥85 años	+3,5
Insuficiencia hepática (INR >1.5)	+2,5
Insuficiencia renal grave (ClCr <30mL/min)	+2,5
Ingreso en UCI	+2,5
Catéter venoso central	+2
Enfermedad reumática	+2
Cáncer activo	+2
Edad 40-84años	+1,5
Varón	+1
Insuficiencia renal moderada (ClCr 30-50 mL/min)	+1
Puntuación:	
≥ 7: Alto riesgo hemorrágico (riesgo de hemorragia >4%)	

Abreviaciones: INR, ratio internacional normalizado; ClCr, aclaramiento de creatinina; UCI, Unidad de Cuidados Intensivos. Adaptado de: Decousus. H, Tapson. V, et al. Factors at admission associated with bleeding risk in medical patients: Findings from the IMPROVE investigators. CHEST. 2011 (75).

En los pacientes en los que decidamos realizar tromboprofilaxis farmacológica, existen varias opciones terapéuticas que se resumen en la *Tabla 10*. La HBPM es la más utilizada, pero en pacientes con antecedente de trombocitopenia inducida por heparina o alergia a las mismas se puede realizar con Fondaparinux (76,77). A su vez, en aquellos pacientes que rechacen la terapia parenteral, se puede realizar también con Rivaroxabán a las dosis descritas en la *Tabla 10* (78).

Aunque se ha descrito que el riesgo aumentado de ETV se mantiene hasta 30-45 días tras el alta hospitalaria, las principales guías de práctica clínica no recomiendan, con la evidencia generada hasta el momento, el uso de tromboprofilaxis extendida en los pacientes médicos, por lo que el tratamiento se realizará durante el ingreso hospitalario (76,77).

En los pacientes en los que la tromboprofilaxis farmacológica esté contraindicada por tener un riesgo alto de sangrado, se realizará tromboprofilaxis mecánica utilizando preferentemente medias compresivas o dispositivos de compresión neumática intermitente, en función de la disponibilidad. En el momento en que la contraindicación a la tromboprofilaxis farmacológica desaparezca, se deberá iniciar nuevamente (76,77).

Tabla 10: Estrategias de tromboprofilaxis farmacológica en pacientes médicos hospitalizados.

Fármacos	Dosis ClCr>30 ml/min	Dosis ClCr<30 ml/min
Heparina de Bajo Peso Molecular		
Bemiparina	3500 UI/día SC	2500 UI/día SC
Enoxaparina	40 mg/día SC	20 mg/día SC
Tinzaparina	3500 UI/día SC	Si ClCr 20-30 ml/min no ajustar. Si ClCr<20 ml/min monitorizar con niveles de anti-Xa
Pentasacáridos		
Fondaparinux	2,5 mg/día SC	Evitar
Anticoagulantes de acción directa		
Rivaroxaban	10 mg/día VO	Precaución si ClCr 15-30 ml/min

Abreviaciones: ClCr, Clearence de creatinina; sc, subcutánea; vo, vía oral. Producción propia.

1.12 Infección por SARS-CoV2 y su asociación con la Enfermedad Tromboembólica Venosa

Desde 2019, en contexto de la pandemia por SARS-CoV-2 (del inglés *Severe Acute Respiratory Syndrome Coronavirus 2)*, no solo se ha descrito un aumento del riesgo de ETV asociada a la infección sino que, a su vez, los pacientes con SARS-CoV-2 que presentaban una ETV asociada presentaban una mayor mortalidad (79). Las tasas de trombosis en pacientes con esta infección varían entre los diferentes estudios dada la variabilidad en los protocolos de diagnóstico y de screening de ETV en cada hospital, en función de si se trata de pacientes ambulatorios, ingresados en sala convencional o pacientes ingresados en unidades de cuidados intensivos (UCI); y en función del uso o no de tromboprofilaxis (así como de las dosis empleadas). En el metaanálisis publicado

por Nopp et al en 2020, que incluyó un total de 28.173 pacientes, la prevalencia estimada de ETV fue de 14,1% (95% intervalo de confianza (IC) 11,6-16,9); con un 40,3% (95% IC 27-54,3) si se realizaba screening de TVP mediante ecografía y un 9,5% (95% IC 7,5-11,7) si no se realizaba el screening. El análisis de subgrupos mostró una gran heterogeneidad, con una prevalencia de ETV de 7,9% (95% IC 5,1-11,2) en pacientes hospitalizados sin requerimientos de UCI y 22,7% (95% IC 18,1-27,6) en pacientes de UCI (80). Pese a estas diferencias, lo que sí que parece claro es que la infección por SARS-CoV-2 se asocia a coagulopatía, favoreciendo el desarrollo de ETV por varios mecanismos. En primer lugar, el SARS-CoV-2 interactúa con el receptor de la enzima convertidora de angiotensina en las células endoteliales, lo que da como resultado una mayor liberación del vasoconstrictor angiotensina-II y una disfunción endotelial (81). Además, la respuesta inflamatoria desempeña un papel fundamental a través de la activación del complemento, elevando los niveles de citoquinas proinflamatorias, como la interleucina-6 y la interleucina-17A, que activan las plaquetas, el FT y la coagulación (82,83). Por último, estudios recientes han demostrado alteraciones tanto de la coagulación como de la fibrinólisis por múltiples vías, como la reducción de antitrombina y proteína C y el aumento del PAI-1 (83,84).

Con esta premisa de un aumento de eventos trombóticos asociados a la infección por SARS-CoV-2, y la publicación de estudios observacionales que sugerían una disminución de la mortalidad asociada con la administración de tratamiento anticoagulante a los pacientes con infección grave (85–87), algunas Sociedades Médicas dedicadas a la ETV empezaron a recomendar el uso de dosis intermedias (o incluso dosis plenas) de anticoagulación como tromboprofilaxis en pacientes seleccionados con un mayor riesgo de trombosis (pacientes de UCI, pacientes con peso > 80kg o pacientes con niveles elevados de dímero-D, entre otros) (88–90), aún sin tener evidencia clínica del posible beneficio de esta indicación en ensayos clínicos aleatorizados.

En este contexto, se publicaron posteriormente estudios que describían un aumento en la prevalencia de sangrados en estos pacientes, con especial énfasis en los pacientes de UCI (91–93).

Estos datos pusieron aún más en duda la indicación del uso de dosis mayores de las habituales de tromboprofilaxis e instigaba a la necesidad de realizar estudios aleatorizados prospectivos que evaluaran el riesgo/beneficio del tratamiento anticoagulante en estos pacientes.

2. HIPÓTESIS

1. Establecer las ratios de recurrencia, sangrado mayor, y las tasas de mortalidad tras un primer episodio de trombosis no provocada, puede ayudar en la decisión de mantener o suspender la anticoagulación tras 3-6 meses de tratamiento anticoagulante en estos pacientes.
2. La correcta identificación de los factores de riesgo de recurrencia y de sangrado mayor tras un primer episodio de trombosis no provocada puede ayudar al desarrollo de un score clínico que identifique y clasifique a los pacientes en función de su riesgo, tanto de recurrencia como de sangrado, y ayude en la decisión de mantener o suspender el tratamiento anticoagulante más allá de los 3-6 meses.
3. La mortalidad tras una recurrencia en forma de tromboembolismo pulmonar es mayor que tras una recurrencia en forma de trombosis venosa profunda, por lo que identificar los factores de riesgo independientes, de estos dos eventos, es relevante y puede ayudar en la decisión de mantener o suspender el tratamiento anticoagulante más allá de los 3-6 meses.
4. Los pacientes con edad avanzada, que presentan un riesgo más alto de sangrado mayor, podrían beneficiarse de la suspensión del tratamiento anticoagulante tras 3-6 meses si su riesgo de recurrencia no fuera mayor que el de los pacientes más jóvenes.
5. La colocación de filtros de vena cava sin una clara indicación y la no retirada de los mismos, está asociado a un aumento de complicaciones en estos pacientes entre las que se incluye, entre otros, la recurrencia trombótica.
6. En los pacientes oncológicos, las tasas de no retirada y de complicaciones de los filtros de vena cava podrían ser mayores que en los pacientes no oncológicos.
7. La utilización de dosis intermedias o dosis plenas de anticoagulación como tromboprofilaxis en pacientes no críticos, ingresados con infección activa por SARS-CoV-2, puede estar asociado con un aumento del riesgo de sangrado en estos pacientes sin un mayor beneficio en términos de prevención de eventos trombóticos y/o necesidad de ingreso en una unidad de cuidados intensivos y/o mortalidad.

3. OBJETIVOS

1. Evaluar las tasas de recurrencia y sangrado mayor, así como la tasa de letalidad (*Case Fatality Rate, CFR*) a los 10 días de estos eventos, tras la suspensión del tratamiento anticoagulante, en pacientes con un primer episodio de trombosis no provocada.
2. Identificar factores de riesgo predictores de recurrencias y sangrado mayor tras la suspensión del tratamiento anticoagulante en pacientes con un primer episodio de trombosis no provocada.
3. Evaluar de forma independiente los factores de riesgo de recurrencia en forma de trombosis venosa profunda y tromboembolismo pulmonar en pacientes con un primer episodio de trombosis no provocada.
4. Evaluar las tasas de recurrencia y sangrado mayor tras la suspensión del tratamiento anticoagulante en pacientes mayores de 75 años con un primer episodio de trombosis.
5. Caracterizar los motivos de colocación de los filtros de vena cava y las complicaciones derivadas de la no retirada de los mismos en un hospital terciario.
6. Comparar las tasas de retirada y complicaciones de los filtros de vena cava entre pacientes oncológicos y no oncológicos.
7. Evaluar la eficacia y seguridad de la tromboprofilaxis farmacológica a diferentes dosis en pacientes hospitalizados (no críticos) con infección por SARS-CoV-2.

4. MATERIAL, MÉTODOS Y RESULTADOS

Artículo 1

Para el **primer, segundo** y **tercer objetivo** se llevó a cabo un estudio con datos del registro RIETE (*Registro Informatizado de Pacientes con Enfermedad TromboEmbólica)*, donde evaluamos las tasas de recurrencia y de sangrado mayor, al suspender el tratamiento anticoagulante, en 8.261 pacientes tras un primer episodio de ETV no provocada. Tras una media de seguimiento de casi 1 año tras la suspensión del tratamiento anticoagulante, las tasas de recurrencia (9,8 eventos/pacientes/año) fueron mucho mayores que las tasas de sangrado mayor (0,6 eventos/pacientes/año), pero la tasa de mortalidad a los 10 días de estos eventos, fue mucho más elevada en los pacientes con un sangrado mayor (24%) que en los pacientes con recurrencias en forma de TEP (4,6%) y TVP (0,4%). A su vez, se analizaron los factores de riesgo de recurrencia de TEP, TVP y sangrado en estos pacientes y vimos que estos factores difieren. Los pacientes con TEP inicial y demencia son más propensos a recurrir en forma de TEP y aquellos con TVP inicial, depresión y uso concomitante de corticoesteroides son más propensos a recurrir en forma de TVP. Por contra, la edad avanzada, la enfermedad inflamatoria intestinal y la anemia se asociaron con un mayor riesgo de sangrado mayor. Con estos factores pronósticos obtenidos, desarrollamos un score clínico de riesgo de recurrencias en forma de TEP y otro para la predicción de sangrado mayor y estratificamos a los pacientes en alto o bajo riesgo de cada uno de estos eventos.

Artículo 1: Cristina Gabara, Jesus Aibar, Yuji Nishimoto, Yugo Yamashita, Paolo Prandoni, Geoffrey D Barnes, Behnood Bikdeli, David Jiménez, Pablo Demelo-Rodríguez, Mª Luisa Peris1, Son Truong Nguyen, Manuel Monreal and the RIETE Investigators. *Clinical outcomes after discontinuing anticoagulant therapy in patients with first unprovoked venous thromboembolism*. Journal of Thrombosis and Haemosthasis. 2024; 22 (8):2234-2246. doi: 10.1016/j.jtha.2024.05.007. Epub 2024 May 16. PMID: 38762019.

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ORIGINAL ARTICLE

Clinical outcomes after discontinuing anticoagulant therapy in patients with first unprovoked venous thromboembolism

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Abstract

Background: The duration of anticoagulation for a first episode of unprovoked venous thromboembolism (VTE) should balance the likelihood of VTE recurrence against the risk of major bleeding.

Objectives: Analyze rates and case-fatality rates (CFRs) of recurrent VTE and major bleeding after discontinuing anticoagulation in patients with a first unprovoked VTE after at least 3 months of anticoagulation.

Methods: We compared the rates and CFRs in patients of the Registro Informatizado Enfermedad Trombo Embólica (RIETE) and Contemporary management and outcomes

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in patients with venous thromboembolism registries. We used logistic regression models to identify predictors for recurrent pulmonary embolism (PE) and major bleeding.

Results: Of 8261 patients with unprovoked VTE in RIETE registry, 4012 (48.6%) had isolated deep vein thrombosis (DVT) and 4250 had PE. Follow-up (median, 318 days) showed 543 recurrent DVTs, 540 recurrent PEs, 71 major bleeding episodes, and 447 deaths. The Contemporary management and outcomes in patients with venous thromboembolism registry yielded similar results. Corresponding CFRs of recurrent DVT, PE, and major bleeding were 0.4%, 4.6%, and 24%, respectively. On multivariable analyses, initial PE presentation (hazard ratio [HR], 3.03; 95% CI, 2.49-3.69), dementia (HR, 1.47; 95% CI, 1.01-2.13), and anemia (HR, 0.72; 95% CI, 0.57-0.91) predicted recurrent PE, whereas older age (HR, 2.11; 95% CI, 1.15-3.87), inflammatory bowel disease (HR, 4.39; 95% CI, 1.00-19.3), and anemia (HR, 2.24; 95% CI, 1.35-3.73) predicted major bleeding. Prognostic scores were formulated, with C statistics of 0.63 for recurrent PE and 0.69 for major bleeding.

Conclusion: Recurrent DVT and PE were frequent but had low CFRs (0.4% and 4.6%, respectively) after discontinuing anticoagulation. On the contrary, major bleeding was rare but had high CFR (24%). A few clinical factors may predict these outcomes.

KEYWORDS
bleeding, mortality, recurrence, unprovoked, venous thromboembolism

1 | INTRODUCTION

The optimal management of venous thromboembolism (VTE) following a first unprovoked episode is a multifaceted challenge that extends beyond the initial treatment phase [1–14]. Clinicians face the difficulty of predicting and preventing recurrent events, which tend to follow the presentation of the initial episode. Patients with an initial deep vein thrombosis (DVT) are more likely to experience subsequent DVT, while those who suffer a pulmonary embolism (PE) are at a higher risk for another PE [6]. This pattern of recurrence is not merely a matter of frequency but also of severity, as the case-fatality rates (CFRs) of recurrent DVT and PE are notably different, with PE carrying a more substantial risk of mortality [15].

The intricacy of postanticoagulation care is further heightened by the nonnegligible risk of major bleeding, which remains substantial even after anticoagulants are withdrawn [16]. This persistent threat of bleeding adds a critical dimension to the risk–benefit analysis that must be carefully weighed against the possibility of recurrent VTE. The decision to discontinue anticoagulation is thus a delicate balance, necessitating an approach informed by robust evidence and patient-specific factors.

Acknowledging these complexities, we utilized data from the international Registro Informatizado Enfermedad Trombo Embólica (RIETE) registry to systematically assess the rates of recurrence for both DVT and PE patients, their respective CFRs, and the rates and CFR of major bleeding following the cessation of anticoagulant therapy. Cross-validation with the Contemporary management and outcomes in patients with venous thromboembolism (COMMAND-VTE) registry was done to reinforce the robustness of our findings. Additionally, we aimed to identify independent predictors for these critical outcomes (distinguishing between the types of VTE recurrence), offering a nuanced approach to postanticoagulation risk assessment and informing the complex decision-making process to both patients and clinicians. This effort aims to provide clinicians with a clearer framework for navigating the challenging landscape of long-term VTE treatment and ultimately enhance patient-centered care strategies.

2 | METHODS

The RIETE registry represents a comprehensive and ongoing database, capturing the experiences of consecutive patients with objectively confirmed VTE. Spanning 207 enrolling centers across 28 countries from Europe, North and South America, Asia, and Africa, RIETE currently includes over 120 000 patients with VTE. The methodology of RIETE is detailed extensively in prior publications [17]. The COMMAND-VTE registry is a physician-initiated, multicenter cohort study in which consecutive patients with acute symptomatic VTE among 29 centers in Japan were included between January 2010 and August 2014 [18]. They enrolled consecutive patients who met the definition of acute symptomatic VTE diagnosed within 31 days from symptom onset during the study period.

2.1 | Eligibility criteria

We enrolled consecutive patients presenting with acute, symptomatic PE or isolated lower-limb DVT, confirmed through objective testing methods such as helical computed tomography (CT) scan, ventilation-perfusion lung scintigraphy, or angiography for PE, and compression ultrasonography or contrast venography for DVT, into the RIETE registry. In March 2009, a comprehensive list of comorbidities was integrated into the RIETE registry; thus, our analysis included only patients enrolled after this enhancement. Patients were excluded if they were engaged in blinded therapeutic clinical trials. Informed consent was obtained from all patients or their proxies, according to local ethical standards. For patients with cognitive impairments, such as those with dementia, proxies provided consent on behalf of the patients, ensuring adherence to ethical guidelines.

The current study considered patients with a first episode of unprovoked VTE who had undergone at least 3 months of anticoagulant therapy and subsequently discontinued anticoagulation. Exclusions were prior VTE, any VTE-related events (recurrent VTE or major bleeding) or death appearing during anticoagulation, the use of an inferior vena cava filter, or lack of follow-up posttherapy discontinuation before/by the time of discontinuation. Unprovoked VTE was defined in the absence of cancer, recent immobilization or surgery, pregnancy, postpartum period, hormone therapy, or prolonged travel.

2.2 | Study outcomes

The main study outcomes were the incidence and severity of recurrent VTE and that of major bleeding. We also separately explored recurrent DVT and recurrent PE. Each episode of clinically suspected recurrent VTE was investigated by repeat compression ultrasonography, lung scan, helical CT scan, or pulmonary angiography, as appropriate. Recurrent PE was defined as a new ventilation-perfusion mismatch on a lung scan or a new intraluminal filling defect on spiral CT of the chest in patients with respiratory symptoms, suggesting a new PE. Recurrent DVT was defined as a new noncompressible vein segment or an increase in the vein diameter of at least 4 mm from the last available measurement on venous ultrasound. Major bleeding events were defined as overt bleeding requiring the transfusion of 2 or more units of blood, occurring at a critical site, or contributing to death, which are closely similar to the definition by the International Society of Thrombosis and Haemostasis criteria [19]. All outcomes were classified as reported by the clinical centers. Among patients with recurrent VTE or with major bleeding, we also ascertained the CFR of PE, DVT, and major bleeding following discontinuation of anticoagulant therapy. CFR was defined as the proportion of all events (nonfatal and fatal) that were fatal within the first 10 days, as in previous studies on the same topic [1]. Considering the incidence and CFR of the events, we also provided the total number of deaths due to PE and major bleeding in this population.

2.3 | Baseline variables

At the initial VTE episode, we collected data on demographics, initial VTE presentation, vital signs, imaging tests, concurrent conditions, medications, laboratory results, and treatment specifics. Dementia was defined as the loss of memory, language, problem-solving, and other thinking abilities that were severe enough to interfere with patients' daily lives. Anemia was defined as a hemoglobin level of less than 13 g/dL in men and less than 12 g/dL in women. Follow-up data included outcomes observed after cessation of anticoagulant therapy.

2.4 | Treatment and follow-up

Patient management reflected the practices of each participating center. The specifics of anticoagulant therapy, including drug choice, dosing, and duration, were at the discretion of the treating clinicians. Follow-up consisted of outpatient or telephonic consultations, with assessments for signs or symptoms of recurrent VTE or major bleeding.

2.5 | Statistical analysis

We present categorical variables as percentages and continuous variables as means and SDs or medians with IQR for nonnormally distributed data. Considering the large sample size, we anticipated that many pairwise hypothesis tests (P values) would be highly statistically significant. To identify comparisons of clinical relevance, rather than those that will show statistical significance of unclear clinical relevance, we reported standardized differences (STDs). STD > 0.1 in absolute value was considered relevant. In the case of continuous variables, the STD was estimated as mean differences divided by a common SD (square root of the sum of variances of each group divided by 2).

Incidence rates were calculated per 100 person-years with corresponding CIs. Time-to-event regression models, considering competing risks, facilitated the exploration of associations between baseline variables and the risks for recurrent PE, recurrent DVT, or major bleeding. The COMMAND-VTE registry served as external validation of our findings.

The risk of developing recurrent PE and major bleeding after discontinuing anticoagulation was assessed using logistic regression models. Covariates entering the models were selected by a significance level of P on univariable analyses. We built 2 prognostic scores (1 for recurrent PE and 1 for major bleeding), assigning points to each independent variable according to regression coefficients β. Then, we tried to identify patients at high risk for every outcome. We did not build a prognostic score for recurrent DVT since its CFR was found to be near zero. Discrimination was quantified by calculating sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratio, and area under the receiver operating characteristic curve. SPSS software (version 22, SPSS Inc) was used for the statistical management of the data.

TABLE 1 Baseline clinical characteristics, treatment, and outcomes during anticoagulation in 32 510 patients with unprovoked venous thromboembolism. Comparison between included vs excluded patients in the study.

	Patients without exclusion criteria		Patients with exclusion criteria, *n* (%)
	Discontinued anticoagulation, *n* (%)	Continued with anticoagulation, *n* (%)	
Patients, *N*	8261	15 930	8319
Male sex	4564 (55)	8908 (56)	4489 (54)
Age, y (mean ± SD)	66 ± 16	67 ± 16	68 ± 16[a]
Body weight, kg (mean ± SD)	78 ± 16	80 ± 17[a]	79 ± 17
Comorbidities			
Hypertension	4055 (49)	8089 (51)	4338 (52)
Chronic lung disease	967 (12)	1696 (11)	1054 (13)
Chronic heart failure	384 (4.6)	936 (5.9)	633 (7.6)[a]
Prior VTE	0	0	6126 (74)[c]
Initial VTE presentation			
Isolated, distal lower-limb DVT	664 (8.0)	745 (4.7)[a]	468 (5.6)
Isolated, proximal lower-limb DVT	3347 (41)	4886 (31)[b]	2921 (35)[a]
Isolated PE	3254 (39)	7733 (49)[a]	3554 (43)
Concomitant DVT and PE	996 (12)	2566 (16)[a]	1376 (17)[a]
Laboratory tests			
Anemia	1819 (22)	3323 (21)	2103 (25)
Platelet count < 100 000/μL	145 (1.8)	276 (1.7)	227 (2.7)
CrCl levels < 60 mL/min	2438 (30)	4807 (30)	2860 (34)[a]
Concomitant drugs			
Corticosteroids	537 (6.5)	1031 (6.5)	675 (8.1)
Antiplatelets	1187 (14)	2556 (16)	1720 (21)[a]
Statins	2043 (25)	3894 (24)	2080 (25)
Initial therapy			
Low-molecular-weight heparin	7454 (90)	13 067 (82)[b]	6718 (81)[b]
Unfractionated heparin	191 (2.3)	809 (5.1)[a]	450 (5.4)[a]
Direct oral anticoagulants	371 (4.5)	1147 (7.2)[a]	562 (6.8)
Inferior vena cava filter	0	0	513 (6.2)[b]
Long-term therapy			
Vitamin K antagonists	4940 (60)	8623 (54)[a]	4286 (52)[a]
Direct oral anticoagulants	1404 (17)	4723 (30)[b]	1894 (24)[a]
Low-molecular-weight heparin	1811 (22)	2396 (15)[a]	1611 (19)
Duration of anticoagulation			
Days, median (IQR)	199 (120-341)	211 (117-430)[b]	211 (102-505)[b]
Outcomes during anticoagulation			
VTE recurrences	0	0	660 (7.9)[b]
Major bleeding	0	0	643 (7.7)[b]
Death	0	0	1259 (15)

CrCl, creatinine clearance; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Comparisons between included and excluded patients in the study: [a]standardized differences (STD), 0.1-0.2; [b]STD, 0.21-0.5; [c]STD, >0.5.

3 | RESULTS

3.1 | Study overview and exclusion criteria

Between March 2009 and August 2023, 32 510 patients with unprovoked VTE were enrolled in the RIETE registry. Of these, 8319 (25.6%) were excluded due to previous VTE (6126 patients), inferior vena cava filter placement (513), complications during anticoagulation (recurrent VTE 660, major bleeding 643), or death (1259). An additional 15 930 patients (49%) were continuing anticoagulant therapy. The analysis thus focused on the 8261 patients (25.4%) who ceased anticoagulant therapy and had a minimum of 30 days follow-up. The clinical characteristics at the time of the index VTE event were mostly similar across included and excluded patients, with a notable exception that a higher proportion of the included patients initially presented with isolated DVT as opposed to PE (Table 1).

In the COMMAND-VTE registry, from January 2010 to August 2014, out of 1340 patients with unprovoked VTE, 469 (35%) were excluded from the study. Moreover, 552 (41.2%) did not discontinue anticoagulant therapy or lacked post discontinuation follow-up. The study ultimately included 319 patients (23.8%). The proportions of patients with follow-up data postanticoagulation discontinuation and those meeting exclusion criteria were notably similar in both registries (Supplementary Figure).

3.2 | Baseline characteristics of the study population

In the RIETE registry, the mean age of the patients was 66 years, with 55% being male. The patients exhibited various comorbidities, the most prevalent being hypertension (49%). At their initial VTE event, 4011 patients (49%) presented with isolated lower-limb DVT (proximal 3347, distal 664), and 4250 (51%) had PE (isolated PE 39%, concomitant DVT and PE 12%). Those initially presenting with isolated DVT were less likely to have chronic heart failure, prior artery disease, or chronic lung disease compared with those with PE, but no significant differences were observed in other variables (Table 2). Similar patterns of baseline characteristics were observed in COMMAND-VTE registry patients who discontinued anticoagulation compared with those who continued with anticoagulation, with a higher incidence of isolated distal DVT in those who discontinued (Supplementary Table).

3.3 | Outcomes after discontinuing anticoagulation

After anticoagulation was stopped (median follow-up, 318 days), 1083 patients experienced a recurrent VTE event (DVT 543, PE 540), 71 had major bleeding (intracranial 27, gastrointestinal 21, other sites 23), and 447 patients died (Table 3). Respective rates were 9.82 VTE

TABLE 2 Clinical characteristics of the patients included in the study, according to initial venous thromboembolism presentation.

	Isolated lower-limb DVT, *n* (%)	PE with or without DVT, *n* (%)	STD
Patients, *N*	4011	4250	
Male sex	2315 (58)	2249 (53)	0.097
Age, years (mean ± SD)	65 ± 16	67 ± 16	0.093
Body weight, kg (mean ± SD)	78 ± 16	78 ± 16	0.048
Comorbidities			
Current smoking	627 (16)	575 (14)	0.060
Hypertension	1876 (47)	2179 (51)	0.090
Diabetes	578 (14)	653 (15)	0.027
Chronic heart failure	106 (2.6)	278 (6.5)	0.187
Recent major bleeding	26 (0.65)	42 (0.99)	0.038
Prior artery disease	404 (10)	578 (14)	0.109
Leg varicosities	783 (20)	682 (16)	0.091
Chronic lung disease	384 (9.6)	583 (14)	0.129
Gastroduodenal ulcer	38 (0.95)	43 (1.0)	0.007
Hiatal hernia	116 (2.9)	182 (4.3)	0.075
Inflammatory bowel disease	34 (0.85)	34 (0.80)	0.005
Chronic liver disease	71 (1.8)	55 (1.3)	0.039
Chronic alcoholism	48 (1.2)	69 (1.6)	0.036
Dementia	176 (4.4)	162 (3.8)	0.029
Depression	236 (5.9)	323 (7.6)	0.068
Schizophrenia	57 (1.4)	82 (1.9)	0.040
Parkinson disease	46 (1.1)	63 (1.5)	0.029
Epilepsy	49 (1.2)	49 (1.2)	0.006
Laboratory tests			
Anemia	876 (22)	943 (22)	0.008
Platelet count < 100 000/μL	81 (2.0)	64 (1.5)	0.039
CrCl levels < 60 mL/min	1122 (28)	1316 (31)	0.066
Concomitant drugs			
Statins	981 (24)	1062 (25)	0.012
Antiplatelets	515 (13)	672 (16)	0.085
Corticosteroids	248 (6.2)	289 (6.8)	0.025

CrCl, creatinine clearance; DVT, deep vein thrombosis; PE, pulmonary embolism; STD, standardized difference.

TABLE 3 Clinical outcomes during follow-up, according to initial venous thromboembolism presentation.

		Isolated lower-limb DVT		PE with or without DVT		
	N	*N*	Events per 100 patient-years (95% CI)	*N*	Events per 100 patient-years (95% CI)	Rate ratio (95% CI)
RIETE registry						
Patients, *N*	**8261**	**4011**		**4250**		
Days, median (IQR)		316 (123-747)		319 (129-671)		
Outcomes						
Recurrent PE	540	131	2.20 (1.85-2.61)	409	7.06 (6.40-7.77)	0.31 (0.26-0.38)
Recurrent DVT	543	429	7.76 (7.05-8.52)	114	1.89 (1.56-2.26)	4.12 (3.36-5.08)
Major bleeding	71	27	0.45 (0.30-0.64)	44	0.71 (0.53-0.95)	0.62 (0.38-1.00)
Intracranial	27	10	0.16 (0.08-0.29)	17	0.28 (0.17-0.43)	0.60 (0.26-1.30)
Gastrointestinal	21	8	0.13 (0.06-0.25)	13	0.21 (0.12-0.35)	0.63 (0.25-1.51)
Hematoma	7	3	0.05 (0.01-0.13)	4	0.06 (0.02-0.16)	0.76 (0.14-3.70)
Other sites	16	6	0.10 (0.04-0.21)	10	0.16 (0.08-0.29)	0.61 (0.21-1.68)
All-cause death	447	156	2.57 (2.19-2.99)	291	4.70 (4.18-5.26)	0.55 (0.45-0.66)
Death within 10 d						
Fatal VTE	27	8	0.13 (0.06-0.25)	19	0.31 (0.19-0.47)	0.43 (0.18-0.96)
Fatal bleeding	17	6	0.10 (0.04-0.21)	11	0.18 (0.09-0.31)	0.56 (0.19-1.50)
COMMAND-VTE registry						
Patients, *N*		**156**		**153**		
Days, median (IQR)		907 (426-1440)		815 (424-1353)		
Outcomes						
Recurrent PE	21	2	0.53 (0.13-2.12)	19	7.75 (3.69-16.3)	0.09 (0.02-0.41)
Recurrent DVT	18	14	3.71 (2.20-6.27)	4	1.18 (0.44-3.13)	3.16 (1.04-9.59)
Major bleeding	6	2	0.49 (0.12-1.97)	4	1.07 (0.40-2.84)	0.46 (0.84-2.52)
All-cause death	28	19	4.68 (2.99-7.34)	9	2.40 (1.25-4.62)	1.95 (0.88-4.31)
Death within 10 d						
Recurrent VTE	0	0	-	0	-	-
Major bleeding	0	0	-	0	-	-

Results are expressed as rates per 100 patient-years and 95% CIs (in parentheses).

CI, confidence intreval; COMMAND-VTE, Contemporary management and outcomes in patients with venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; RIETE, Registro Informatizado Enfermedad Trombo Embólica; VTE, venous thromboembolism.

recurrences per 100 patient-years (95% CI, 9.24-10.4): 4.60 recurrences per 100 patient-years in the form of PE (95% CI, 4.22-5.00), 4.69 in the form of DVT (95% CI, 4.31-5.10), and 0.58 major bleeds per 100 patient-years (95% CI, 0.46-0.73). The CFRs within 10 days were 0.4% for recurrent DVT, 4.6% for recurrent PE, and 24% for major bleeding. Overall, VTE-related fatalities marginally surpassed those related to bleeding (27 vs 17 deaths).

Compared with patients who initially presented with PE, those with DVT had a lower rate of recurrent VTE in the form of PE (rate ratio [RR], 0.31; 95% CI, 0.26-0.38), all-cause mortality (RR, 0.55; 95% CI, 0.45-0.66), and VTE-related death (RR, 0.43; 95% CI, 0.18-0.96; Table 3 and Figure 1). The rates of major bleeding were nonsignificantly different (RR, 0.62; 95% CI, 0.38-1.00), while the rate of recurrent VTE in the form of DVT was significantly higher (RR, 4.12; 95% CI, 3.36-5.08). The index DVT being proximal or distal appeared to influence the outcomes marginally (Figure 2). Outcomes varied slightly between patients initially presenting with isolated PE vs concomitant DVT and PE.

