

## ORIGINAL RESEARCH

# Cancer-Associated Thrombosis

## Trends in Clinical Features, Treatment, and Outcomes From 2001 to 2020



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## ABSTRACT

**BACKGROUND** Despite advances in cancer and venous thromboembolism (VTE) management, the epidemiology of cancer-associated thrombosis management over time remains unclear.

**OBJECTIVES** We analyzed data from the RIETE (Registro Informatizado de la Enfermedad Trombo Embólica) registry spanning 2001 to 2020 to investigate temporal trends in clinical characteristics and treatments for cancer-associated thrombosis.

**METHODS** Using multivariable survival regression, we examined temporal trends in risk-adjusted rates of symptomatic VTE recurrences, major bleeding, and death within 30 days after incident VTE.

**RESULTS** Among the 17,271 patients with cancer-associated thrombosis, there was a progressive increase in patients presenting with pulmonary embolism (from 44% in 2001-2005 to 55% in 2016-2020;  $P < 0.001$  for trend), lung (from 12.7% to 18.1%;  $P < 0.001$ ) or pancreatic cancer (from 3.8% to 5.6%;  $P = 0.003$ ), and utilization of immunotherapy (from 0% to 7.4%;  $P < 0.001$ ). Conversely, there was a decline in patients with prostate cancer (from 11.7% to 6.6%;  $P < 0.001$ ) or carcinoma of unknown origin (from 3.5% to 0.7%;  $P < 0.001$ ). At the 30-day follow-up, a reduction was observed in the proportion of patients experiencing symptomatic VTE recurrences (from 3.1% to 1.1%;  $P < 0.001$ ), major bleeding (from 3.1% to 2.2%;  $P = 0.004$ ), and death (from 11.9% to 8.4%;  $P < 0.001$ ). Multivariable analyses revealed a decreased risk over time for VTE recurrence (adjusted subdistribution HR [asHR]: 0.94 per year; 95% CI: 0.92-0.98), major bleeding (asHR: 0.98; 95% CI: 0.96-0.99), and death (aHR: 0.97; 95% CI: 0.96-0.98).

**CONCLUSIONS** In this multicenter study of cancer patients with VTE, there was a decline in thrombotic, hemorrhagic, and fatal events from 2001 to 2020. (Registro Informatizado de la Enfermedad Trombo Embólica [RIETE]; [NCT02832245](https://doi.org/10.1016/j.jacc.2023.09.003)) (J Am Coll Cardiol CardioOnc 2023;5:758-772) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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Cancer significantly increases the risk of thrombosis, including venous thromboembolism (VTE), defined by deep vein thrombosis (DVT) and pulmonary embolism (PE). Overall, about 1 of 5 VTE events occurs in patients with cancer.<sup>1</sup> In clinical practice, diagnosing VTE in patients with cancer encounters delays because of the symptoms attributable to VTE not being consistently recognized.<sup>2</sup> Furthermore, the presence of cancer-associated VTE poses challenges because it is associated with an increased risk of both VTE recurrence and bleeding compared with VTE patients without cancer.<sup>3</sup> VTE in patients with cancer adds to the burden of disease and contributes to mortality and long-term morbidity.<sup>4</sup>

In recent decades, significant advances have been made in both cancer and VTE management. Cancer patients have experienced improved quality of life and survival because of new therapies.<sup>5-8</sup> In parallel, awareness surrounding cancer-associated VTE has grown as well as an increased knowledge of its epidemiology and risk factors. Also, the advent of direct oral anticoagulants (DOACs) has introduced new possibilities for treating cancer-associated VTE. DOACs have undergone comparison with low molecular weight heparin (LMWH) in several head-to-head trials,<sup>9-12</sup> leading to updates in most international guidelines.<sup>13-17</sup> Despite these advancements in cancer and VTE management, trends in the clinical characteristics, management, and VTE-related outcomes of patients with cancer presenting with acute VTE in clinical practice have not been well-defined. Although data from a multicenter multinational registry have indicated improved short-term outcomes in individuals with VTE,<sup>18,19</sup> these trends have remained unexplored in patients with cancer-associated VTE despite the potential temporal changes in cancer care and VTE care.

The RIETE (Registro Informatizado de la Enfermedad Trombo Embólica) registry, an ongoing multicenter registry, comprises consecutive patients with objectively confirmed acute VTE.<sup>20</sup> Data from this registry have previously been used to evaluate

outcomes after VTE, such as the frequency of recurrent VTE, major bleeding, or mortality, along with the risk factors associated with these outcomes. The aims of the current study are to compare the 30-day rates of symptomatic VTE recurrences, major bleeding events, and death in cancer patients with acute VTE over the last 20 years as well as to explore any changes in their clinical characteristics and treatments.

## METHODS

### BRIEF SUMMARY OF THE RIETE REGISTRY.

The RIETE registry is an ongoing, multicenter compilation of consecutive patients with objectively confirmed acute VTE (NCT02832245). The rationale and methodology of RIETE have been previously described.<sup>20</sup> Briefly, it includes consecutive patients with objectively confirmed acute VTE. For each patient included, baseline characteristics, such as comorbidities and concomitant drugs, as well as diagnostic information, VTE risk factors, biological results, and initial management (including anticoagulant therapy and modalities, use of inferior vena cava filters, and so on) are prospectively recorded. Every patient is followed for a minimum of 3 months unless they die. During the follow-up period, information on therapeutic management approaches (drugs, compression therapy, surgery, and so on) and outcomes (death, recurrent VTE, bleeding, arterial events, chronic thromboembolic pulmonary hypertension, post-thrombotic syndrome, and so on) is collected. S & H Medical is the coordinating center and oversees data monitoring, audits, and queries.

Since its establishment in Spain in 2001, the RIETE registry has gained participation from many countries. At present, more than 180 centers across 20 countries contribute to the RIETE registry, which includes more than 100,000 patients with acute VTE. Having prospective clinical data from a multitude of centers across several countries has enabled the

## ABBREVIATIONS AND ACRONYMS

<b>asHR</b>	= adjusted subdistribution HR
<b>CrCl</b>	= creatinine clearance
<b>CT</b>	= computed tomography
<b>DOAC</b>	= direct oral anticoagulant
<b>DVT</b>	= deep vein thrombosis
<b>LMWH</b>	= low molecular weight heparin
<b>PE</b>	= pulmonary embolism
<b>VKA</b>	= vitamin K antagonist
<b>VTE</b>	= venous thromboembolism

