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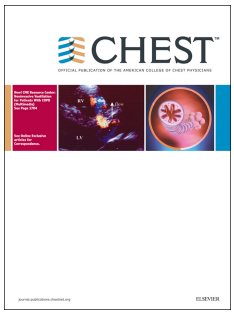

Deep vein thrombosis management and outcome trends, 2001 to 2014

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PII: S0012-3692(16)47594-X

DOI: 10.1016/j.chest.2016.03.046

Reference: CHEST 412

To appear in: *CHEST*

Received Date: 13 February 2016

Revised Date: 8 March 2016

Accepted Date: 29 March 2016

Please cite this article as: Morillo R, Jiménez D, Aibar MÁ, Mastroiacovo D, Wells PS, Sampériz Á, de Sousa MS, Muriel A, Yusen RD, Monreal M, for the RIETE investigators, Deep vein thrombosis management and outcome trends, 2001 to 2014, *CHEST* (2016), doi: 10.1016/j.chest.2016.03.046.

Word count: 2,850

Abstract word count: 240

Deep vein thrombosis management and outcome trends, 2001 to 2014

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Running head: Acute DVT mortality

Keywords: Deep vein thrombosis, survival, prognosis.

Tables: 5

Figures: 3

ABBREVIATION LIST

CI, confidence interval

CT, computerized tomography

DVT, deep vein thrombosis

PE, pulmonary embolism

RIETE, Registro Informatizado de la Enfermedad TromboEmbólica

VQ, ventilation-perfusion

VTE, venous thromboembolism

ABSTRACT

Background: A comprehensive evaluation of temporal trends in the treatment of patients who have deep vein thrombosis (**DVT**) may assist with identification of modifiable factors that contribute to short-term outcomes.

Methods: We assessed temporal trends in length of hospital stay and use of pharmacological and interventional therapies among 26,695 adults with DVT enrolled in the RIETE registry between 2001 and 2014. We also examined temporal trends in risk-adjusted rates of all-cause, PE-related, and bleeding-related death to 30-days after diagnosis.

Results: The mean length of hospital stay decreased from 9.0 days in 2001-2005 to 7.6 days in 2010-2014 (P <0.01). For initial DVT treatment, the use of low-molecular weight-heparin decreased from 98% to 90% (P <0.01). Direct oral anticoagulants use increased from 0.5% in 2010 to 13.4% in 2014 (P <0.001). Risk-adjusted rates of 30-day all-cause mortality decreased from 3.9% in 2001-2005 to 2.7% in 2010-2014 (adjusted rate ratio per year, 0.84; 95% confidence interval [**CI**], 0.74 to 0.96; P <0.01). VTE-related mortality showed a non-statistically significant downward trend (adjusted rate ratio per year, 0.70; 95% CI, 0.44 to 1.10; P =0.13), whereas 30-day bleeding-related mortality significantly decreased from 0.5% in 2001-2005 to 0.1% in 2010-2014 (adjusted rate ratio per year, 0.55; 95% CI, 0.40 to 0.77; P <0.01).

Conclusions: This international registry-based temporal analysis identified reductions in length of stay for adults hospitalized for DVT. The study also found a decreasing trend in adjusted rates of all-cause and bleeding-related mortality.

INTRODUCTION

Venous thromboembolism (**VTE**) remains a worldwide major health issue (1). Patients who have VTE, consisting of pulmonary embolism (**PE**) and or deep vein thrombosis (**DVT**), have a reduced survival, and VTE independently predicted reduced survival for up to 3 months after diagnosis (2, 3).

Changes in the approach to the care of patients with VTE may influence short-term clinical outcomes. Following changes in health-care services and their delivery (4), health-care providers are discharging hospitalized patients earlier (5). Particularly, advances in therapeutic strategies that include the use of direct oral anticoagulants have facilitated treating a proportion of patients with VTE as outpatients, especially those who have DVT (6-9). A comprehensive evaluation of temporal trends in the treatment of patients with DVT may assist with identification of modifiable factors that contribute to improved short-term outcomes (10). Although a recent report (11) examined temporal trends in PE treatment from 2001 to 2013 and found significant reductions in all-cause and PE-related mortality over time, there is a paucity of data from robust population-based surveillance studies describing changing trends in death rates for acute DVT (12, 13). Therefore, we used the Registro Informatizado de la Enfermedad TromboEmbólica (**RIETE**) (14-16) to define temporal changes in hospital management of patients with acute DVT (i.e., length of hospital stay, use of evidence-based treatments) and to describe contemporary mortality trends.