In the COMMAND-VTE registry, the outcomes after discontinuing anticoagulation (median follow-up, 870 days; IQR, 424-1381 days) were as follows: 21 patients (6.6%) had recurrent PE, 18 (5.6%) had recurrent DVT, and 6 (1.9%) experienced major bleeding. Among

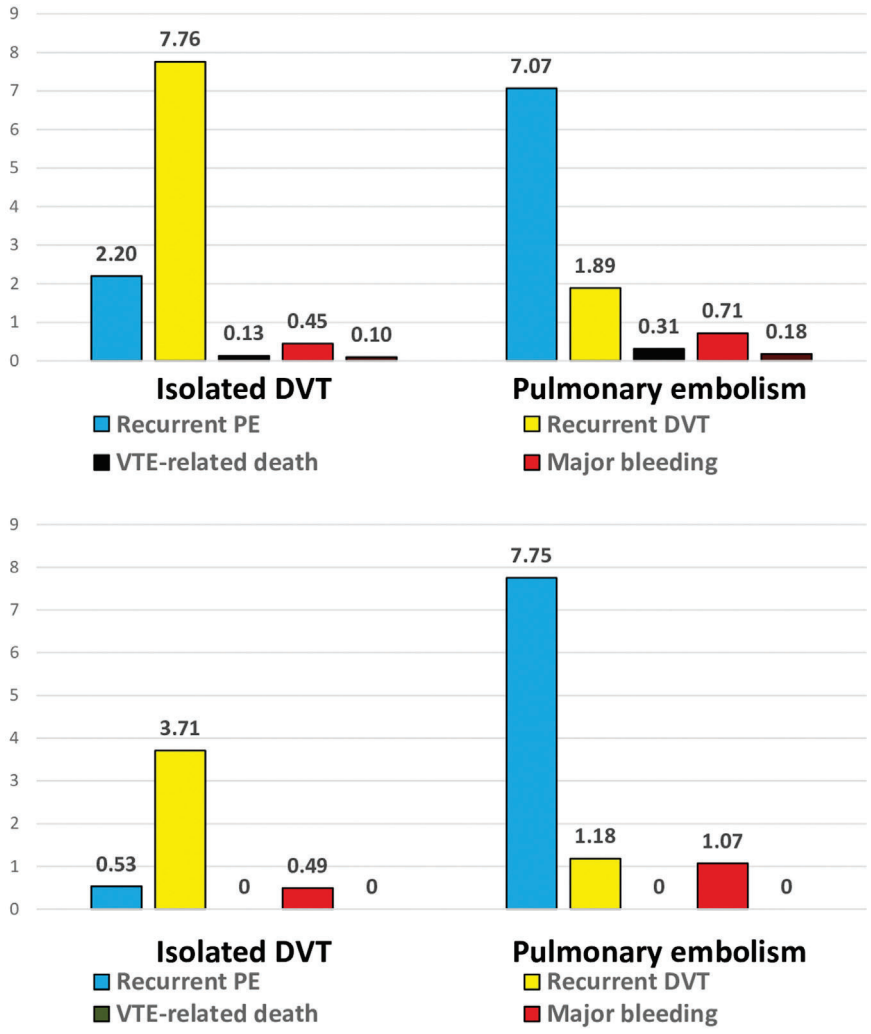


FIGURE 1 Incidence rates of recurrent pulmonary embolism (PE), recurrent deep vein thrombosis (DVT), major bleeding, and mortality associated with these events, according to initial presentation in patients in the Registro Informatizado Enfermedad Trombo Embólica (RIETE) (above) and Contemporary management and outcomes in patients with venous thromboembolism (COMMAND-VTE) (below) registries. Results are expressed as number of events per 100 patient-years.

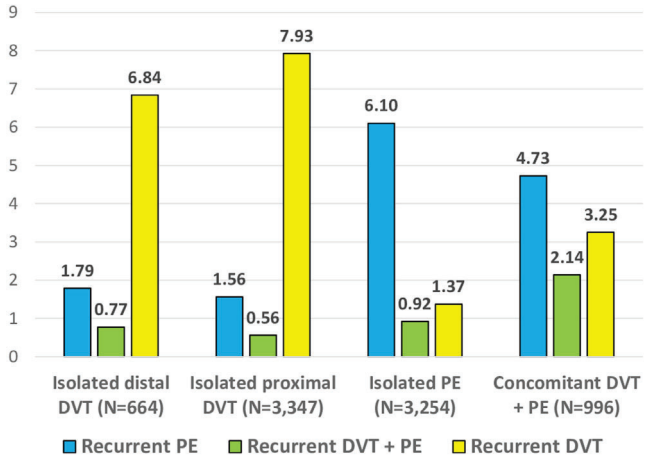


FIGURE 2 Incidence rate of recurrent pulmonary embolism (PE), recurrent deep vein thrombosis (DVT) + PE, or recurrent DVT, according to initial presentation in patients in the Registro Informatizado Enfermedad Trombo Embólica (RIETE) registry. Results are expressed as number of events per 100 patient-years.

those initially presenting with DVT (166 patients), the following were observed: 14 recurrent DVTs (8.4%), 2 PEs (1.2%), and 2 major bleeding events (1.2%). Among patients initially presenting with PE (153 patients), the outcomes were 4 DVTs (2.6%), 19 recurrent PEs (12.4%), and 4 major bleedings (2.6%). Notably, no deaths occurred within the first 10 days following these events (Table 3 and Figure 1).

3.4 | Predictors of outcomes in the RIETE cohort

Multivariable analyses identified that an initial VTE presentation as PE (hazard ratio [HR], 3.03; 95% CI, 2.49-3.69), dementia (HR, 1.47; 95% CI, 1.01-2.13), and baseline anemia (HR, 0.72; 95% CI, 0.57-0.91) were independent predictors of recurrent PE (Table 4). In contrast, initial presentation as PE (HR, 0.24; 95% CI, 0.20-0.30), depression (HR, 1.49; 95% CI, 1.12-1.98), and corticosteroid use (HR, 1.46; 95% CI, 1.08-1.96) were associated with an increased risk for recurrent DVT. Additionally, predictors for major bleeding included older

TABLE 4 Multivariable analyses (with competing risk analysis) for recurrent pulmonary embolism, recurrent deep vein thrombosis, and major bleeding.

	Recurrent PE HR (95% CI)	Recurrent DVT HR (95% CI)	Major bleeding HR (95% CI)
Demographics			
Male sex	0.95 (0.80-1.13)	1.09 (0.92-1.31)	-
Age >75 y	1.07 (0.86-1.33)	0.92 (0.76-1.12)	2.11 (1.15-3.87)
Comorbidities			
Current smoking	-	1.09 (0.87-1.38)	-
Hypertension	1.16 (0.90-1.38)	-	1.03 (0.57-1.86)
Diabetes	-	0.81 (0.63-1.06)	1.15 (0.62-2.14)
Chronic heart failure	-	0.70 (0.42-1.17)	1.25 (0.53-2.94)
Prior artery disease	-	0.94 (0.68-1.30)	1.52 (0.79-2.90)
Gastroduodenal ulcer	-	-	2.87 (0.90-9.13)
Inflammatory bowel disease	-	-	4.39 (1.00-19.3)
Chronic liver disease	-	1.50 (0.86-2.62)	-
Dementia	1.47 (1.01-2.13)	-	-
Depression	-	1.49 (1.12-1.98)	1.51 (0.73-3.10)
Anemia	0.72 (0.57-0.91)	-	2.24 (1.35-3.73)
CrCl levels < 60 mL/min	1.05 (0.84-1.30)	-	0.96 (0.54-1.71)
Initial VTE presentation			
Isolated DVT	Ref.	Ref.	Ref.
Pulmonary embolism	3.03 (2.49-3.69)	0.24 (0.20-0.30)	1.35 (0.82-2.21)
Concomitant drugs			
Antiplatelets	-	0.96 (0.71-1.28)	1.53 (0.81-2.90)
Corticosteroids	-	1.46 (1.08-1.96)	-

Rates are expressed as number of events per 100 patient-years and 95% CIs (in parentheses).

CrCl, creatinine clearance; DVT, deep vein thrombosis; HR, hazard ratio; PE, pulmonary embolism; Ref., reference; VTE, venous thromboembolism.

age (HR, 2.11; 95% CI, 1.15-3.87), inflammatory bowel disease (HR, 4.39; 95% CI, 1.00-19.3), and anemia (HR, 2.24; 95% CI, 1.35-3.73).

In the development of the 2 prognostic scores (1 for recurrent PE and another for major bleeding), specific point values were assigned to each predictor based on their statistical significance and relative weights in the regression model. The detailed point attribution for each predictor is as follows: for recurrent PE: dementia +0.4 points; anemia −0.3 points; and initial presentation as PE +1.1 points. For major bleeding: age >75 years +0.7 points; inflammatory bowel disease +1.5 points; and anemia +0.8 points. Subsequently, patients were categorized based on their total score: a total score above 0 points for each model was considered indicative of a high-risk category.

In the cohort, 4426 patients (53.6%) were classified as high risk for recurrent PE based on the score. Of these high-risk patients, 423 (9.6%) experienced a recurrent PE. In contrast, among the 3835 patients (46.4%) classified as low risk, only 117 (3.1%) experienced recurrent PE (Table 5). For major bleeding events, 56 of 3794 patients (1.5%) were deemed high-risk bled compared with 15 of 4467 low-risk patients (0.3%). The predictive accuracy of the scores was quantified using the C statistic, which was 0.63 (95% CI, 0.61-0.66) for the recurrent PE score and 0.69 (95% CI, 0.63-0.75) for the major bleeding score. Cumulative incidence rates of recurrent PE and major bleeding over the initial 3-year period postindex event are depicted in Figure 3.

Stratification of the patients revealed the following: 2222 (26.9%) were at high risk for recurrent PE and low risk for major bleeding, 1590 (19.2%) were at low risk for PE and high risk for bleeding, 2204 (26.7%) were at high risk for both, and 2245 (27.2%) were at low risk for both (Table 5). The rate of PE recurrences was 25 times higher than major bleeding in the first subgroup, while it was only 2.7 times higher in the second subgroup. PE-related deaths outnumbered bleeding-related deaths in the first subgroup (8 vs 3 deaths), whereas

TABLE 5 Application of the 2 prognostic scores for recurrent pulmonary embolism and for major bleeding in the Registro Informatizado Enfermedad Trombo Embólica (RIETE) cohort and in the COMMAND-VTE cohort.

	Recurrent PE		Major bleeding	
	Events/number of patients at risk	Events per 100 patient-years (95% CI)	Events/number of patients at risk	Events per 100 patient-years (95% CI)
RIETE cohort				
All patients	**540/8261**	**4.60 (4.22-5.00)**	**71/8261**	**0.58 (0.46-0.73)**
Low risk for recurrent PE (≤0 points)	117/3835	2.05 (1.71-2.45)	-	-
High risk for major bleeding (>0 points)	-	-	56/3794	1.04 (0.79-1.34)
Low risk for bleeding (≤0 points)	-	-	15/4467	0.22 (0.13-0.35)
Identification of high-risk patients				
C statistics	0.63 (0.61-0.66)		0.67 (0.61-0.72)	
Sensitivity	78.3 (74.9-81.8)		78.9 (69.4-88.4)	
Specificity	48.2 (47.0-49.3)		54.4 (53.3-55.4)	
Positive predictive value	9.56 (8.69-10.4)		1.48 (1.09-1.86)	
Negative predictive value	96.9 (96.4-97.5)		99.7 (99.5-99.8)	
Rates of outcomes in subgroups				
High risk for PE + low risk for bleeding	213/2222	6.76 (5.89-7.71)	9/2222	0.27 (0.13-0.49)
Low risk for PE + high risk for bleeding	53/1590	2.33 (1.77-3.03)	20/1590	0.86 (0.54-1.31)
High risk for PE + high risk for bleeding	210/2204	7.26 (6.33-8.29)	36/2204	1.17 (0.83-1.60)
Low risk for PE + low risk for bleeding	64/2245	1.87 (1.45-2.37)	6/2245	0.17 (0.07-0.36)
COMMAND-VTE cohort				
Rates of outcomes in subgroups				
High risk for PE + low risk for bleeding	14/77	8.49 (5.03-14.3)	2/77	1.03 (0.26-4.11)
Low risk for PE + high risk for bleeding	1/107	0.41 (0.06-2.90)	2/107	0.75 (0.19-3.02)
High risk for PE + high risk for bleeding	5/76	2.86 (1.19-6.86)	2/76	1.11 (0.28-4.44)
Low risk for PE + low risk for bleeding	1/49	0.76 (0.11-5.37)	0/49	-

Recurrent PE score: dementia: +0.4 points; anemia: −0.3 points; initial presentation as PE: +1.1 points.

Major bleeding score: age >75 years: +0.7 points; inflammatory bowel disease: +1.5 points; anemia: +0.8 points.

CI, confidence interval; COMMAND-VTE, Contemporary management and outcomes in patients with venous thromboembolism; PE, pulmonary embolism; RIETE, Registro Informatizado Enfermedad Trombo Embólica; VTE, venous thromboembolism.

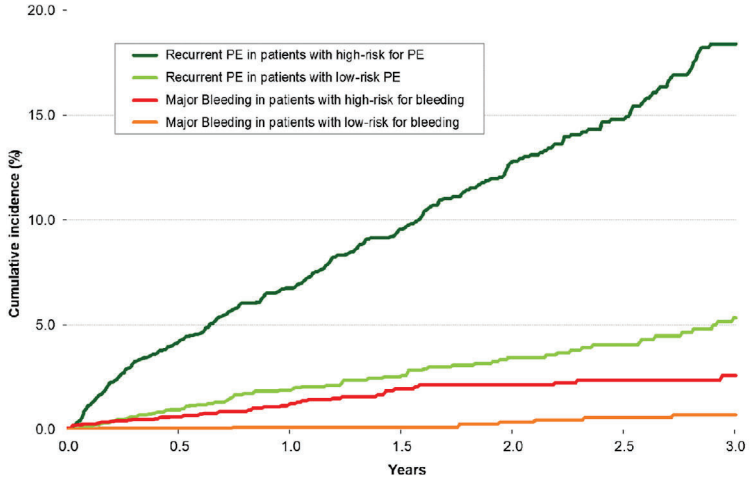
the trend was reversed in patients at low risk for PE and high risk for bleeding (3 vs 5 deaths).

3.5 | Validation of the prognostic scores in the COMMAND-VTE cohort

The COMMAND-VTE registry did not record data on inflammatory bowel disease or dementia. When applying the scores to these patients, 77 (24.9%) were at high risk for recurrent PE and low risk for major bleeding, 107 (34.6%) were at low risk for PE and high risk for bleeding, 76 (24.6%) were at high risk for both, and 49 (15.9%) were at low risk for both. The incidence of PE recurrences was 8.2 times higher than that of major bleeding in the first subgroup, whereas it was half as frequent as major bleeding in the second subgroup (Table 5).

4 | DISCUSSION

In our cohort of patients with a first unprovoked VTE, the rate of VTE recurrences after discontinuing anticoagulation (9.82 per 100 patient-years; 95% CI, 9.24-10.4) is similar to that found in previous studies [1]. Moreover, our study provides novel insights into these outcomes. When we analyze predictors of recurrence, our findings suggest that independent predictors for recurrent PE and DVT may differ. First, it corroborates the well-documented observation that the initial type of VTE significantly influences the probability of recurrent events, with patients initially suffering from a PE being more prone to subsequent PE events and those with DVT more inclined to face further DVT occurrences [6]. Our data extend these data to a similar pattern in patients with unprovoked VTE after discontinuation of anticoagulant therapy. Moreover, other than the initial VTE presen-



Time (months)		6	12	18	24	30	36
At-risk patients		*6,904*	*4,537*	*3,153*	*2,273*	*1,646*	*1,230*
Recurrent PE	**High-risk**	160 (4.2%)	223 (6.8%)	272 (9.5%)	312 (13%)	330 (15%)	356 (18%)
	Low-risk	30 (0.9%)	50 (1.9%)	61 (2.6%)	71 (3.4%)	76 (4.0%)	84 (5.3%)
Major bleeding	**High-risk**	21 (0.6%)	33 (1.2%)	43 (1.9%)	45 (2.1%)	47 (2.4%)	48 (2.6%)
	Low-risk	3 (0.1%)	4 (0.1%)	4 (0.1%)	7 (0.4%)	9 (0.6%)	10 (0.7%)

FIGURE 3 Cumulative rates of recurrent pulmonary embolism (PE) and major bleeding after discontinuing anticoagulant therapy, according to the prognostic scores.

tation, we found that patients with dementia had a higher risk of recurrent PE, while those with depression and concomitant use of corticosteroids had a higher risk of recurrent DVT. Despite the association of dementia and a higher VTE recurrent risk making clinical sense and may be related to reduced mobility or dehydration, to our knowledge, it has not yet been well established in the literature. On the other hand, depression and the concomitant use of glucocorticoids have been previously associated with an increased risk of recurrent VTE but not particularly with a higher risk of DVT [20,21].

Additionally, our study reports an almost negligible mortality associated with recurrent DVT and a lower mortality following recurrent PE than typically documented during the initial months of anticoagulant therapy. These findings carry important implications, as most studies in the literature concentrated on the incidence of VTE recurrences without duly considering the mortality of these recurrent events. The insights extracted from our large, geographically, and ethnically diverse cohort support the need for personalized follow-up strategies tailored to the features of the initial VTE event, which could potentially improve outcomes.

Moreover, our analysis also highlights that the incidence of major bleeding postanticoagulation in nonselected patients with unprovoked VTE is not negligible. Our rate of 0.58 major bleeds per 100 patient-years (95% CI, 0.46-0.73) is nonsignificantly higher than the rate of 0.35 (95% CI, 0.20-0.54) major bleeds observed in a recent meta-analysis of randomized trials and cohort studies [16]. This risk, while sometimes sidelined, is far from being inconsequential. We found that although major bleeding occurs less frequently than VTE recurrence, it exhibits a notably higher CFR when it does manifest, a concerning fact given that these events appeared postanticoagulation. We also found that older age, inflammatory bowel disease, and anemia independently predicted the risk of major bleeding, as suggested in the literature [22,23]. Therefore, the prognostic scores devised from our research serve not merely as academic tools but as practical instruments to guide this decision-making process. Given that nearly half of our cohort (45.9%) falls into the high-risk category for major bleeding, these scores are particularly relevant. They offer a systematic approach to estimate whether the benefits of extended prevention of VTE recurrence outweigh the risks of potential life-threatening bleeding complications. This consideration is especially pertinent for patients at high risk for major bleeding but at concurrently low risk for recurrent PE. In such cases, halting anticoagulation might be a critical, potentially life-saving intervention. Our findings thus endorse a prudent approach, suggesting that for patients with a lower likelihood of experiencing another PE episode, the peril of ongoing anticoagulation (primarily the threat of major bleeding) may eclipse its advantages. Nonetheless, while the prognostic scores exhibit respectable predictive value, the C statistics indicate there is room to enhance predictive precision. This indicates the potential benefit of incorporating additional variables or biomarkers into risk assessment models for a more refined analysis.

The present study has a number of limitations that should be discussed. As RIETE is observational in nature, we cannot exclude the potential influence of uncontrolled variables on the outcomes. Additionally, the decision to discontinue anticoagulation was not dictated by any study protocol but was decided by the physician taking care of the patient. This could have led to an underestimation of the association between VTE recurrences and treatment discontinuation if patients perceived at higher risk were more likely to continue anticoagulation. Conversely, the incidence of bleeding after discontinuation may be overestimated if those perceived at higher risk for bleeding were less likely to remain on anticoagulant therapy. However, it is noteworthy that there were no major differences in the patient population included vs those excluded from the study. Finally, dementia and inflammatory bowel disease, which together account for one-third of the items of the scores, were not captured in the COMMAND-VTE registry. However, the prevalence of dementia (4.1%) and inflammatory bowel disease (0.8%) in our study population is low. As such, while the absence in the COMMAND-VTE registry is a limitation, it is unlikely to have substantially impacted the prognostic accuracy for the vast majority of patients.

Our study also has some strengths not commonly found in previous research, such as a substantial sample size, consistent definition of unprovoked VTE, and the corroboration of findings through 2 independent registries. Additionally, our study provides novel insights into the predictors of outcomes, such as the initial VTE presentation, patient age, and certain comorbidities. The external validation provided by the COMMAND-VTE registry not only strengthens our conclusions but also highlights geographic and demographic variations in VTE management outcomes. Although our study did not record mortality within 10 days postoutcome in the COMMAND-VTE cohort, this does not detract from the global significance of the early mortality risks associated with these events.

In summary, our study underscores that while major bleeding is less common than recurrent VTE after anticoagulation is stopped, it is associated with a substantially high mortality rate. These results emphasize the necessity to consider not just the frequency but also the severity of potential outcomes when deciding whether to continue or discontinue anticoagulation in patients with unprovoked VTE. Future research should focus on refining risk stratification tools and exploring the benefits of personalized treatment durations to optimize patient care.

APPENDIX

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AUTHOR CONTRIBUTIONS

C.G. was involved in the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, and final approval of the version to be submitted.

J.A. was involved in the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, revising it critically for important intellectual content, and final approval of the version to be submitted.

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DECLARATION OF COMPETING INTERESTS

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SUPPLEMENTARY MATERIAL

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Artículo 2

Para el **cuarto objetivo** se llevó a cabo un estudio con datos del registro RIETE, donde se analizó el papel de la edad avanzada en el riesgo de recurrencia en pacientes con ETV. Para ello se incluyeron 23.218 pacientes, de los cuales, 7.208 (31%), eran mayores de 75 años. Al hacer la comparación entre grupos, las recurrencias fueron ligeramente más frecuentes en los pacientes mayores que en los jóvenes (12% vs 10% respectivamente), pero al realizar el análisis tras ajustar por otros factores clínicos (características basales, factores de riesgo de trombosis, extensión y localización de la ETV, comorbilidades…); y teniendo en cuenta el riesgo de sangrado y mortalidad, estas diferencias desaparecían. Con todo , nuestros datos sugieren que la edad avanzada no aumenta el riesgo de recurrencia, con respecto a los pacientes más jóvenes, pero sí que aumenta el riesgo de sangrado mayor, incluso tras la suspensión del tratamiento anticoagulante.

Artículo 2: Prandoni P, **Gabara C**, Bilora F, Aibar J, Pesavento R, Villalobos A, Campello E, Miguel PL, Tormene D, Monreal M; RIETE Investigators. *Age over 75 does not increase the risk of recurrent venous thromboembolism: Findings from the RIETE registry*. Thrombosis Research. 2023; 222: 16-19. doi: 10.1016/j.thromres.2022.12.005. Epub 2022 Dec 17. PMID: 36549192.

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Letter to the Editors-in-Chief

Age over 75 does not increase the risk of recurrent venous thromboembolism: Findings from the RIETE registry

ARTICLE INFO

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Dear Editor,

Based on current evidence, in most patients with an episode of venous thromboembolism (VTE) extended anticoagulation is generally recommended beyond the initial 3–6 months provided the bleeding risk is acceptably low [1]. Among factors that are expected to increase the risk of (major) bleeding complications is the elderly age. In a recent overview and meta-analysis of 27 prospective cohort and randomized clinical trials, older patients were found to exhibit a higher risk of major or clinically relevant bleeding complications, even with the use of the direct oral anticoagulants (DOAC) [2]. Not surprisingly, therefore, the prolongation of anticoagulation beyond the initial 3–6 months in patients over 75 years old is generally discouraged [3]. This recommendation, however, can only be justified if the risk of recurrent VTE in patients in whom anticoagulation is discontinued does not exceed that expected in younger individuals. As far as we know, no study has addressed the risk of recurrent VTE beyond the age of 75. Hence, this key question is still unanswered.

As in the framework of the international RIETE registry, aimed at collecting information on the initial and long-term follow-up of unselected patients with deep-vein thrombosis (DVT), pulmonary embolism (PE) or both, a considerably high number of patients aged at least 75 years had their anticoagulation discontinued after the first months, we have the opportunity to report here the rate of recurrent VTE occurring in the subsequent follow-up as compared to that observed in younger individuals.

The Computerized Registry of Patients with Venous Thromboembolism (RIETE, NCT: 02832245) is a large prospective registry enrolling consecutive patients, including pregnant women, with objectively confirmed VTE since 2001 [4]. The main objective of RIETE is to provide information to help physicians to improve their knowledge on the natural history of thromboembolic disease, including epidemiologic, diagnostic, prophylactic and therapeutic information. Participants in the RIETE registry are requested to provide accurate information on patient's short and long-term outcome after the index event. All recurrent symptomatic VTE events are diagnosed according to objective tests and validated criteria for their interpretation. All enrollees provide written or verbal informed consent according to the local ethics protocols of enrolling centers. The institutional review board at each enrolling center approves participation in RIETE for the site investigators and allows the entry of de-identified patient information into the RIETE database.

Out of 96,701 eligible patients with VTE recruited in the RIETE registry between March 2001 and September 2022, we excluded 38,552 because of: active cancer (17,870), indications for long-term anticoagulation such as a personal or familiar history of VTE and atrial fibrillation (16,249), or the development of thromboembolic, bleeding events or death during anticoagulation (4433). Of the remaining 58,149 patients, information on the clinical course following discontinuation of anticoagulation was available in 23,218 patients, of whom 7208 (31.0 %) were aged 75 or older.

Table 1 shows the main demographic and clinical characteristics of these patients. As expected, older patients were more likely to be women, to have an unprovoked VTE and to have a higher rate of comorbidities. As shown in the table, the duration of anticoagulation prior to discontinuation was similar in the two study groups (on average, 236 days in both subgroups), whereas the duration of the subsequent follow-up (on average, 547 and 469 days, respectively) was longer in the older patients. The baseline characteristics of patients who were not followed-up beyond the first three months were comparable to those of recruited patients, except for a slightly higher prevalence of unprovoked VTE (data not shown).

As shown in Table 2, after discontinuing anticoagulation objectively proven symptomatic VTE recurrences (a composite of symptomatic DVT, fatal and non-fatal PE) developed more frequently in older than in younger patients: 861 of 7208 (11.9 %), accounting for 10.6 events per 100 patient-years, and 1581 of 16,010 (9.9 %), accounting for 7.3 events per 100 patient-years, respectively (crude hazard ratio [HR] = 1.22; 95 % CI, 1.11–1.34). However, when the analysis was adjusted for baseline characteristics, risk factors of thrombosis, extent and location of VTE, risk factors of thrombosis, renal failure and other comorbidities, duration of follow-up, and was repeated after taking into account the competing risk of bleedings and death, the difference disappeared

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Table 1
Main characteristics of the study patients.

Features	Patients aged ≥75 (*N* = 7208)	Patients aged <75 (*N* = 16,010)	*P*-value
Demographics			
Age (mean ± SD)	79 ± 17	53 ± 15	
Males	2635 (36.6 %)	8505 (53.1 %)	<0.001
Body mass index >30	1424 (19.8 %)	3902 (24.4 %)	<0.001
Known thrombophilia[a]	29 (0.40 %)	244 (1.5 %)	<0.001
Index episode			
- Proximal DVT	2891 (40.1 %)	6171 (38.5 %)	0.024
- Isolated calf DVT	514 (7.1 %)	1965 (12.3 %)	<0.001
- PE alone or associated with DVT	3803 (52.8 %)	7874 (49.2 %)	0.004
Risk factors of thrombosis			
- Recent trauma/surgery (<30 days)	626 (8.7 %)	2280 (14.2 %)	<0.001
- Immobilization (≥4 days)	2168 (30.1 %)	3618 (22.6 %)	<0.001
- Hormonal therapy	51 (0.7 %)	1799 (11.2 %)	<0.001
- Pregnancy/puerperium	0	516 (3.2 %)	<0.001
- Long travel (≥8 h)	83 (1.2 %)	674 (4.2 %)	<0.001
- Unprovoked	4306 (59.7 %)	7843 (49.0 %)	<0.001
Comorbidities			
- Diabetes mellitus	1101 (15.3 %)	1334 (8.3 %)	<0.001
- Varicose veins	1451 (20.1 %)	2348 (14.7 %)	<0.001
- Renal failure[b]	4729 (65.6 %)	1783 (11.1 %)	<0.001
- Anemia[c]	2469 (34.3 %)	4017 (25.1 %)	<0.001
Anticoagulant treatment			
- Heparin(s) alone	2007 (27.8 %)	3663 (22.9 %)	<0.001
- Heparin(s) followed by VKA	4395 (61.0 %)	9513 (59.4 %)	0.026
- DOAC with or without heparin(s)	571 (7.9 %)	2198 (13.7 %)	<0.001
- Others	235 (3.3 %)	636 (4.0 %)	0.028
Duration of anticoagulation prior to discontinuation			
Mean ± SD, days	236 ± 139	236 ± 260	0.91
- Up to three months	876 (12.2 %)	1643 (10.3 %)	
- Up to six months	2472 (34.3 %)	5438 (34.0 %)	
- Longer than six months	3860 (53.6 %)	8929 (55.8 %)	
Duration of follow-up after discontinuation of anticoagulation			
Mean ± SD, days	547 ± 790	469 ± 625	<0.001
- Up to six months	3088 (42.8 %)	6534 (40.8 %)	
- Up to one year	1451 (20.1 %)	3028 (18.9 %)	
- Up to two years	1173 (16.3 %)	2767 (17.3 %)	
- Up to three years	662 (9.2 %)	1487 (9.3 %)	
- Longer than three years	834 (11.6 %)	2194 (13.7 %)	

SD = standard deviation; DVT = deep-vein thrombosis; PE = pulmonary embolism; VKA = vitamin K antagonists; DOAC = direct oral anticoagulants.
Data are presented as n (%) unless otherwise specified.
[a] Deficiency of antithrombin, protein C or S, factor V Leiden, prothrombin G20210A mutation, antiphospholipid antibody syndrome.
[b] Creatinine clearance <50 ml/min.
[c] Hb concentration < 10 g/dl.

(adjusted HR = 1.03; 95 % CI, 0.92–1.17).

Our findings are somewhat surprising. Elderly age, a very well-known risk factor of VTE [5], does not seem to increase the risk of recurrent VTE in patients older than 75 who develop a first thromboembolic episode. This conclusion is consistent with that coming from a recent uncontrolled observation conducted in Switzerland in patients older than 65 [6]. As the risk of (major) bleeding complications occurring during extended anticoagulation in patients older than 75 (whichever the drug employed) definitely exceeds that reported in younger people [2], the decision as to discontinue anticoagulation after the first 3–6 months seems justified [3]. In this regard, it is interesting to note that even in our cohort of patients in whom anticoagulation had been stopped, the rate of major bleeding complications occurring during the long-term follow-up of older people was substantial and exceeded by 2.5 times that occurring in younger individuals. While waiting for drugs, such as the inhibitors of factor XIa, which are expected to possess a more favorable therapeutic profile [7], based on the results of the SURVET study an alternative option beyond the first months of conventional therapy in older patients with an episode of unprovoked or weakly provoked VTE could be the use of sulodexide, a glycosaminoglycan that is devoid of bleeding risk [8]. An Italian multicenter, double-blind, placebo-controlled clinical trial addressing the value of sulodexide for secondary prevention of VTE in patients older than 75 is currently ongoing [9].

The strength of our observation lies in the high number of patients with a first episode of VTE who were recruited, in the long duration of patients' follow-up and in the careful documenting and recording of recurrent VTE. However, it should not be forgotten that our findings come from a registry where the therapeutic choices in terms of type, intensity and duration of treatment were left to the discretion of

Table 2
Main clinical outcomes following discontinuation of anticoagulation in patients older and younger than 75.

Features	Patients aged ≥75 (*N* = 7208)	Patients aged <75 (*N* = 16,010)	Crude HR (95 % CI)	Adjusted HR (95 % CI)
VTE recurrences[a]	861 (10.6; 9.95–11.4)	1581 (7.31; 6.96–7.68)	1.22 (1.11–1.34)	1.03 (0.92–1.17)
- DVT alone	401	909		
- PE	460	672		
Major bleedings[a]	89 (0.97; 0.78–1.19)	73 (0.31; 0.24–0.38)	2.50 (1.77–3.54)	
Deaths[a]	931 (10.1; 9.44–10.7)	354 (1.48; 1.33–1.64)	6.74 (5.87–7.75)	
- Due to PE	21	14		
- Due to bleeding	27	16		

CI = confidence intervals; DVT = deep-vein thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.
[a] Data in parenthesis indicate the rate per 100 patient-years and its 95 % CI.

attending physicians. In addition, the rate of patients managed with DOAC was low.

In conclusion, the risk of recurrent VTE in patients aged over 75 years does not exceed that expected in younger individuals. Our results have the potential to inform the long-term management of these patients.

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None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Artículo 3

Para el **quinto objetivo** se llevó a cabo un estudio retrospectivo donde se incluyeron 185 pacientes en los que se había colocado un FVC entre 2015 y 2020 en un hospital terciario. Encontramos una alta tasa de colocación de FVC sin indicación clara en ninguna guía (38%) y una tasa de no retirada del 41%. Las tasas de trombosis del FVC fueron más bajas que las descritas en revisiones previas recientes y encontramos una tasa de recurrencia del 18%, ocurriendo casi la mitad de estos eventos mientras el FVC estaba aún colocado. Al realizar la comparación entre grupos (recurrencia de ETV vs no recurrencia), los pacientes con trombosis de vena cava o vena ilíaca en contexto del FVC y aquellos con más complicaciones previas relacionadas con el filtro (sobre todo la trombosis del filtro) tuvieron unas tasas de recurrencia más elevadas.

Artículo 3: Gabara C, Montoya-Rodes M, López N, Zamora-Martínez C, Ortiz M, Morancho A, Moisés J, Osorio J, Coloma E, Font C, Jiménez S, Zarco F, Burrel M, Bermúdez P, Barrufet M, Aibar J. *Inferior Vena Cava Filters: Adherence to Clinical Practice Guidelines Recommendations, Retrieval Rates, and Filter Complications in a Tertiary Hospital.* Angiology. 2023; 20: 33197231190184. doi: 10.1177/00033197231190184. Epub ahead of print. PMID: 37470426**.**

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Inferior Vena Cava Filters: Adherence to Clinical Practice Guidelines Recommendations, Retrieval Rates, and Filter Complications in a Tertiary Hospital

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Abstract

The present study evaluated the adherence to guideline recommendations regarding the indication for inferior vena cava filter (IVCF) placement, retrieval rates, complications, thrombotic recurrences, and mortality. Patients in whom an IVCF was placed between 2015 and 2020 in a tertiary hospital were retrospectively included. We considered absolute indication of IVCF placement if all the guidelines evaluated agreed on the indication, relative indication if only some guidelines recommended it and without indication if none of the evaluated guidelines recommended it. From the 185 patients included; 47% had an absolute indication, 15% a relative indication, and 38% had no indication. Filter-associated complications and non-removal rates were 12.4% and 41%, respectively. Venous thromboembolism recurrence rate was 17.8%, being filter-associated complications (24.2 vs 9.8%, P = .02) and thrombosis of the inferior cava or iliac veins (12.1 vs 2.6%, P = .03) more frequent in this group. The mortality rate was 40%, with higher mortality risk in patients with co-existing cancer. Previous major bleeding, filter-associated complications, and mortality were associated with a major risk of non-removal. In conclusion, the adherence to guidelines regarding the indication of IVCF placement is still low and IVCF complications are not negligible. This fact is of special concern in the elderly, comorbid, and cancer patients.