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

<b>TABLE 1 Trends in Baseline Characteristics in 17,271 Patients With Active Cancer and Acute VTE</b>					
	<b>2001-2005 (n = 3,068)</b>	<b>2006-2010 (n = 4,266)</b>	<b>2011-2015 (n = 4,864)</b>	<b>2016-2020 (n = 5,073)</b>	<b>P Value for Trend</b>
<b>Clinical characteristics</b>					
Female	1,373 (44.8)	1,946 (45.6)	2,366 (48.6)	2,483 (48.9)	<0.01
Age, y	67.6 ± 0.2	67.4 ± 0.2	67.3 ± 0.2	67.2 ± 0.2	0.12
Body weight, kg	70.9 ± 0.2	71.7 ± 0.2	73.1 ± 0.2	73.6 ± 0.2	<0.01
Inpatients	893 (29.5)	1,288 (30.5)	1,378 (29.5)	1,474 (30.3)	0.97
Initial VTE presentation					
Symptomatic PE	1,356 (44.2)	2,207 (51.7)	2,467 (50.7)	2,783 (54.9)	<0.01
<b>In patients with PE</b>					
SBP levels <90 mm Hg	61 (2.0)	92 (2.2)	107 (2.2)	97 (1.9)	0.91
Heart rate >100 beats/min	433 (14.1)	701 (16.4)	831 (17.1)	860 (17.0)	<0.01
Saturated O <sub>2</sub> levels <90%	318 (10.4)	379 (8.9)	346 (7.1)	258 (5.1)	<0.01
sPESI >0 points	1,731 (56.4)	2,414 (56.6)	2,664 (54.8)	2,982 (58.8)	0.04
Isolated DVT	1,712 (55.8)	2,059 (48.3)	2,397 (49.3)	2,290 (45.1)	<0.01
Lower limb, proximal	1,333 (43.4)	1,492 (35.0)	1,654 (34.0)	1,409 (27.8)	<0.01
Lower limb, distal	162 (5.3)	212 (5.0)	224 (4.6)	284 (5.6)	0.52
Upper extremity DVT	192 (6.3)	304 (7.1)	508 (10.4)	609 (12.0)	<0.01
<b>Additional risk factors</b>					
Recent surgery	492 (16.0)	615 (14.4)	691 (14.2)	670 (13.2)	<0.01
Recent immobility ≥4 d	571 (18.6)	762 (17.9)	720 (14.8)	750 (14.8)	<0.01
Estrogen use	87 (2.8)	175 (4.1)	406 (8.3)	425 (8.4)	<0.01
Pregnancy or postpartum	1 (0.03)	5 (0.1)	6 (0.1)	6 (0.1)	0.20
None of the above	1,937 (63.1)	2,755 (64.6)	3,155 (64.9)	3,343 (65.9)	0.01
Prior VTE	437 (14.2)	474 (11.1)	553 (11.4)	538 (10.6)	<0.01
<b>Underlying conditions</b>					
Chronic heart failure	122 (4.0)	212 (5.0)	292 (6.0)	239 (4.7)	0.19
Chronic lung disease	316 (10.3)	462 (10.8)	623 (12.8)	537 (10.6)	0.65
Recent major bleeding	95 (3.1)	128 (3.0)	151 (3.1)	142 (2.8)	0.53
<b>Blood tests</b>					
Anemia	1,775 (57.9)	2,614 (61.3)	3,085 (63.4)	3,033 (59.8)	0.03
Leukocyte count >11,000/μL	947 (30.9)	1,208 (28.3)	1,351 (27.8)	1,374 (27.1)	<0.01
Platelet count <100,000/μL	168 (5.5)	227 (5.3)	329 (6.8)	277 (5.5)	0.32
CrCl levels <60 mL/min	1,438 (46.9)	1,723 (40.4)	1,460 (30.0)	1,378 (27.2)	<0.01
<b>Concomitant drugs</b>					
Corticosteroids	384 (12.5)	516 (12.1)	794 (16.3)	856 (16.9)	<0.01
Antiplatelets	228 (7.4)	447 (10.5)	764 (15.7)	676 (13.3)	<0.01
<b>Countries</b>					
Spain	3,007 (98.0)	3,083 (73.3)	2,935 (60.3)	3,328 (65.6)	<0.01
Rest of Europe	50 (1.6)	840 (19.7)	1,089 (22.4)	1,327 (26.2)	<0.01
America	11 (0.4)	43 (1.0)	199 (4.1)	175 (3.4)	<0.01
Asia	0	287 (6.7)	638 (13.1)	188 (3.7)	<0.01

Values are n (%) or mean ± SEM. P values for trend are obtained from linear or logistic regression models.  
CrCl = creatinine clearance; DVT = deep vein thrombosis; PE = pulmonary embolism; SBP = systolic blood pressure; sPESI = simplified Pulmonary Embolism Severity Index; VTE = venous thromboembolism.

RIETE registry to harness the advantages of prospective cohorts, characterized by individual inclusion of well-phenotyped patients, combined with the strength of administrative databases, providing access to a large number of patients.<sup>20</sup>

**INCLUSION CRITERIA.** Consecutive cancer patients with acute, symptomatic lower or upper limb DVT, and/or PE confirmed by objective tests (compression ultrasonography for suspected DVT; helical computed tomography [CT] scan, ventilation-perfusion lung

scintigraphy, or conventional angiography for suspected PE) were eligible for inclusion. Patients were not included in the registry if they were currently participating in a blinded therapeutic clinical trial (a situation that did not occur in the setting of cancer-associated thrombosis during the study period). All patients (or their relatives) provided written or oral informed consent for participation in the registry in accordance with local ethics committee requirements.

**TABLE 2 Cancer Characteristics**

	<b>2001-2005</b> (n = <b>3,068</b> )	<b>2006-2010</b> (n = <b>4,266</b> )	<b>2011-2015</b> (n = <b>4,864</b> )	<b>2016-2020</b> (n = <b>5,073</b> )	<b>P Value</b> <b>for Trend</b>
Time from cancer diagnosis, mo	4 (0-18)	4 (0-19)	4 (0-19)	4 (0-24)	<0.01
Metastases					
Yes	1,529 (49.8)	2,302 (54.0)	2,664 (54.8)	2,855 (56.3)	<0.01
Sites of cancer					
Lung	390 (12.7)	679 (15.9)	835 (17.2)	916 (18.1)	<0.01
Colorectal	417 (13.6)	635 (14.9)	693 (14.2)	633 (12.5)	0.01
Breast	366 (11.9)	499 (11.7)	623 (12.8)	755 (14.9)	<0.01
Prostate	358 (11.7)	402 (9.4)	372 (7.6)	336 (6.6)	<0.01
Hematologic	206 (6.7)	327 (7.7)	410 (8.4)	353 (7.0)	0.53
Bladder	207 (6.7)	235 (5.5)	221 (4.5)	238 (4.7)	<0.01
Brain	172 (5.6)	194 (4.5)	164 (3.4)	170 (3.4)	0.59
Stomach	136 (4.4)	185 (4.3)	184 (3.8)	179 (3.5)	0.02
Uterine	128 (4.2)	174 (4.1)	178 (3.7)	218 (4.3)	0.99
Pancreas	118 (3.8)	193 (4.5)	273 (5.6)	285 (5.6)	<0.01
Ovary	101 (3.3)	142 (3.3)	167 (3.4)	224 (4.4)	<0.01
Kidney	71 (2.3)	94 (2.2)	100 (2.1)	133 (2.6)	0.32
Unknown origin	107 (3.5)	110 (2.6)	81 (1.7)	37 (0.7)	<0.01
Oropharynx	43 (1.4)	81 (1.9)	76 (1.6)	89 (1.8)	0.59
Biliary tract	42 (1.4)	44 (1.0)	86 (1.8)	48 (0.9)	0.53
Melanoma	13 (0.4)	42 (1.0)	44 (0.9)	58 (1.1)	0.95
Liver	19 (0.6)	29 (0.7)	46 (0.9)	42 (0.8)	0.20
Esophagus	28 (0.9)	46 (1.1)	58 (1.2)	47 (0.9)	0.66
Other sites	146 (4.8)	155 (3.6)	253 (5.2)	312 (6.2)	<0.01
Therapy for cancer					
Chemotherapy	1,552 (51.3)	2,164 (52.2)	2,324 (52.2)	2,370 (52.1)	0.79
Radiotherapy	309 (10.2)	496 (12.0)	709 (16.7)	693 (16.1)	<0.01
Chemo- and radiotherapy	189 (6.3)	311 (7.5)	471 (11.2)	421 (9.9)	<0.01
Hormonal therapy	315 (34.2)	334 (23.4)	569 (14.0)	588 (13.9)	<0.01
Immunotherapy	0	2 (2.8)	13 (2.7)	243 (7.4)	<0.01
None of the above	1,212 (39.5)	1,713 (40.2)	1,916 (39.4)	1,935 (38.1)	0.22

Values are median (Q1-Q3) or n (%). P values for trend are obtained from linear or logistic regression models.

For this study, only patients with active cancer at baseline were considered. We defined active cancer when the diagnosis of malignancy was made within 6 months before the index VTE event or in patients with metastatic disease or receiving active therapy (chemotherapy, radiotherapy, hormonal therapy, or supportive or palliative care) at the time of VTE.

**OUTCOMES.** The primary outcomes considered in this study were the development of symptomatic, objectively confirmed VTE recurrences; major bleeding events; or death within the first 30 days after VTE diagnosis. The secondary outcomes included fatal PE and fatal bleeding. During each visit, any signs or symptoms suggestive of VTE recurrences or bleeding complications were noted. Each episode of clinically suspected recurrent DVT or PE was investigated through repeat compression ultrasonography, lung scintigraphy, helical CT scan, or pulmonary angiography as deemed appropriate. Recurrent DVT was defined as a new noncompressible vein segment

or an increase in the vein diameter by at least 4 mm compared with the last available measurement on venous ultrasonography. Recurrent PE was defined as a new ventilation-perfusion mismatch on a lung scan or a new intraluminal filling defect on a spiral CT of the chest. Fatal PE, in the absence of autopsy, was defined as any death appearing within 10 days after PE diagnosis without any alternative cause of death. Bleeding events were classified as major if they were overt and required a transfusion of 2 or more units of blood or if they occurred in the retroperitoneum, pericardium, spinal column, or intracranially or were fatal.<sup>20</sup> Fatal bleeding was defined as any death occurring <10 days after a major bleeding episode without any alternative cause of death.