METHODS

Study design

We conducted a retrospective cohort study that used prospectively collected data from patients enrolled in the RIETE registry. All patients provided written or oral consent for participation in the registry in accordance with local ethics committee requirements.

Data source

Previous publications have described the design and conduct of the RIETE registry (17, 18). Briefly, at each participating RIETE site, investigators aimed to enroll consecutive patients who had confirmed acute symptomatic or asymptomatic VTE (e-**Appendix**). Confirmatory testing consisted of high probability ventilation-perfusion (**V/Q**) scintigraphy (19), positive contrast-enhanced, PE-protocol, chest computerized tomography (**CT**) [single or multi-detector CT] (20), lower limb venous compression ultrasonography (21) or CT venography positive for proximal DVT (22). The RIETE registry only excluded patients that enrolled in blinded randomized VTE treatment clinical trials.

Data quality control

To ensure the validity of the information entered into the database, one of the specially trained monitors visited each participating hospital and compared information in 25 to 50 randomly chosen patient records with the information entered into the RIETE database. For data quality assessment, monitors assessed 4,100 random records from all participating hospitals that included 1,230,000 measurements. These data showed a 95% overall agreement between the registered information and patient records. RIETE also used electronic data monitoring to detect inconsistencies or errors and attempted to resolve discrepancies by contacting the local coordinators.

Eligibility

This study included adult patients enrolled in RIETE with a diagnosis of acute symptomatic DVT from January 1, 2001, through December 31, 2014. Since we were interested in examining trends in mortality over time, we excluded patients at hospitals with fewer than 3 years of data submission and patients at hospitals with low case volumes (less than 30 DVT during the study period).

Variables

Patients enrolled in RIETE had data collected from around the time of VTE diagnosis that included but was not limited to: age; gender; body weight; presence of coexisting conditions such as chronic heart or lung disease; recent (<30 days prior to VTE) major bleeding; presence of risk factors for PE including active cancer (defined as newly diagnosed cancer or cancer undergoing

treatment [i.e. surgery, chemotherapy, radiotherapy, hormonal, or support therapy]), recent immobility (defined as non-surgical patients assigned to bed rest with bathroom privileges for ≥4 days in the 2-months prior to VTE diagnosis), surgery (defined as those who had undergone major surgery in the 2 months prior to VTE); clinical signs and symptoms on admission; and laboratory results at hospital admission that included hemoglobin, platelet count and serum creatinine. We defined outpatients as those who were discharged from the Emergency Department within 24 hours of diagnosis.

Study outcomes

The primary outcome was 30-day all-cause mortality (defined as death from any cause within 30 days following the diagnosis of DVT). Since studies have shown that most deaths occur soon (i.e., during the first 7 days) after DVT diagnosis and initiation of treatment, and to better understand the association between specific phases of treatment and mortality, we also examined rates of death from any cause within 7 days following the diagnosis of DVT. In addition, we examined temporal trends in VTE-related and bleeding-related mortality through 30-days after DVT diagnosis. We chose 7-day and 30-day mortality assessment periods because they reflect variations related to changes in length of stay and evidence-based treatments, and because they are standard measurements of quality of care (23). In addition, we examined rates of nonfatal VTE recurrences and nonfatal bleeding events within 30 days following the diagnosis of DVT. The RIETE investigators used medical record review to assess vital status. For patients that died, further medical record review, and proxy interviews when necessary, assisted with determining date and cause of death.

Statistical analysis

We examined patient demographic and clinical characteristics across three time periods (2001–2005, 2006–2009, and 2010–2014). To evaluate changes in baseline characteristics by calendar period, we used the Mantel–Haenszel test of trend for categorical variables and linear regression for continuous variables. We used the Cochran-Armitage trend test to determine the statistical

significance of changes over time in the binary outcomes and the Cuzick nonparametric test in the continuous outcomes.