Keywords

inferior vena cava filter, pulmonary embolism, deep vein thrombosis, recurrence, mortality

Introduction

Inferior vena cava filters (IVCF) are used to reduce the risk of pulmonary embolism (PE) in patients with deep vein thrombosis (DVT) or pulmonary embolism (PE) who have a contraindication to anticoagulation.[1] Despite the lack of data regarding their benefit in terms of mortality, IVCF have become an important part of venous thromboembolic disease therapy.[2-4]

Currently, most guidelines recommend the IVCF placement as an absolute indication in patients with acute venous thromboembolism (VTE) and contraindication to anticoagulation (such as active gastrointestinal bleeding, acute hemorrhagic stroke, presence of brain lesions, coagulation disorders, etc.); but there is a disparity of opinions regarding

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relative indications like treatment of iliofemoral DVT, patients with free-floating thrombus or poor cardiopulmonary reserve and prophylactic indications such as bariatric and trauma surgical patients.[5-10] This lack of consensus is probably responsible for the heterogenic indications of IVCF placement.

Moreover, only one-third of the IVCF are retrieved, and previous reports have described high rates of IVCF long-term complications such as filter migration (10–25%), perforation (22–93%), filter thrombosis (3.5–50%) or DVT (5–18%) in these patients. Most of these complications occur >30 days after IVCF placement when these are not removed, which favors removal within 30–60 days after placement.[9-15] Until now, patient, clinical, and filter characteristics associated with IVCF non-retrieval, thrombotic recurrences, and mortality have not been well described.

The present study aimed to evaluate the adherence to different guideline recommendations regarding the indication of IVCF placement and to assess retrieval rates, IVCF complications, thrombotic recurrences, and mortality rates in a tertiary hospital.

Methods

Patients and Data Collection

We conducted a non-randomized, observational retrospective cohort study including all patients (inpatients and ambulatory patients) aged >18 years old in whom an IVCF was placed between 2015 and 2020 in a tertiary hospital.

The local institutional ethics committee approved the study, waiving the need for informed consent from individual patients because of its retrospective nature (HCB/2020/0273). All participants gave their informed consent for the IVCF placement before the procedure.

Demographic Data and Comorbidities

Demographic data (gender, age) and the main comorbidities were recorded. The Charlson Comorbidity Index score was calculated for each patient.[16]

Bleeding and Thrombotic Events

Bleeding and thrombotic events previous to the IVCF placement were recorded. Bleeding events were graded according to the International Society of Thrombosis and Haemostasis (ISTH) definition, being categorized as major bleeding for those with: (1) Fatal bleeding, and/or, (2) Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or, (3) Bleeding causing a fall in hemoglobin level of ≥2.0 g/dL, or leading to the transfusion of ≥2 units of whole blood or red cells. Non-major bleeding was defined as that which did not meet any of the criteria for major bleeding but required medical attention and/or a change in antithrombotic treatment.[17] PE and DVT were confirmed with a CT pulmonary angiogram and Doppler ultrasound, respectively.

Indication for IVCF Placement

We considered absolute indication of IVCF placement if all the guidelines evaluated agreed on the indication, relative indication if only some guidelines recommended it and without indication if none of the evaluated guidelines recommended it.[5,18-22] Table 1 summarizes the recommendations of each clinical guideline we evaluated.[5,18-22]

IVCF Characteristics Complications and Removal Rates

Among the IVCF characteristics, the type of filter (removable or permanent), the commercial brand [Optease (Cordis Corp, Hialeah, FL, USA), Celect (Cook Medical, Bloomington, Ind, USA) or non-specified], and the site of insertion were recorded.

Complications during filter insertion, filter-associated complications (fracture, migration, penetration, epithelization, and thrombosis of the IVCF) detected in phlebography or CT angiography, the presence of thrombosis of the inferior cava or iliac veins due to the presence of IVCF, as well as the rate of filter removal, number of trials to removal, time since placement until removal and complications associated with removal were also investigated.

Anticoagulant treatment after IVCF placement, VTE recurrence, bleeding events after IVCF insertion, and mortality were also recorded.

Statistical Analysis

Continuous variables are presented as mean and standard deviation (SD) if they had a normal distribution and as median and interquartile range otherwise. Normality was assessed with the Shapiro–Wilk test. Categorical data are shown as frequencies and percentages. In comparisons that included quantitative continuous variables with a normal distribution, a *t* test was used. Chi-squared or Fisher tests were used to compare qualitative variables.

We performed a logistic multivariable regression to evaluate the association between no removal of IVCF and mortality with clinical and IVCF characteristics. Variable selection was based on clinical relevance. Dependent variables were no removal of IVCF and mortality. Independent variables were age, sex, a Charlson Comorbidity Index higher than three, history of cancer, thrombophilia, VTE, and bleeding events before the IVCF placement, IVCF complications, reintroduction of anticoagulant treatment after IVCF placement, VTE recurrences and bleeding complication after IVCF placement.

Table 1. Indications for IVC Filter Use Depending on the Guidelines.

	ACCP (2016) [5]	BCSH (2006) [18]	AHA (2011) [19]	ICSI (2013) [20]	TC (2021) [21]	NICE (2020) [22]
Acute DVT and CI to AC	✓	✓	✓	✓	✓	✓
29 to 90 days from DVT and CI to anticoagulation	✗	✗	✗	✗	✗	✗
More than 90 days from DVT and CI to anticoagulation	✗	✗	✗	✗	✗	✗
Acute PE and CI to anticoagulation	✓	✓	✓	✓	✓	✓
29 to 90 days from PE and CI to anticoagulation	✗	✗	✗	✗	✗	✗
More than 90 days from PE and CI to anticoagulation	✗	✗	✗	✗	✗	✗
CTEPH undergoing pulmonary endarterectomy	✓	✓	✗	✗	✗	✗
Recurrent VTE despite therapeutic anticoagulation	✓	✓	✓	✓	✗	✓
PE prophylaxis in those with high VTE risk and CI to anticoagulation	✗	✗	✗	✗	✗	✗
Recent VTE and ECT	✗	✗	✗	✗	✗	✗
Superficial venous thrombosis and CI to anticoagulation	✗	✗	✗	✗	✗	✗
Acute VTE without CI to anticoagulation	✗	✗	✗	✗	✗	✗
Thrombectomy of chronic DVT	✗	✗	✗	✗	✗	✗

Abbreviations: *AC, anticoagulation; ACCP, American College of Chest Physicians; AHA, American Heart Association; BCHS, Brithish Committee for Standards in Hematology; CI, contraindication; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep venous thrombosis; ECT, electroconvulsive therapy; ICSI, Institute for Clinical Systems Improvement; NICE, National Institute for Health and Care Excellence; PE, pulmonary embolism; TC, Thrombosis Canada; VTE, venous thromboembolism;* ✓, indication in the guideline; ✗, no indication in the guideline.

All tests were performed with a 2-sided significance level of $P < .05$. Analyses were performed using SPSS v25 (IBM Corp. Armonk, New York, USA).

Results

Epidemiological and Clinical Characteristics of the Patients

One hundred eighty-five patients were enrolled in the study. The mean age was 63.4 years (SD 15), 63.4% were men, and 51.3% had a Charlson Comorbidity Index ≥4. The most frequent comorbidities were hypertension (46.5%) and a history of active cancer (45%).

IVCF Indications, Characteristics and Complications

Sixty patients (32.4%) had a previous VTE (46% PE, 20% DVT, and 33% both PE and DVT). Seventy-five (40%) patients had a bleeding event previous to filter placement (82.7% major bleeding and 17.3% non-major bleeding). The most frequent locations were cutaneous and soft tissues (11.4%) and gastrointestinal tract (10.8%).

Regarding filter placement indication (Table 2), the most frequent was the diagnosis of DVT in the last 28 days with a contraindication for anticoagulation (26%); followed by the PE diagnosis in the last 28 days with a contraindication for anticoagulation (21%), PE diagnosis in the last 29–90 days, with contraindication for anticoagulation (14.6%) and previous to pulmonary endarterectomy in patients with pulmonary hypertension (11.9%).

According to the revised guidelines, from the 185 patients in which an IVCF was placed, 70 (38%) patients had no indication, 28 (15%) had a relative indication, and 87 (47%) had an absolute indication. In those patients with no indication according to the guidelines, the main reasons were >90 days from PE and contraindication to anticoagulation (38.6%), >90 days from DVT and contraindication to anticoagulation (18.6%), between 29 and 90 days from DVT and contraindication to anticoagulation (14.3%), and between 29 and 90 days from PE and contraindication to anticoagulation (11.4%). Other indications were PE prophylaxis in those with high VTE risk and contraindication to anticoagulation (7%), recent VTE and electroconvulsive therapy (4.3%), superficial venous thrombosis and contraindication to anticoagulation (3%), acute VTE without contraindication to anticoagulation (1.4%), and thrombectomy of chronic DVT (1.4%).

Most of the IVCF inserted were removable (97%); the most frequent type was Optease (Cordis Corp, Hialeah, FL, USA) (72%). The most frequent venous access for insertion was the right femoral vein (85.4%). There were no acute complications associated with filter insertion. Anticoagulant treatment was reintroduced after the filter placement in 84.3% of the patients, with a mean time of 13.7 (SD 45) days.

In 23 patients (12.4%), a filter-associated complication was observed: penetration in two (1%), epithelization in eight

Table 2. IVCF Indications.

Patients (n = 185)	
Filter indication	
Acute (0–28 days) DVT and CI to AC, n (%)	48 (26)
29 to 90 days from DVT and CI to anticoagulation, n (%)	10 (5.4)
More than 90 days from DVT and CI to anticoagulation, n (%)	13 (7)
Acute PE (0–28 days) and CI to anticoagulation, n (%)	39 (21)
29 to 90 days from PE and CI to anticoagulation, n (%)	8 (4.3)
More than 90 days from PE and CI to anticoagulation, n (%)	27 (14.6)
CTEPH undergoing pulmonary endarterectomy, n (%)	22 (11.9)
Recurrent VTE despite therapeutic anticoagulation, n (%)	6 (3.2)
PE prophylaxis in those with high VTE risk and CI to anticoagulation, n (%)	5 (2.7)
Recent VTE (0–90 days) and ECT, n (%)	3 (1.6)
Superficial venous thrombosis and CI to anticoagulation, n (%)	2 (1)
Acute VTE without CI to anticoagulation, n (%)	1 (.5)
Thrombectomy of chronic DVT	1 (.5)
Indication for the IVCF insertion according to guidelines	
Non-indicated, n (%)	**70 (38)**
29 to 90 days from DVT and CI to anticoagulation, n (%)	10 (14.3)
More than 90 days from DVT and CI to anticoagulation, n (%)	13 (18.6)
29 to 90 days from PE and CI to anticoagulation, n (%)	8 (11.4)
More than 90 days from PE and CI to anticoagulation, n (%)	27 (38.6)
PE prophylaxis in those with high VTE risk and CI to anticoagulation, n (%)	5 (7)
Recent VTE (0–90 days) and ECT, n (%)	3 (4.3)
Superficial venous thrombosis and CI to anticoagulation, n (%)	2 (3)
Acute VTE without CI to anticoagulation, n (%)	1 (1.4)
Thrombectomy of chronic DVT	1 (1.4)
Relative indication, n (%)	**28 (15)**
CTEPH undergoing pulmonary endarterectomy, n (%)	22 (78.6)
Recurrent VTE despite therapeutic anticoagulation, n (%)	6 (21.4)
Absolute indication, n (%)	**87 (47)**
Acute (0–28 days) DVT and CI to AC, n (%)	48 (55)
Acute PE (0–28 days) and CI to anticoagulation, n (%)	39 (45)

Abbreviations: AC, anticoagulation; CI, contraindications; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep venous thrombosis; ECT, electroconvulsive therapy; IVCF, inferior vena cava filter; n, number of participants; PE, pulmonary embolism; VTE, venous thromboembolism.
The bold means the head of a section.

(4%), and filter thrombosis in 15 (8%); most of them were with the Optease (Cordis Corp, Hialeah, FL, USA) filter (87%). Thrombosis of the inferior cava or iliac veins due to the presence of the filter was observed in eight (4.3%) patients.

In 109 (59%) patients, the filter was removed, with successful removal on the first try in 97% of the patients. The mean time between placement and removal was 53 (SD 52) days (range 4–290): 44 (SD 33) days (range 8–186) for Optease (Cordis Corp, Hialeah, FL, USA) and 77 (SD 79) days (range 4–290) for Celect (Cook Medical, Bloomington, Ind, USA) filters. There were no complications associated with filter removal. In 76 patients (41%), the filter was not removed, and in four patients (2%) removal information was missing. The main reasons for no removal were patient death in 19 patients (25%) and poor prognosis in 13 patients (17%). In two patients (2.6%), the filter was not removed due to the prolonged time since the placement, in six (8%) due to IVCF thrombosis, in eight (10.5%) due to non-thrombotic complications, in seven (9%) due to loss of follow-up and in 17 (32%) there was no specific reason recorded. Only in four patients (5%), the filter was not removed due to the persistence of contraindication for anticoagulation.

Table 3 shows the epidemiological, clinical, and IVCF characteristics and complications associated with non-filter removal. The non-removed IVCF patients had more frequently a Charlson Comorbidity Index >3 points (76.3 vs 61.5%, $P < .03$), a permanent IVCF (5.4 vs 0%, $P < .01$), a higher rate of bleeding events previous to IVCF placement (48.7 vs 23%, $P < .001$), in fewer cases anticoagulation was reintroduced (69.7 vs 94.5%, $P < .001$) and they had a higher mortality rate (55.3 vs 29.4%, $P = .001$). Patients with an absolute IVCF placement indication had a higher rate of non-removal than those without indication (59.2 vs 29%, $P = .01$).

Table 3. Epidemiological, Clinical, and IVCF Characteristics and Complications Associated With Non Filter Removal.

	Non-removal (n = 76)	Removal (n = 109)	P Value
Male, n (%)	42 (55.3)	66 (60.6)	.47
Age, mean (SD)	63.53 (15.5)	63.22 (14.6)	.74
Charlson Comorbidity Index			**.03**
≤3 points, n (%)	**18 (23.7)**	**42 (38.5)**	
>3 points, n (%)	**58 (76.3)**	**67 (61.5)**	
Cancer, n (%)	40 (52.6)	43 (39.4)	.08
Thrombophilia, n (%)	**6 (7.9)**	**21 (19.3)**	**.03**
VTE event, n (%)	20 (26.3)	40 (36.7)	.14
History of PE +/− DVT, n (%)	14 (18.4)	34 (31.2)	.05
History of isolated DVT, n (%)	5 (6.6)	7 (6.4)	.97
Bleeding event			
Major bleeding, n (%)	**37 (48.7)**	**25 (22.9)**	**<.001**
Non-major bleeding, n (%)	5 (6.6)	8 (7.3)	.84
Indication for the IVCF insertion according to guidelines			**.02**[a]
Non-indicated, n (%)	**22 (28.9)**	**48 (68.6)**	
Relative indication, n (%)	9 (11.8)	19 (67.9)	
Absolute indication, n (%)	**45 (59.2)**	**42 (48.3)**	
Type of filter			**.01**
Removable, n (%)	**70 (94.6)**	**109 (100)**	
Permanent, n (%)	**4 (5.4)**	**0 (0)**	
Non-specified, n (%)	**2 (2.6)**	**0 (0)**	
Specific filter			.27
Optease (Cordis Corp, Hialeah, Fla), n (%)	56 (73.7)	77 (70.6)	
Celect (Cook Medical, Bloomington, Ind), n (%)	17 (22.4)	31 (28.4)	
Non-specified, n (%)	3 (3.9)	1 (80.9)	
Reintroduction of AC, n (%)	**53 (69.7)**	**103 (94.5)**	**<.001**
Filter-associated complications, n (%)	13 (17.3)	10 (9.2)	.11
Thrombosis of the inferior cava or iliac veins due to the presence of IVCF	6 (7.9)	2 (1.8)	.06
VTE recurrence, n (%)	16 (21.1)	17 (15.6)	.34
Bleeding complication, n (%)	10 (13.2)	16 (14.7)	.77
Mortality, n (%)	**42 (55.3)**	**32 (29.4)**	**<.001**

Abbreviations: AC, anticoagulation; DVT, deep venous thrombosis; IVCF, inferior vena cava filter; n, number of participants; PE, pulmonary embolism; SD, standard derivation; VTE, venous thromboembolism.

[a]Comparison between absolute indication and non-indication: $P = .01$; comparison between relative indication and non-indication: $P = .94$; comparison between absolute and relative indication: $P = .07$.

The bold means: a) the head of a section and b) data that are statistically significant.

In the multivariate analysis, major bleeding events previous to the IVCF placement (odds ratio (OR), 3.5; 95% confidence interval [CI], 1.6–7.8), filter-associated complications (OR, 4.6; 95% CI, 1.6–13.4) and mortality (OR, 3.04; 95% CI, 1.3–6.9) were associated with a major risk of non-removal; while the reintroduction of anticoagulation was associated with a lower risk (OR, .28; CI .09–.8).

VTE Recurrence, Bleeding Complications, and Mortality

Thirty-three patients (17.8%) had a VTE recurrence: 11 (33.3%) had a PE, 19 (57.6%) a DVT and three (9%) had both PE and DVT. The mean number of days between the placement of IVCF and VTE recurrence was 279 (SD 402). Of the 33 patients who had thrombotic recurrences, in 17 patients (51.5%), the IVCF had been previously removed. Table 4 shows epidemiological, clinical, and IVCF characteristics and complications associated with VTE recurrences. More filter-associated complications were observed in the recurrence group (24.2 vs 9.8%, $P = .02$); the most frequent one was IVCF thrombosis (21.2%). Thrombosis of the inferior cava or iliac veins due to the presence of IVCF was also associated with a higher risk (12 vs 2.6%, $P = .03$) of VTE recurrences.

Twenty-six patients (14%) suffered a bleeding event after the IVCF placement; again the most frequent location was cutaneous and soft tissues (27%) and gastrointestinal tract (27%). In 24 patients (92.3%), the anticoagulant treatment had been reintroduced before the bleeding event.

Table 4. Epidemiological, Clinical, and IVCF Characteristics and Complications Associated With VTE Recurrence.

	No Recurrence (n = 152)	Recurrence (n = 33)	P Value
Male, n (%)	88 (58)	20 (60.6)	.77
Age, mean (SD)	63.71 (14.8)	61.67 (15.5)	.56
Charlson Comorbidity Index			.48
≤3 points, n (%)	51 (33.5)	9 (27.3)	
>3 points, n (%)	101 (66.4)	24 (72.7)	
Cancer, n (%)	68 (44.7)	15 (45.4)	.94
Thrombophilia, n (%)	22 (14.5)	5 (15)	.92
VTE event, n (%)	52 (34.2)	8 (24.2)	.27
History of PE and/or DVT, n (%)	14 (18.4)	34 (31.2)	.05
History of isolated DVT, n (%)	43 (28.3)	5 (15.2)	.12
Bleeding event			
Major bleeding, n (%)	50 (33)	12 (36.4)	.7
Non-major bleeding, n (%)	9 (6)	4 (12)	.21
Indication for the IVCF insertion according to guidelines			
Non-indicated, n (%)	55 (36.2)	15 (45.5)	.32
Relative indication, n (%)	25 (16.4)	3 (9)	.42
Absolute indication, n (%)	72 (47.4)	15 (45.5)	.84
Type of filter			.51
Removable, n (%)	146 (96)	33 (100)	
Permanent, n (%)	4 (2.6)	0 (0)	
Non specified, n (%)	2 (1.3)	0 (0)	
Specific filter			.91
®Optease (Cordis Corp, Hialeah, Fla), n (%)	109 (71)	24 (72.7)	
®Celect (Cook Medical, Bloomington, Ind), n (%)	40 (26.3)	8 (24.2)	
Non-specified, n (%)	3 (2)	1 (3)	
Reintroduction of AC, n (%)	131 (86)	25 (75.7)	.13
Filter-associated complications, n (%)	**15 (9.8)**	**8 (24.2)**	**.02**
VCF penetration, n (%)	0 (0)	1 (3)	
VCF epithelization, n (%)	7 (4.6)	1 (3)	
VCF thrombosis, n (%)	8 (5.3)	7 (21.2)	
Thrombosis of the inferior cava or iliac veins due to the presence of IVCF	**4 (2.6%)**	**4 (12%)**	**.03**
IVCF removed, n (%)	92 (60.5)	17 (51.5)	.34
Bleeding complication, n (%)	23 (15)	3 (9)	.36
Mortality, n (%)	60 (39.5)	14 (42.4)	.75

Abbreviations: AC, anticoagulation; DVT, deep venous thrombosis; IVCF, inferior vena cava filter; n, number of participants; PE, pulmonary embolism; VTE, venous thromboembolism.
The bold means: a) the head of a section and b) data that are statistically significant.

The mortality rate was 40%. Mean days between IVCF placement and mortality were 354 (SD 460). Comparing patients according to survival (Table 5), patients who died were older (67 (SD 12) vs 61 (SD 16) years, $P < .001$), had more frequently a Charlson Comorbidity Index >3 (86.5 vs 55%), $P < .001$) and more frequently had cancer (74.3 vs 25.2%, $P < .001$). In contrast, in fewer cases, anticoagulation was reintroduced (70.3 vs 93.7%, $P < .001$), and in fewer cases the filter was removed (43.2 vs 69.4%, $P < .001$).

In the multivariate analysis, the presence of co-existing cancer was associated with a major risk of mortality (OR, 6.7; 95% CI, 2.7–16.3). Contrary, the reintroduction of anticoagulation (OR, .29; 95% CI, .09–.9) and the IVCF removal (OR, .3; 95% CI, .1–.7) were associated with a lower risk of mortality.

Discussion

The present study evaluated the adherence to different guideline recommendations regarding the indication of IVCF placement and assessed its management and complications in a tertiary hospital.

IVCF placement according to all guidelines evaluated was only 47%, which is consistent with previous works.[23,24] We found a high rate of IVCF placement without a clear indication

Table 5. Epidemiological, Clinical and IVCF Characteristics and Complications Associated With Mortality.

	Non-mortality Group (n = 111)	Mortality Group (n = 74)	P Value
Male, n (%)	63 (57)	45 (61)	.58
Age, mean (SD)	**60.62 (16)**	**67.4 (12)**	**.001**
Charlson Comorbidity Index			**<.001**
≤3 points, n (%)	**50 (45)**	**10 (13.5)**	
>3 points, n (%)	**61 (55)**	**64 (86.5)**	
Cancer	**28 (25.2)**	**55 (74.3)**	**<.001**
Thrombophilia, n (%)	**22 (19.8)**	**5 (6.8)**	**.014**
VTE event, n (%)	41 (37)	19 (25.7)	.11
History of PE and/or DVT, n (%)	34 (30.6)	14 (19)	.075
History of isolated DVT, n (%)	7 (6.3)	5 (6.8)	.9
Bleeding event			
Major bleeding, n (%)	36 (32.4)	26 (35)	.7
Non-major bleeding, n (%)	8 (7.2)	5 (6.8)	.91
Indication for the IVCF insertion according to guidelines			
Non-indicated, n (%)	42 (37.8)	28 (37.8)	1
Relative indication, n (%)	**23 (20.7)**	**5 (6.8)**	**.009**
Absolute indication, n (%)	46 (41.4)	41 (55.4)	.06
Type of filter			.074
Removable, n (%)	110 (99)	69 (93.2)	
Permanent, n (%)	1 (.9)	3 (4)	
Non-specified, n (%)	0 (0)	2 (2.7)	
Specific filter			.34
®Optease (Cordis Corp, Hialeah, Fla), n (%)	76 (68.5)	57 (77)	
®Celect (Cook Medical, Bloomington, Ind), n (%)	33 (29.7)	15 (20.3)	
Non-specified, n (%)	2 (1.8)	2 (2.7)	
Reintroduction of AC, n (%)	**104 (93.7)**	**52 (70.3)**	**<.001**
Filter-associated complications, n (%)	17 (15.3)	6 (8)	.15
IVCF removed, n (%)	**77 (69.4)**	**32 (43.2)**	**<.001**
VTE recurrence, n (%)	19 (17)	14 (19)	.75
Bleeding complication, n (%)	13 (11.7)	13 (17.6)	.26

Abbreviations: AC, anticoagulation; DVT, deep venous thrombosis; IVCF, inferior vena cava filter; n, number of participants; PE, pulmonary embolism; VTE, venous thromboembolism.The bold means: a) the head of a section and b) data that are statistically significant.

in any guideline (37.8%). The main reason was >90 days from PE or DVT and contraindication to anticoagulation.

Our IVCF thrombosis rates were lower than those described in recent reviews, which may be in part explained due to the high rates of anticoagulation reintroduction after IVCF placement and the relative early mean time of removal.[11,25] Also, other small retrospective studies have described similar rates.[26,27]

Regarding retrieval rates, in 59% of the patients the IVCF was removed. This rate is better than those described in previous studies, which vary between 20 and 30%.[11,15,28,29] The removal was successful on the first try in almost all patients (97%), which is consistent with previous works.[11,15,30] The mean time between placement and removal was 53 days, according to the current recommendations of retrieval within 29–54 days of placement.[12,31] Nevertheless, in 41% of the patients, the filter was not removed, probably because nearly half of the patients had active cancer or a high Charlson Comorbidity Index. This fact warns of the need to carefully review the indications of IVCF placement in this subgroup of patients, considering the real benefit since these patients often had a poor short-term prognosis.

When we explored clinical variables associated with non-removal, a previous major bleeding event, filter-associated complications, and mortality were associated with higher risk, while the reintroduction of anticoagulation was associated with a lower risk.

The increased risk of recurrent DVT after an IVCF placement has been previously described and varies between and 35%.[2,4,13,15,30] We found a recurrence rate of VTE of 18% (6% PE, 10.2% DVT, 1.6% both PE and DVT), but only nearly half of the patients (48.5%) recurred while IVCF was placed. We observed more filter-associated complications, especially filter thrombosis, and more inferior cava and iliac vein thrombosis in the recurrence group.

Finally, we found a significant mortality rate of 40%, which was more frequent in older patients, patients with comorbidities, and those with cancer. In this sense, while these patients may have the highest mortality, they may also have the maximum benefit for

the placement of the IVCF, so the decision of IVCF placement should be taken carefully and individualized to each case.

The present study has some limitations, and the results must be interpreted with caution. First, this is a retrospective study, so it lacks the rigor of a prospective randomized study. Second, as it was a non-interventional study, treatment strategies and management were conditioned by the clinical practice. Lastly, it is a single-center study.

Conclusions

Despite we obtained higher removal rates than those described in previous works, the adherence to current guidelines regarding the indication of IVCF placement is still low and IVCF complications are not negligible. This fact is of special concern in the elderly, comorbid, and cancer patients, who seem to have lower rates of IVCF removal and higher mortality rates.

Author Contributions

All authors contributed to: (1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and, (3) final approval of the version to be published.

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Artículo 4

Para el **sexto objetivo** se llevó a cabo un estudio retrospectivo donde se incluyeron 185 pacientes en losque se había colocado un FVC entre 2015 y 2020 en un hospital terciario. Se comparó la adherencia a las guías de práctica clínica, las tasas de retirada y las complicaciones entre los pacientes con (48%) y sin cáncer de nuestra cohorte y vimos que en los pacientes con cáncer se colocaron más FVC con indicación relativa y sin indicación según las guías revisadas. No hubo diferencias entre grupos en cuanto a las complicaciones derivadas del filtro, pero en los pacientes oncológicos la tasa de reinicio de la anticoagulación fue menor (75% vs 93%) mientras que la tasa de no retirada del FVC fue mayor (67% vs 51%).

Artículo 4: Nestor López, Carles Zamora-Martinez, Marc Montoya-Rodes, **Cristina Gabara**, María Ortiz, Jesús Aibar. *Comparison of inferior vena cava filter use and outcomes between cancer and non-cancer patients in a tertiary hospital*. Thrombosis Reserch. 2024; 236:136-143. doi: 10.1016/j.thromres.2024.02.020. Epub 2024 Feb 28. PMID: 38447420.

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*-LeEdthdLehA*1K)iesi)j L3irA G-t -dRF EiseTdI ihdiAEERu diu AsiesiRu-ir Rh-dREziL dG-oir Rh-dREiu I iul5u-oio R-Eiesi)j L3irA G-t -dR F hRueTRI hdI hC Rhedi dI iAeF-oi dRkCe 5TA Rhedio-ETt r Rhedi dI i)j L3io-Rdh-n Ao RheEci I-Er hR-i Cet r AC RhedEiF-o-iEt hA oihdiNeRui5oeTr Ezii

Age ovr75e e dsnr

j-deTEiRucet Ne-t NeAEt i.j (x2iEi iAss-ORuo-R dhd5iCedI hRhediF hRui iEh5dlf C dRI hE-E-iNTol-dzi(uhEiHi-Er-Ch AAViht reoR dR t ed5iC dG-oi r Rh-dREciEhdG-ihREiRo-Rt-dRkC diN-iI hsf CTAkI T-iReiRu-ihdCo-E-I iokEMesi NA-I hd5zi)ds-oheoin-d iC n if AR-oi.)j L32irA G-t -dRkEETE-sTAF u-diRu-o-i hEi iCedRo hdI hC RhediRei dRkCe 5TA Rhedziw ARueT5uiRu-o-ihEi iCedE-dETEi ediRu-it hdihdI hC RhedEiseoi hREiTE-diRu-o-i o-iI hECo-r dCh-Ei t ed5iRu-i I hss-o-dRl5TH-Akd-Ei dI i)j L3io-Rdh-n Ao R Eio-t hdi AeF dI-Er hR-iRu-i -t -o5-dG-iesio-Rdh-n NA i)j L3zi(uhEiHi-Er-Ch AAvideR NA ihdiRu-iC dG-oi r erTA Rhedzi)diRuhEiERTI ViF-iI-t edERo R I iRu R)j L3irA G-t -dRF hRueTRI iCA oihdI hC RhediF Eit eo-iso-7T-dRkdiRu-iC dG-oi5oeTr i dI oI-Er hR-iRu-i NE-dG-iesi I hss-o-dG-EihdiCet r AC Rhedio R EiedCeAe5hCir Rh-dREiu I i AeF-oio R Eiesi)j L3io-Rdh-n A dIio-ETt r Rhediesi dRkCe 5TA Rhedzi

ti cahskf5uhgkar

j-deTEiRucet Ne-t NeAEt i.j (x2ihdCATI hd5ir TA ed oVi-t NeAEt i .6x2i dI iI--rin-hdiRucet NeEHEi.kj (2ciHEi ireR-dRh AAVis R A Ced I hRhedi F hRui di ddT AkdCh I-dG-iesi NeTRfifiq–fi9' ir-oifi%%%%%ir-oEedE,V- oi /fiWdi)RkHEio-5 oI-I i EiRu-iRuhoI it eERCet t ediC TE-iesiC oI hen ECTA oi I hE-E-i/4Wdj (xilhEiesir oRkCTA oihdR o-EHt ed5ir Rh-dREiF hRuiC dG-oci Ei Ru-Vi o-iseToORei E-n-dQeA it eo-iAtM-AViRei I-n-Aeri di-t NeAEt iRu di r Rh-dREiF hRueTHC dG-oi/SWdI3ToRu-ot eo-diC dG-oOEEeCh R I iRucet NeEHEi hEi Ru-iE-Ced I i A I hd5iC TE-iesi I-Ruihdi C dG-oir Rh-dREi sR oi I hE-E-i roe5o-EEhedi/:Wdi dI i hREi Ro-Rt-dRkC di N-i Cu AAd5hd5i I T-i Rei Ru-i hdCo-E-I i ohEMesi NA-I hd5i E-Ced I oVi Rei Ru-i I hE-E-i hRE-Asi eoi Ru-i Ced Cet hR dRt-I hC RhedEzi

(u-iERdI oI it d 5-t -dRkesij (xiHEiN E-I iedirоet r RhIhdHh Rhediesi dRkCe 5TA dRkRo-Rt-dRkhdieoI-oiRei ro-n-dRkF eoE-dhd5cio-CToo-dG-i dI i

y Leoo-EredI hd5i TRueoai
*BHJ radsrDDowhhA*Cl t eo X CAdhCzC R.Lzia t eo Qg oRkd-l2zii

uRRtEJ; I ehaeo5; fi%%fi%fi9; GRucet o-Ez4%4: z%4z%4%
K-G-hn-I i0i1-r R t N-oi4%4SfIK-G-hn-I ihdio-nhE-I iseot ifiqi3-NoT oVi4%4: flwCG-r R I ifi' i3-NoT oVi4%4: iii
Available online 28 February 2024

S. Ltwswsrds Ehvwrdvvhvvhvvh

íSS myrydyErdsrerdhds

K-ETABEi o-i-ýro-EE-Ii Eit - di dIiERdI oIiI-nhPkedi.1k2iseoi 7T dPkRPkn-in oh NAEiRu PuseAteF i ideot AIhERdhNTPkedi dIi Eit -Ih di dIio d5-ieoihdRo7T oRhAio d5-ieRu-oF hE-ziJT AtRPkn-in oh NAEi o-i -ýro-EE-Ii Eir-oG-dR5-Ei.8 2zimeot AtRViF Ei EE-EE-IiF hRuiRu-i1ur rhoeO] hAMRERzi