**OTHER DATA ELEMENTS.** The following parameters were recorded when the qualifying episode of VTE was diagnosed: baseline characteristics, including demographic characteristics, other VTE risk factors,

**TABLE 3 Venous Thromboembolism Treatment Strategies**

	2001-2005 (n = 3,068)	2006-2010 (n = 4,266)	2011-2015 (n = 4,864)	2016-2020 (n = 5,073)	P Value for Trend
<b>Initial therapy</b>					
LMWH	2,823 (92.0)	3,881 (91.0)	4,409 (90.6)	4,424 (87.2)	<0.01
Unfractionated heparin	208 (6.8)	252 (5.9)	237 (4.9)	178 (3.5)	<0.01
DOACs	0	0	35 (0.7)	149 (2.9)	<0.01
Rivaroxaban	0	0	34 (0.7)	97 (1.9)	<0.01
Apixaban	0	0	1 (0.02)	42 (0.8)	<0.01
Fondaparinux	0	68 (1.6)	85 (1.7)	67 (1.3)	<0.01
Thrombolytic drugs	19 (0.6)	29 (0.7)	35 (0.7)	32 (0.6)	0.66
Inferior vena cava filter	124 (4.0)	232 (5.4)	255 (5.2)	235 (4.6)	0.46
Pulmonary embolectomy	9 (0.3)	18 (0.4)	25 (0.6)	33 (0.7)	0.01
Mechanical thrombolysis	0	0	5 (0.3)	26 (0.6)	0.04
<b>Long-term therapy</b>					
LMWH	1,510 (49.2)	2,690 (63.1)	3,525 (72.5)	3,476 (68.5)	<0.01
Vitamin K antagonists	1,332 (43.4)	1,144 (26.8)	823 (16.9)	455 (9.0)	<0.01
DOACs	0	1 (0.02)	94 (1.9)	623 (12.3)	<0.01
Rivaroxaban	0	1 (0.02)	82 (1.8)	249 (5.3)	<0.01
Apixaban	0	0	7 (0.2)	216 (4.6)	<0.01
Dabigatran	0	0	2 (0.04)	20 (0.4)	<0.01
Edoxaban	0	0	3 (0.06)	138 (2.9)	<0.01
Fondaparinux	0	66 (1.5)	71 (1.5)	56 (1.1)	<0.01

Values are n or n (%). P values for trend are obtained from logistic regression models; proportions are crude rates.  
DOAC = direct oral anticoagulant; LMWH = low molecular weight heparin.

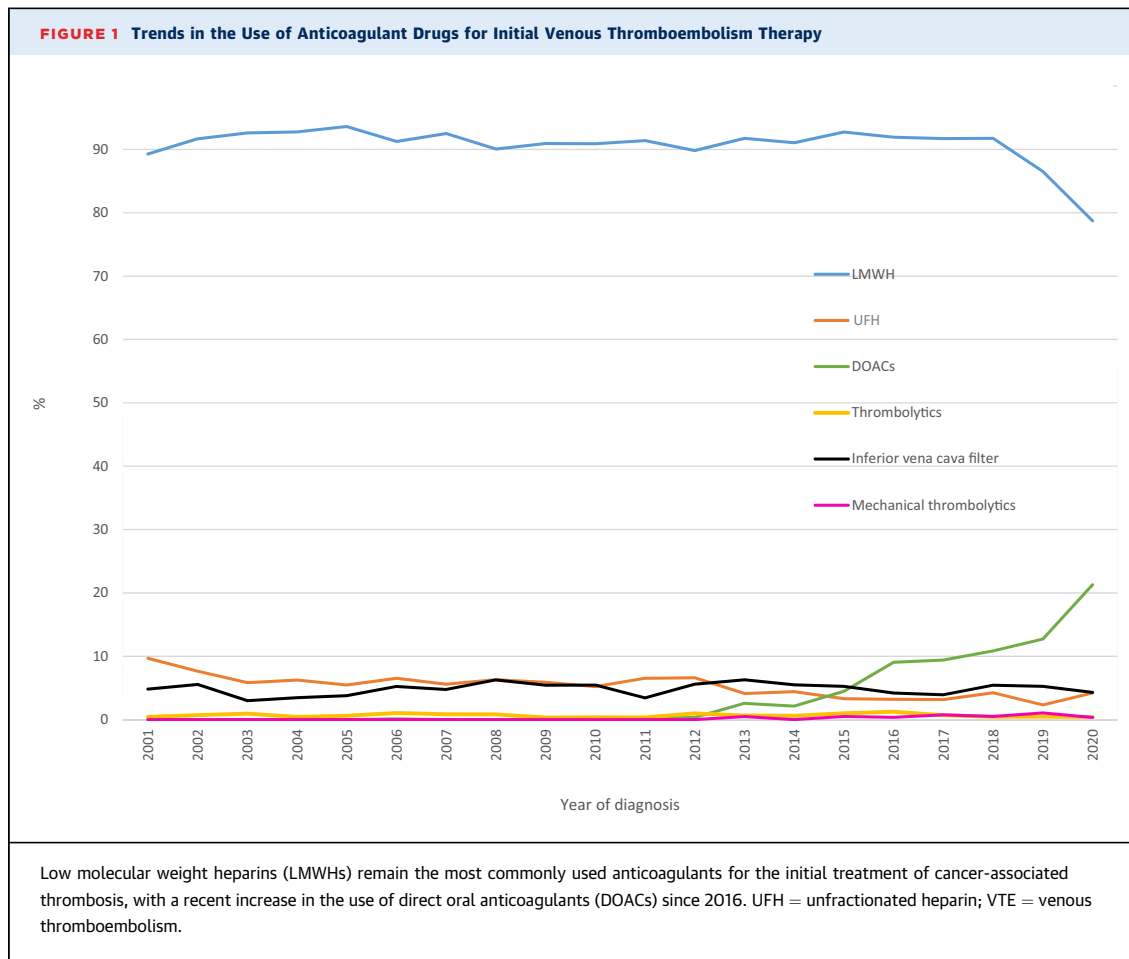
and comorbidities; signs and symptoms of VTE; cancer site, presence of metastases, and type of oncologic therapy (chemotherapy, radiotherapy, immunotherapy, hormonal therapy, or combinations thereof); anticoagulant therapy administered upon VTE diagnosis (drug, dose, start date, and discontinuation date for each drug); concomitant drugs; and outcomes within the first 30 days. Immobilized patients were defined as nonsurgical patients who had been bedridden (ie, total bed rest with or without bathroom privileges) for 4 or more days in the 2 months before the index VTE. Surgical patients were defined as those who had undergone a surgical procedure in the 2 months before the VTE event. Recent major bleeding was considered if it occurred within 30 days before the index VTE. Anemia was defined as hemoglobin levels <13 g/dL for men and <12 g/dL for women. Creatinine clearance (CrCl) levels were measured according to the Cockcroft-Gault formula.<sup>20</sup>

**TREATMENT AND FOLLOW-UP.** Patients received management in accordance with the clinical practices of each participating hospital, with no central standardization of treatment. The type, dose, and duration of anticoagulant therapy were determined by the treating clinicians and recorded by the study staff. After VTE diagnosis, patients were monitored for at least 3 months or until death.

**STATISTICAL ANALYSIS.** Data are presented as counts expressed as percentages for categorical variables and as mean ± SEM of the mean for continuous variables.

To evaluate changes in baseline characteristics over time, we used linear regression for continuous variables and logistic regression for categorical variables. For simplicity of representation, baseline characteristics are grouped in 5-year intervals (2001-2005, 2006-2010, 2011-2015, and 2016-2020). However, linear regression (or logistic regression where appropriate) tested for trends for each individual year.

To assess the 30-day death rates over time, we performed Cox regression analysis for the overall cohort. The 30-day rates of VTE recurrences, major bleeding, fatal PE, and fatal bleeding were calculated separately, assuming death as a competing risk using Fine-Gray regression models. Non-PE death was considered the competing risk for VTE recurrence, and nonbleeding death was the competing risk for bleeding events. Our subdistribution hazards regression models adjusted for the following variables: sex, age, body weight, initial VTE presentation (PE vs isolated DVT), chronic heart or lung disease, recent major bleeding, prior VTE, blood tests at baseline (including anemia, leukocytosis, thrombocytopenia, and CrCl levels), cancer site, presence of metastases,



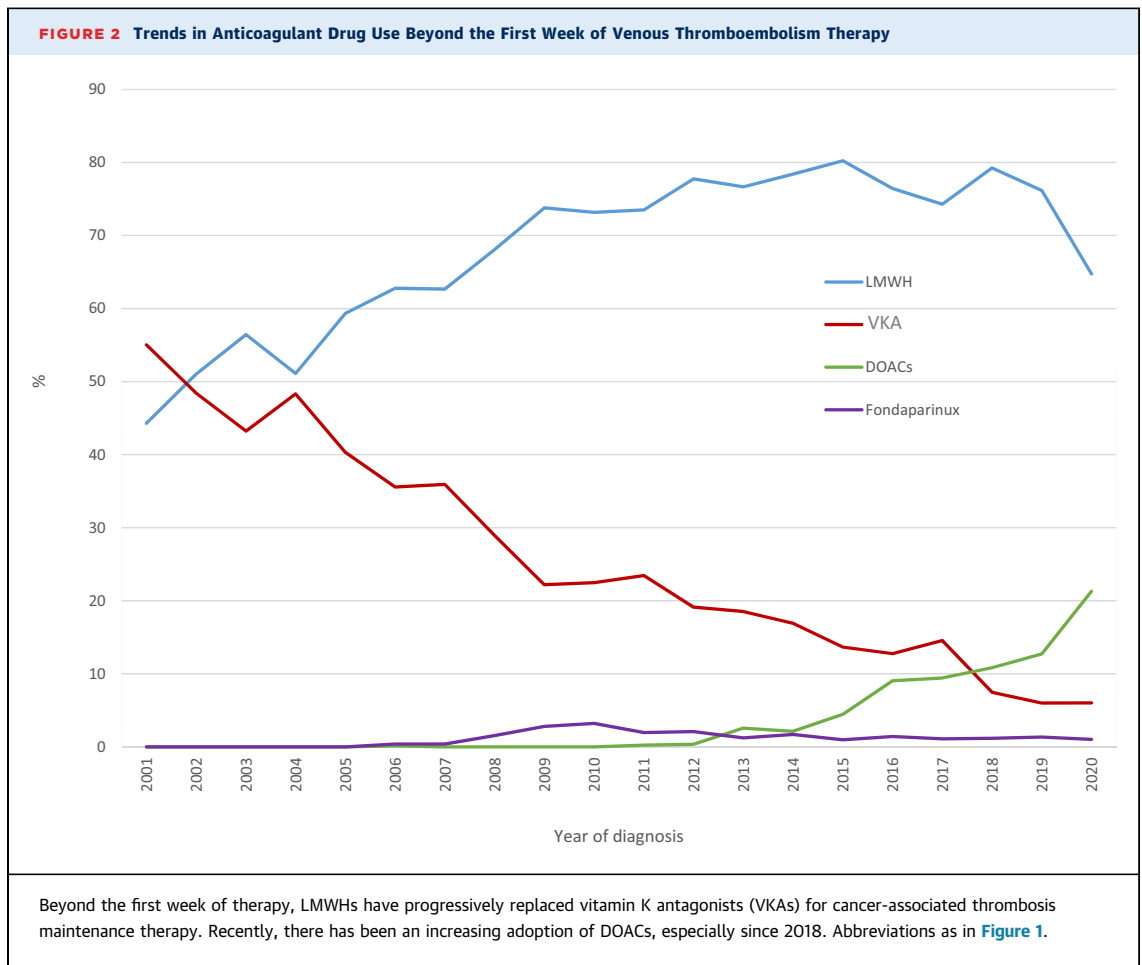
oncologic therapy, long-term anticoagulant therapy with LMWH, DOACs or vitamin K antagonists (VKAs), concomitant therapy with corticosteroids or antiplatelet drugs, and the country of enrollment. The selection of these potential confounders was based on consensus among the steering committee of the study, and they were chosen before conducting the analyses. The annual trends were calculated by assessing the statistical significance of the coefficient in the regression models (logistic, linear, Cox, or Fine-Gray regression model) for the year variable (calendar year) using 2001 as the reference period. Statistical analyses were conducted with SPSS for Windows Release (version 22, IBM Corp). For data sharing inquiries, contact the corresponding author via direct e-mail.

## RESULTS

**TREND ANALYSES FOR BASELINE CHARACTERISTICS AND VTE THERAPY.** As of December 2020, the RIETE registry enrolled 17,271 patients with active cancer and symptomatic VTE. Initially, the number of

participating hospitals in RIETE increased from 129 centers with 3,072 patients in the first period from 2001 to 2005 to a relatively stable number of approximately 180 centers with over 4,000 patients in the subsequent 5-year periods (Table 1). Among these patients, 8,168 (47%) were women, with a mean age of  $67 \pm 0.2$  years. A total of 8,813 (51%) presented initially as PE (with or without associated DVT), and 9,350 (54%) had metastases. The most common types of cancer included lung (2,820 cases), colorectal (2,378 cases), breast (2,243 cases), prostate (1,468 cases), and hematologic cancer (1,296 cases) (Table 2).

Over the 20-year study period, there was a progressive increase in patients initially presenting with PE (from 44.2% in 2001-2005 to 54.9% in 2016-2020;  $P < 0.001$  for trend) or with upper extremity DVT (from 6.3% in 2001-2005 to 12.0% in 2016-2020;  $P < 0.001$  for trend). In contrast, the proportion of patients with proximal DVT of the lower limbs decreased (Supplemental Figure 1). Additionally, the proportion of women increased significantly during the study period (from 44.8% initially to 48.9% in



the last period;  $P < 0.001$  for trend), along with an increase in estrogen use (from 2.8% initially to 8.4% in the last period;  $P < 0.001$  for trend). Furthermore, we observed an increase in patients receiving corticosteroids (from 12.5% to 16.9%;  $P < 0.001$  for trend) or antiplatelet drugs (from 7.4% to 13.3%;  $P < 0.001$  for trend) and a progressive decrease in patients with CrCl levels  $<60$  mL/min at baseline (from 46.9% to 27.2%;  $P < 0.001$  for trend) ([Table 1](#)).

There was also a progressive increase in patients with metastases (from 49.8% to 56.3%;  $P < 0.001$  for trend) ([Table 2](#)). Concerning cancer sites, we observed a progressive increase in patients with lung cancer (from 12.7% to 18.1%;  $P < 0.001$  for trend) or pancreatic cancer (from 3.8% to 5.6%;  $P = 0.003$  for trend). In contrast, there was a progressive decrease in patients with prostate cancer (from 11.7% to 6.6%;  $P < 0.001$  for trend), brain cancer (from 5.6% to 3.4%;  $P < 0.001$  for trend), or carcinoma of unknown origin (from 3.5% to 0.7%;  $P < 0.001$  for trend). There was also a progressive

increase in patients receiving radiotherapy (from 10.2% to 16.1%;  $P < 0.001$  for trend) or immunotherapy (from 0% to 7.4%;  $P < 0.001$  for trend) and a decrease in patients on hormonal therapy (from 34.2% to 13.9%;  $P < 0.001$  for trend).

Regarding the initial therapy of VTE, there was a progressive decrease in the use of LMWH (from 92.0% to 87.2%;  $P < 0.001$  for trend) or unfractionated heparin (from 6.8% to 3.5%;  $P < 0.001$  for trend) along with an increase in the use of DOACs (from 0% to 2.9%;  $P < 0.001$  for trend) or pulmonary embolectomy (from 0.3% to 0.7%;  $P = 0.014$  for trend) ([Table 3](#), [Figure 1](#)). After the first week of therapy, there was a progressive increase in the use of LMWH (from 49.2% to 68.5%;  $P < 0.001$  for trend) or DOACs (from 0% to 12.3%;  $P < 0.001$  for trend) and a progressive decrease in the use of VKAs (from 43.4% to 9.0%;  $P < 0.001$  for trend) ([Table 3](#), [Figure 2](#)).