J T AtRPkn-in oh NAEiF-o-iCet r o-IiTEhd5iRu-i LuhOE7T o-i RERzi J T dPkRPkn-in oh NAEiF-o-iCet r o-IiTEhd5iRu-i1RTI-dREiyPkREPkseoiRu-i n oh NAEiF hRui ideot AIhERdhNTPkedi dIiRu-ig ddi] uhRd-Vi*bs*RERPkseoi RuEE-iF hRui ided Qdeot AIhERdhNTPkedzi

wAtRERBiF-o-ir-oseot -IiF hRui iNhARo AEh5dlf C dG-iAn-A*iesits*< %#%qzij oh NAEiF hRuiERPkERPkC AtViEh5dlf C dRI hss-o-dG-EihdiRu-iTdln oh Ri t eI-AF-o-ihdCATI-IihdiRu-it TAtn oh RiAe5hERPkCio-5o-EERediRei-n AT Ri NeRuihdI-r-dI-dRIoEMs CReoEiseoideio-Roh-n A*iesi*)j L3i dIit eoRAtRVzi 1RPkERPkC A d AVEhEiF Eir-oseot -IiTEhd5iRu-i1611ij 49iEesRF o-ir CM5-i *.mMmmsKéESN- gdErCLNSK Nbmf* 2zi

Ri I v75dV7r

: SUS mycDIst Ltcdr ydLesreDsvrhwdewsEgr or EywodyEPhs

(u-it hdi-rhI-t heAe5hCi dIiCAdthC A I Ri esiRu-ifiHqir Pkh-dREi hdCATI-IihdiRu-iERTI Vi o-iEueF dihdi(NAi4zi

(u-it - di 5-iesiRu-iERTI VirerTA PkrediF Ei9SiV- oEi.1kUfiqiV- oE2ci dIi: fizfii8 iF-o-iF et -dzixl5uRVQdhd-ir Pkh-dREi.: Hzfii8 2iu I ii di CRkn-i u-t PeAe5hC A dI;eoiEeAdiieo5 diC dG-oi Pk Ru-i t et -dPkIesi)j L3i r AG-t -dRzib-TM-t h iF EiI h 5deE-I ihdiSir Pkh-dREi.Sz i8 iesiRu-iC dG-oi CeueoRziAVt ruet ihdiqi.qz9i8 2i dIiEeAdiieo5 did-er A Eh ihdiHSi.' SzSi 8 2zi)diRu-iEeAdiieo5 did-er A Eh iCeueoRi: %ir Pkh-dREi.: : : z i8 2i F-o-i t -RERPkCi PkRu-iRt -iesiRu-i)j L3ir AG-t -dRzi(u-it eERso-7T-dPkEeAdi d-er A Eh iF EiCeAeo-CR AC dG-oi.49zqi8 2iseAteF-I iNVi5 ERohCiC dG-oi .fiqzOi8 2ciATd5iC dG-oi.fiSzSi8 2i dIiTohd oViRo CRC dG-oi.Hz i8 2zi

L dG-oir Pkh-dREiF-o-ieA-oiRu dided QC dG-oir Pkh-dREi.99iV- oEi.1ki fiS2inEzi9%iV- oEi.1kifi92*its*= %#%fi2ciu I ii iul5u-oiCet eoNhIRVihdI-ýi .t -Ih diesiOinEziSirehdREihdi 5-OI CTER-I iLu oAtediLet eoNhIRVi)dI-ýi ECeo-o*its*< %#%fi2i dI i iul5u-oiNA-I hd5ioh EM.t -Ih diesi: inEziSirehdREihdi wLL6iNA-I hd5ihdI-ýdiri< %#%fi2zi

v diRu-ieRu-oiu dIidedQC dG-oir Pkh-dREiu I ii iul5u-oihdCh I-dG-iesi Ced5-ERkn-iu- oRs hATo-i.44z i8 inEzi' i8 ci*ts*= %#%fi2iCedd-CRkn-iRERET-i I hE-E-Ei.0zSi8 inEzifizfii8 ci*ts*= %#%2i dI ihdu-oRhI iRuoet NeruhAn i.fi' zHi8 i nEzi' i8 ciri= %#%2iRu diC dG-oir Pkh-dREzi3ToRu-ot eo-oiRuhEi5oeTriu I i i ul5u-oio RiesiroheoIj (xi-n-dREi.: %9i8 inEzi4Szqi8 ci*ts*= %#%fi2i dI iAtNhAi)dRod Pkred Atmeot Atl-I iK Pkei.)mK2ihdiRueE-io-G-hmhd5inhRt hdiúi dO R5edhEREi.j úw2iRo-Rt -dRI.fiSzqi8 inEzi: zqi8 ci*ts*= %#%S2zi

meieRu-oiERPkC AtViEh5dlf C dRI hss-o-dG-EiF-o-iseTdIiN-RF--di 5oeTrEzi

: SIS K- sœDdErydLehNEgr or EywodyEPhNreDsEL, tdErydLehsowdrywDsyLs dywos œhwoydLes

(u-it eERso-7T-dRI)j L3ir AG-t -dRIhdIhC PkredEiF-o-ikj (iIh 5deEPkEi hdiRu-iAERI4HiI VEiF hRui iCedRo hdIhC PkrediRei dRtCe 5TAPkredi.4qz i8 2zi 6xiIh 5deEPkEi hdiRu-i AERI 4HiI VEi F hRui iCedRo hdIhC PkrediRei dRtO Ce 5TAPkredi.4fiz9i8 2i dIi>'%iI VEisoet iRu-i6xiIh 5deEPkEi F hRui i CedRo hdIhC PkrediRei dRtCe 5TAPkredi.fi: z9i8 2zi(NAiSiEueF Ei AtRu-ihdO IhC PkredEiseoi)j L3ir AG-t -dRIesiRu-ir Pkh-dREihdiCATI-IihdiRu-iERTI Vi dI i Ru-hoiAn-Aiesio-Cet t -dI Pkredzi

wCCeoIhd5iReiRu-io-nhE-Ii5ThI-Atd-Eei t ed5iRu-ifiHqir Pkh-dREihdiF uhCui Ru-i)j L3iF Eir AG-t -dciH0i.: 0i8 2iu I iERed5AVio-Cet t -dI-I ihdIhC PkredEzi meiEh5dlf C dRI hss-o-dG-EiF-o-iseTdIiN-RF--di5oeTrEio-5 oIhd5iERed5i hdIhC PkredEi.: : : z i8 ihdiRu-iC dG-oi5oeTrinEzi:' i8 ihdiRu-ided QC dG-oi 5oeTrci*ts*> %#%q2zi)diCedRo ERi)j L3ir AG-t -dRIesiRu-ir Pkh-dREihdiCATI-IihdiRu-iERTI Vi dI i Ru-hoiAn-Aiesio-Cet t -dI-I ihdIhC PkredEiF Ei eNE-on-I ihdifiSi8 iesir Pkh-dREien-o At dI iF Eit eo-iso-7T-dRI t ed5ided QC dG-oir Pkh-dREi.fi' zHi8 inEziqz9i8 ci*ts* < %#%fi2it hdAViN-C TE-iesiRu-ifiHir Pkh-dREi F hRui L(6xPirohroiRei

: dFovmr

[E-Atd-iCu o CRohERPkCEiesiC dG-oin-oETEidedQC dG-oir Pkh-dREziii

	v n-o At*es*= fiHqzi	6 Pkh-dREiF hRui C dG-oi*es*= H zi	med QC dG-oi r Pkh-dREi*es*= '9zi	*t*O j AT-i
w5-dV- oEcit - di.1kzi	9Si.fiqzi	99i.fiSzi	9%i.fi9zi	%#%fii
3-t Ai5-dI-ocidi.8 zi	09i.: fizfizi	: %i.: : z zi	S9i.SOzqzi	%sS%i
Led5-ERkn-iu- oRs hATo-cidi.8 zi	S%i.fi9z4zi	Hi.' zi	44i.44z zi	%#%fii
LucedhCirTA ed oVi IhE-E-cidi.8 zi	fi' i.fi%sSzi	' i.fi%fizi	fi%i.fi%z zi	%z qi
khN-REit -AtRTEcidi .8 zi	4qi.fiSzqzi	fiSi.fi: z9zi	fi4i.fi4zqzi	%z ' i
P-t hrA5h cidi.8 zi	qi.4zOzi	4i.4z4zi	Si.Szfizi	%tOfii
Ledd-CRkn-iREEET-i IhE-E-cidi.8 zi	Hi.: zSzi	fii.fizfizi	0i.0zSzi	%#%i
LucedhCiAn-oiIhE-E-cidi.8 zi	fi%i.qz zi	qi.qz9zi	qi.qz4zi	%z %i
Lúki.-D3Ki≤ S%tcidi .8 zi	' i.: z zi	: i.: zqzi	qi.qz4zi	%tH4i
wCRkn-iATM-t h cidi .8 zi	Si.fiz9zi	Si.Sz zi	%i	mwi
wCRkn-iAVt ruet cidi .8 zi	qi.4zOi8 zi	qi.qz9zi	%i	mwi
wCRkn-iEeAtiC dG-ocidi .8 zi	HSi.: : z zi : Si.4Sz4zi	HSi.' SzSzi : Si.: HzSzi	%i	mwi
OmedO1-RERPkCcidi .8 zi	: %i.4fiz9zi	: %i.: : z zi		
Og-RERPkCcidi.8 zi				
w5-OI CTER-I i Lu oAtediECeo-ci t -Ih di.o d5-zi	qi.%–fifizi	0i.4—fifizi	Si.%-HZi	<%#%fii
b NhAi)mKi.hsi Ro-Rt -dRIFhRui dRtO nhRt hdiú2idi.8 zi	fi0i.' z4zi	: i.: zqzi	fiSi.fiSzqzi	%#%Si
P-t eoou 5hCi IhRu-EPkcidi.8 zi	9Hi.S9zHZi	S: i.SHz4zi	S: i.Sqz zi	%tO%i
LucedhCim1w)kEcidi .8 zi	fifii.qz zi	0i.0z zi	: i.: z4zi	%z4' i
wdPkrARARi Ro-Rt -dRidi.8 zi	fi: i.0z9zi	qi.qz9zi	' i.' z zi	%sSSi
1VERt hCi 5ATCeCeoRtCeHEcidi .8 zi	4Si.fi4z zi	fi4i.fiSzqzi	fifii.fifizqzi	%#9Hi
6o-nhe TEit Ceoi NA-I hd5 cidi.8 zi	94i.SSzqzi	40i.S%sSzi	Sqi.S9zqzi	%sSHi
6o-nhe TEiLKmg [Ncidi .8 zi	fiSi.0zi	: i.: zqzi	' i.' z zi	%fi' i
6ARARAEcit -I h di .o d5-zi	4: Si× fi%; bi .' i× fi%; i	4: : i× fi%; bi .4%i× fi%; i	4: Si× fi%; bi .' i× fi%; i	%z ' ii
OrARARAEi≤ fi%i× fi%; bcidi.8 zi	b–HqSi× fi%; b zi	b–0q4i× fi%; i b zi	b–HqSi× fi%; i b zi	%tfi4i %tq4i
OrARARAEi≤ q%i× fi%; bcidi.8 zi	Hi.: zSzi Si.fizqzi	9i.9zOzi 4i.4z4zi	4i.4zfizi fii.fizi	
P-t e5AeNhdi≤ fi%i5; i Ibcidi.8 zi	9Si.S: zfizi	4' i.S4z9zi	S: i.Sqz zi	%z9' i
)du-dRIi Rucet NeruhAncidi .8 zi	40i.fi: z9zi	Hi.' zi	fi' i.fi' zHZi	%#%i
K-G-dRIETc5-oVcidi.8 zi	40i.fi: z9zi	fi4i.fiSzqzi	fiqi.fiqz9zi	%9Hi
wLL6iNA-I hd5ioh EM ECeo-ct -Ih di .o d5-zi	Si.%-HZi	: i.fi–HZi	Si.%-HZi	<%#%fii
6o-nhe TEij (xcidi.8 zi	9%i.S4z zi	4fii.4Szqzi	S' i.: %9zi	%#%fii
O6xcidi.8 zi	4Hi.fiqzfizi	fi%i.fifizi4zi	fiHi.fiH0zi	
Okj (cidi.8 zi	fi4i.9zqzi	qi.qz9zi	0i.0zSzi	
O[eRucidi.8 zi	4%i.fi%zHZi	9i.9zOzi	fi: i.fi: z9zi	

1kUERdI oIiI-nhPkedcLúkUCucedhCiMHd-ViIhE-E-fl-D3KU-ss-CRkn-i5Aet -oTAoi f ARoPkredio Rfl)mKUihdRod Pkred Atdeot Atl-I io Pkrefim1w)kEcidedERoeHi A dRtO hdü t t PeoViIoT5EfiLKmg [UiCAdthC AtVio-An dRdedO1 CeoiNA-I hd5flmwümeRi rr AtC NAi

rQ AT-i≤ %#%qiF EiCedEHi-o-I iERPkERPkC AtViEh5dlf C dRi

g CeoiNA-I hd5iF EiI-f d-I i Eii.fi2is RAtNA-I hd5ci dI;eoi.42iEVt rRet PkCi NA-I hd5ihdi iCoPkC A o-ieoieo5 dciETCui EihdRo Co dh AtihdRo Erhd AtihdRo eCTA oci o-Roer-oPked-AtihdRo OoPkCTA oieoir-ohC oIh Atieoihd Rot TECTA oiF hRui Cet r oRO t -dPkEVdI oet -ci dI;eoi.S2iNA-I hd5iC TEhd5i is AtAhdiu-t e5AeNhdiAn-Atiesi4z%5;i

Ibieoit eo-dieoiA Ihd5iReiRo dEsTEhediesiRF eieoit eo-iTdlhREiesiF ueAiNAeeIieoio-IiNAeeIiG-AEzi

[N] LKmg [iF EiI-fd-Iiii EiNA-Ihd5iRu RIe-EideRsTAfAtRu-iCdR-ohiesit Cdeoi NA-Ihd5iNTHo-7Tho-Eit -IhC AhdRon-dRhediNVi iu- ARuC o-iroes-EEhed AtiA IEiRei ueErhRAtl Rhedi eoi hdCo- E-IiAn-AiesiC o-ieoi o-7Tho-Ei rœt rFl ro-E-dRhA -n AT Rhedzi

: dFovrRr

)dIhC Rhedi dIiERo-d5RuiesiCTEHf C Rhediesi)j L3irAG-t -dRhdiC dG-oin-oETEidedCO C dG-oir Rh-dREziii

	vn-o AA .di= fiHq2i	6 Rh-dREi FhRuiC dG-oi .di= H 2i	medCC dG-oi r Rh-dREi.di = '92i	rO j AT-i
EAhskaTomsvuke e vaf vf r gafgudhgka7yrar1S Dr	**pwr1xwDr**	**x2r1xxi Dr**	**xwr1x Dr**	**2i r**
wCTRikj(i.<4HiI VEzi dIiL)iReiwLcidi.8 2i	:0i.4qz 2i	fi0i.fi' zfi2i	S%.SfizS2i	
wCTRi6xi.<4HiI VEzi dIiL)iReiwLcidi.8 2i	:%.4fiz92i	4Si.4qzHDi	fi0i.fi0z02i	
Er kaE7hskaTomr svuke e vaf vf r gafgudhgka7yrar1S Dr	**mxr1tRDr** fiHi.'z02i 9i.Sz42i	**r1 i Dr** %i qi.qz92i	**t r1t ipDr** fiHi.fiHHDi fii.fi2i	**<2i2tr** <%%fii %%Hi
L(x6PirdeoiRei -dI oRo-CRet Vcidi.8 2i K-CTco-dRhj(xiI-ErhRi wLcidi.8 2i	**wxr1x2Dr**	**xxr1 i Dr**	**R2r1x2i Dr**	**2i2tr**
Er kasvuke e vaf dhgka ir				
4'iRei'%I VEiEhdG-ij(xiRei)j L3irAG-t -dRydi.8 2i	fiHi.'z02i	fifii.fi4z 2i	0i.0zS2i	<%%fii
3cet ikj(i dIiL)iReiwLcidi .8 2i	fi%i.qz 2i Hi.:zS2i	qi.qz92i 9i.9zHDi	qi.qz42i 4i.4zfi2i	
3cet i6xi dIiL)iReiwLcidi .8 2i				
geo-iRu di'%I VEiEhdG-i j(xiRei)j L3irAG-t -dRidi .8 2i	:%.4fiz92i	S%.SSz02i	fi%.fi%z 2i	<%%fii
3cet ikj(i dIiL)iReiwLcidi .8 2i	fiSi.02i 40i.fi:z92i	fi%.fifiz42i 4%.44zq2i	Si.Szfi2i 0i.0zS2i	
3cet i6xi dIiL)iReiwLcidi .8 2i				
vRu-oihdIhC RhedEidi.8 2i	fi9i.Hz92i	Si.Sz 2i	fiSi.fiSzq2i	%%fii
L(x6Pi dIiL)iReiwLcidi .8 2i	:i.4z42i qi.4z02i	%i fii.fizfi2i	:i.:z42i :i.:z42i	
6xirœruVAýHEiiuh5uij(xi dHEMi dIiL)iReiwLcidi.8 2i	Si.fiz92i	%i	Si.Szfi2i	
K-G-dRhj(xi dIixL(cidi .8 2i	4i.fizfi2i fii.%q2i	4i.4zS2i %i	%i fii.fi2i	
1Tr-of Ch An-deTEi Ruœt NeEHEi dIiL)iReiwLcidi.8 2i	fii.%q2i	%i	fii.fi2i	
wCTRij(xiF hRueTHL)iReiwLcidi.8 2i				
(uœt N-CRet Viesi CuoedhCIkj(cidi.8 2i				

kj(UI--rin-deTEiRuœt NeEHEfiL)UCedRo hdIhC RhedfiwLU dRhCe 5TARhedfl6xU rTAted oVi-t NeAEt fiL(x6PUCuoedhCiRuœt Ne-t NeAtCirTAted oViuVr-oRdO Ehedflj(xUin-deTEiRuœt Ne-t NeAEt flxL(U-ACRoeCednTAEn-iRu-o rVzi rO AT-i≤%%qiF EiCedEHi-o-IiER REERC AAViEh5dlf C dRzi

-dI oRo-CRet Vi.fiHzHi8 2ihdiRu-i5oeTriF hRueTHC dG-ozi)j L3irAG-t -dRi Rei neHid-Fi-n-dREihdir Rh-dREiF hRuio-CToo-dRj(xiI-ErhRiN-hd5iedi dRhCe 5TAdRRo- Rt -dRLSz4i8 ien-o A2ZF Eit eo-iso-7T-dRIhdiRu-iC dG-oi 5oeTriCNTRIdeiEH5dlf C dRIER REERC AIhss-o-dG-EiF-o-iseTdIi.qz9i8 inEzifii 8 cits=%%Hzi3hd AAVci)j L3irAG-t -dR4'iI VEi sRoiRu-ij(xi-n-dRF Ei t eo-iso-7T-dRIhdiRu-iC dG-oi5oeTri.:9zfiinEzifi0z0i8 cits<%%fi2ir oRCO TAoAVihdiRueE-iF hRui6xi.4'z4i8 inEzi'z i8 cits=%%fi2zi

(u-it -Ihdi Rt -isoet ij(xiIh5deEHEiRei)j L3irAG-t -dRF Ei4qiI VEi .o d5-i%I VEiReifiqz0iV- oE2diF hRuideiIhss-o-dG-EiN-RF--di5oeTrEi.40i I VEihdiRu-iC dG-oi5oeTrinEzifi9zqiI VEcits>%%q2im-n-oRu-AEEci iETNO 5oeTri d AVEHEi-ýCATIhd5iRu-ir Rh-dREiF hRuiL(x6PiEueF-Ii it -Ih diesi fi0iI VEisoet iRu-i-n-dRREi)j L3irAG-t -dRiF hRuiER REERC AAViEH5dlf C dRI Ihss-o-dG-EiN-RF--di5oeTrEi.49iI VEihdiRu-iC dG-oi5oeTrinEziHI VEihdiRu-i dedCC dG-oi5oeTrcits=%%2i(u-it hdiCedRo hdIhC RhedEiRei dRhO Ce 5TARhediF-o-i it -IhC AtCedIhRhediETCui EiNA-Ihd5i.:Sz4i8 2i dIi TrCet hd5iuh5uQhEMETo5-oVi.:fizfii8 2i(uhEiAEHo-EediF Eit eo-iso-7T-dRI t ed5iRu-ir Rh-dREiF hRuiC dG-oi.q0zSi8 inEzi49i8 cits<%%fi2ik Ri o-5 olhd5iRt -isoet ij(xiRei)j L3irAG-t -dRI dIiCedRo hdIhC RhedEiRei dRhCe 5TARhedi o-iETt t odI-Iihdi(NAi:zi

g eEHesiRu-i)j L3ihdE-oRiiF-o-io-Roh-n NAi.'9zHi8 2iN-hd5iRu-i *TtywrhwS.-LoDdhs-LotNPardwrgN d*-2i.04i8 2iRu-it eERso-7T-dRIRVr-zi(u-i t hdin ECTAoi CC-EEiF EiRu-ioh5uRls-t eo An-hdi.Hqz i8 2iwt ed5iRu-i fi00ir Rh-dREiF hRueTHseAteF CTriAeEEci Cet rAtC RhedEio-AR-IiRei fARoi hdE-oRhedi.ETCui Ei)j L3iRuœt NeEHEci-rHRu-AI Rhedieoit h5o Rhed2iF-o-i seTdIihdi49i.fiSz9i8 2imeiEH5dlf C dRIhss-o-dG-EiF-o-iseTdIiN-RF--di 5oeTrEi.fi%%4i8 ihdiRu-iC dG-oi5oeTrinEzifi9z i8 cits>%%q2zi(uœt NeEHEiesi Ru-ihds-oheoin-d iC n ieoihAn Cin-hdEiF-o-iEtt hAoihdiNeRui5oeTrEi.4zSi8 ihdi Ru-idedCC dG-oi5oeTrinEzi9z0i8 cits=%%fiq2fiIeiEH5dlf C dRIhss-o-dG-Ei F-o-iseTdIihdio-ARhediReiRt -iReiRu-ihAeC n ARuœt NeEHEzi

k Rio-5 olhd5iI-nhG-iCu o CR-ohEHRCEi n ECTAoi CC-EEi dIi)j L3Oi o-ARIiCet rAtC RhedEi o-iETt t odI-Iihdi(NAi:zi

: S S f eydELrCcdydLesowhc, tydLesreDsK - sowycowRrdcorywhs

wdRhCe 5TARhedio-ETt rRhediF Eit eo-iCet t edihdiRu-idedCC dG-oi

: dFovrxr

Lu o CR-ohEHRCEi dIi EEeChRIiCet rAtC RhedEiesi)j L3irAG-t -dRhdiC dG-oin-oETEi dedCC dG-oir Rh-dREziii

	vn-o AA.di = fiHq2i	6 Rh-dREi FhRuiC dG-oi .es= H 2i	medCC dG-oi r Rh-dREi.es = '92i	tO j AT-i
dn7rske r : nfgdTak7g7r hkrc r oduve valyr e vf gdar1sdaTvDr	4qi .%-q0Sfi2i	40i .%-:9S42i	fi9zqi .%-q0Sfi2i	%zHO%
: n vrk r crhkr				
6oheoiReiETo5-oVcidi.8 2i	09i.:fizfi2i	qfii.q0zS2i	4qi.492i	<%%fii
Ph5uicHEMr eERQETo5-oVcidi .8 2i	0i.SzHDi fiHi.'z02i	fii.fizfi2i %i	9i.9zS2i fiHi.fiHHDi	%%Oi <%%fii
6oheoiRei-dI oRo-CRet Vcidi.8 2i	HP%i.:Sz42i :i.:zq2i	S9i.:%z 2i fii.fizfi2i	::i.:qzHDi Si.Szfi2i	%z 9i %%94i
medCETo5hC Aidi.8 2i				
6eERGeAVRo Tt cidi.8 2i				
: n vrk rc r				
medCo-Roh-n NAi)j L3cidi .8 2i	:i.4z42i fi0'i	:i.:zq2i HSi.'SzS2i	%i '9i.fi%%zi	%%Sii
K-Roh-n NAi)j L3cidi.8 2i	.'9zHDi	4i.4z42i	%i	%%Si
meiI Rin hANAcidi.8 2i	4i.fizfi2i			
c ruke e vsuglorFsdaf r				%zq4i
® *TtyBrhws.-LoDdhs-LotN PardwrgN d*-2Nes.8 2i	fiSSi .0fiz 2i	94i.9'z02i 4:i.402i	0fii.0:2i 4qi.4q2i	%O9i
® *-wdwEys.-LLFs wDdErdN CdLL, œGyLeNKéD2Nes.*8 2i	:Hi.4qz 2i :i.4z42i	Si.Sz 2i	fii.fi2i	
meRIr-Cf-Icidi.8 2i				
d7u5odsrduuv77r				
Kh5uRls-t eo An-hdcidi.8 2i	fiqHi .Hqz 2i	09i.Hqz 2i :i.:zq2i	H4i.Hqz 2i 0i.0zS2i	fii %z 4i
b-sRls-t eo An-hdcidi.8 2i	fifii.qz 2i	'i.fi%fi2i	9i.9zS2i	%S:i
Kh5uHCT5TAoin-hdcidi.8 2i	fiqi.Hzfi2i fii.%q2i	%ii	fii.fi2i	%%Ssi
c Esvodlhvf r uke qgudhgkar	4: i.fiSz92i fi:i.0zHDi	' i.fi%%42i qi.qz02i	fiq i.fi9z 2i ' i.' z 2i	%%4i
)j L3iRuœt NeEHEcidi.8 2i	Hi.:zq2i	:i.:zq2i	:i.:z 2i	
)j L3i-rHRu-AI Rhedcidi.8 2i	4i.fizfi2i	%i	4i.4z42i	
)j L3it h5o Rhedcidi.8 2i				
: l ske Fk7g7rk rud d ggdur vga7yrar1S Dr	H i.:zq2i	4 i.4zS2i	9 i.9z02i	%fiqi
dn7r ske rc r oduve valrHkr hl ske Fk7g7rk rud d ggdur vga7yre vf gdar1sdaTvDr	:fizqi .4–:9:2i	9fii.fi–fi4%zi	:fizqi .4fi–:9:2i	%zqfii

j(xUin-deTEiRuœt Ne-t NeAEt fl)j L3Uhds-oheoin-d iC n if ARofiL)UCedRo hdIhO C RhedfiwLU dRhCe 5TARhedzi

tO AT-i≤%%qiF EiCedEHi-o-IiER REERC AAViEH5dlf C dRzi

(u-iHir Rh-dREiAeEHReiseAteF CTriF-o-i-ýCATI-IUfiiF hRuiC dG-oi dIi0iF hRueTRzi

5oeTri.' 4z0i8 inEzi0qzSi8 dts< %e%fi2i ARueT5uideiEhss-o-dG-EiF-o-iseTdIihdiRu-idedC0 C dG-oi5oeTri.99z0i8 inEziq%e9i8 dts= %e%S2iF hRueTRHE5dlf C dRHIhss-oO-dG-Eio-5 oIhd5iRt-iTdRhAo-Roh-n A.SqiI VEinEziS0iI VEdts> %e%q2zi(u-it hdio-EedEiseoideHo-t enhd5iRu-i)j L3iF-o-iAeFiAs-i-ýr-CR dCVi.fi0zfii 8 2i dIi-oAViI-Rui.4qi8 2iF uhCuiF Eit eo-iso-7T-dRhdiC dG-oiRu dihdi dedCC dG-oir Rh-dREi.S:zfii8 inEzifi4zqi8 dts= %e%S2i

(u-i Ae5hERhCi o-5o-EEhedi d AVEhEi EueF-i i Ru R1 o-ERoRhd5i dRhO Ce 5TARhediF Ei EEeChR1iFhRui dihdCo-E-Iio Riesi)j L3io-Roh-n A. eIIEio Rhei.v K2ziSzfi4fl' qi8 iCedfI-dG-ihdRon A.L)2diFi-' z9HfIts= %e%q2zi FuhAi)j L3Co-ARIiCet rAtC RhediEi.v KUi%efi9fl' qi8 iL)Ui%e%9–%z 0fIts< %e%fi2i dIiI-Rui.v KUi%e40fl' qi8 iL)Ui%efifi–%e9fIri< %e%fi2iF-o-i EEeChRIi FhRui iI-Co-E-Iio Riesi)j L3io-Roh-n Ai

g eo-iI Rio-5 oIhd5iCTEHf C RhedEiseoideR0j L3io-Roh-n A o-iEueF dihdi (NAiqzi

: dFovr r

LAdhC AeTRCet-Eci dRhCe 5TARhedio-ERoR1 dIi)j L3io-Roh-n Ao RiEihdiC dG-oi n-oETEidedCC dG-oir Rh-dREziii

	v n-o AS.es = fiHq2i	6 Rh-dREiF hRui C dG-oi.di= H 2i	medCC dG-oi r Rh-dREi.es = ' 92i	rO j AT-i
rsv7hdshyrar1S Dr	fiq9i.H-tzS2i	90i.0qzS2i	H i.' 4z02i	<%e%fii
dn7rhkr rsv7hdshyr e vf gdar1sdaTvDr	Si.%-: 9: 2i	Si.%-49%2i	4i.%-: 9: 2i	%e90i
c rsvhsgv doyrar1S Dr	fi%i.qHz 2i	: qi.q%e92i	9: i.99z02i	%e%Si
dn7rhkrc rsvhsgv doyr e vf gdar1sdaTvDr	Sqi.: –4' %2i	S0i.: –4' %2i	Sqi.%-fiH92i	%a0%i
57tg udhgkark rakhr				
c rsvhsgv dor	fi' i.4q2i	fiqi.S:zfi2i	: i.fi4zq2i	%e%Si
0x oAViI-Rudidi.8 2i	fiSi.fi0zfi2i	' i.4%q2i	: i.fi4zq2i	%zS9i
0beFiAs-i-ýr-CR dCVdi di.8 2i	: qi.q' 2i	4fii.: 0z02i	4: i.0q2i	%e%fii
	0i.' z42i	4i.: zq2i	qi.fiqz92i	
0vRu-oiC TE-Edidi.8 2i	9i.0z 2i	Si.9zHZi	Si.' z 2i	
medORucet NeEHE0 o-ARIiCet rAtC Rhedi di.8 2i	: i.qzS2i	Si.9zHZi	fii.Szfi2i	
	4i.4z92i	fii.4zS2i	fii.Szfi2i	
	fiHi.4Sz02i	fifii.4q2i	0i.4fiz 2i	
)j L3iRucet NeEHEidi .8 2i	Hi.fi%q2i	fii.4zS2i	0i.4fiz 2i	
L)iReiwLir-oEHERdG-idi .8 2i				
)dCo-E-Iii)j L3i IF-Atd5iRt-idi.8 2i				
meiCTEHf C Rhedi Hi-dRf-Iidi.8 2i				
beEEiReiseAteF CTridi .8 2i				
dve kssl dTgur uke qgudhgkayrar1S Dr	49 i.fi:z02i	fi4 i.fiSz92i	fi: i.fiqz02i	%e9'i
dn7rske rc r oduve vahrhkr	fi%qi .fi–fi%fi2i	fi4i.: –fi%fi2i	9i.fi–qfi2i	%e40i
l dve kssl dTgur uke qgudhgkayr e vf gdar1sdaTvDr				
: rsvu5ssvauvyrar1S Dr	4Hi.fiqzHZi	fi: i.fiqz 2i	fi: i.fiqz02i	%z 0i
6xidi.8 2i	fifii.9z42i	Hi.' zfi2i	Si.Sz 2i	%efi4i
kj(idi.8 2i	fi0i.' z92i	9i.9zHZi	fifii.fi4z 2i	%e4fii
dn7rske rc r oduve vahrhkr : r svu5ssvauvyre vf gdar 1sdaTvDr	fi: %i .fi0–fiqq: 2i	fiHqzqi .S9–fifi' HZi	fifi4i .S4–fiqq: 2i	%e4: i
vdHyrar1S Dr	0: i.: %i	q9 i.9Sz92i	fiH i.4%e42i	<%e%fii
dn7rske rc r oduve vahrhkf vdHyr e vf gdar1sdaTvDr	fi9%qi .4–fiHfiHZi	fi' Si .4–fiHfiHZi	H-tzqi .0–fi90' 2i	%a00i

wLUi dRhCe 5TARhedfl)j L3Uihds-oheoin-d iC n if AR-oflL)UiCedRo hdIhC Rhedflj(xUi n-deTEiRucet Ne-t NeAEt zi

*t*0) AT-i≤ %e%qiF EiCedEHi-o-IiERHERhC AAViEH5dlf C dRi

(u-iHir Rh-dREiAeEHReiseAteF CTriF-o-i-ýCATI-IUfiiF hRuiC dG-oi dIi0iF hRueTRi

: S S´ *BsowEcoowEwNgw, LoogrGEsEL, tdErydLehNireDs, Loyrdyls*

wid-Fij(xi-n-dHF EiI-RCR-IihdifiqzHi8 iesiRu-ir Rh-dREiF ueiCeTAiN-i seAteF-IiiTrzimeiIhss-o-dG-EiF-o-iseTdIiN-RF--di5oeTrEi.fiqz i8 ihdiRu-i C dG-oi5oeTrinEzifiqz0i8 dts> %e%q2id-hRu-oiIhss-o-dG-ihdio-ARhediReiRu-i Rt-iTdRhARu-ij(xio-CToo-dG-i.fi:%i VEien-o AtifiHqzqiI VEihdiRu-i C dG-oi5oeTrinEzififi4iI VEdiri> %e%q2zi