Evaluating crude rates during the first 30 days of therapy, we found that 319 patients (1.8%) developed VTE recurrences (recurrent PE, 177; DVT, 145), 414 (2.4%) experienced major bleeding (gastrointestinal,



**TABLE 4** Thirty-Day Outcomes

	2001-2005	2006-2010	2011-2015	2016-2020	P Trend
All patients	3,068	4,266	4,864	5,073	
PE recurrences	50 (1.6)	48 (1.1)	44 (0.9)	35 (0.7)	<0.01
DVT recurrences	45 (1.5)	34 (0.8)	43 (0.9)	23 (0.5)	<0.01
VTE recurrences	95 (3.1)	81 (1.9)	86 (1.8)	57 (1.1)	<0.01
Major bleeding	95 (3.1)	114 (2.7)	92 (1.9)	113 (2.2)	<0.01
Gastrointestinal	43 (1.4)	47 (1.1)	48 (1.0)	44 (0.9)	0.01
Intracranial	11 (0.4)	9 (0.2)	6 (0.1)	20 (0.4)	0.59
Genitourinary	15 (0.5)	16 (0.4)	6 (0.1)	8 (0.2)	0.01
Hematoma	14 (0.5)	15 (0.4)	9 (0.2)	13 (0.3)	0.06
Retroperitoneal	1 (0.0)	9 (0.2)	9 (0.2)	11 (0.2)	0.20
Overall death	364 (11.9)	514 (12.0)	454 (9.3)	428 (8.4)	<0.01
Fatal PE	77 (2.5)	87 (2.0)	41 (0.8)	30 (0.6)	<0.01
Fatal initial PE	67 (2.2)	76 (1.8)	34 (0.7)	29 (0.6)	<0.01
Fatal recurrent PE	10 (0.3)	11 (0.3)	7 (0.1)	1 (0.0)	<0.01
Fatal bleeding	33 (1.1)	30 (0.7)	17 (0.3)	15 (0.3)	<0.01
PE patients	1,356	2,207	2,467	2,783	
PE recurrences	35 (2.6)	25 (1.1)	20 (0.8)	15 (0.5)	<0.01
DVT recurrences	16 (1.2)	10 (0.5)	18 (0.7)	10 (0.4)	<0.01
VTE recurrences	51 (3.8)	35 (1.6)	38 (1.5)	25 (0.9)	<0.01
Major bleeding	46 (3.4)	60 (2.7)	59 (2.4)	62 (2.2)	<0.01
Overall death	197 (14.5)	327 (14.8)	283 (11.5)	283 (10.2)	<0.01
Fatal PE	74 (5.5)	82 (3.7)	39 (1.6)	29 (1.0)	<0.01
Fatal initial PE	67 (4.9)	76 (3.4)	34 (1.4)	29 (1.0)	<0.01
Fatal recurrent PE	7 (0.5)	6 (0.3)	5 (0.2)	0	<0.01
Fatal bleeding	10 (0.7)	14 (0.6)	12 (0.5)	9 (0.3)	<0.01
DVT patients	1,712	2,059	2,397	2,290	
PE recurrences	15 (0.9)	23 (1.1)	24 (1.0)	20 (0.9)	0.79
DVT recurrences	29 (1.7)	24 (1.2)	25 (1.0)	13 (0.6)	<0.01
VTE recurrences	44 (2.6)	46 (2.2)	48 (2.0)	32 (1.4)	<0.01
Major bleeding	49 (2.9)	54 (2.6)	33 (1.4)	51 (2.2)	<0.01
Overall death	167 (9.8)	187 (9.1)	171 (7.1)	145 (6.3)	<0.01
Fatal PE	3 (0.2)	5 (0.2)	2 (0.1)	1 (0.04)	<0.01
Fatal bleeding	23 (1.3)	16 (0.8)	5 (0.2)	6 (0.3)	<0.01

Values are n or n (%). Proportions are crude rates not adjusted for competing risks. P values for trend are obtained from Cox regression for overall death and separate competing risk Fine-Gray regression models for all other outcomes.  
Abbreviations as in Table 1.

182; hematoma, 51; intracranial, 46; genitourinary, 45), and 1,760 (10.2%) died (Table 4, Supplemental Table 1 for results according to cancer sites). Of these, 235 (13.4%) died of PE (the index PE, 206; recurrent PE, 29) and 95 (5.4%) died of bleeding. There was a progressive decrease in patients with VTE recurrences (from 3.1% to 1.1%;  $P < 0.001$  for trend), major bleeding (from 3.1% to 2.2%;  $P = 0.004$  for trend), all-cause death (from 11.9% to 8.4%;  $P < 0.001$  for trend), fatal PE (from 2.5% to 0.6%;  $P < 0.001$  for trend), and fatal bleeding (from 1.1% to 0.3%;  $P < 0.001$  for trend) (Figures 3 and 4). The decrease in most of these outcomes was similar in patients initially presenting with PE or with isolated DVT. The 30-day mortality rate decreased from 14.5% to 10.2% ( $P < 0.001$  for trend) in patients with PE and

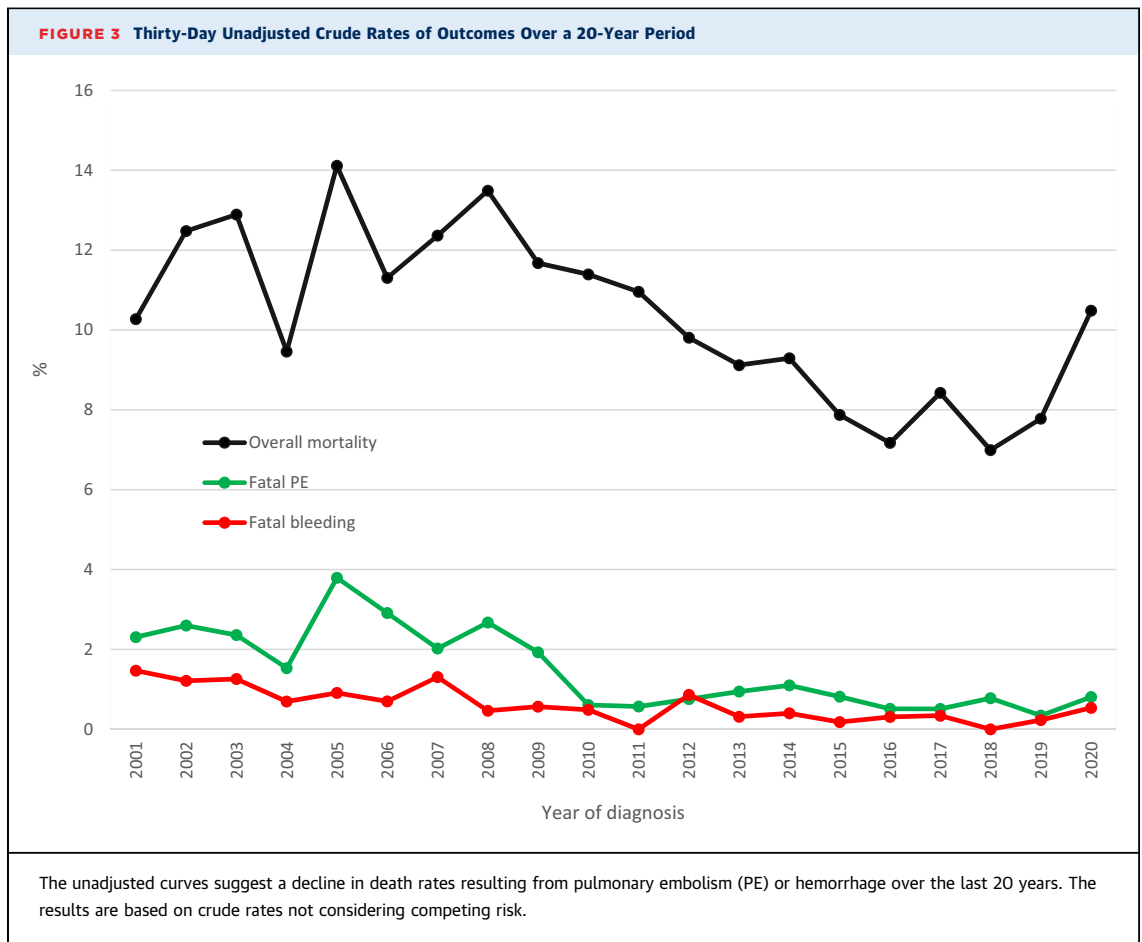
from 2.9% to 2.2% ( $P < 0.001$  for trend) in those with isolated DVT (Table 4).

#### TRENDS ANALYSIS FOR CLINICAL OUTCOMES.

Fourteen patients (0.08%) had missing values for anemia, 18 (0.1%) for leukocytosis, 17 (0.1%) for thrombocytopenia, and 1 patient (0.005%) had no information on body weight; these cases were excluded from the multivariable analysis.

In the multivariable analyses, we observed a progressive decrease in the risk of VTE recurrences (adjusted subdistribution HR [asHR]: 0.94 per year; 95% CI: 0.92-0.96), major bleeding (asHR: 0.98 per year; 95% CI: 0.96-0.99), all-cause death (asHR: 0.97 per year; 95% CI: 0.96-0.98), fatal PE (asHR: 0.89 per year; 95% CI: 0.87-0.92), and fatal bleeding





(asHR: 0.91 per year; 95% CI: 0.88-0.95) (Table 5, Figures 5 and 6). Similarly, after adjusting for temporal trends in patient characteristics around the time of VTE diagnosis, from 2001 to 2005 to 2016 to 2020, the HRs (or subdistribution HRs for competing risk analysis) for VTE recurrences decreased by 0.42 (95% CI: 0.28-0.64), major bleeding by 0.66 (95% CI: 0.45-0.97), all-cause death by 0.60 (95% CI: 0.48-0.74), fatal PE by 0.19 (95% CI: 0.08-0.46), and fatal bleeding by 0.37 (95% CI: 0.20-0.68).

## DISCUSSION

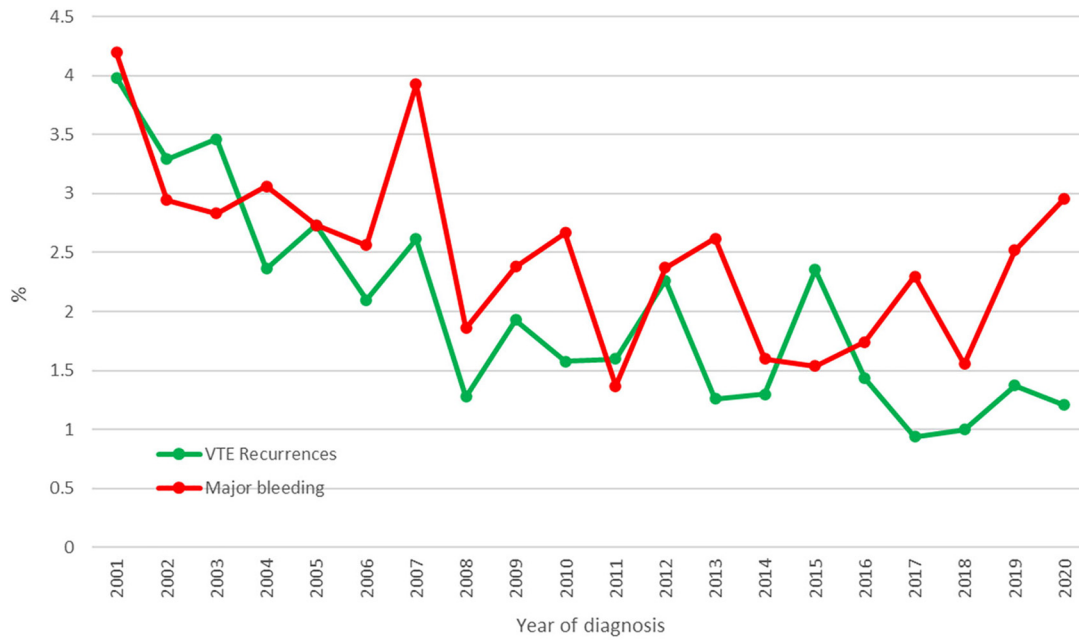
Our study, which analyzed a large cohort of consecutive patients with active cancer and symptomatic VTE, has identified several significant changes over time that suggest advances in the management of patients with cancer-associated thrombosis (Central Illustration). We observed a progressive increase in patients initially presenting with PE or upper extremity DVT and a decrease in patients presenting with lower limb DVT. Furthermore, there was an

increase in patients receiving radiotherapy or immunotherapy and a decrease in those prescribed hormonal therapy (with the exception of estrogen use). Concerning the treatment of VTE, the progressive increase in DOAC use has been matched by a decrease in VKA use. However, the most clinically relevant findings pertain to the progressive decrease in patients experiencing VTE recurrences, major bleeding events, and all-cause death as well as death caused by bleeding or PE during the first 30 days of therapy. These findings remain robust even after thorough multivariable adjustment. This progressive improvement in 30-day outcomes remains consistent among patients initially presenting with PE or isolated DVT.

The possible reasons behind the increase in PE and upper extremity DVT are not clear. Several hypotheses could explain these results. One possibility is the potential increase in the use of central catheters during the study period, which might contribute to an increased risk of upper limb thrombosis.<sup>21</sup>

Concerning the increase in the number of PEs, technological improvements, such as the widespread

**FIGURE 4** Thirty-Day Unadjusted Crude Rates of Symptomatic VTE Recurrences and Major Bleeding Over a 20-Year Period



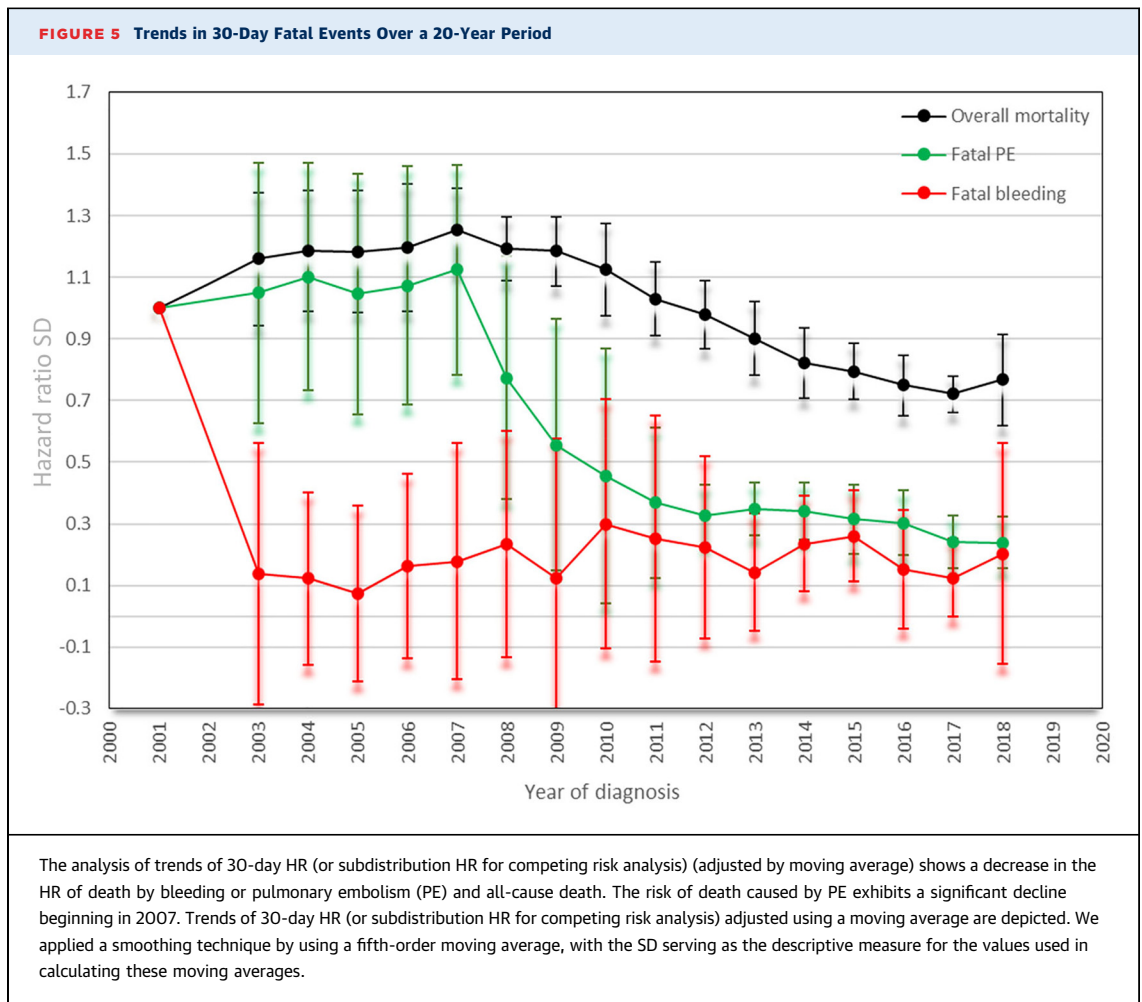
The unadjusted curves suggest a decrease in the rates of symptomatic cancer-associated thrombosis recurrence and bleeding events over the last 20 years. The results are based on crude rates not considering competing risk. VTE = venous thromboembolism.