[A-Ihd5isRoi)j L3irAG-t-dRiF EiseTdIihdifi:z0i8 ir Rh-dREien-o Ati F hRueTRIhss-o-dG-EiN-RF--di5oeTrEi.fiSz9i8 ihdiRu-iC dG-oi5oeTrinEzifiqz0i 8 dts> %e%q2ziP-t eoou 5hCiCet rAtC RhediF EiI-RCR-Iifi%qiI VEi sRoi)j L3irAG-t-dRiF hRueTRIER RhERhC AIhss-o-dG-EiN-RF--di5oeTrEi.fi4iI VEi t ed5iRu-ir Rh-dREiF hRuiC dG-oinEzi9iI VEdts> %e%q2zi

g eoRAtRViF Eiuh5u-oihdiRu-iC dG-oi5oeTri.9Sz9i8 inEzi4%e4i8 dts< %e%fi2zi

xi g7u577gkar

]-i ht-IiRei-n AT RiRu-i Iu-o-dG-iReiIhss-o-dRI5ThI-Atd-io-Cet O t-dI RhedEio-5 oIhd5iRu-ihdIhC Rhediesi)j L3irAG-t-dRIdIiRei EE-EEihREi t d 5-t-dRIdIiCet rAtC RhedEiCet r ohd5iC dG-oi dIidedCC dG-oir O Rh-dREihdi iRoRhoViueErhRAti

)di IIhRhediReiRu-is CRiRu RIC dG-oir Rh-dREiF-o-ieAI-oiRu didedC0 C dG-oir Rh-dREi.99inEzi9%iV-oE2diRu-ircedeTdG-IiIhss-o-dG-EiN-RF--di 5oeTrEiediLu oAEediLet eoNhIhRVi)dI-ýiECeo-i.0inEziS2iCeTAiN-i-ýr Ahd-I i NViRu-iEH5dlfC dRiuh5u-oiF-h5uRiesit-REREhCIC dG-oiCet r o-IiReieRu-oi t-IhC ACedIhRhedEihdiRuhEiECeo-diFuhCuiF-o-it eo-iCet t edihdiRu-idedC0 C dG-oi5oeTrzi1-n-o AlERTIh-Eiu n-iI-ECohN-IiRu RIC dG-oir Rh-dREiF hRui Rucet NeRhCi-rhEeI-Eiu n-it eo-iRucet NeRhCio-CToo-dG-EihsiRu-Vi o-iedi dRhCe 5TAdRIRo-Rt-dRIF hRuij úwiRu diF hRuiAeFit eACTAoiF-h5uRI u-r ohdi.bg] P2ziwIIhRhed AAVdit dViesiRu-t i o-iediRo-Rt-dRIF hRui Cu-t eRu-o rVi.F hRui i5o-Roiso-7T-dCViesinet hRhd5ci deo-ýh di-RCZ2ieoi r o-E-dRhdReAo dG-iReieo AhdRMiIT-iReiRu-iIhE-E-ihRE-Aszi(u-o-seo-ci AA Ru-E-i o-EedEiC di-ýr AhdiFuVir Rh-dREiF hRueTRI C dG-oi o-it eo-i so-7T-dRAViedi dRhCe 5TAdRIRo-Rt-dRIF hRuij úwi dIiETNE-7T-dRAVi r o-E-dRIt eo-iANhAi)mKzi

]-iseTdIiRu Rt 0i8 iesiRu-ir Rh-dREihdieToiERTIViF-o-i-At5hNAiseoi)j L3i rAG-t-dRhN E-Iiedi iERoed5AVio-Cet t-dI-IihdIhC RhedüRu-iIh5deEHEiesi CTRikj(i dI;eoi6xi dIiCedRo hdIhC RhediRei dRhCe 5TARhedzi(uhEHI Ri hEiEht hAoiReir o-nheTEAVio-reoRIio-ETAREi.:: –00i8 2i/fi9cfiHc4' cS%WdNTRI IT-iReio-G-dRCu1 d5-Eihdi5ThI-Atd-EciEet-iesiRu-iro-nheTEAVihdCATI-I i hdIhC RhedEi o-ideiAed5-oi CC-rRIzi3eoihdERdG-ciwNRuh di-RI Ai/fi9W I-ECohN-IiRu R9fizSi8 iesi)j L3irAG-t-dREihdiRu-hoiERTIViF-o-iETrreoRIi NViseot-oin-oEhedEiesiwLL6ci1eCh-RViesi)dRon-dRhed AIK IheAe5Vi.1)K2i dIiwt-ohC diP-oRIwEEeChRhedi.wPw2i5ThI-Atd-Ei/qcSficS4WdIFuhCui hdCATI-Iio-CToo-dRIj(xiI-ErhRi dRhCe 5TARhedzi)RIhEi MdeF di Ru RI o-CToo-dRIj(xit ViN-iIT-iReit dVis CReoEiETCui EiETNerRht At-IhC O Rhedi Iu-o-dG-cihdI-7T RiIeE 5-ieoiIoT5ORe0oT5ihdRo CRhedEci dIi Ru-o-seo-ciEet-iCToo-dR5ThI-Atd-EiCedEHi-oiRu RI)j L3iEueTAideRIN-i oeTRhd-AVirAG-IiiN-seo-i EE-EEhd5iRu-idedC0 eIIf NAid RTo-iesiRu-i o-CToo-dG-ci-Er-ChAAVi Fu-diRu-ireRdRhAoiEMiesiC oIherTAted oVi I-RoReo RhediN-C TE-iesi id-Fi6xieTRF-h5uEiRu-ioEMEi EEeChRIiF hRui)j L3irAG-t-dRI/4:c4HWdi

)dieToiERTIVciRu-ien-oAAt-IhdiRt-isoet ij(xiIh5deEHEiRei)j L3i rAG-t-dRIF Ei4qiI VEdiFhRuideiIhss-o-dG-EiN-RF--di5oeTrEzi)dieToi CeueoRdi)j L3iF EirceruVACRhC AAVirAG-IirdreoiReirTAted oVi-dIO oRo-CRet ViIhdi iEr-CIfCiETN5oeTriesir Rh-dREiF hRuiL(x6PiN E-Iiedi -ýr-oRIerIhdIhedi/S:WdI-ErhRi iACMiesiuh5uO7T AtRVi-nhI-dG-iI-t edO ERo Rtd5i iEH5dlfC dRIo-ITCRhediIhdi6xio-CToo-dG-iFhRuiCeoo-CRIdRhCe 5O TAdRIRo-Rt-dRI/SqWdiwsRoi-ýCATIhd5iRu-E-ir Rh-dREisoet iRu-i d AVEHEdi AAesiFuet iN-Aed5-IiReiRu-idedC0 dG-oi5oeTrdiF-ieNE-on-IiRu RIRu-i t-IhdiRt-iI-Co-E-IiReifi0iI VEien-o AA dIiReiHiI VEihdiRu-idedC0 C dG-oi5oeTrziv diRu-ieRu-oiu dIidhdiRu-iC dG-oi5oeTrdiF-iH-dRf-Iii t-IhdiRt-iesi49iI VEisoet iRu-i-n-dRhRei)j L3irAG-t-dRIdIiiuh5u-oi so-7T-dCViesi)j L3irAG-t-dRIN-VedIiRu-ifoERIdIiRuhoIit edRui.Eet-i TRueoEiCedEHi-oiRu-i CTRij(xiru E-i EiRu-ifoERISit edRuEisRoiRu-i -n-dRZi/SSWd(u-ioEMesio-CToo-dG-iIirce5o-EEhediesiRu-iRucet NITEihEi

ul5u-oiFhRuhdiRu-ifoEHF--MEfiRu-o-seo-ci sRoiRuhEir-ohe IdiRu-o r-THCi)j L3irAG-t -dRlhEideiAed5-oiTE-sTA dIihEideRlhdIhC RIihdiRu-iCToo-dRl 5ThI-Atd-Ei /4Sc4: c49–4HWi(u-E-iIhss-o-dG-Eit ViN-i RohNTRIiRei 5o- RoiCTRtedited5iruVEhChdEiRei nehIij(xio-CToo-dG-ihdi irerTO ARtedi FhRui i uVr-oCe 5TARtedi ERRi Fu-di dRtCe 5TARtedi hEi CedRo hdIhC RIzi

(u-i)j L3iF Eio-Roh-n-IihdiqHz i8 iesiRu-ir Rh-dREciFuhCuihEiul5u-oi Ru diRu RI-ECohN-IihdiRo-nheTEiERTIh-Ei.Sz0–:0zfii8 2i/fi9c4' cS%cS9–S' W NTHEht hAoiReiRu-i NeTRI9%i8 io-Roh-n Ao RiI-ECohN-IihdiRu-iERTIViesi 6-RoEedi-RI Ai/SSWag eo-en-ociRu-it -Ih diRt -iscet i)j L3irAG-t -dRlRei hREio-Roh-n AF EiSqiI VEciFuhCuihEiCedEHERdRlFhRuiRu-iRt -ir ce reE-IiNVi g eo AEi-RI Ai.4' –q:iI VE2i EiRu-iRt -iFu-diRu-ioHEMesi)j L3iCet rAtO C RtediHEiAeF-EH/:%Wi

1-n-o AERTIh-Eiu n-i d AVl-IiRu-iohEMs CReoEiesi)j L3idedCo-Roh-n Ai EueFhd5iRu RI 5-i dIiC dG-oi o-ihdI-r-dI-dRIohEMs CReoEiesidedCO o-Roh-n A/SScS0cS' Wi)diRuhEiE-dE-diRHEiht reoRdRIeideRiRu RihdieToi ERTIVcir Rh-dREiFhRuiC dG-oiu Ii iERHEHC AAViEH5dlf C dRlAeF-oio Riesi)j L3io-Roh-n ARu dir Rh-dREiFhRueTRIC dG-oi.q%e9i8 inEzi99z0i8 cits= %e%S2ihdi CCeoI dG-iFhRuiro-nheTEAVio-reoRIio-ETAREi/fi9WiwdeRu-oi hdRo-EHd5iERTIVisoet ixITrT5 dRi-RI AF uhCuihdCATI-Ii4fiffiiir Rh-dREi FhRuiC dG-oi dIij(xiFueiTdI-oF-dR)j L3irAG-t -dRlEueF-Ii iAeFi o-Roh-n Ao Ri.0zqi8 2i dIiseTdIiRu RuI5u-oit ed-ViIdCet -iF Ei EEeChO RIiRei iul5u-oio Ri/:fiWim-n-oRu-AEEciRu-i)j L3io-Roh-n Ao RiI-ECohN-Ii hdieToiCeueoRI t ed5iRu-irerTARtediFhRuiC dG-oiF EiCedEHI-o NAViul5u-oi Ru diro-nheTEAVi I-ECohN-Iio REi.4–SHi8 2i/fiqcfi9c fic 4WiroeN NAVi N-C TE-ihdieToiERTIViF-iseTdIi iul5u-oi dRtCe 5TARtedio-ERoRo RiRu di Fu Ru Eiro-nheTEAViN--dio-reoRIihdiRu-iARo RTo-ithdiNeRuiRu-i5-d-o A rerTARtedi.'4z0i8 inEzi9SzHi8 2i/S%WdIiC dG-oir Rh-dREi.0qzSi8 inEziS:i 8 2i/fiSc fiWi(u-iAeF-oio RiesioERoRd5i dRtCe 5TARtedihdiC dG-oir O Rh-dREio-reoRIihdiRu-iARo RTo-it ViN-iIT-iReiRu-is CRuRu Ru ro-nheTEi ERTIh-EiI-ECohN-IiuI5u-oiNA-Ihd5io REihdiRu-E-ir Rh-dREi/:Sc :WiFuhAi hdieToiERTIViRu-o-iF-o-ideiIhss-o-dG-EihdiNA-Ihd5i-n-dREiN-HF--di 5oeTrEi.fiSz9i8 ihdiRu-iC dG-oi5oeTrinEzifiqzOi8 cits> %e%q2i

k-ErhRiCeoo-CHRo-Rt -dRIdIi di)mKiFhRuhdiRu-iRu-o r-THCio d5-ihdi r Rh-dREio-G-lnhd5ij úwiRo-Rt -dRiRu-iohEMesij(xio-CToo-dG-io-t hdEi ul5ui t ed5ir Rh-dREiFhRuiC dG-oi/fific qWi6o dIedhi-RI Ai/:SWiI-ECohN-Ii ifi4O edRuiCTt TARhn-ihdCHI-dG-iesio-CToo-dRlRucet Ne-t NeAEet ihdi C dG-oir Rh-dREiesi4%zOi8 in-oETEi9zHi8 ihdir Rh-dREiFhRueTHC dG-ozi)dieToi CeueoRideiIhss-o-dG-EiF-o-iseTdIiN-HF--diC dG-oi dIiededCC dG-oir O Rh-dREihdio-5 oIiReij(xio-CToo-dG-i sRoi)j L3irAG-t -dRLfiqz inEfiqzOi8 ci ts> %e%q2iFhRui5AeN Ao-ETAREiEht hAoiReiRueE-iro-nheTEAViI-ECohN-IiFhRui ul5uin oh NhARVi.9–Sqi8 2i/:cqcfi:cfi9c qWi

v n-o AtiRu-iso-7T-dCViesiRucet NeEHEiesiRu-ihds-oheoin-d iC n ieoihAn Ci n-hdEL:zqi8 2iF EiEht hAoiReiro-nheTEio-reoREihdir Rh-dREiFhRuio-Roh-n NAi)j L3i/fi9cSHWaimeiIhss-o-dG-EiN-HF--di5oeTrEiF-o-iseTdIihdieToiERTIVihdi -hRu-oi)j L3iRucet NeEHEiHi-dRf-IiNViht 5hd5ieoi Ro-Roh-n Ai

)dieToiERTIVciF-iseTdIis-Fit -Cu dhCAiCet rAtC RtediEciFhRuiEht hAoi o RiEi Rei RueE-i I-ECohN-Ii hdi Ru-i AtRo RTo-i /:c4qc4' cS%cSScS9cSHc %c 0–q%WdIi AEeiFhRueTRIhss-o-dG-EiN-HF--di C dG-oi dIiededCC dG-oir Rh-dREi/fi9c 4Wibe5HERhCio-5o-EEhedi d AVEHEi EueF-IiRu Ro-ERoRd5i dRtCe 5TARtediF Ei dihdI-r-dI-dRls CReoi EEeChRIiFhRui)j L3io-Roh-n A.v KüSzfi42i(uHEif dIhd5iC diN-i-ýr Ahd-Ii N-C TE-iedG-iRu-iCedRo hdIhC RtediRei dRtCe 5TARtediHio-EeAn-IciRu-o-i hEideid--IiReit hdRhdi io-Roh-n NAi)j L3iReiro-n-dRRu-iroe5o-EEhediRei i 6xci dIihRC diN-iE s-AVio-t en-Izi

v diRu-ieRu-oiu dIci)j L3Oo-ARIiCet rAtC RtediEi.v KU%fi92i dIiI-Rui .v KUi%e402iF-o-i EEeChRIiFhRui iI-Co-E-Iio Riesi)j L3io-Roh-n Ai g-Cu dhCiCet rAtC RtediEiesi)j L3iu n-iN--di EEeChRIiFhRui iAed5-oi)j L3iIF-Atd5iRt -iRu RI-ýG-IEiCet t -oChAiNo dIio-Cet t -dI RtediEi /4qcS%cSScS0c %c 9–:HWiRu-o-seo-ir Rh-dREihdieToiCeueoRIReiFuet iRu-i)j L3iF EideHo-t en-Ii-ýr-oh-dG-Iit eo-iCet rAtC RtediEzi)diRot Eiesi t eoRARVcir Rh-dREiFhRui ireeo-oiEueoRORot iroe5deEHEi-ýuhNhRIi i 5o- RoiRdI-dCViReideRu n-iRu-i)j L3io-t en-Izi

i Ahsva Th l 7rdaf rqge ghdhgka7r

(eieToiMdeFAI5-diRuhEiEiRu-ifoEHERTIViReiCet r o-iRu-i Iu-o-dG-iRei Ru-it eEHTrI RIij(xi5ThI-Atd-EiN-HF--diC dG-oi dIiededCC dG-oir O Rh-dREzim-n-oRu-AEEcieToiERTIViu EiEet -iAt hRRtedEzivd-iAt hRRtedihEi Ru HN-C TE-iesiRu-iCu d5-EihdiRu-ij(xi5ThI-Atd-EihdiRu-iAEHV-oEci Iu-o-dG-iReiRu-E-i5ThI-Atd-EihdieToiCeueoRIhdCATIhd5ir Rh-dREiEhdG-i 4%fiqiRei4%4%t ViN-iTdI-o-ERt RIzi)diRuhEiE-dE-diRu-iCet r oRtediesi Iu-o-dG-io RiEiFhRuiro-nheTEiERTIh-EiCeTAiN-iNh E-Izi3hd AAVci EiRuhEi F Ei iEhd5ACC-dRo-iERTIVciRu-idTt N-oiesir Rh-dREihdCATI-iF EideHAo5-ci FuhCuit l5uRu n-i ss-CR-IiRu-iEl5dlf C dG-iesiEet -io-ETAREzi

i ka uc57gka7r

]-iseTdIiRu RIhdiAEEiRu diu AsiesiRu-ir Rh-dREiERTIh-Ii)j L3irAG-O t -dRLF EiETrreoR-IiNVi iERoed5AVio-Cet t -dI-IihdIhC RtediFhRueTRI ERHEHC AAViEH5dlf C dRlIhss-o-dG-EiN-HF--diC dG-oi dIiededCC dG-oir O Rh-dREzi)diC dG-oir Rh-dREiRu-ihdE-oRtediesi di)j L3iFhRueTRI iCA oihdIhO C Rtedi CCeoIhd5iReiCToo-dRl5ThI-Atd-EiHit eo-iso-7T-dRlRu dihdiedCO C dG-oir Rh-dREciFuhAi dRtCe 5TARtedio-ERt rRtedi dIi)j L3io-Roh-n A o RiEi o-iAeF-ozi]-iET55-EHRu RI it TARhHCh r Atd oVi rroe CuihdCATIhd5i j(xi-ýr-oREiCeTAiht roen-i Iu-o-dG-iRei5ThI-Atd-Ei dIiRu-io RiEiesi dRtCe 5TARtedio-ERt rRtedi dIi)j L3io-Roh-n AIhdieoI-oiReineHiCet O rAtC RtediEi EEeChRIiFhRuiAd5RuViIF-AAtd5iRt -Eci-Er-Ch AAVihdiC dG-oi r Rh-dREzi3hd AAVcit eo-iul5uO7T ARVi-nHi-dG-ihEid--I-IiRei5ThI-iCAdlhO Ch dEihdiRu-iTE-iesi)j L3ihdiRu-E-ir Rh-dREzi

5afgaTr

(uhEio-E-oCuio-G-ln-Iidei-ýRod AsTdIhd5zi

ca7hgk5hgkadorI v gv r kdsfr7hdhve vahr

(u-iERTIViF EiCedITCRIihdi CCeoI dG-iFhRuiRu-ik-CAo RtediesiP-AEhdMni dIi rroen-IiNViRu-ixRuhCEiLet t hRR-iesiPeErhRALAdlhCiesi [oG-Aed i.PL[;4%4%%40S2i

ca kse vf ruka7va hr7hdhve vahr

)dIlnhIT Ar Rh-dRIhdseot -IiCedE-dRLF EiF hn-IiNViRu-iAeC AIhdERtO RTRted A-RuhCEiCet t hRR-iN-C TE-iesihHEio-RoeEr-CRln-id RTo-zi

g7uodge vs 5Fqg7l vs7rakhvr

(u-iERRt -dREcierhdhedEi dIiI RiCedRhd-IihdiAArTNACRtediEi o-i EeAAViRueE-iesiRu-ihdIlnhIT A TRueoi.E2i dIiCedRohNTReo.E2i dIideRiesi g k6)i dI;eoiRu-i-IhReo.E2i g k6)i dI;eoiRu-i-IhReo.E2iIhECAht io-O EredEHNhARViseoi dVihdCToViRei-er Aieoir cer-oRVio-ETARhd5iscet i dVi hI-Ecit -RueIEcihdERoTCRtedEieoir ceITCREio-s-oo-IiReihdiRu-iCedRdRzi

I vf g rd5hI ks7l g ruka hsgF5hgkar7hdhve vahr

v7hksr k v r] ohRhd5i–o-nh-Fi&-IhRhd5ci] ohRhd5i–ed5hd AIo sRi g-RueIeAe5Vci3eot A d AVEHEcik RiCTo RtediLedG-rRT AtI Rtedzi dsov7r de ksdIBdshga v r] ohRhd5i–o-nh-Fi&-IhRhd5ci] ohRhd5i–ed5hd AIo sRi 1Tr-onhEtediig-RueIeAe5Vci3eot A d AVEHEcik RiCTo RtediLedG-rRTO AtI Rtedzib dsurb kahkndBHkfv7rg-RueIeAe5Vci3eot A d AVEHEcik Ri CTo RtediLedG-rRT AtI Rtedzi sg7hgadr dFdsd r] ohRhd5i–o-nh-Fi& -IhRhd5dig-RueIeAe5VciLedG-rRT AtI Rtedzib ds dr shg r] ohRhd5i–o-nh-Fi & -IhRhd5zi v7 7r gFds r] ohRhd5i–o-nh-Fi&-IhRhd5ci] ohRhd5i–ed5hd AIo sRi1Tr-onhEtediig-RueIeAe5VciLedG-rRT AtI Rtedzi

vuodsdhgkark ruke vhgaTrgahvsv7hr

(u-i TRueoEiI-CAo-iRu RuRu-Viu n-ideiMdeFdiCet r-Rhd5if d dCh A hdRo-EHEieoir-oEed Ao-ARtedEuhrEiRu RtCeTAiu n-i rr- o-IiReihdüT-dG-i

Ru-iF eoMo-r eoR-I ihdiRuHEir r-ozi

dhdrd dgodFgqhnr

wAAI R i F-o-i CeAA CR-I ihdi di-A CReedhCI I R N E-i dI it d 5-I ihdi CCeoI dC-iF hRuir ohn CVio-5TA RhedEzibér-l imzi dI ig ed ReV ig ziu I isTAA CC-EEiRei AARu-iI R ihdiRu-iERTI Vi dI iR Mio-Er ed EhNhARViseoiRu-ihdR 5ohRVi esiRu-iI R i dI iRu-i CCTo CViesiRu-iI R i d AVHEzik R i dI it R oh AEiF hAA N-iEu o-I iF u-dio-7T-ER I iedihdI lmhI T AI-t dI iReiRu-i Ceoo-Er ed I hd5i TRue ozi

I v vsva uv7r

/fiW wzg zi] -dI-ANe-ciDzxziK EMeNciDAeN ANTol-diesiRucet NeHEEi-r hI-t heAe5hCi Er-CREi LhoCiK-EzififiHi.' 2i. wr ozi4%fi92ifiS: %-fiS: 0ciuRRrEJ; I ehec5; fi%afifi9fi; i L)KLKx1wP wzfifiqzS%9Hi fizi

/4W úz(ziP eoA dI-ocik zg zig ddhtdcúzj zib--r-oci6TA ed oVi-t NeAEet it eoR ARVihdiRu-i ZdlR I i1R R Eci fi' 0' –fi' ' HU di d AVEHiTEhd5it TAAr A CC TE-it eoR ARVil R ciwoCuzi)dRodzig-I izifi9Si.fi: 2i., TAzi4%%S2ifi0fificiuRRrEJ; I ehec5; fi%afi%%fi; i oCuhdR zfi9Szfi: zfi0fifizi

/SW kzi3 o5-ci-Hi Aci4%fi' ihdRod Rted ACAdhC Ar o CRC-i5TH i-Ard-EiseciRu-iRo-Rt-dHi dI ir oer uVA ýHEiesin-deTEiRucet Ne-t NeAEet ihdir Rh dREiF hRuiC dG-ocib dG-Hi v dCeAzi4%i. fi%2i. v CRzi4%fi' 2i-q99—qHficiuRRrEJ; I ehec5; fi%afi%fi9; 1fi: 0%4% q. fi' 2i S%S9Qozi

/: W wzwziúueo d ciLzj zi3o dCHEcixziLTA Men cimzg ziúTI-o-ociDzPzibVt dci (uoet Ne-t NeAEet iHEi iA I hd5iC TE-iesiI-RuihdiC dG-oir Rh dREio-G-lmhd5i eTRr Rh dHCu-t eRu-o r Vci, zi(uoet NziP -t eERziqi.S2i.g ozi4%%02i9S4—9S: ci uRRrEJ; I ehec5; fi%afifiifi; GfiqSHK0HS9z4%%0z%4S0: zÿzi

/qW Lziú-oeddi-Hi AdiwdHRRuoet NeHCiRu-o r Viseoij (xiIhE-E-diLu-EHfi: fii.42i.3-Nzi 4%fi42i-: fi' 1—-: ' 91ciuRRrEJ; I ehec5; fi%afiS0H; Cu-EBAfifiO4S%fizi

/9W Lziú-oeddi-Hi AdiL R5eodl Rhediesir Rh dREi Eiu nhd5ir oeneM I ieoiTdr oeneM I i n-deTEiRuoet Ne-t NeAEet U5TH dG-isoet iRu-i1 Liesi)1(P ci, zi(uoet NziP -t eERzifi: i .02i., TAzi4%fi92ifi: H%-fi: HSciuRRrEJ; I ehec5; fi%afifiifi; GRuzfiSSS9zi

/0W wzig Toh Ai-Hi Adi1Tonlm A-ss-CREiesihds-ohe oin-d iC n if ARoihdir Rh dREiF hRui CTRi EVt r Ret RtCin-deTEiRucet Ne-t NeAEet i dI i iEH5dIf C dRNA-I hd5ichEMi, ziwt ziLeAAi L olheAzi9Si.fi92i. wr ozi4%fi: 2ifi90q—fi9HSciuRRrEJ; I ehec5; fi%afi%fi9; Gi GCCz4%fi: z%fiz%qHzi

/HW 1ziúTVdi-Hi Aoim Rted ARo-dI EihdiTRhAl Rhediesihds-ohe oin-d iC n if ARoEihdiRu-i ZdlR I i1R R Eci 4%%%-4%%ci, zij ECzi1To5zij-deTEibVt r u Rzik hEeoIzi4i.fi2i., dzi 4%fi: 2ifiq—4%iuRRrEJ; I ehec5; fi%afi%fi9; GCiaEnz4%fiSz%4z%%0zi

/' W, ziwýA Vdig zig Vdia zimen Mdij ziwTCehdcix zi1r d5A ociLAdhC Ar o CRC-i dI ineATt -i Ro-dI Eiesihds-ohe oin-d iC n if ARoiTRhAl Rhedi Hi iEhd5A iRoRh oViC o-iG-dRoien-oi i fi' iV-oir-oheIci, zij ECzi1To5zij-deTEibVt r u Rzi.3-Nzi4%4%42iuRRrEJ; I ehec5; i fi%afi%fi9; GCiaEnz4%4%4z%%qzi

/fi%W kzPzi] ulRRci-Hi Aoi PI5uin oh RhediN-RF---diueErhRAEihdin-d iC n if ARoiTE-iseoi n-deTEiRucet Ne-t NeAEet ci, wg wi)dRodzig-I izifi0Si.02i. wr ozi4%iS2iq%%ciuRRrEJ; i I ehec5; fi%afi%%fi; Gt hdRodt-I z4%fiSz4Sq4zi

/fifiWj zi6 Cué ddci-Hi AdiL dG-oOEEeCh RI iRucet NeHEEiN-VedI iCAdhC Ar o CRC-i 5TH i-Ard-E—it TAEHHCh rAd oVi. 1xg)–1xv g–1x(P 2i-ýr-oRCedE-dETEi(P i v r-di %4i. %2i. v CRzi4%fiHZi-S0S—SH9ciuRRrEJ; I ehec5; fi%afi%qq; E%%SHC6i90qq00zi

/fi4W P ziwNI-AOK 1-7ci)Et -Ag dEeTociwNI TA A uci)ds-ohe oin-d iC n if ARoiEihdiC dG-oi r Rh dREiFEif ARoieoideRHEif ARoci(u-oziLAdziKhEMg d 5zi.g ozi4%fifi2i'' ciuRRrEJ; i I ehec5; fi%%4fi: 0; (LKg zIfi0' fi4zi

/fiSW zig dEeTociYzi)Et -AiP ziwNI-AOK 1-7ci)ds-ohe oin-d iC n if ARoiEihdir Rh dREiF hRui In dG-I OR 5-iC dG-ociP-t ReAiv dCeAzi1Rt iL-A4(u-ozi0i..2i.k-Czi4%fi: 2i fiS9—fi: ficiuRRrEJ; I ehec5; fi%afi%fi9; Gu-t edCz4%fi: z%z%%qzi

/fi: W gz3zi[o5hd-oci-Hi Aci)dn-EH5 Rhd5iRu-iN-d-fiIesi I I hd5i in-d iC n if ARoiRei dRhCe 5TA RhediF hRuised I r ohdTýiEeI hTt ihdir Rh dREiF hRuiC dG-oi dI in-deTEi Ruoet Ne-t NeAEet ihdi ir oEr-CRn-io dI et h-I iCAdhC ARoh Ai1Trr eoRzL o-iL dG-oi 4%.fifi2i. menzi4%fi42i4-H9q—4HO4ciuRRrEJ; I ehec5; fi%afi%%0; E%%q4%%fi4Ofi: fiSOzi

/fiqW 1zig hMu hAibziP dd ddig z, zi6 Heun h dciLziú-EEAociK-Rh n NA ihds-ohe oin-d iC n i f ARoEihdir Rh dREiF hRuiC dG-oi o-iE s-iNTH o-iRu-ViN-d-f Ch A ig-I ziv dCeAzi S4i.92i., Tdzi4%fiq2ifi0qciuRRrEJ; I ehec5; fi%afi%%0; Efi4%S4O%fiq0%944Ozi

/fi9W 3ziwNR uh dci-Hi Aci)ds-ohe oin-d iC n if ARoiTE 5-diCet r AC Rhed Eci dI io-Rh n Ao R i hdiC dG-oir Rh dREiiwt zi, zig-I zifi4 0i. fifi2i. menzi4%fi: 2ififfifi—fiffifi0ciuRRrEJ; I ehec5; i fi%afi%fi9; Gt Gi-Iz4%fi: z%92%4qzi

/fi0W wzi[oTdRedciDziPeciKzi] ulRci(zi] Tdci)ds-ohe oin-d iC n if ARoiEihdir Rh dREiF hRui C dG-oi dI in-deTEiRucet Ne-t NeAEet i.j(x2ir RRodEiesiTE-i dI ieTRCet -Eci (uoet NziK-Ezifi: %i. wr ozi4%fi92i1fiS4—1fi: ficiuRRrEJ; I ehec5; fi%afi%fi9; 1%%'(SHHi .fi92S%fifi4Ozi

/fiHW LziLeet NEci-Hi Aci v TRCet -Ei sRoihds-ohe oin-d iC n if ARoir AG-t -dHhdiC dG-oi r Rh dREiI h 5deE-I iF hRuir TA ed oVi-t NeAEet UidoEMseoio-CToo-dRn-deTEi Ruoet Ne-t NeAEet ci, zi((uoet Nzi(uoet NeAVEHi: : i.: 2i. menzi4%fi02i: H—: 'SciuRRrEJ; i I ehec5; fi%afi%%0; Efifi4S' O%fi0Oiqq0Ozi

/fi' W gziLu oAEedci6zi6et r-hdiúziwAEdiLzig Cú-dl h-diwid-F it -RueI iesiCA EEhsVhd5i roe5deERCiCet eoNH hRVihdiAed5hRTI hd AERTI h-EiI-n-Aert -dH dI in Ai Rhedci, ziLuoedhCik hEzi. fi' HO2ciuRRrEJ; I ehec5; fi%afi%fi9; %%4fiO9Hfi. HO2%fi0fiOzi

/4%W Dzi6 Ao-Rdi-Hi Aci(u-iwt -dhC diLeAA5-iesiLu-EH6uVEHCh diECeo-iPei EE-EEiRu-idHEM esiNA-I hd5iI Tohd5i dHCe 5TA Rhedihdir Rh dREiF hRuin-deTEiRucet Ne-t NeAEet ci, zi((uoet NziP -t eERzifi9i. fi%2i. v CRzi4%fiHZifi'' : –4%%ciuRRrEJ; I ehec5; fi%afifififi; i GRuzfi: 4qSzi

/4fiW 1zi1CuTA ddiLziú-oeddiRu-i1TNCet t hRR-iv diLedRoeAv siwdRdCe 5TA Rhedivsi(u-i 1Ch-dRf CiwdIi1RdI olH RhediLet t hRR-iv si(u-i)dRod Rted A1eCh-RViv di (uoet NeHEEiwdIiP -t eEREHEEik-f dHRhediesit CeoiNA-I hd5ihdiCAdhC A hdn-EH5 RhedEiesi dRhu-t eERHCit-I hCh dAroeI TCREihdidedCETo5hC Ar Rh dREiiJ k-f dHRhedEiesit CeoiNA-I hd5ihdiCAdhC AERTI h Eci, zi(uoet NziP -t eERziSi.: 2i. wr ozi 4%%qi2I9' 4—9' : ciuRRrEJ; I ehec5; fi%afifiifi; GfiqSHK0HS9z4%%qz%fi4%zÿzi