**TABLE 5** Multivariable HRs for Main Clinical Outcomes at 30 Days

	Recurrent VTE	Major Bleeding	All-Cause Death	Fatal PE	Fatal Bleeding
Patients	319	414	1,760	235	95
Clinical characteristics					
Age >70 y	0.51 (0.38-0.67)	1.01 (0.80-1.28)	1.06 (0.96-1.18)	1.12 (0.83-1.52)	1.47 (0.92-2.34)
Initial VTE presentation					
Pulmonary embolism	0.80 (0.64-1.01)	1.17 (0.96-1.44)	1.49 (1.35-1.64)	20.5 (11.2-37.6)	0.93 (0.61-1.40)
Blood tests					
Anemia	1.02 (0.81-1.29)	1.96 (1.56-2.46)	1.63 (1.47-1.81)	1.26 (0.96-1.66)	2.28 (1.40-3.71)
WBC >11,000/ $\mu$ L	1.82 (1.44-2.30)	1.63 (1.33-2.01)	2.59 (2.35-2.86)	2.18 (1.68-2.83)	1.85 (1.20-2.87)
Platelet count <100,000/ $\mu$ L	1.34 (0.86-2.09)	1.75 (1.24-2.48)	2.55 (2.19-2.96)	2.88 (1.91-4.35)	2.09 (1.10-4.00)
CrCl levels <60 mL/min	0.84 (0.64-1.10)	1.58 (1.26-1.99)	1.76 (1.58-1.96)	1.85 (1.38-2.46)	1.63 (1.03-2.58)
Concomitant drugs					
Corticosteroids	0.86 (0.62-1.19)	1.46 (1.13-1.89)	1.64 (1.46-1.84)	1.87 (1.37-2.56)	1.75 (1.04-2.95)
Cancer characteristics					
With metastases	1.28 (1.01-1.63)	1.35 (1.09-1.66)	2.85 (2.53-3.21)	2.61 (1.91-3.58)	1.73 (1.09-2.73)
Site of cancer					
Breast	Reference	Reference	Reference	Reference	Reference
Gastrointestinal	1.60 (0.99-2.59)	1.38 (0.94-2.03)	1.75 (1.42-2.15)	1.03 (0.64-1.66)	2.56 (0.91-7.21)
Genitourinary	1.50 (0.93-2.44)	1.48 (1.01-2.16)	1.22 (0.98-1.51)	1.07 (0.66-1.72)	2.06 (0.72-5.91)
Lung	2.30 (1.42-3.73)	0.99 (0.64-1.53)	1.97 (1.60-2.44)	0.97 (0.59-1.60)	2.15 (0.68-6.81)
Other sites	1.55 (0.95-2.55)	1.29 (0.86-1.94)	1.60 (1.29-1.99)	1.10 (0.67-1.81)	2.88 (0.99-8.36)
Cancer therapy					
Chemotherapy	0.69 (0.54-0.87)	0.62 (0.50-0.76)	0.75 (0.67-0.83)	0.82 (0.62-1.09)	0.77 (0.49-1.20)
Influence of time					
Per year	0.94 (0.92-0.96)	0.98 (0.96-0.99)	0.97 (0.96-0.98)	0.89 (0.87-0.92)	0.91 (0.88-0.95)

Values are n or adjusted HR (or subdistribution HR for competing risk analysis) (95% CI). Multivariable time-to-event regression models at 30 days for the respective outcomes of recurrent VTE, major bleeding, all-cause death, fatal PE, and fatal bleeding. Models were adjusted for sex, age, body weight, VTE presentation (PE vs DVT), chronic heart or lung disease, recent major bleeding, prior VTE, anemia, leukocytosis, thrombocytopenia, CrCl, cancer site, metastases, oncologic therapy, anticoagulant type, antiplatelet therapy, corticosteroids, and country. This table is the global results of the 5 multivariable analyses, one for each clinical outcome, with adjusted outcomes models using HR (or asHR) as the effect measure for each outcome.

asHR = adjusted subdistribution HR; WBC = white blood cell; other abbreviations as in Table 1.

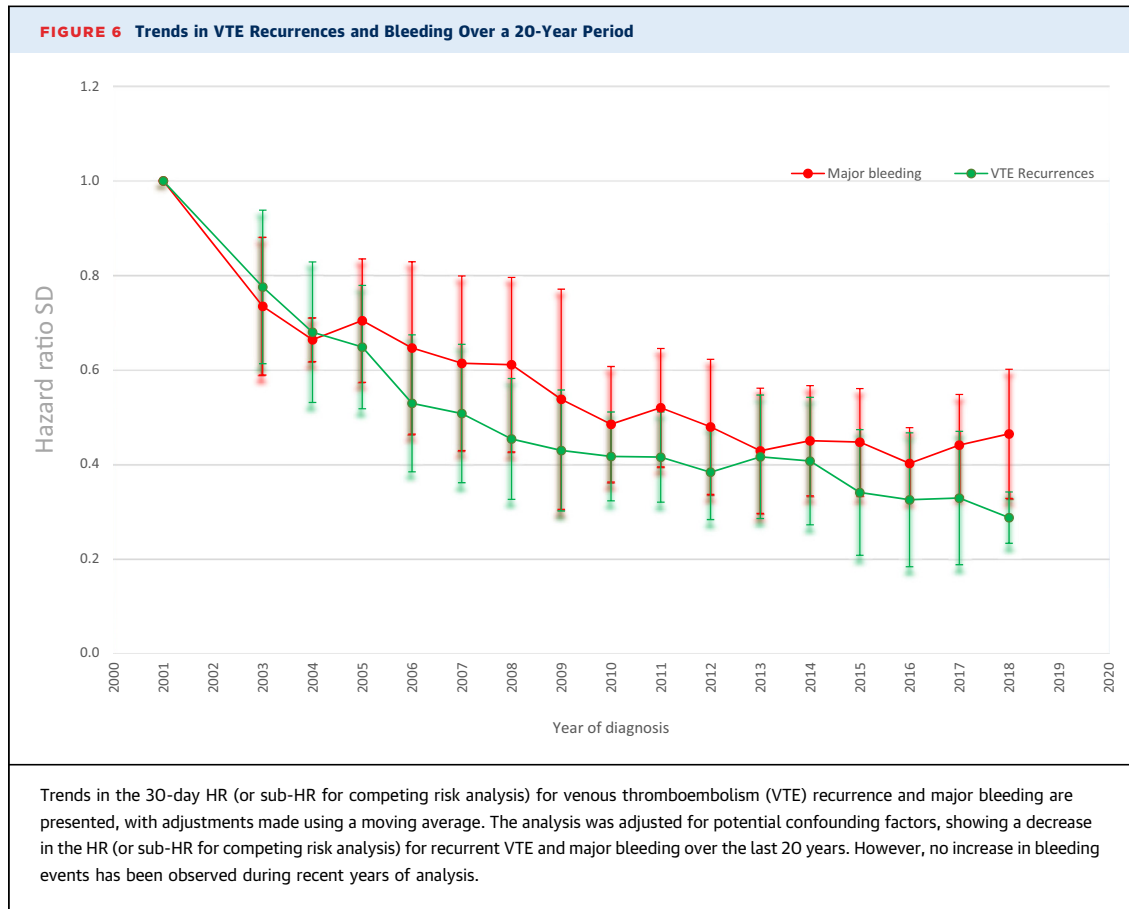


use of multidetector CT, could also play a role. Previous studies have shown that such technological improvements might account for part of the rise in diagnosed PEs.<sup>22,23</sup>

From 2001 to 2005, the proportions of patients developing VTE recurrences or major bleeding within 30 days were similar, each at 3.1%. However, the progressive decrease in VTE recurrences (0.94 per year) was more pronounced than the decrease in major bleeding (0.98 per year). The decrease in fatal PE (0.89 per year) was also higher than the decrease in fatal bleeding (0.91 per year). Consequently, during the 2016 to 2020 period, the proportion of patients developing VTE recurrences within the first 30 days was half that of patients with major bleeding (1.1% vs 2.2%, respectively). Similarly, although the rate of fatal PE in 2001 to 2005 was more than 2-fold higher than that of fatal bleeding (2.5% vs 1.1%, respectively), both rates were similar in the 2016 to 2020 period (0.6% vs 0.4%).

In other words, if the major challenge in cancer patients with VTE 20 years ago was to prevent fatal PE and VTE recurrences, the current major challenge should be to avoid major (and fatal) bleeding without compromising treatment efficacy. Promising anti-factor XI drugs<sup>24</sup> are expected to offer improved safety benefits while maintaining similar efficacy. Ongoing studies in the field of cancer-associated VTE will likely assess these compounds. Another key element involves identifying high-risk patient subgroups for bleeding events, including potential bleeding sites, and monitoring them closely.<sup>25</sup>

There could be several potential explanations for the reduction in recurrent VTE events, bleeding events, and mortality over time. During the 20-year study period, there was a progressive increase in patients initially presenting with PE, having metastases, or using corticosteroids or antiplatelet therapies. There also was a progressive decrease in patients



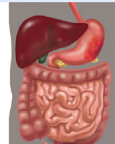
with renal insufficiency. However, the progressive decrease in adverse outcomes was consistently observed in patients initially presenting with PE and those with isolated DVT. The reduced all-cause mortality rates (and possibly some of the reduction in VTE recurrences and bleeding) may be also attributable to effective cancer therapies, including the increased use of radiation therapy and immunotherapy in more recent years.<sup>26</sup> Moreover, the increasing use of various therapies and interventions, including DOACs, pulmonary embolectomy, and mechanical thrombolysis, was associated with a statistically significant decrease in the rates of death, nonfatal VTE recurrences, and nonfatal major bleeding. Although this study does not imply causality, the decline in VTE-specific and treatment-related complications may reflect the more widespread use of therapies shown in trials and meta-analyses to lower the risk of VTE recurrences and bleeding complications. LMWH has been shown to be more efficient than VKAs in preventing recurrent VTE,<sup>27</sup> and DOACs have demonstrated greater efficiency than dalteparin.<sup>12</sup> Using administrative claims,

Ording et al<sup>28</sup> also found a progressive decrease in 30-day mortality (from 15.1% in 2006-2008 to 12.7% in 2015-2017) in 8,167 Danish patients with cancer-associated VTE. However, that study was unable to estimate VTE recurrences or bleeding rates or event rates for fatal PE and fatal bleeding. To our knowledge, the current study is the largest and most comprehensive study reporting the trends in presentation and outcomes specifically for cancer-associated VTE.