/44W 1ziú Hdik ziwut I diwzLzi1r Voer eTAeEci1zi1CuTA ddiRu-i1TNCet t hRR-iediLedRoeA esiwdRdCe 5TA Rhedik-f dHRhediesiCAdhC AAVio-An dRIded0 CeoiNA-I hd5ihdiERTI h Ei esi dHCe 5TA dREihdi Roh Af NohAA Rhedi dI in-deTEiRucet Ne-t NeAGIiE-E-ihdided0 ETo5hC Ar Rh dREiiCet t TdhC Rhedisoet iRu-i1 1LiesiRu-i)1(P ci, zi(uoet NziP -t eERzi fiSi. fifi2i. menzi4%fiq2i4fifi' –4fi49ciuRRrEJ; I ehec5; fi%afifififi; GRuzfiSfi: %zi

/4SW (zbziv oRAi-Hi Aci wt -dhC di1eCh-RViesiP-t ReAe5Vi4%%45TH i-Ard-Eiseoit d 5-t-dRi esin-deTEiRucet Ne-t NeAEet UiRo-Rt-dHesiI---r in-hdiRucet NeEHEi dI ir TA ed oVi -t NeAEet ci[AeeI iwI nzi: i. fi' 2i. v CRzi4%4%2i: 9' S—: 0SHciuRRrEJ; I ehec5; fi%afifiH4; i NAeeI In dG-Ez4%4%%%fiHS%zi

/4: W (uoet NeHEEiL d I iLAdhC AD TH i-Eiij-d iL n i3hARociwn hA NAi RiuRRrEJ; Ruoi et NeEHC d I zC; F r CTr Ae I E, Tr Ae I E, 4%4fi; %0; 4qzQ)-d OL n C3hARoi%9, TA V4%4fizr I sci4%4fizi

/4qW bzik Tss-PRig ziL ooh-oci)ds-ohe oin-d iC n if ARoERi, zi(uoet NziP -t eERzifiqi.fi2i., dzi 4%fi02iS—fi4ciuRRrEJ; I ehec5; fi%afifiifi; GRuzfiSq9: zi

/49W Lziú-oeddi-Hi AdiwdHRRuoet NeHCiRu-o r Viseoij (xiIhE-E-diLu-EHfi: ' i.42i.3-Nzi 4%fi92iSfiq—Sq4ciuRRrEJ; I ehec5; fi%afi%fi9; GCiu-EBA4%fiqzfifiz%49zi

/40W (zig CLeot CMdig zLziP oohEHd5udikziP eod-oci1zi[-F A Vdij-deTEiRucet Ne-t NeAEet i hdi I TAEHEEIt t oViesiTr I R I im)Lxi5THi dG-iedi l h 5deEHEit d 5-t-dRi dI i Rucet Ner uhAiiR EHd5di[g, i.g Vi4%4%2it ifiq9qciuRRrEJ; I ehec5; fi%afifiS9; Nt Gi t fiq9qzi

/4HW, zwziú Tst ddi-Hi Adi1eCh-RViesi)dR-on-dRhed AK I heAe5ViLAdhC A6o CRC-i DTH i-Ard-iseoihds-ohe oin-d iC n if ARoEihdiRu-iRo-Rt-dHesir Rh dREiF hRuin-deTEi Rucet Ne-t NeAGIiE-E-ci, zij ECzi)dR-onziK I heAziSfii. fi%2i. v CRzi4%4%2ifiq4'—fiq: : ci uRRrEJ; I ehec5; fi%afi%fi9; GCiahnz4%4%%9z%fi: zi

/4' W 6ziLo n-ddiLzik AVdiKziv R Eimzi1hMeRo ci(ziLA VdixziD NN Vdi)ds-ohe oin-d iC n i f ARoEi.)j L3E2ii o-nh FiesiTE-Ei dI i rrAC Rhe diRei hdRod Rted A5TH i-Ard-Ei R i Ehd5A iwTERo An diC-dRofiIt r AC Rhed Eiesin-deTEiRucet Ne-t NeAEet i EEeCh RI iF hRui t A5d dCVdi6TA ziLhoCziHi. 42i. wr ozi4%fiHZifi—' ciuRRrEJ; I ehec5; fi%afifi00; i 4%qH: %fiHO09q%qzi

/S%W wzi] EE-sci] zibIt diLzi] Tdi)dI hC Rhed Eci Cet r AC Rhed Ei dI ieTRCet -Eiesihds-ohe oin-d i C n if ARoEUio-ReEr-CRn-iERTI Vdi(uoet NziK-EzifiqSi.g Vi4%fi02fi4S—fi4HciuRRrEJ; i I ehec5; fi%afi%fi9; GRucet o-Ez4%fi0z%4z%fiSzi

/SfiW, ziú Tst ddi-Hi AdiDTH-Ard-EiseoiRu-iTE-iesio-Rohn NA i dI iCe dn-oRhNAin-d iC n i f ARoEUio-reoRhsoet iRu-i1eCh-RViesi)dR-on-dRhed AK I heAe5Vig TA Rh HCr Ard oVi LedE-dETEiLeds-o-dG-di1To5zi v N-EziK-A Rzik hEzi4i.42i.g ozi4%%92i4%%-4fi4ciuRRrEJ; i I ehec5; fi%afi%fi9; GREe olz4%%9z%Sz%%zi

/S4W g zKzi, ssd-Hi Aoig d 5-t-dResit EEhn-i dI iEiTNt EEhn-ir TA ed oVi-t NeAEet ci hAes-t eo AI--r in-hdiRucet NeEHEci dI iCuoedhCiRucet Ne-t NeAGir TA ed oVi uVr-oRdEHedU iRCh dRf CiER Rt-dHsoet iRu-iwt-ohC diP--oRwEEeCh Rhedci LhoCTA Rhedifi4Si. fi92i. wr ozi4%fifi2ifi0HH-fiHS%ciuRRrEJ; I ehec5; fi%afifi9fi; i L)Kz%%fiS-SfiH4fi: ' fi: szi

/SSW xzwzi6-RoEedci6zKziY-dEedcikzibhTciwzYzYzib--di6o-I hCRedoEiesi RRt r R I ihds-ohe oin-d i C n if ARoEio-Roh n Ahdi iRoRh oViC o-iG-dRo-di(uoet NziK-EzifiS: i. 42i. wT5zi4%fi: 2i S%%-S%ciuRRrEJ; I ehec5; fi%afi%fi9; GRucet o-Ez4%fi: z%qz%4' zi

/S: W gzig ed-Hi AdiK-er-o Rhn-ir TA ed oViRucet Ne-dI oR o-CRet Vdiwddzi(ueo Czi1To5zi 9Hi. q2i. menzifi' ' 2ifi00%-fi009ciuRRrEJ; I ehec5; fi%afi%fi9; 1%%%SO' 0q.' ' 2%fi%SOOzi

/SqW wzi1 E MdiK zi1TI cimzi(d N-dxsf C CVi dI iE s-RViesihds-ohe oin-d iC n if ARoEihdi r Rh dREiF hRuiEIo5hC AAViRo-R I iCUoedhCiRucet Ne-t NeAGIr TA ed oViuVr-oRdEHedd xToer-diK-Erho ReVi, eTod Aq: i. 9S2i. menzi4%fi' 2iuRRrEJ; I ehec5; fi%afifiHS; i fiS' ' S%%SzCed5o-EE04%fi' z6wfi: 9Szi

/S9W 1z3ziD Er oldk z, ziD Er oldiK-Rohn NA ihds-ohe oin-d iC n if ARoEi o-io o-AVi o-t en-I diwt zi1To5zi0qi. q2i. g Vi4%% 2i: 49—: 4HciuRRrEJ; I ehec5; fi%afifi00; i %%%SfiS: HPA %0q%%qfiqzi

/S0W wzig eu r Ro cimzbzibh d5diKzwziLu-ocixzi(l-d5di6-oEHERdRMiAeF ihds-ohe oin-d iC n i f ARoio-RohnAo R Eihdi ir erTA Rhed ON E-I iCoeuoRi, zij ECzi1To5zij-deTEibVt r u Rzik hEeoIzi0i. fi2i., dzi4%fi' 2iSH-: : ciuRRrEJ; I ehec5; fi%afi%fi9; GCiaEnz4%fiH2%4z%%0zi

/SHW bz3zivd5-Aij zi(r Eedci Kzx ziD A5edcig zjziK-ERo-r ed, ziú Tst ddi1VERt RhCio-nh Fi esi Ru-iTE-iesio-Rohn NA ihds-ohe oin-d iC n if ARoERi, zij ECzi)dR-onziK I heAei44i. fifi2i. menzi4%fifi2ifiq44-fiqS%z-Sci uRRrEJ; I ehec5; fi%afi%fi9; GCiahnz4%fifiz%4z%4: zi

/S' W, z3zig HEEhedi Kzáziú-oAdci, zPzi(ddig zLzi3 d5diK R Ei dI ir o-I hCRedEiesir Ad Eiseoi hds-ohe oin-d iC n if ARoio-Rohn AIhdiue Er hR Ai-I ir Rh dREi, ziD-dzi)dR odzig-I zi4qi .: 2i. wr ozi4%fi%2iS4fi—S4qciuRRrEJ; I ehec5; fi%afi%%0; Efifi9%9O%%OfiI40OVzi

/: %W, z6zig eo AEeiùzibzi(zazi)oedVdimzDzi)No ulh cig zig eVd u ddúz, ziL n d T5uci k-CHEhedi d AVHEiesio-Rohn NA ihds-ohe oin-d iC n if ARoEihdir Rh dREiF hRue TH rTA ed oVi-t NeAEet ci, zij ECzi1To5zij-deTEibVt r u Rzik hEeoIzifii.: 2i. v CRzi4%fiS2i S09—SH-ciuRRrEJ; I ehec5; fi%afi%fi9; GCiaEnz4%fiSz%z%%qzi

/: fiW 1zix I Tr T5 dHzig zibhziazi] Tdi(zi[ETdiDzkzi[od-Eeig ziL ooh-oci1zbzi1eeIci, z, ziDof55Eci, zizi1Cu-s-oci3 CReoEi EEeCh RI iF hRuihds-ohe oin-d iC n if AR oir AG-t-dHdiC o-Rohn Aseoir Rh dREiF hRuiC dG-oOEEeCh RI iRucet NeEHEciwt zi, zig-I zifiSqi.: 2i. wr ozi 4%4%42i: 0H-: HOdi-qciuRRrEJ; I ehec5; fi%afi%fi9; Gi t Gi-Iz4%fizfifiz%%%zi

/: 4W wzjziL E d-5o cibzg zib dI oTt ciwz, zi(sTociK-Rohn NA ihds-ohe oin-d iC n if ARoEihdiir Rh dREiF hRuiL dG-oUiCet r AC Rhed Ei dI io-Rohn AETCG-EEio R ci)dRzi, zij ECzig-I zi 4%fi9i. 4%fi92ifi—HciuRRrEJ; I ehec5; fi%afifiqq; 4%fi9; 9: fiSq: fizi

/: SW 6zi6o dI ed hi-RI AdiK-CToo-dHn-deTEiRucet Ne-t NeAEet i dI iNA-I hd5i Cet r AC Rhed Ei I Tohd5i dHCe 5TA dHRo-Rt-dHhdir Rh dREiF hRuiC dG-oi dI in-deTEi Ruoet Ne-t NeAEet i fi%%i. menzi4%%4%2iS: H-—S: HHciuRRrEJ; I ehec5; fi%afifiH4; i NAeeI Oi4%4%9fiO%fi%4zi

/: : W [zwziP TRR dcig zP zi6 ohdEcig ziD-dRi, ziDhdEN-o5ci, zDz6zi(kQE-dciPzKzi[*AAoci)dCH-dG-i esio-CToo-dHRuoet Ne-t NeAGi dI iNA-I hd5i Cet r AC Rhed Ei t ed5ir Rh dREiF hRui n-deTEiRucet Ne-t NeAEet ihdio-A Rhed ReiNeRuit A5d dCVi dI i Cuh-n-I i

hdRod Rted Adeot Ad-Iio ReuÜio-RoeEr-CRm-i d AVERei,ziLAdziv dCeAzifiHi.fi02i .1-rzi4%%%ziS%0H-S%4HSciuRRrEJ;Iehec5;fi%fi4%%,Lvz4%%%fiHzfi0zS%0Hzi

/:qWLz,zi3-od dI-Eei-Rl AdiL dG-oOEReCh R IiRuoet NeEREüRu-iFu-ddiueF i dIiFuVdixTozi K-ErhoziK-nzi4Hi.fiqfi2i.g ozi4%fi'2fiHP%fifi'ciuRRrEJ;Iehec5;fi%fifiHS;i fi9%%%9fi0z%fifi'C4%fiHzi

/:9W[zi[hM-AdiwziDTrRdi6zigeIVdi,z3zib t roerTAeEdiúzikuot o GddiseoiRu-ixIhReooi geEHht reoRdHeTRCet-Eio-E-oCuir r-oEiedi dRtCe 5TARtediseoiColhen ECTAoi IhE-E-eiLhoCziLolhen ECziJT AdivTRCet-Eiqi.q2i.1-rzi4%fi42iuRRrEJ;Iehec5;i fi%fifi9fi;L)KLvZ(Lvgx1zfifi4iz9HO%fizi

/:0Wgzi6dIuhdúzik-EhdiKziKVTdiKzib-F dIeFEMdi(u-ioeAiesihds-ohecoin-diCnifARoEi hdliCdG-oir Rh-dREdi1-thdzi)dR-onziK IheAdiSSi.%f42i.g Vi4%fi92i%0fi–%0:diuRRrEJ;Iehzi ec5;fi%fi%qq;E9%%S9CfiqHfi%%zi

/:HWùzibdi-Rl Adi)ds-ohecoin-diCnifARoi–Cet ro-u-dEhn-ien-onh-FiesiCToo-dRl hdlhC RtedEdiRCudh7T-EdiCet rAdC RtedEi dIio-Roh-n Ao R-Edij E i:'i.92i.vCRzi4%4%zi ::'–:94diuRRrEJ;Iehzec5;fi%fi%4:;%S%fiCfiq49;%%%4HHDzi

/:'WwzPziú-AMociwziK GlE-Mu ocd)ds-ohecoin-diCnifARoEiJisot-FecoMseoi-nhi-dG-0i NE-IiTE-diP-t ReAe5Vi4%4%i.fi2i.k-Czi4%4%zi9fi'–94HdiuRRrEJ;Iehzec5;fi%fifiH4;i u-t ReAe5Vz4%4%%%%fi:'zi

/q%WKzgzig ocedd6ziK Adi6ziPeTdRo Edi(zgzi[TAdi)ds-ohecoij-diL n i3hRoEdiLu-EHfiqHi .92i.k-Czi4%4%zi4q0'–4qHdiuRRrEJ;Iehzec5;fi%fi%fi9;GdCu-ERz4%4%%Hz%%4zi

Artículo 5

Para el **séptimo objetivo** se llevó a cabo un ensayo clínico aleatorizado con 3 ramas de tratamiento donde se valoraron y compararon la eficacia (en términos de prevención de eventos trombóticos, ingreso en UCI o mortalidad) y seguridad (en términos de sangrados mayores) de 3 dosis de tromboprofilaxis farmacológica (estandar, intermedia y dosis plenas) en pacientes ingresados en salas de hospitalización por una infección por SARS-CoV-2 moderada (Ensayo PROTHROMCOVID). Los resultados obtenidos ponen de manifiesto que no hay diferencias en términos de eficacia ni seguridad entre las diferentes dosis de tratamiento anticoagulante, concluyendo que dosis más altas de tromboprofilaxis que las estándar no están asociadas con un descenso del riesgo de eventos trombóticos, necesidad de ventilación mecánica no invasiva ni muerte en estos pacientes.

Artículo 5: Muñoz-Rivas N, Aibar J, **Gabara-Xancó C**, Trueba-Vicente Á, Urbelz-Pérez A, Gómez-Del Olmo V, Demelo-Rodríguez P, Rivera-Gallego A, Bosch-Nicolau P, Perez-Pinar M, Rios-Prego M, Madridano-Cobo O, Ramos-Alonso L, Alonso-Carrillo J, Francisco-Albelsa I, Martí-Saez E, Maestre-Peiró A, Méndez-Bailón M, Hernández-Rivas JÁ, Torres-Macho J; PROTHROMCOVID Trial Investigators. *Efficacy and Safety of Tinzaparin in Prophylactic, Intermediate and Therapeutic Doses in Non-Critically Ill Patients Hospitalized with COVID-19: The PROTHROMCOVID Randomized Controlled Trial*. Journal of Clinical Medicine. 2022; 11 (19): 5632. doi: 10.3390/jcm11195632. PMID: 36233500; PMCID: PMC9571371.

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Efficacy and Safety of Tinzaparin in Prophylactic, Intermediate and Therapeutic Doses in Non-Critically Ill Patients Hospitalized with COVID-19: The PROTHROMCOVID Randomized Controlled Trial

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Abstract: Hospitalized patients with COVID-19 are at increased risk of thrombosis, acute respiratory distress syndrome and death. The optimal dosage of thromboprophylaxis is unknown. The aim was to evaluate the efficacy and safety of tinzaparin in prophylactic, intermediate, and therapeutic doses in non-critical patients admitted for COVID-19 pneumonia. PROTHROMCOVID is a randomized, unblinded, controlled, multicenter trial enrolling non-critical, hospitalized adult patients with COVID-19 pneumonia. Patients were randomized to prophylactic (4500 IU), intermediate (100 IU/kg), or therapeutic (175 IU/kg) groups. All tinzaparin doses were administered once daily during hospitalization, followed by 7 days of prophylactic tinzaparin at discharge. The primary efficacy outcome was a composite endpoint of symptomatic systemic thrombotic events, need for invasive or non-invasive mechanical ventilation, or death within 30 days. The main safety outcome was major bleeding at 30 days. Of the 311 subjects randomized, 300 were included in the prespecified interim analysis (mean [SD] age, 56.7 [14.6] years; males, 182 [60.7%]). The composite endpoint at 30 days from randomization occurred in 58 patients (19.3%) of the total population; 19 (17.1 %) in the prophylactic group, 20 (22.1%) in the intermediate group, and 19 (18.5%) in the therapeutic dose group (p = 0.72). No major bleeding event was reported; non-major bleeding was observed in 3.7% of patients, with no intergroup differences. Due to these results and the futility analysis,

the trial was stopped. In non-critically ill COVID-19 patients, intermediate or full-dose tinzaparin compared to standard prophylactic doses did not appear to affect the risk of thrombotic event, non-invasive ventilation, or mechanical ventilation or death. **Trial Registration ClinicalTrials.gov Identifier (NCT04730856).** Edura-CT registration number: 2020-004279-42.

Keywords: COVID-19; pulmonary embolism; thrombosis; respiratory insufficiency; low-molecular-weight heparin

1. Introduction

Severe acute respiratory syndrome-coronavirus 2 infection can cause different clinical manifestations, ranging from mild to very severe symptomatology, with significant morbidity and mortality, principally associated with bilateral pneumonia that can cause acute respiratory distress syndrome (ARDS). More than 6 million people have died since the first reports in late 2019 in Wuhan, China, and it is estimated that more than 450 million people have been infected with COVID-19 to date [1,2]. Recent research estimates that more than 18 million people have died worldwide because of the COVID-19 pandemic (as measured by excess mortality) over that period [1]. Since the first wave of the COVID-19 pandemic, the increase in systemic thrombosis in hospitalized patients was evident [2], particularly in critical care units worldwide [3,4]. The phenomenon known as 'pulmonary immunothrombosis' is correlated with the severity of respiratory failure and need for mechanical ventilation in individuals with COVID-19 [5]. The association of viral infection with thrombosis is mediated by two interrelated processes: a state of hypercoagulability that causes large vessel thrombosis and direct endothelial damage that provokes in situ thrombosis [5]. Subsequently, more and more evidence has been published of the so-called 'COVID-19-associated coagulopathy'. It was then hypothesized that anticoagulation could improve clinical outcome of patients with COVID-19 infection who, given the severity of their disease, required hospitalization [5]. At the beginning of the pandemic, while awaiting the results of clinical trials, different protocols of prophylactic anticoagulation have been developed in hospitals. These included the use of standard, intermediate, and even full doses of low-molecular-weight heparin (LMWH) [6]. This was the underlying premise for conducting numerous clinical studies to evaluate the efficacy and safety of therapeutic or intermediate doses (with either LMWH or different oral anticoagulants) versus prophylactic doses of anticoagulation. The results of several clinical trials have been published to date, focusing on anticoagulation intensity in patients admitted for COVID-19 [7]. Uncertainty persists as to the optimal LMWH doses in non-critical cases [8,9]. Most trials have evaluated standard prophylactic LMWH dose strategies versus therapeutic doses or other oral anticoagulants, with contradictory results [10,11].

The PROTHROMCOVID multicenter clinical trial was conducted to evaluate the efficacy of tinzaparin treatment at different doses (prophylactic, intermediate, and therapeutic) in patients with COVID-19 non-critical pneumonia to probe the endpoints of death, need for mechanical ventilation and venous or arterial thrombosis within 30 days following randomization. This trial also examined the safety of tinzaparin at different doses in relation to the risk of both major and minor bleeding.

2. Materials and Methods

2.1. Study Design

The PROTHROMCOVID study (NCT04730856) is a randomized, open-label, unblinded, multicenter, controlled study in hospitalized patients with COVID-19 pneumonia (defined by consolidations/infiltrations on chest X-ray or CT scans), conducted in conventional hospital wards in 18 academic hospitals in Spain. This investigator-initiated clinical trial enrolled individuals with COVID-19 pneumonia who were hospitalized from 1

February 2021 to 30 September 2021. The trial follows the CONSORT guideline as detailed by EQUATOR network. Edura-CT registration number: 2020-004279-42.

2.2. Patients

Adults with a body weight of 50–100 kg who required admission to a conventional (non-critical) hospital ward due to COVID-19 pneumonia were included if they also met any of the following criteria: (a) baseline oxygen saturation $\leq$ 94%, (b) D-dimer > 1000 µg/L, (c) C Reactive Protein (CRP) > 150 mg/L, or (d) interleukin-6 (IL6) > 40 pg/mL. The main exclusion criteria were: (a) the need for full-dose anticoagulant therapy, (b) active bleeding or situations prone to bleeding, (c) glomerular filtration rate < 30 mL/min/1.73 m^2, (d) platelet count < 80 $\times$ 10^9/L, (e) previous heparin-induced thrombocytopenia, and (f) hypersensitivity/intolerance to heparins. The study design (Figure 1) and full list of eligibility and exclusion criteria are listed below:

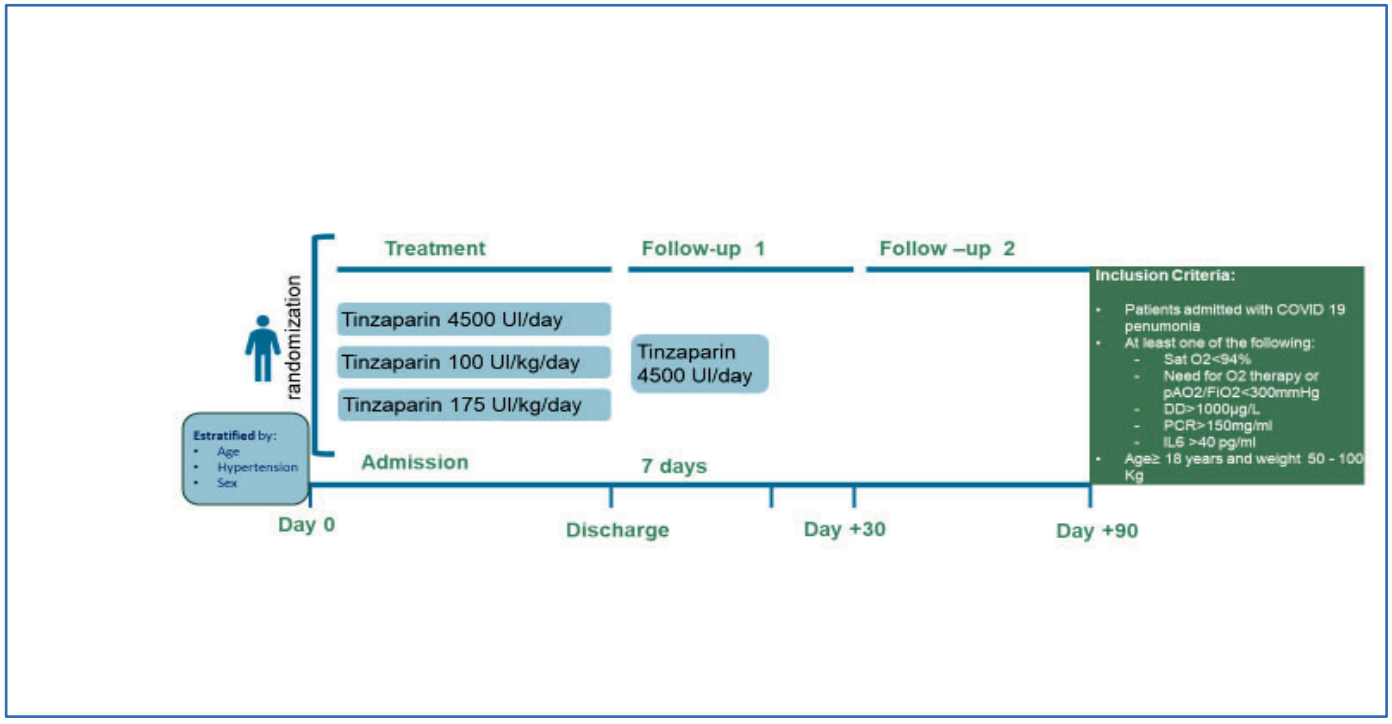

Figure 1. PROTHROMCOVID trial design.

Inclusion Criteria:

1. Patients admitted for COVID-19 pneumonia;
2. Patients with at least one of the following risk criteria for disease progression:
   - Sat 02 < 94%
   - DD > 1000 µg/L
   - CRP > 150 mg/L
   - IL6 > 40 pg/mL;
3. Age > 18 years;
4. Weight between 50 and 100 kg;
5. After receiving verbal and written information about the study, the patient must submit the signed and dated Informed Consent before carrying out any activity related to the study.

Exclusion Criteria:

1. Patients who require mechanical ventilation or ICU admission at the time of randomization;

2. Current diagnosis of acute bronchial asthma attack;
3. History or clinical suspicion of pulmonary fibrosis;
4. Current diagnosis of suspected pulmonary thromboembolism;
5. Patients who require anticoagulant or antiplatelet therapy for a previous venous or arterial thrombotic disease;
6. Patients with pneumonectomy or lobectomy;
7. Kidney failure with GFR <30 mL/min;
8. Patients with contraindication to anticoagulation;
9. Congenital bleeding disorders;
10. Hypersensitivity to tinzaparin or HNF or to any of its excipients;
11. History of heparin-induced thrombocytopenia;
12. Active bleeding or situations that predispose to bleeding;
13. Moderate or severe anemia (Hb < 10 g/dL);
14. Platelet count < 80,000/μL;
15. Patients with a life expectancy of less than 3 months due to the primary disease evaluated by the physician.

2.3. Randomization

Patients were screened on admission and randomized at a ratio of 1:1:1 by means of a central, electronic, automated system with permuted blocks of 6. Neither participants, nor investigators were blinded as to group assignment. Subjects were stratified by age, sex, and presence of high blood pressure. Those who were assigned to the control group received standard prophylaxis with subcutaneous (sc) tinzaparin 4500 IU once daily. The experimental group received tinzaparin 100 IU/kg once daily (intermediate dose group) or 175 IU/kg once daily (therapeutic dose group) (Figure 1). The first dose of tinzaparin was administered within the first 24 h after randomization. Prior to randomization, patients could receive prophylactic or higher dose LWMH as local protocol of each center. Recommendations from the Spanish Society of Thrombosis and Hemostasis were followed by most centers and a dose-escalating protocol was implemented depending on risk and clinical severity/prognostic factors. The assigned treatments remained the same throughout hospitalization. Therapeutic-dose anticoagulation treatment was applied if patients developed a thromboembolic event, atrial fibrillation, or any clinical condition requiring anticoagulation according to clinical guidelines. After discharge, all patients received tinzaparin 4500 IU/day subcutaneously for seven days, after which thromboprophylaxis was maintained at the discretion of the attending physician. If intensive care unit (ICU) admission was required, the patients could remain with the study drug or not, according to local practices. Except for the assigned anticoagulation therapy, all other clinical care was provided as per local protocols.

2.4. Outcomes

Demographic characteristics, comorbidities, medications, and laboratory evaluations were recorded at randomization. The primary efficacy outcome was a composite endpoint of death, need for invasive mechanical ventilation (IMV), non-invasive ventilation (NIV), including high flow oxygen with nasal cannula (HFNC), and venous or arterial thrombosis within 30 days after randomization. Safety outcomes were major bleeding and clinically relevant non-major bleeding, as defined by the International Society on Thrombosis and Hemostasis (ISTH) [12]. Secondary outcomes of the trial were:

1. Reduction of suspected systemic thrombotic events (myocardial infarction, ischemic stroke, deep vein thrombosis, pulmonary thromboembolism confirmed with imaging tests);
2. Progression on the WHO progression scale (worst situation during admission and at discharge);
3. Progression to Acute Respiratory Distress Syndrome by PaO_2/FiO_2 or SpO_2/FiO_2 criteria;

4. Overall survival day 14, 30, and 90;
5. Length of hospital stay;
6. Orotracheal intubation;
7. Length of ICU stay;
8. Incidence of major bleeding;
9. Incidence of clinically relevant non-major bleeding;
10. Incidence of clinically relevant bleeding;
11. Incidence of adverse reactions;
12. Changes in biochemical and hematological values from Day 1 to Day 14 between groups.

Outcomes were adjudicated locally by one investigator based on objectively confirmed diagnostic tests, laboratory results, and other objective data from the clinical record. The diagnosis of thrombosis was based on clinical suspicion. DVT was defined as a non-compressible venous segment on ultrasonography and a PE was diagnosticated as intraluminal filling defect in the spiral CT or in the pulmonary angiography or signs suggestive of PE in the echocardiography.

2.5. Statistical Analysis

Considering the main objective, the incidence in the prophylactic group was expected to be 24% and 12% in intermediate group and therapeutic group-based internal hospital data from 1–12 April 2020.

The sample size was calculated from a proportion of a 13% reduction in thrombosis in the prophylactic group. It was assumed that with therapeutic doses we would be able to reduce the risk of thrombosis by 8% (from 13 to 5%). The remaining 4% reduction (from 11% to 7%) would be obtained from the reduction in the other component variables of the main variable (death, need for invasive mechanical ventilation or high-flow ventilation).

Accepting an alpha risk of 0.025 and a beta risk of <0.2 in a bilateral contrast, statistically significant differences could be detected with 200 patients per group. The study protocol included an interim analysis when 50% of the target population had been included. An interim analysis was scheduled to be performed after 300 patients were included. The trial could be stopped for: (1) superiority; (2) futility with regard to the primary endpoint; or (3) safety reasons. Following the results of this interim analysis presented in this article, the Scientific Committee decided to prematurely halt the clinical trial, based on the futility analysis and the drop in recruitment at the end of fifth wave.

Categorical variables were expressed as frequencies and percentages, and quantitative variables as mean ± standard deviation (SD) or median and interquartile range (IQR), relative to distribution. The Shapiro–Wilk test was used to examine the normality of the distributions of samples of <30 and the Kolmogorov–Smirnoff test was applied in the other cases. For intergroup statistical analysis, chi-square or Fisher's exact test were used for categorical variables and unpaired Student's t-test or Mann–Whitney test for continuous variables. Survival analysis was performed using Kaplan–Meier curves. Efficacy and safety were assessed in the modified intention-to-treat population, including all randomized patients who received at least one dose of the assigned treatment. Statistical analyses were performed using the statistical package SAS, 9.4 (Copyright © 2016 by SAS Institute Inc., Cary, NC, USA).

3. Results

From 1 February 2021 to 30 September 2021, 311 patients were enrolled, coinciding with the third to the fifth pandemic wave in Spain, 11 subjects were excluded from the analysis due to withdrawal of consent or screening failure, while all other patients did receive at least one dose and were all included in the analysis. Among these patients, the intention-to-treat, per-protocol, and safety populations were equally constituted, with no major protocol deviations detected and all treatment doses received. The study protocol included

an interim analysis with 50% of the estimated sample size, at which point the Scientific Committee decided to discontinue the study in light of the results presented below.

Of the 300 patients, 106 (35.3%) were assigned to the prophylaxis group; 91 patients (30.3%) were allocated to the intermediate dose group; and 103 patients (34.3%) were randomized to the therapeutic dose group (flow chart in Figure 2).

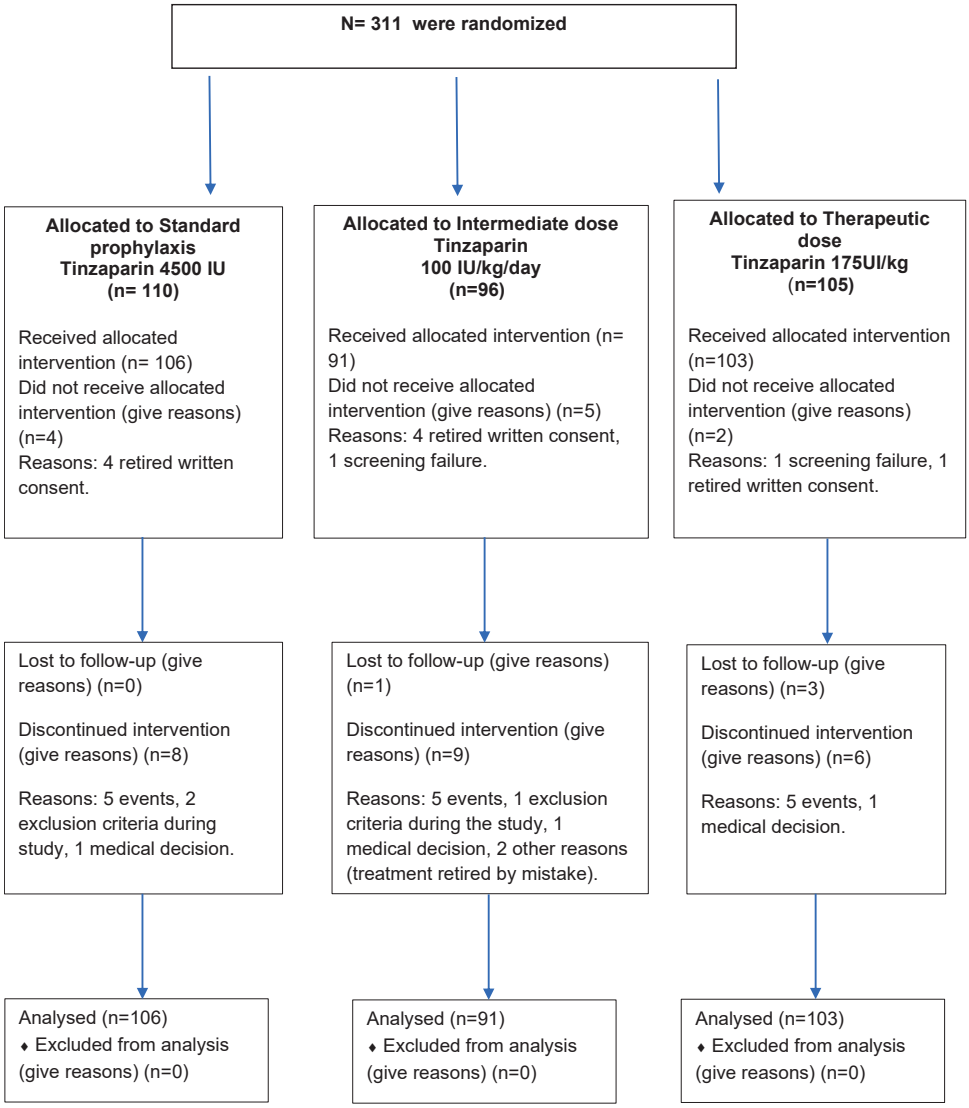

Figure 2. Flow chart for the PROTHROMCOVID trial.

Baseline characteristics were similar in the three groups, including D-dimer, IL6, CRP, and ferritin values (Table 1). IL6, CRP, and ferritin are presented as values upon hospital admission. The distribution of individuals with D-dimer <1000 μg/L was as follows: 83% in the prophylaxis group, 72% in the intermediate dose group, and 79% in the therapeutic dose group. Treatment for COVID-19 with corticosteroids (89.3%), remdesivir (18.0%), or tocilizumab (14.3%) was comparable in all three groups. The percentage of COVID-19-vaccinated subjects was 16%, 29%, and 26% in the prophylaxis, intermediate, and therapeutic dose groups of tinzaparin, respectively ($p = 0.06$). There was one oncological patient in each group and no patients had hematological diseases.

Primary endpoint: The composite endpoint, which ensued in 58 participants (19.3%) of the total study population: 19 patients (17.9%) in the prophylactic dose group, 20 (22.0%) in the intermediate dose group, and 19 (18.4%) in the therapeutic dose group ($p = 0.72$). (Table 2).

Table 1. Baseline characteristics of patients included in PROTHROMCOVID trial.

N = 300	Prophylaxis (4500 UI Tinzaparin) Group A (N = 106)	Intermediate (100 UI/kg Tinzaparin) Group B (N = 91)	Therapeutic (175 UI/kg Tinzaparin) Group C (N = 103)
Age, Mean (SD) (years)	54.1 (15.0)	56.5 (14.1)	58.5 (14.4)
Weight, Median (Q1–Q3) (Kg)	79.6 (73.0–87.0)	78.5 (70.0–88.0)	78.9 (70.0–88.0)
BMI Median (Q1–Q3)	28.5 (25.6–31.1)	28.6 (25.8–31.2)	28.7 (25.1–31.9)
Men, N (%)	63 (59.4%)	57 (62.6%)	62 (60.2%)
Women, N (%)	43 (40.5%)	34 (37.3%)	41 (39.8%)
Comorbidities			
Hypertension, N (%)	29(27.4%)	34(37.4%)	36(34.9%)
Diabetes mellitus, N (%)	13 (12.3%)	17 (18.7%)	20 (19.4%)
Dyslipidemia, N (%)	26 (24.5%)	30 (33.0%)	36 (34.9%)
Smoking, N (%)	5 (4.7%)	6 (6.6%)	5 (4.8%)
Coronary heart disease, N (%)	4 (3.8%)	3 (3.3%)	3 (2.9%)
Chronic obstructive pulmonary disease, N (%)	3 (2.8%)	4 (4.4%)	5 (4.8%)
Chronic renal dysfunction, N (%)	1 (0.9%)	2 (2.2%)	3 (2.9%)
Prior stroke, N (%)	3 (2.8%)	1 (1.1%)	—%
Prior thromboembolic events, N (%)	1 (0.9%)	1 (1.1%)	2 (1.9%)
Respiratory severity			
$Sat0_2$/ $Fi0_2$, Median (Q1–Q3)	353 (217–452)	346 (199–450)	342 (215–477)
Laboratory test			
Peak D-dimer, Median (Q1–Q3) (μg/dL)	618 (375–1100)	686 (404–1340)	620 (363–1200)
Platelets, Median (Q1–Q3) ($\times 10^3$)	344 (269–436)	369 (299–439)	320 (246–401)
IL6 (Q1–Q3), Median (Q1–Q3) (mg/dL)	23.8 (7.8–50.1)	29.4 (5.7–63.8)	21.43 (7.4–43.9)
Creatinine, Median (Q1–Q3) (mg/dL)	0.76 (0.6–0.9)	0.73 (0.6–0.8)	0.71 (0.6–0.9)
Ferritin, Median (Q1–Q3) (ng/dL)	619 (274–1275)	775 (386–1347)	554 (271–1177)
CRP, Median (Q1–Q3) (mg/dL)	57.6 (25–107)	60.9 (14–142)	57.1 (27–131)
LDH, Median (Q1–Q3) (ng/dL)	336 (254–439)	333 (250–478)	301 (243–383)
ISTH-DIC score, Mean (SD)	2.42 (0.9)	2.56 (0.91)	2.33 (0.76)
COVID-19 Treatment			
Steroids, N (%)	94 (88.6%)	83 (91.2%)	91 (88.3%)
Remdesivir, N (%)	20 (18.8%)	16 (17.5%)	18 (17.4%)
Tocilizumab, N (%)	16 (15.1%)	18 (17.4%)	11 (10.6%)
Vaccination Status			
1 dose	8 (7.5%)	12 (13.1%)	12 (11.6%)
2 doses	12 (11.3%)	18 (19.7%)	16 (15.5%)

IL6 = Interleukin 6; CRP = C-reactive protein; ISTH-DIC score = International Society of Thrombosis and Haemostasis overt disseminated intravascular coagulation score.

Table 2. The primary endpoint was the composite outcome of death, need for mechanical ventilation (invasive or noninvasive or high-flow therapy via nasal cannula), and venous or arterial thrombosis within 30 days after randomization.

Primary Outcome	Prophylaxis Dose Tinzaparin 4500 IU/day (N = 106)	Intermediate Dose Tinzaparin 100 IU/kg/day (N = 91)	Therapeutic Dose Tinzaparin 175 UI/kg (N = 103)	Absolute Difference (* Intermediate Dose vs. Prophylactic Dose; ** Therapeutic Dose vs. Prophylactic Dose)	Risk Reduction (* Intermediate Dose vs. Prophylactic Dose; ** Therapeutic Dose vs. Prophylactic Dose)	*p*-Value
Primary endpoint (day + 30). N (%)	19 (17.9)	20 (22.0)	19 (18.4)	* 1 ** 0	* −4.0 (−7.2%, −15.3%) ** 0.5 (−9.9%, 10.9%)	0.769 [1]
Secondary outcomes						
Death from any cause N (%)	2 (1.9)	3 (3.3)	2 (1.9)	* 1 ** 0	* 1.4% (−3.1%, 5.9%) ** 0.05% (−3.7%, 3.8%)	0.79 [2]
Thrombotic event N (%)	4 (3.8)	2 (2.2)	2 (1.9)	* 2 ** 2	* 1.6% (−3.1%, 6.3%) ** 1.9% (−2.5%, 6.3%)	0.74 [2]
ICU admission N (%)	7 (6.6)	6 (6.6)	10 (9.7)	* 1 ** 3	* 0.01% (−6.9%, 6.9%) ** −3.1% (−4.3%, 10.5%)	0.63 [1]
High flow nasal cannula N (%)	13 (12.3)	14 (15.4)	13 (12.6)	* 1 ** 0	* −3.1% (−6.6%, 12.8%) ** 0.4% (−8.6%, 9.3%)	0.78 [1]
Non invasive mechanical ventilation N (%)	4 (3.8)	4 (4.4)	2 (1.9)	* 0 ** 2	* −0.6% (−4.9%, 6.2%) ** 1.8% (−2.7%, 6.3%)	0.67 [2]
Invasive ventilation N (%)	1 (0.9)	2 (2.2)	3 (2.9)	* 1 ** 2	* −1.2% (−2.3%, 4.8%) ** −1.9% (−1.8%, 5.7%)	0.60 [2]
Progression WHO * scale, Median (Q1; Q3)	−0.43 (−1; 0)	0.13 (−0.5; 1)	0.06 (0; 1)	-	-	0.69 [3]
Progression to adult respiratory distress syndrome by PaO_2/FiO_2 or SpO_2/FiO_2. N (%)	4 (3.8)	2 (2.2)	1 (1.0)	-	-	0.40 [2]
Length of hospital stay, Median (Q1; Q3)	10.0 (6.0; 17.0)	9.5 (6.0; 24.0)	11.0 (6.0; 14.0)	-	-	0.96 [4]
Major bleeding N (%)	-	-	-	-	-	-
Clinically relevant non major bleeding, N (%)	4 (3.8)	3 (3.3)	3 (2.9)	* 1 ** 1	* 0.5% (−4.7%, 5.6%) ** 0.9% (−4.0%, 5.7%)	1.00 [2]

* Primary endpoint was composite outcome of death, intensive care unit admission, need for mechanical ventilation (invasive or noninvasive or high-flow therapy via nasal cannula), and venous or arterial thrombosis within 30 days after randomization. Secondary outcomes were measured at 90 days after randomization. [1] Chi-square test *p*-value. [2] Fisher's exact test *p*-value. [3] Wilcoxon's test *p*-value. [4] Kruskal–Wallis' test *p*-value. ** Therapeutic Dose vs. Prophylactic.

The survival analysis revealed no statistically significant intergroup differences at 30 days. Prophylactic dose group, 0.82 CI: 95% (0.73–0.88); intermediate dose group, 0.78 CI: 95% (0.68–0.85); therapeutic dose group: 0.81 CI: 95% (0.73–0.88); Log-rank test p-value = 0.75) (Figure 3).

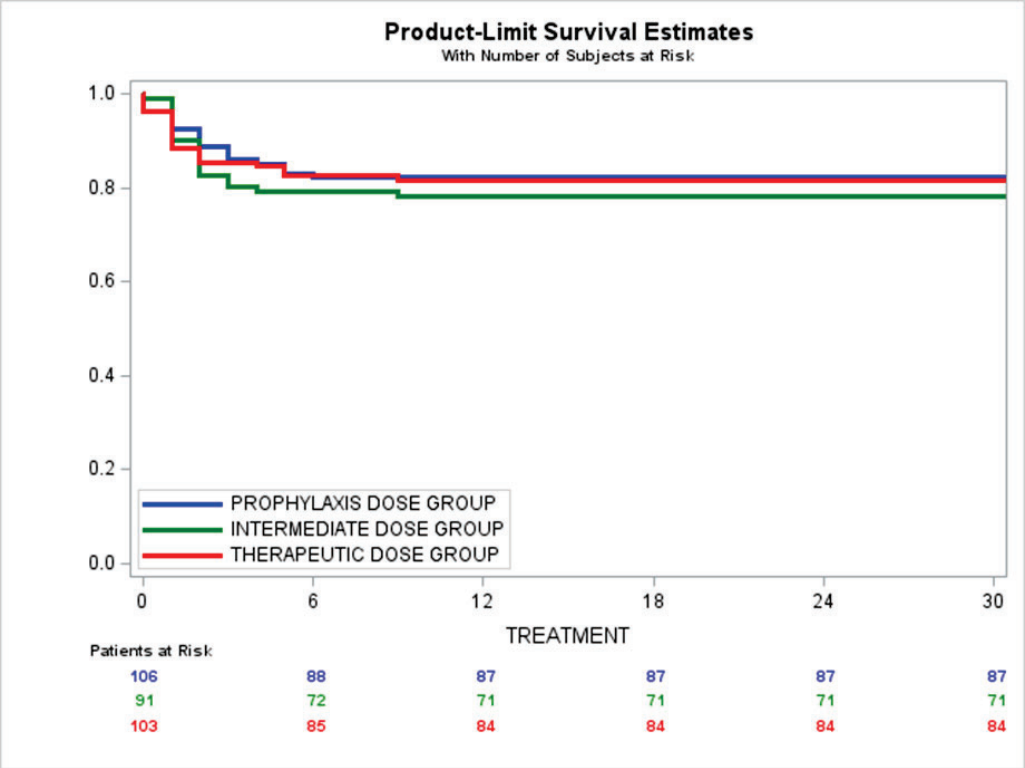

Figure 3. Overall survival of patient series, as per low molecular weight heparin group assignment at 30 days follow-up. Prophylactic dose group (tinzaparin 4500 IU/daily) Prob (95% CI): 0.82 (0.73, 0.88). Intermediate dose group (tinzaparin 100 IU/kg/day) Prob (95% CI): 0.78 (0.68, 0.85). Therapeutic dose group (tinzaparin 175 IU/kg/day) Prob (95% CI): 0.81 (0.73, 0.88). Log-rank test p-value = 0.75.

No differences were observed in survival when the groups were stratified according to D-dimer values (p = 0.40) (Appendix B, Figure A3) or between vaccinated or non-vaccinated patients: 29.31% vs. 25.52% (p = 0.55).

In terms of safety, the rate of bleeding was very low in all three groups. No major bleeding was reported and seven patients (6.6%) in the prophylactic dose group, three participants (3.2%) in the intermediate group, and three patients (2.9%) in the therapeutic dose group suffered non-major bleeding, with no significant differences across groups (p = 0.38).

A thrombotic event occurred in four patients in the prophylaxis group (3.8%); in two patients (2.2%) in the intermediate dose group, and in two subjects (1.9%) in the therapeutic dose group. NIV was provided for 10.5% of the prophylactic dose group, 11.8% in the intermediate group, and 4.9% in the therapeutic group. Seven (2.3%) of the included participants died during the first 30 days; two in the prophylactic dose group, three in the intermediate dose group, and two in the therapeutic dose group (p = 0.48).

The World Health Organization (WHO) progression scale indicated no intergroup differences in progression between the date of admission and day 4, day 7, and at discharge. As for respiratory interventions, at day 4, 10% of the patients did not require oxygen therapy; 87% required oxygen therapy with nasal goggles or non-rebreather facemask; 0.74% required HFNC or NIV; 0.4% needed NIV, and 0.4% required IMV. The Wilcoxon paired signs test showed no differences in progression between groups.

The results of a per-protocol analysis were similar to the intention-to-treat analysis.

Futility analysis showed that there was no evidence of significant differences between the prophylactic dose group and the therapeutic dose group ($Z = -0.09$, $p = 0.92$); comparing prophylactic dose group and intermediate dose group, the results obtained were very close to entering the zone of non-rejection of the null hypothesis, ($Z = -0.71$, $p = 0.48$) and boundary values: $\alpha = -2.72$; $\beta = -0.70$ (Supplementary File, Appendix A).

4. Discussion

The results of the PROTHROMCOVID trial did not show differences during treatment with tinzaparin in relation to prophylactic, intermediate, or therapeutic doses in relation to the probability of death, thrombotic event, or non-invasive ventilation or invasive mechanical ventilation in patients with COVID-19 pneumonia. In this regard, the results of our trial provide evidence on the use of LMWH, indicating that there seems to be no advantage of a higher dose although the risk of major bleeding appears to be low regardless of dose in hospitalized and non-critical patients with pneumonia due to COVID-19. This study tested these three strategies of different LMWH doses that coexisted *de facto* in different hospitals in the absence of solid evidence of the most suitable dose and faced with the high rate the high rate of thrombosis and respiratory failure recorded in the first wave of the pandemic.

The results of the PROTHROMCOVID trial are in line with a previous study published by Lópes et al. The ACTION trial, conducted at the end of first and second waves of the pandemic, included 615 patients and used a hierarchical statistical analysis structure based on time to death, and it detected no survival benefit or in duration of hospitalization in individuals treated with full-dose enoxaparin or rivaroxaban compared to those who received standard prophylactic LMWH doses [11].

Similarly to our results, the RAPID trial determined that there was no significant difference between therapeutic or prophylactic strategies in non-critically ill patients admitted for COVID-19 in the combined endpoint of death, mechanical ventilation, or ICU admission [13]. Moreover, the BEMICOP clinical trial, a small study conducted with bemiparin, did not find any differences in the primary endpoint between cases randomized to therapeutic doses in comparison with prophylactic doses [14]. In contrast, the results of REMAP-CAP, ACTIV-4a, and ATTAC multiplatform collaborative trials support an early strategy of full-dose anticoagulant doses of heparin in non-critically ill subjects by demonstrating an increased in organ-free support days evaluated on an ordinal scale that combined in-hospital death and the number of days free of cardiovascular or respiratory organ support up to day 21 among patients who survived to hospital discharge (98.6% vs. 95.0%, respectively) in comparison to standard doses of LMWH thromboprophylaxis [10]. Despite being the clinical trial that has included the largest number of patients, statistical significance was barely reached and there were no statistical differences in other outcomes among groups, including thrombosis, survival to hospital discharge, and bleeding. Moreover, the percentage of patients who received intermediate doses in the prophylaxis group was high (26%), which may have biased the results [15]. The HEPCOVID trial, with a dose design similar to PROTHROMCOVID trial, showed a decrease in events, thromboembolism, and death in the therapeutic-dose LMWH in hospitalized, but not in ICU patients, with no differences at the intermediate-dose level [16]. It should be noted that the HEPCOVID trial was conducted in May 2020, during the first wave, with a higher percentage of events than those observed in our trial and in those conducted in later stages of the pandemic. It is worth mentioning that PROTHROMCOVID recruitment began in February 2021, in the middle of the third wave of the pandemic in Spain and up to and including the fifth wave. Consequently, patients were at lower risk of mortality, given the widespread use of corticosteroids and the beginning of vaccination against COVID-19 (unlike other studies), with the first dose of tinzaparin administered within the first 24 h after randomization and with concomitant treatment, mainly corticosteroids, most of which were homogeneous across the patients included. This profile is more similar to current clinical presentations than those of the first wave of the pandemic.

In line with our results, two clinical trials have analyzed standard prophylactic versus intermediate-dose LMWH. The INSPIRATION trial [17] tested the effect of intermediate versus standard dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to ICU. Likewise, Perepu et al. [18] published the results of their trial that examined standard prophylactic versus intermediate-dose enoxaparin in adults with severe COVID-19; both trials did not find significant intergroup differences. The lack of efficacy of the intermediate or full doses compared to standard doses could be due to differences in the clinical situation of the subjects included after the first wave, in which patients displayed more inflammation and received fewer doses of corticosteroids, monoclonal antibodies, immunomodulators, and antivirals that have demonstrated benefit in the evolution of the disease. In addition, the severity of symptoms in individuals affected by COVID-19 variants with lower mortality rates in the last months of recruitment may account for these data. Similarly, the incidence of thrombosis recorded during the first wave [19] in our own setting was higher than data collected during the second wave.

A meta-analysis including 49 studies concluded that prophylactic anticoagulation was recommended rather than intermediate to therapeutic anticoagulation, considering insignificant survival benefits but higher risk of bleeding when higher doses were used [20]. The PROTHROMCOVID study confirms the non-superiority of intermediate doses and therapeutic doses with respect to standard prophylactic LMWH doses; consequently, the accumulated evidence suggests that this strategy should be abandoned in this patient group.

However, the recommendations of the different guidelines have not been unanimous either. The American Society of Hematology favored a prophylactic dose over intermediate or therapeutic dose for patients with critical illness related to COVID-19 or acute illness without confirmed or suspected thromboembolic disease [21], while the National Institute for Health and Care Excellence (NICE) guidelines put forth the conditional recommendation to consider a therapeutic dose of LMWH for young people and adults with COVID-19 who need low-flow oxygen and who do not have an increased bleeding risk [22].

In terms of safety, the risk of bleeding tends to be higher in most of the studies in which the anticoagulation strategy is more intense [23]. In multiplatform trials, the risk of major bleeding was 1.8% in controls receiving standard prophylaxis versus 3.7% in those receiving therapeutic doses [10]. The PROTHROMCOVID study participants had no major bleeding events, perhaps because of the smaller sample size than in the collaborative trials, the characteristics of the included population, or the type of heparin used [6].

We believe our safety data to be of the utmost importance because it does not appear from our results that the option of therapeutic anticoagulation or intermediate doses generates an increased risk of major bleeding in a subset of non-critically ill patients where upcoming ASH or ISTH guidelines may suggest full-dose LMWH as NICE guidelines does.

Our study has certain limitations. For instance, neither investigators, nor patients were blinded. The main weakness of our results, however, is not having reached the estimated sample size, given that the researchers chose to interrupt the study on September 2021 due to both the slow recruitment rate and the results of the interim analysis. After the first 300 patients, we conducted the planned interim analysis. At this point, there were 19 combined outcome events in the 103 patients who received standard prophylaxis tinzaparin 4500 IU/kg, 20 combined events in patients who received intermediate-dose tinzaparin 100 IU/kg/day, and 19 combined events in patients who received therapeutic-dose tinzaparin 175 IU/kg/day. It revealed a lower absolute number of events than expected, as well as a smaller relative difference between intermediate and therapeutic versus standard prophylaxis, so it was unlikely that significant differences could have been reached with the complete sample originally planned. We determined that we would need at least 2592 patients per group to achieve a statistically significant difference.

These results should not be extrapolated to other more severe hospitalized patients with COVID-19.

The strengths of our study include the low number of withdrawals of informed consent by patients, the very early use of tinzaparin in all three arms of the study, which may have influenced in the safety outcomes, and the fact that the three strategies of anticoagulation were with the same LMWH. In Spain, LMWH such as tinzaparin, enoxaparin, or bemiparin, among others, are approved for the prophylaxis and treatment of venous thromboembolic disease. We consider that very few results had been reported on the use of tinzaparin in the prophylaxis of thromboembolism associated with COVID-19. Therefore, we consider that this fact could provide more evidence in this field.

Similarly, this was a multicenter study conducted in academic and general care centers. Furthermore, the study was conducted during a phase of the pandemic in which the incidence of thrombosis and mortality were lower than before; thus, the findings of our study might be more applicable to future waves of the pandemic, which are expected to be milder due to generalized immunization, fewer pathogenic variants of COVID-19, and better treatment options [24].

5. Conclusions

In conclusion, in non-critically ill COVID-19 pneumonia patients, intermediate, or full-dose tinzaparin does not appear to offer any benefit over standard, prophylactic doses, on the risk of thrombotic events, use of invasive or non-invasive ventilation, high-flow oxygen with nasal cannula, or death. However, the risk of bleeding related to intermediate or full heparin doses appears to be low in these patients.

PROTHROMCOVID trial (NCT04730856).

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11195632/s1. File S1: Clinical Trial Protocol Summary.

Author Contributions: N.M.-R., J.Á.H.-R. and J.T.-M. had full access to all the study data and take responsibility for the integrity of said data and the accuracy of the data analyses. Both N.M.-R. and J.Á.H.-R. are corresponding authors. Concept and design: N.M.-R., J.Á.H.-R. and J.T.-M. Drafting of the manuscript: N.M.-R., J.Á.H.-R., M.M.-B. and J.T.-M. The manuscript was critically reviewed by all the authors J.A., C.G.-X., Á.T.-V., A.U.-P., V.G.-D.O., P.D.-R., A.R.-G., P.B.-N., M.P.-P., M.R.-P., O.M.-C., L.R.-A., J.A.-C., I.F.-A., E.M.-S. and A.M.-P., who approved the final version. Members of the PROTHROMCOVID Trial and participant centers are included in Appendix B. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The Foundation for Biomedical Research and Innovation of the Infanta Leonor University Hospital and the Southeast University Hospital sponsored the study. The trial was conducted in accordance with the Declaration of Helsinki and local regulatory requirements. The protocol was approved 21th December 2020 by the Ethical Committees for Drug Research at the Gregorio Marañón General University Hospital (nº 27/2020) and, subsequently, by the local Drug Research Ethics Committees and the Spanish Agency for Medicines and Health Products.

Informed Consent Statement: Written Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data supporting reported results can be shared under request at www.prothromcovid.org or nmunozr@salud.madrid.org.

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Conflicts of Interest: The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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Appendix A

Futility Analysis PROTHROMCOVID Trial Report

To evaluate the possibility of continuing with the study, the following futility analysis was proposed, considering the hypotheses:

H0. *There are no statistically significant differences between treatments.*

H1. *There are statistically significant differences between the treatments.*

In case of rejecting the null hypothesis, it is concluded that the treatments behave significantly differently, and differences could be reached if the study continues.

If the null hypothesis is not rejected, it is concluded that the treatments behave in a similar way, so it would be futile to continue with it.

Table A1. The POWER Procedure.

Pearson Chi-Square Test for Proportion Difference	
Fixed Scenario Elements	
Distribution	Asymptotic normal
Method	Normal approximation
Number of Sides	L
Alpha	0.025
Group 1 Proportion	0.13
Group 2 Proportion	0.05
Nominal Power	0.8
Null Proportion Difference	0
Computed N per Group	
Actual Power	N per Group
0.801	200

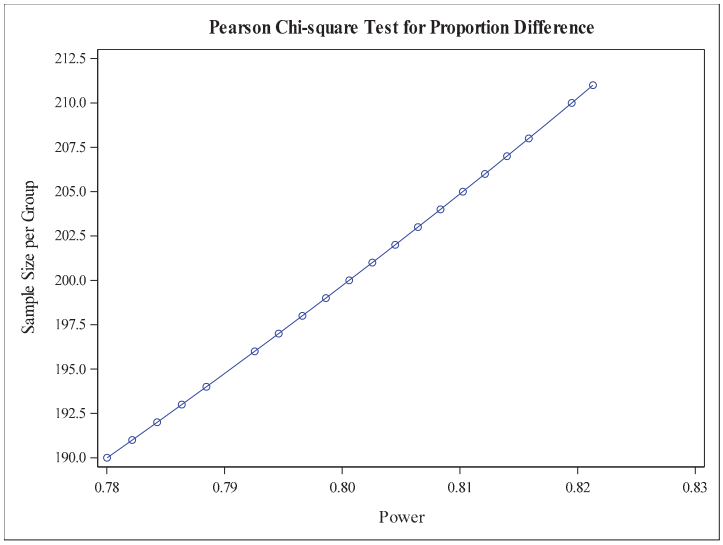

Figure A1. Power procedure of the futility analysis.

Table A2. The SEQDESIGN Procedure.

Design: One-Sided O'Brien–Fleming	
Design Information	
Statistic Distribution	**Normal**
Boundary Scale	**Standardized Z**
Alternative Hypothesis	**Lower**
Early Stop	Accept/Reject Null
Method	O'Brien-Fleming
Boundary Key	Both
Alternative Reference	−0.08
Number of Stages	2
Alpha	0.025
Beta	0.2
Power	0.8
Max Information (Percent of Fixed Sample)	105.8601
Max Information	1298.255
Null Ref ASN (Percent of Fixed Sample)	65.61561
Alt Ref ASN (Percent of Fixed Sample)	88.24682
Adj Design Alpha	0.025
Adj Design Beta	0.19907
Adj Design Power	0.80093
Adj Design Max Information (Percent of Fixed Sample)	105.8615
Adj Design Max Information	1301.37
Adj Design Null Ref ASN (Percent of Fixed Sample)	65.70521
Adj Design Alt Ref ASN (Percent of Fixed Sample)	88.12149

Table A3. Method Information of the SEQDESIGN Procedure.

Method Information								
Boundary	**Method**	**Alpha**	**Beta**	**Rho**	**Unified Family Tau**	**C**	**Alternative Reference**	**Drift**
Lower Beta	O'Brien-Fleming	.	0.20000	0.5	0	0.94812	−0.08	−2.8825
Lower Alpha	O'Brien-Fleming	0.02500	.	0.5	0	1.93438	−0.08	−2.8825

Boundary Information (Standardized Z Scale) Null Reference = 0						
Stage				**Alternative**	**Boundary Values**	
	Information Level			**Reference**	**Lower**	
	Proportion	**Actual**	**N**	**Lower**	**Alpha**	**Beta**
1	0.5000	649.1273	208.4997	−2.03824	−2.73563	−0.69739
2	1.0000	1298.255	416.9994	−2.88250	−1.93438	−1.93438

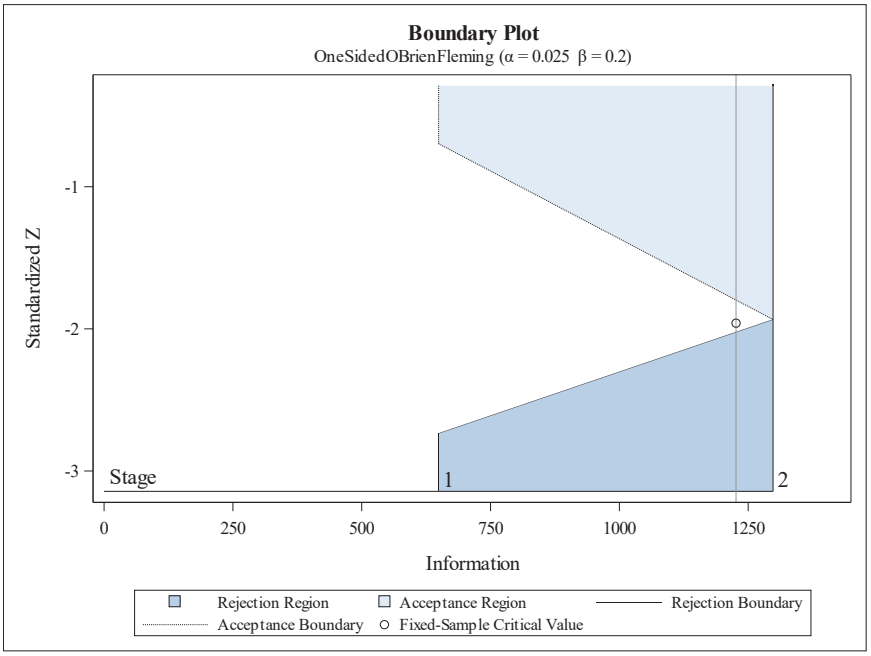

Figure A2. Boundary plot.

Table A4. Ceiling-Adjusted Design Boundary Information.

Ceiling-Adjusted Design Boundary Information (Standardized Z Scale) Null Reference = 0						
Stage				**Alternative**	**Boundary Values**	
	Information Level			**Reference**	**Lower**	
	Proportion	**Actual**	**N**	**Lower**	**Alpha**	**Beta**
1	0.5024	653.7983	210	−2.04556	−2.72960	−0.70352
2	1.0000	1301.37	418	−2.88596	−1.93473	−1.93473

According to these results, Z test values below −2.72960 result in a rejection of the null hypothesis, while Z values above −0.70352 accept the null hypothesis.

Group Prophylactic Dose vs. Group Intermediate Dose

The statistic Z = −0.7118 falls within the interval (−0.70352, −2.72960), that is, in a zone of indeterminacy, which, although the results obtained indicate that it is very close to entering the zone of non-rejection of the null hypothesis, that is to say that it is about to enter the zone of deciding to stop the study.

Group Prophylactic Dose vs. Group Therapeutic Dose

The statistic Z = −0.0978 > −0.70352, that is, in the zone of acceptance of the null hypothesis, which implies stopping the study.

Appendix B

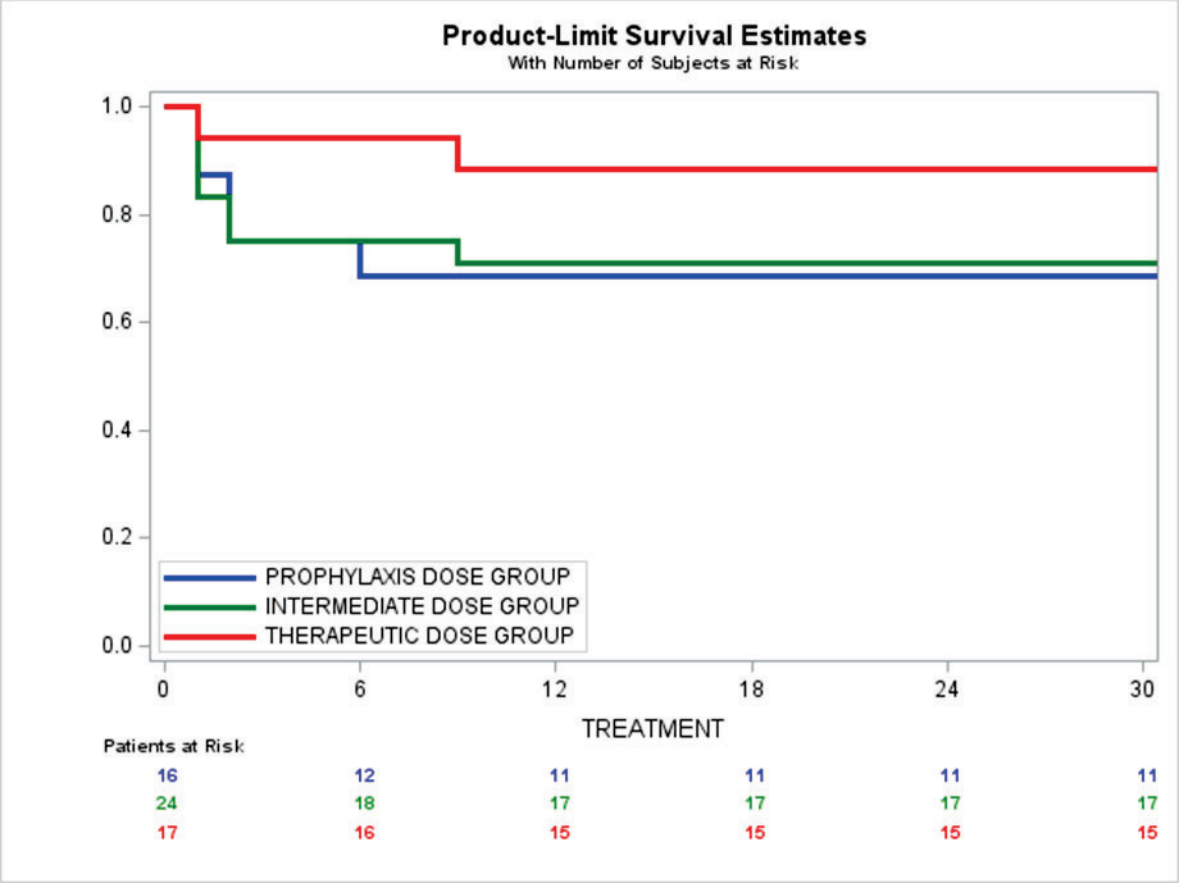

Figure A3. Survival analysis stratified by D Dimer ≥ 1000.