**STUDY LIMITATIONS.** This study has several limitations that should be acknowledged. First, we could not control for certain potential confounders, such as specific cancer details, biomarkers, lifestyle factors, or the use of central vein catheters or surgery within the first 30 days. It is possible that these variables may have influenced event rates. Additionally, the RIETE registry did not systematically collect information on race, which may be a relevant factor. Second, the generalizability of our findings should be considered, and caution should be exercised in extrapolating the results to centers with limited resources. However, it is important to note that the RIETE registry has enrolled

**CENTRAL ILLUSTRATION** Advancements in Cancer-Associated Thrombosis Management Over a 20-Year Period

Trends in clinical characteristics, treatment, and 30-day outcomes in cancer patients with cancer-related thrombosis: RIETE Registry, 2001-2020

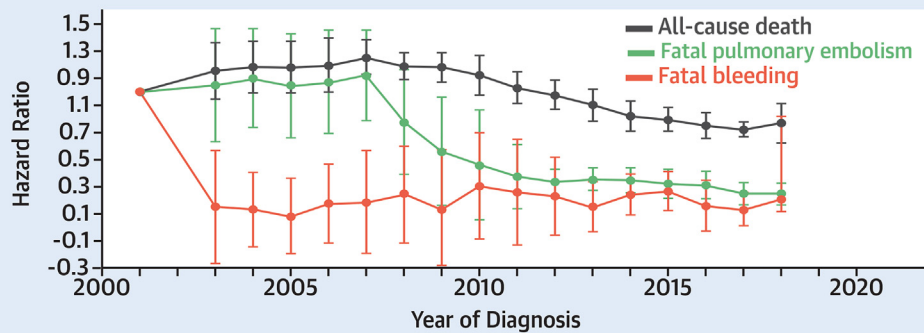
17,271 patients with venous thromboembolism (VTE) over 20 years  
Evaluation at 30-day follow-upVTE  
recurrenceMajor  
bleeding

Death

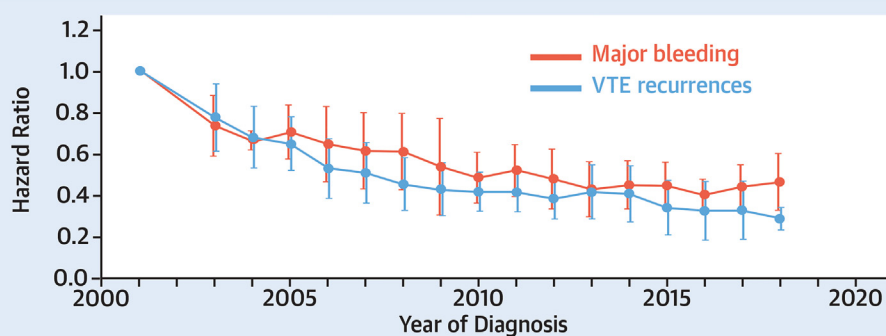


Prevalence	2001-2005	2016-2020
Pulmonary embolism	44.2%	54.9% ↑
Upper extremity DVT	6.3%	12.0% ↑
Lung cancer	12.7%	18.1% ↑

Trends of 30-day adjusted HR of all-cause death, fatal PE, and fatal bleeding



Trends of 30-day adjusted HR of VTE recurrences and major bleeding

Bertoletti L, et al. *J Am Coll Cardiol CardioOnc.* 2023;5(6):758-772.

This illustration portrays the trends in the 30-day adjusted HR (or subdistribution HR for competing risk analysis) of symptomatic venous thromboembolism (VTE) recurrences and major bleeding over a 20-year time period. The analysis was adjusted for potential confounding factors, showing a decrease in the HR (or subdistribution HR for competing risk analysis) for the recurrence of cancer-associated thrombosis and major bleeding, which has remained constant throughout the entire 20-year period. However, there has been no increase in bleeding events during the recent years of analysis. Trends are presented with adjustments made using a moving average. DVT = deep vein thrombosis; PE = pulmonary embolism; RIETE = Registro Informatizado de la Enfermedad Trombo Embólica.

patients from 27 countries, including a diverse range of local, regional, and referral hospitals. Third, the data from randomized trials suggesting the safety and efficacy of DOACs in various subgroups of patients with cancer have only emerged recently, and updates by regulatory authorities or guideline committees require additional time. This, along with reservations for use of DOACs in certain luminal cancers, may account for the limited utilization of DOACs in our study despite a growing trend in their use. As such, future analyses in subsequent years should assess whether thrombotic and hemorrhagic outcomes continue to change as clinical practice increasingly adopts DOACs. Finally, our results suggest an association between trends rather than a direct causality. We were not able to control for confounding factors, such as variations in cancer management or the diagnostic approach to VTE.

## CONCLUSIONS

Our study reveals a progressive decline in the 30-day rates of VTE recurrences, major bleeding events, and death in cancer patients with VTE from 2001 to 2020. Interestingly, the decrease in VTE recurrences was more pronounced than the decrease in major bleeding events. This observation may have therapeutic consequences given that in the last 5 years the rate of major bleeding events was 2-fold higher than that of VTE recurrences. Further prospective studies are warranted to externally validate these findings and determine the best therapeutic approach moving forward.

**ACKNOWLEDGMENTS** The authors thank all the members of the RIETE organization (see [Supplemental Appendix](#)). They also express our gratitude to Sanofi Spain, LEO PHARMA and ROVI for supporting this Registry with an unrestricted educational grant. They also thank the RIETE Registry Coordinating Center, S&H Medical Science Service, for their quality control data, logistic and administrative support and Prof.

Salvador Ortiz, Universidad Autónoma Madrid, Statistical Advisor in S&H Medical Science Service for the statistical analysis of the data presented in this paper.

## FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Bertoletti has received personal fees and nonfinancial support from Aspen, Bayer, BMS-Pfizer, and Léo-Pharma and Johnson & Johnson; and has received grants, personal fees, and nonfinancial support from Merck Sharp & Dohme outside the submitted work. Dr Jimenez has received grants or contracts from Daiichi-Sankyo, Sanofi, and ROVI; and has received personal fees and honoraria for lectures from Bayer, Boehringer Ingelheim, BMS, Daiichi-Sankyo, Léo-Pharma, Pfizer, ROVI, and Sanofi outside the submitted work. Dr Bikkeli is supported by the Scott Schoen and Nancy Adams IGNITE Award from the Mary Horrigan Connors Center for Women's Health and Gender Biology at Brigham and Women's Hospital and a Career Development Award from the American Heart Association (#938814). Dr Ay has received honoraria for lectures from Bayer, BMS, Daiichi-Sankyo, Pfizer, and Sanofi outside the submitted work; and has served on Advisory Boards of Bayer, BMS, Daiichi-Sankyo, Pfizer, and Sanofi. Dr Trujillo-Santos has received personal fees and honoraria for lectures from Bayer, Boehringer Ingelheim, BMS, Daiichi-Sankyo, Léo-Pharma, Pfizer, ROVI, and Sanofi outside the submitted work. Dr Sigüenza has received support for attending meetings for Sanofi, ROVI, and Viatrix. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** Over the past 20 years, the rates of VTE recurrences, major bleeding, and overall death consistently decreased in cancer patients with VTE.

**TRANSLATIONAL OUTLOOK:** Further research is needed to confirm the recent trend toward an increased rate of major bleeding and determine the optimal management strategies to further improve morbidity and mortality.

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**KEY WORDS** anticoagulant, bleeding, cancer, survival, thrombosis

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**APPENDIX** For a list of the coordinators of the RIETE registry as well as supplemental tables and a figure, please see the online version of this paper.