A subanalysis was performed evaluating only those patients with a D-dimer value ≥1000. The combined event of presenting Thrombotic Event and/or NIMV and/or death from any cause and/or High Flow and/or ICU before 30 days from randomization was considered; those patients who did not present an event were censored at 31 days. No statistically significant differences in survival were detected between the three treatment groups. The *p*-value associated with the Wald statistic (1.8037) is 0.4058 > 0.05.

Appendix B.1. Members of the PROTHROMCOVID Trial

Ahmad Sánchez, N., Aibar Gallizo, J., Alonso Carrillo, J., Anchorena Díaz, C.O., Araújo Ameijeiras, A., Ausin García, C., Aznar Ruiz de Alegría, M.L., Bara Ledesma, N., Barbagelata López, C., Béjar Béjar, M.J., Boán Pérez, J., Bosch Nicolau, P., Bou, M., Casillas Ramos, N., Castro Guardiola, A., Cerezo Benichou, E., Cervilla Muñoz, E., Chouza Piñeiro, A., Coloma, E., Daponte Angueira, S., De Carranza López, M., De Moya Romero, J.R., Del Toro Cervera, J., Demelo-Rodríguez, P., Encabo González, M.V., Escribano Stable, J.C.,

Espadas, N., Espinosa Pereiro, J., Fabregate Fuente, M., Fajardo Megías, A., Fernández Gómez, B., Fernández Poncela, E., Fernández Soler, C., Francisco Albesa, I., Franco Moreno, A.I., Gabara Xancó, C., Galeano-Valle, F., García Delicado, E., Gómez del Olmo, V., Gómez Guerra, R., Hernández Rivas, J.A., Hurtado Ganoza, A., Iranzo Alcolea, M.P., Jiménez Esteban, J., Lalueza Blanco, A., Lima Rodríguez, O., López Cisneros, O.A., López Domínguez, A.M., López Lallave, S., Madridano Cobo, O., Maestre Peiró, A., Manzano Varela, S., Marín Gonzalez, M., Martí Sáez, E., Martín, M., Martín Hurtado, M.J., Martínez Merchan, C., Méndez-Bailón, M., Mestre Gomez, B., Moisés, J., Molina Mejías, P., Molina Ruano, A., Morello González, D., Moreno Martínez, M.E., Moya Mateo, E., Muñoz-Rivas, N., Nieto Rodríguez, J.A., Pérez-Pinar, M., Oblitas, C.M., Ordieres Ortega, L., Peña Rodríguez, M., Pérez Gonzalez, A., Pérez Pinar, M., Pousada Fernández, G., Pueyo, C., Quezada Reynoso, A., Ramos Alonso, L., Ramos de Ascanio, V., Rexach Fumanya, M., Rey García, J., Ríos Prego, M., Rivera Gallego, A., Rodríguez-Calderita Facundi, M.A., Rodríguez-Núñez, O., Salvador Vélez, F., Sánchez Díaz, C., Sánchez Montalvá, A., Sánchez Serrano, I., Sanchiz Cruz, M., Segado Soriano, A., Suárez Carantoña, C., Such Díaz, A., Torres Macho, J., Torrijos Sen, R., Trueba Vicente, A., Urbelz Pérez, A., Varona Torralvo, N., Zamora, C.

Appendix B.2. Participant Centers

Hospital Universitario Infanta Leonor. Madrid. Spain.
Hospital Clínic. Barcelona. Spain.
Hospital de Emergencias Enfermera Isabel Zendal. Madrid. Spain.
Hospital Universitario Ramón y Cajal. Madrid. Spain.
Hospital General Universitario Gregorio Marañón. Madrid. Spain.
Hospital Álvaro Cunqueiro. Vigo, Pontevedra. Spain
Hospital Universitario Vall d'Hebron. Barcelona. Spain.
Hospital Virgen de la Luz. Cuenca. Spain.
Complexo Hospitalario Universitario de Pontevedra. Pontevedra. Spain.
Hospital Universitario Infanta Sofía. San Sebastián de los Reyes, Madrid. Spain.
Hospital Universitario A Coruña. A Coruña. Spain.
Hospital Universitario 12 de Octubre. Madrid. Spain.
Hospital Universitari de Girona Dr. Josep Trueta. Girona. Spain.
Hospital Clínico Universitario de Valencia. Valencia. Spain.
Hospital Universitario de Vinalopó. Elche, Alicante. Spain.

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5. DISCUSIÓN

La presente tesis doctoral, compuesta por 4 artículos originales y 1 carta al editor, trata de valorar e identificar factores de riesgo asociados tanto al riesgo de recurrencia trombótica como al riesgo de sangrado en pacientes con enfermedad tromboembólica venosa.

Tal y como hemos visto en la introducción, actualmente, dada la ausencia de evidencia robusta referente a los factores de riesgo de recurrencia y de sangrado, la decisión de mantener o suspender el tratamiento anticoagulante tras un primer evento de ETV, sobre todo si es no provocado, es un reto en la práctica clínica habitual. Para la toma de esta decisión, las guías de práctica clínica recomiendan tener en cuenta tres pilares fundamentales: el riesgo de recurrencia, el riesgo de sangrado y las preferencias del paciente; pero la correcta categorización de estos riesgos es uno de los principales temas de debate e investigación actual en el ámbito de la ETV. Como punto de partida, en nuestro artículo publicado a partir de los datos del *Registro Informatizado de Pacientes con Enfermedad TromboEmbólica* (RIETE), evaluamos las tasas de recurrencia y de sangrado mayor, al suspender el tratamiento anticoagulante, en 8.261 pacientes tras un primer episodio de ETV no provocada. Tras una media de seguimiento de casi 1 año tras la suspensión del tratamiento anticoagulante, las tasas de recurrencia (9,8 eventos/pacientes/año) fueron mucho mayores que las tasas de sangrado mayor (0,6 eventos/pacientes/año), pero la tasa de mortalidad a los 10 días de estos eventos, fue mucho más elevada en los pacientes con un sangrado mayor (24%) que en los pacientes con recurrencias en forma de TEP (4,6%) y TVP (0,4%). Nuestras tasas de recurrencia son similares a las descritas previamente (42), sin embargo, nuestro estudio reporta una mortalidad casi insignificante asociada con la recurrencia en forma de TVP y una mortalidad más baja que las descritas previamente tras una recurrencia en forma de TEP. Estos hallazgos tienen implicaciones importantes, ya que la mayoría de los estudios en la literatura se concentran en la incidencia de recurrencias de ETV sin considerar debidamente la mortalidad asociada a estas recurrencias. En cuanto a los sangrados mayores, nuestro estudio también resalta que la incidencia de sangrado mayor tras suspender la anticoagulación en pacientes no seleccionados con ETV no provocada no es insignificante. De hecho, nuestra tasa de sangrado mayor es ligeramente más alta que la tasa de 0,35 (IC 95%,

0,20-0,54) de sangrados mayores observada en un metaanálisis reciente de ensayos aleatorizados y estudios de cohorte (56), aunque esta diferencia no es significativa. Este riesgo, aunque a veces se pasa por alto, está lejos de ser inconsecuente y, más, si tenemos en cuenta que los pacientes con un sangrado mayor presentan una tasa de letalidad notablemente más alta que aquellos con recurrencias cuando se manifiesta. Por tanto, estos datos, obtenidos a partir de una larga cohorte de pacientes de vida real, ponen de manifiesto la necesidad de categorizar de forma correcta a estos pacientes.

Con esta premisa, nuestro siguiente objetivo fue intentar identificar los factores de riesgo asociados a recurrencias en forma de TEP y TVP de forma independiente (dada la diferente implicación pronóstica de estos eventos), y observamos que estos factores difieren. En primer lugar, este estudio corrobora que la presentación inicial de la ETV, en pacientes con ETV no provocada, influye de forma significativa en la forma de recurrencia: los pacientes con TEP inicial son más propensos a recurrir en forma de TEP y aquellos con TVP inicial son más propensos a recurrir en forma de TVP. Además, encontramos que los pacientes con demencia tenían un mayor riesgo de sufrir recurrencias en forma de TEP, mientras que aquellos con depresión y uso concomitante de corticoesteroides tuvieron un mayor riesgo de recurrencia en forma de TVP. Aunque la relación entre demencia y un mayor riesgo de recurrencia parece tener sentido clínico (por la inmovilización y mayor deshidratación en estos pacientes), hasta la fecha aún no se ha establecido esta asociación de forma clara en la literatura. Por otro lado, la depresión y el uso concomitante de glucocorticoides sí que se han asociado previamente con un mayor riesgo de recurrencia de ETV, pero no particularmente con un mayor riesgo de TVP (94,95). En cuanto a los factores de riesgo asociados a sangrado mayor, encontramos que la edad avanzada, la enfermedad inflamatoria intestinal y la anemia se asociaban a un mayor riesgo de estos eventos, tal y como sugiere la literatura publicada hasta la fecha (51,96).

Con estos factores pronósticos obtenidos, desarrollamos un score clínico de riesgo de recurrencias en forma de TEP y otro para la predicción de sangrado mayor y estratificamos a los pacientes en alto o bajo riesgo de cada uno de estos eventos. Aunque el c-estadístico obtenido de estos scores (entre 0,6 y 0,7) muestra que hay aún

margen de mejora, en los pacientes clasificados como de alto riesgo de recurrencia en forma de TEP y bajo riesgo de sangrado, la tasa de recurrencia fue 25 veces mayor que la de sangrado, mientras que en los pacientes clasificados como bajo riesgo de recurrencia y alto riesgo de sangrado, la tasa de recurrencia fue únicamente dos veces mayor. Con esto, nuestros resultados no sirven simplemente como herramientas académicas sino como instrumentos prácticos para guiar en el proceso de toma de decisiones en estos pacientes, siendo útiles para estimar si los beneficios de la prevención extendida de la recurrencia de ETV superan los riesgos derivados de un sagrado mayor (teniendo en cuenta la alta mortalidad asociada a este evento). Desde nuestro punto de vista, esta consideración es especialmente pertinente para pacientes con alto riesgo de sangrado mayor, pero al mismo tiempo bajo riesgo de recurrencia, en los que, suspender la anticoagulación, podría ser una medida crítica de intervención que podría disminuir la mortalidad. En este sentido, la validación externa de nuestros scores, proporcionada por el registro *Contemporary management and outcomes in patients with venous thromboembolism* (COMMAND-VTE), fortalece nuestras conclusiones y las extrapola a una población geográfica y demográfica diferente.

Pese a sus fortalezas, nuestro estudio también tiene algunas limitaciones que vale la pena mencionar. En primer lugar, dado que el registro RIETE es de naturaleza observacional, no podemos excluir la influencia potencial de variables no controladas en los resultados. En segundo lugar, la decisión de suspender o mantener la anticoagulación tras 3-6 meses de tratamiento en los pacientes fue tomada por cada médico tratante, lo que podría haber llevado a una subestimación de la asociación entre las recurrencias de ETV y la interrupción del tratamiento si los pacientes percibidos como de mayor riesgo tenían más probabilidades de continuar con anticoagulación. Por el contrario, la incidencia de sangrado después de la interrupción puede haberse sobreestimado si aquellos que se consideran con mayor riesgo tenían menos probabilidades de continuar con el tratamiento anticoagulante. Sin embargo, hay que destacar que no hubo grandes diferencias entre la población de pacientes incluidos versus los excluidos del estudio. Por último, mencionar que las variables demencia y enfermedad inflamatoria intestinal, que en conjunto representan un tercio de los ítems de las puntuaciones de los scores, no estaban disponibles en el registro COMMAND-VTE, lo que supone una limitación. Sin embargo, dada su baja prevalencia

en nuestra población (4% y 0,8% respectivamente), es poco probable que haya afectado sustancialmente la precisión pronóstica para la gran mayoría de los pacientes.

En resumen, este primer estudio destaca que, aunque el sangrado mayor es menos frecuente que la recurrencia de ETV después de interrumpir la anticoagulación en pacientes con ETV no provocada, está asociado con una tasa de mortalidad sustancialmente alta. Por tanto, estos resultados enfatizan la necesidad de considerar no solo la frecuencia, sino también la gravedad de los eventos, a la hora de decidir continuar o interrumpir la anticoagulación en estos pacientes. En este sentido, la investigación futura debería centrarse en perfeccionar las herramientas de estratificación de riesgos y explorar los beneficios de las duraciones de tratamiento personalizadas para optimizar el cuidado de los pacientes.

Una subpoblación que merece una mención especial en cuanto al riesgo de recurrencia y sangrado son los pacientes de edad avanzada. Está descrito que la edad avanzada aumenta el riesgo de sangrado (y sangrado mayor) (56) con pacientes con ETV, por lo que, en general, se desaconseja la prolongación de la anticoagulación más allá de los 3-6 meses en pacientes mayores de 75 años (51). Sin embargo, esta recomendación sólo puede justificarse si el riesgo de recurrencia en estos pacientes no excede el riesgo esperado en individuos más jóvenes y, hasta la fecha, no se han publicado estudios concluyentes al respecto. Para intentar dar respuesta a esta cuestión, y como complemento a los datos publicados en el primer artículo, quisimos valorar de forma concreta el papel de la edad avanzada en cuanto al riesgo de recurrencia y de sangrado mayor en pacientes mayores de 75 años con un primer episodio de ETV (tanto provocada como no provocada), que hubieran suspendido el tratamiento anticoagulante tras completar al menos 3-6 meses, del registro RIETE. Tras aplicar los criterios de exclusión, se incluyeron en el análisis un total de 23.218 pacientes, de los cuales, 7.208 (31%), eran mayores de 75 años. Al hacer la comparación entre grupos, las recurrencias fueron ligeramente más frecuentes en los pacientes mayores que en los jóvenes (12% vs 10% respectivamente), pero al realizar el análisis tras ajustar por otros factores clínicos (características basales, factores de riesgo de trombosis, extensión y localización de la ETV, comorbilidades…); y teniendo en cuenta el riesgo de

sangrado y mortalidad, estas diferencias desaparecían. Estos datos son congruentes con los publicados por Lauber et al (97), donde la incidencia acumulada de recurrencia a los 3 años en una cohorte prospectiva de 991 pacientes mayores de 65 años fue del 15%. A su vez, también en línea con los datos publicados del primer artículo y con la literatura hasta el momento, las tasas de sangrado mayor y mortalidad fueron más elevadas en los pacientes mayores de 75 años que en los más jóvenes. Por tanto, pese a que la edad avanzada sí que parece un factor de riesgo claro para un primer episodio de ETV (98), no parece jugar un papel en el riesgo de recurrencia con respecto a los pacientes más jóvenes, pero sí en el riesgo de sangrado mayor, incluso tras la suspensión del tratamiento anticoagulante. Con todo, aunque nuestros datos se han obtenido de una cohorte observacional, con las limitaciones que ello conlleva, son datos derivados de una gran cohorte con un tiempo largo de seguimiento, que apoyan el hecho de que, parece justificado, en este subgrupo de pacientes, el no mantener el tratamiento anticoagulante de forma indefinida.

Siguiendo en la misma línea de investigación, además de los factores epidemiológicos, las comorbilidades y las características del evento inicial, se sabe que hay factores relacionados con el tratamiento de la ETV que se han relacionado con un aumento de la recurrencia trombótica: el no realizar un tratamiento anticoagulante inicial y a largo plazo correctos y la colocación de un FVC (99,100). Como consecuencia, otro de los objetivos de la presente tesis doctoral se centraba por un lado en caracterizar los motivos de colocación de los FVC (valorando la adherencia de la indicación a las principales guías de práctica clínica) y, por otro, en valorar las complicaciones derivadas de la no retirada de los mismos e identificar a los pacientes con más riesgo de presentarlas. Para ello, se llevó a cabo un estudio observacional retrospectivo donde se incluyeron un total de 185 pacientes en los que se había colocado un FVC en un hospital terciario en el periodo comprendido entre 2015 y 2020. En nuestro estudio, casi la mitad de los FVC (47%) se había colocado con una indicación clara acorde con todas las guías de práctica clínica evaluadas, lo que es similar a los resultados obtenidos en trabajos previos publicados (95,96). Sin embargo, encontramos una alta tasa de colocación de FVC sin indicación clara en ninguna guía (38%), siendo la razón principal la colocación de un FVC más de 90 días después de un

TEP o TVP con contraindicación para la anticoagulación. Nuestra tasa de retirada de los FVC fue del 59% (pudiéndose retirar en el primer intento en la práctica totalidad de los pacientes), lo que supone una mejoría con respecto a las tasas descritas en estudios previos, que varían entre el 20 y el 30% (66,69,101,102). El tiempo medio entre la colocación y la retirada fue de 53 días, lo que sigue las recomendaciones actuales de retirada dentro de los 29 a 54 días posteriores a la colocación. Aún y así, un dato preocupante de nuestro estudio es que al 41% de los pacientes no se les retiró el filtro, probablemente porque casi la mitad de los pacientes de la cohorte tenían un cáncer activo o un alto índice de comorbilidad de Charlson. Este hecho advierte de la necesidad de revisar cuidadosamente las indicaciones de colocación de FVC en este subgrupo de pacientes, considerando el beneficio real de esta colocación, ya que estos pacientes a menudo tienen un mal pronóstico a corto plazo. De hecho, cuando exploramos las variables clínicas asociadas con la no retirada del FVC, un sangrado mayor previo a la colocación del FVC, las complicaciones del FVC y la muerte de los pacientes se asociaron con un mayor riesgo de no retirada, mientras que la reintroducción de la anticoagulación se asoció con un menor riesgo. Dentro de las complicaciones asociadas con el FVC, nuestras tasas de trombosis del FVC fueron más bajas que las descritas en revisiones previas recientes, lo que puede explicarse en parte por la alta tasa de reintroducción de anticoagulación después de la colocación del FVC (84%) y por el tiempo medio relativamente corto de retirada (66,103). En cuanto a las recurrencias, tal y como se ha mencionado previamente, el mayor riesgo de recurrencia en forma de TVP tras la colocación de un FVC se ha descrito previamente y varía entre el 6 y 35% según los trabajos publicados (58,60,68,69,104). En nuestro trabajo encontramos una tasa de recurrencia del 18% (6% en forma de TEP, 10% en forma de TVP y 2% como TEP + TVP), ocurriendo casi la mitad de estos eventos (48,5%) mientras el FVC estaba aún colocado. Al realizar la comparación entre grupos, los pacientes con trombosis de vena cava o vena ilíaca en contexto del FVC y aquellos con más complicaciones previas relacionadas con el filtro (sobre todo la trombosis del filtro) tuvieron unas tasas de recurrencia más elevadas. Finalmente, encontramos una tasa de mortalidad elevada (40%), siendo los pacientes que murieron de mayor edad y con más comorbilidad asociada, poniendo en especial relevancia a aquellos con cáncer. Con todo, las conclusiones de nuestro estudio son que a pesar de que obtuvimos una

tasa de retirada superior a las descritas en trabajos anteriores, el cumplimiento de las directrices actuales en materia de la indicación de colocación de los FVC es aún baja, mientras que las complicaciones derivadas de esta colocación no son despreciables. Este hecho es de especial preocupación en los pacientes ancianos, comórbidos y con cáncer, que parecen tener tasas más bajas de retirada de FVC y una mayor mortalidad.

Dados los hallazgos en este primer estudio, y la escasa información publicada hasta la fecha en referencia a la colocación de FVC en pacientes con cáncer, decidimos realizar un segundo estudio con nuestra cohorte de 185 pacientes y comparar la adherencia a las guías de práctica clínica, las tasas de retirada y las complicaciones entre los pacientes con y sin cáncer. Del total de pacientes, 89 (48%) tenían cáncer. En cuanto a las características basales de los pacientes, tal y como era esperable, vimos que los pacientes con cáncer eran más mayores, tenían un Índice de Charlson mayor (en contexto de la alta puntuación en este índice de la presencia de tumores, en especial si son metastásicos) y tenían un mayor riesgo de sangrado medido por la escala de la ACCP de 2016 (51). En relación con las indicaciones de colocación de los FVC, en los pacientes con cáncer se colocaron más FVC con indicación relativa (sobre todo a expensas de las recurrencias de ETV pese a una anticoagulación correcta) y sin indicación (sobre todo en el contexto de colocación de FVC tras el primer mes del evento trombótico) según las guías revisadas. Este hecho puede deberse a varios factores. En primer lugar, los pacientes con cáncer tienen un estado de hipercoagulabilidad mayor (debido tanto al propio tumor como a algunos tratamientos recibidos) que los pacientes sin cáncer, por lo que no es de extrañar que en ellos las recurrencias, incluso con una anticoagulación correcta, sean mayores. Además, son pacientes que no sólo tienen un riesgo de recurrencia o progresión del trombo mayor, sino que también tienen un riesgo aumentado de sangrado (por la localización del tumor, las citopenias derivadas de la quimioterapia o las cirugías) que impide, en muchos casos, el reinicio de la anticoagulación de forma precoz, haciéndolos más susceptibles a intentar buscar tratamientos alternativos. No hubo diferencias entre grupos en cuanto a las complicaciones derivadas del filtro, pero la tasa de reinicio de la anticoagulación fue menor (75% vs 93%) en el grupo de pacientes con cáncer mientras que la tasa de no retirada del FVC fue mayor (67% vs 51%); siendo los principales

motivos de no retirada la baja expectativa de vida y la mortalidad temprana tras la colocación del dispositivo. Nuestros resultados están en línea con los publicados por Abtahian et al (105), quienes describieron tasas similares de complicaciones derivadas del FVC entre pacientes con y sin cáncer, pero con tasas menores de retirada en los pacientes oncológicos. Como conclusión, parece que en pacientes con cáncer la inserción de un FVC sin una indicación clara según las directrices actuales es más frecuente que en los pacientes no oncológicos, hecho relevante teniendo en cuenta que en estos pacientes las tasas de no retirada y, por consiguiente, el riesgo de complicaciones, son más elevadas. En este sentido, un enfoque multidisciplinar y centrado en cada paciente parece necesario para intentar mejorar la atención, manejo y seguimiento de estos pacientes.

Cabe destacar, que estos dos estudios tienen algunas limitaciones y los resultados deben interpretarse con cautela. En primer lugar, se trata de estudios retrospectivos, por lo que carecen del rigor de un estudio prospectivo aleatorizado. En segundo lugar, al tratarse de estudios no intervencionistas, las estrategias de tratamiento y el manejo de los pacientes estuvieron condicionados por la práctica clínica. Por último, se trata de estudios unicéntricos, por lo que la extrapolación de los datos se encuentra más limitada.

Para finalizar, el último objetivo de la presente tesis doctoral estaba centrado en evaluar las tasas de eficacia y seguridad de diferentes dosis de tromboprofilaxis farmacológica (estándar, intermedia y dosis plenas de anticoagulación) en pacientes hospitalizados (no críticos) con SARS-CoV-2, dada la alta prevalencia de eventos trombóticos y complicaciones, en términos de requerimientos de ingreso en UCI y muerte, descrita previamente en estudios observaciones retrospectivos. Los resultados obtenidos de nuestro ensayo clínico multicéntrico PROTHROMCOVID ponen de manifiesto que no hay diferencias en términos de eficacia ni seguridad entre las diferentes dosis de tratamiento anticoagulante, concluyendo que dosis más altas de tromboprofilaxis que las estándar, a pesar de no conllevar un aumento significativo en el número de sangrados, no están asociadas con un descenso del riesgo de eventos trombóticos, necesidad de ventilación mecánica no invasiva ni muerte en estos pacientes. Estos resultados están en línea con los publicados en otros ensayos clínicos:

el ensayo ACTION (106), realizado al final de la primera y segunda ola de la pandemia, incluyó a 614 pacientes y no detectó ningún beneficio en términos de eficacia (medida como un aumento de la supervivencia o menor tiempo de hospitalización) entre individuos tratados con dosis plenas de Enoxaparina o Rivaroxabán en comparación con aquellos que recibieron dosis profilácticas estándar de HBPM; aunque sí que objetivó un aumento en el número de sangrados en los pacientes con dosis plenas. De igual forma, el ensayo RAPID (107), que incluyó 465 pacientes, no encontró diferencias significativas en términos de eficacia (medida con el criterio combinado de muerte, requerimientos de ventilación mecánica o ingreso en UCI) ni seguridad entre estrategias terapéuticas o profilácticas en pacientes no críticos ingresados. Por último, el ensayo COVID-19 y dosis de anticoagulación (COVI-DOSE) aleatorizó a 1005 pacientes hospitalizados con SARS-CoV-2 (80,1% enfermos no críticos y 19,9% enfermos críticos) a una dosis intermedia de HBPM ajustada por peso o a una dosis fija de tromboprofilaxis. Pese a que la tasa de ETV sintomática fue menor de lo esperado (1,2% en el grupo de dosis intermedia frente al 2,1% en el grupo de dosis profilácticas), no hubo diferencias estadísticamente significativas entre grupos en cuanto a los eventos trombóticos, pero sí que hubo un aumento significativo en el sangrado mayor en el grupo de dosis intermedia de HBPM (108).

Por el contrario, los resultados de los ensayos colaborativos multiplataforma REMAP-CAP, ACTIV-4a y ATTAC respaldan una estrategia temprana de dosis completas de anticoagulación versus dosis estándar de tromboprofilaxis en pacientes ingresados no críticos, al encontrar en los pacientes tratados con dosis plenas un aumento en los días sin necesidad de soporte de órganos y un aumento de supervivencia sin necesidad de soporte de órganos a los 28 días. Sin embargo, a pesar de ser el ensayo clínico que ha incluido un mayor número de pacientes (2.219 pacientes incluidos), apenas se alcanzó la significación estadística y no hubo diferencias en otras comparaciones de grupo, incluida la trombosis, la supervivencia hasta el alta hospitalaria y el sangrado. Además, el porcentaje de pacientes que recibieron dosis intermedias en el grupo catalogado como dosis profilácticas fue alto (26%), lo que puede haber sesgado los resultados (109). En el ensayo clínico HEP-COVID (110), donde se comparaban pacientes con dosis plenas versus profilácticas o intermedias se objetivó en descenso en el objetivo

primario del estudio (que incluía eventos trombóticos y muerte) en los pacientes ingresados no críticos con dosis plenas de anticoagulación. En este sentido, cabe destacar que este ensayo clínico se realizó en mayo de 2020, durante la primera ola, donde había un mayor porcentaje de eventos (trombosis y mortalidad), dada la mayor gravedad de los pacientes ante la ausencia de vacunación y opciones terapéuticas. De hecho, el reclutamiento de PROTHROMCOVID se inició en febrero de 2021, en plena tercera ola de la pandemia en España, y finalizó en la quinta ola, momento en que ya se había iniciado la vacunación. Por tanto, el perfil de pacientes incluidos en nuestro estudio es más parecido al tipo de pacientes actuales que a los pacientes incluidos en los ensayos realizados más al inicio de la pandemia. El ensayo FREEDOM (111) aleatorizó a 3.398 pacientes no críticos hospitalizados con COVID-19 entre 2020 y 2022, a Enoxaparina en dosis profiláctica (40 mg una vez al día), Enoxaparina en dosis terapéutica (1 mg/kg dos veces al día), o Apixabán en dosis terapéuticas (5 mg dos veces al día). El objetivo primario fue un compuesto de mortalidad por todas las causas, requerimiento de ingreso en UCI, tromboembolismo o accidente cerebrovascular isquémico a los 30 días de ingreso. No hubo diferencias significativas en el objetivo primario entre los grupos de tratamiento, pero en los pacientes tratados con dosis plenas versus dosis profilácticas la tasa de mortalidad y de requerimientos de ventilación mecánica invasiva fueron menores. Los sangrados mayores fueron infrecuentes en los 3 grupos. Por último, un metaanálisis reciente, publicado en 2023, donde se incluyeron 6 ensayos clínicos de calidad, con un total de 3.397 pacientes hospitalizados no críticos con SARS-CoV-2 encontró que la anticoagulación en dosis terapéuticas con HNF o HBPM, en comparación con dosis profilácticas o intermedias, redujo la mortalidad por todas las causas y el tromboembolismo, sin un impacto significativo en los sangrados mayores (112).

Con la evidencia generada hasta la fecha, actualmente las Guías de la ISTH (International Society of Thrombosis and Haemostasis) de 2023 y las del National Institutes of Health (NIH) recomiendan el uso de HBPM a dosis profilácticas en los pacientes hospitalizados con SARS-CoV-2 no grave, pudiéndose beneficiar de dosis plenas pacientes con requerimientos de oxígeno, niveles elevados de dímero-D y bajo riesgo de sangrado (113,114).

A modo de corolario de esta Tesis Doctoral, debemos destacar que la ETV es una patología compleja y multifactorial, en la que se debe intentar valorar de la forma más objetiva posible el riesgo de recurrencia y de sangrado de cada paciente, así como la gravedad de estos eventos, con el fin de intentar optimizar la duración del tratamiento anticoagulante. Entre los factores de riesgo de recurrencia implicados, la forma clínica de presentación inicial de la ETV juega un papel importante, ya que está implicada en el pronóstico: los pacientes que recurren en forma de TEP tienen una mortalidad a corto plazo mayor que los pacientes que recurren como TVP. Este hecho pone en relevancia la necesidad de identificar, por separado, los factores de riesgo asociados a las recurrencias en forma de TEP y TVP que, tal y como hemos descrito en la presente Tesis Doctoral, difieren. En esta línea, hemos descrito que la edad avanzada, que se ha asociado frecuentemente con un aumento del riesgo de ETV y de sangrado, no parece aumentar el riesgo de recurrencia por sí misma, por lo que suspender la anticoagulación tras 3-6 meses de tratamiento en estos pacientes parece una actitud segura. En cuanto a los factores de riesgo de recurrencia derivados del tratamiento de la ETV, hemos descrito que, los FVC (especialmente si no se retiran de forma precoz), están asociados con un mayor riesgo de complicaciones (entre las que se encuentran las trombosis del filtro y las recurrencias), sobre todo en personas de edad avanzada, comórbidas y con cáncer. Para finalizar, nuestro último trabajo pone de manifiesto que el uso de dosis de tromboprofilaxis más altas de las habituales, en pacientes ingresados no graves con infección por SARS-CoV-2, a pesar de no aumentar el riesgo de sangrado, no representa ningún beneficio en términos de eficacia en estos pacientes.

6. CONCLUSIONES

1. Tras la suspensión del tratamiento anticoagulante en pacientes con un primer episodio de trombosis no provocada, las recurrencias son más frecuentes que los sangrados mayores, pero la tasa de letalidad a los 10 días de estos eventos es mucho más elevada en los pacientes con un sangrado mayor que en los pacientes con recurrencias.
2. Los factores predictores de recurrencia de tromboembolismo pulmonar y trombosis venosa profunda en pacientes con trombosis no provocadas son diferentes: la presentación inicial como tromboembolismo pulmonar y la demencia aumentan el riesgo de recurrencia en forma de tromboembolismo pulmonar; mientras que la presentación inicial como trombosis venosa profunda, la depresión y el uso concomitante de corticoesteroides aumentan el riesgo de recurrencia en forma de trombosis venosa profunda.
3. La edad avanzada, la enfermedad inflamatoria intestinal y la anemia se asocian con un mayor riesgo de sangrado mayor tras la suspensión del tratamiento anticoagulante en pacientes con trombosis no provocada.
4. Al suspender el tratamiento anticoagulante tras un primer episodio de trombosis, los pacientes de edad avanzada no presentan un riesgo aumentado de recurrencia, pero sí de sangrado mayor, en comparación con los pacientes más jóvenes.
5. El cumplimiento de las directrices actuales en relación con la indicación de colocación de los filtros de vena cava, y la tasa de retirada de los mismos, es aún baja, mientras que las complicaciones no son despreciables. Este hecho es de especial importancia en los pacientes ancianos, con comorbilidad y en los pacientes oncológicos, que tienen tasas más bajas de retirada y una mayor mortalidad.
6. En pacientes hospitalizados con infección moderada por SARS-CoV-2, dosis más altas de tromboprofilaxis que las estándar, no incrementan significativamente el riesgo de sangrado, pero tampoco están asociadas con un descenso del riesgo de eventos trombóticos, necesidad de ventilación mecánica no invasiva ni muerte.

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