To assess mortality rates over time, we constructed multivariable regression models for the overall cohort. We adjusted generalized linear models for age, sex, coexisting conditions (i.e., cancer, immobilization, chronic lung disease, chronic heart disease), signs of clinical severity (i.e., heart rate, systolic blood pressure), and laboratory results (i.e., creatinine levels, hemoglobin levels) at hospital admission. These models accounted for clustering of patients within hospitals. We included the independent variable, calendar period, a categorical variable, with 2001-2005 as the reference period. We multiplied the adjusted rate ratio for each period by the observed mortality rate for the reference period to obtain risk-adjusted mortality rates for the study period. These rates represented the estimated mortality for each period if the patient case mix was identical to that in the reference period.

To confirm that any mortality trends were independent of the duration of hospital participation in the registry, we adjusted for the number of years of hospital participation for each patient. We also examined whether mortality trends differed by age group (≥ 65 years vs. < 65 years), and by location of treatment (inpatient vs. outpatient), by including an interaction term with calendar period in the model. To exclude the possibility that our findings were due to enrollment of better-performing hospitals over time, we performed these analyses only for patients at hospitals with at least 5 years of registry participation.

Data were complete for all covariates and outcomes, except heart rate (9.8% missing), systolic blood pressure (7.0% missing), and creatinine levels (1.9% missing) at the time of DVT diagnosis. Missing patient-level covariates were assumed to be missing at random and were imputed with the use of multiple imputation (24).

We conducted statistical analyses with the use of STATA version 13.1 (STATA Corp, College Station, Texas). All hypothesis tests were two-sided, with a significance level of 0.05.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Study population

We identified 28,565 adults at 286 hospitals participating in the RIETE registry that had a diagnosis of acute symptomatic DVT during the time period of January 1, 2001, through December 31, 2014 (**Figure 1**). We excluded 642 patients at 42 hospitals with fewer than 3 years of data submission and 1,228 patients at 106 hospitals with low case volumes (less than 30 DVT). The final study sample included 26,695 patients from 138 hospitals.

Patient characteristics

There was a fairly stable number of approximately 100 sites participating in RIETE that provided more than 8,500 patients in each of the three 5-year periods.

Table 1 shows the patient characteristics for each of the three time periods. During the study, there was a calendar-period trend toward younger age (mean 64 years decreased to 62 years), whereas the sex distribution remained stable (females 47% in 2001-2005 and 50% in 2010-2014; P =0.63). The prevalence of cancer and chronic heart failure increased over time. Conversely, there was a decrease in a history of immobility (26% to 22%). A history of recent bleeding did not significantly change over time (2.1% in 2001-2005 to 1.8% in 2010-2014; P =0.26 for trend).

Regarding time trends for signs of clinical severity, mean heart rate and systolic blood pressure did not vary (P >0.10 for trend for all comparisons), but the

proportion of patients with systolic blood pressure <100 mm Hg significantly increased (7.3% in 2001-2005 to 9.0% in 2010-2014; P <0.01). The proportion of patients with elevated creatinine levels (i.e., creatinine >2 mg/dL) increased from 11.3% (95% confidence interval [**CI**], 10.6 to 12.0%) to 15.9% (95% CI, 15.1 to 16.7%) (P <0.001), whereas mean hemoglobin levels did not significantly change over time (P =0.83 for trend) (**Table 1**).

Temporal trends in length of hospital stay and pharmacological management

Between 2001-2005, 24.6% (95% CI, 23.5 to 25.7%) of patients were managed as outpatients; 35.8% (95% CI, 34.6 to 37.0%) between 2006-2009; and 51.3% (95% CI, 50.1 to 52.5%) between 2010-2014 (P <0.001 for trend). For hospitalized patients, mean length of hospital stay decreased from 9.0 days (95% CI, 8.2 to 9.8 days) in 2001-2005 to 7.6 days (95% CI, 7.3 to 7.8 days) in 2010-2014 (16% relative reduction, P <0.01) (**Figure 2**). Regarding in-hospital treatments known to influence outcomes, the use of unfractionated heparin (3.2% in 2001-2005 to 3.5% in 2010-2014) did not change significantly over time, but the use of low-molecular weight-heparin decreased from 98% to 90% (P <0.01 for trend), probably accounted for by the increased use of direct oral anticoagulants from 0.5% in 2010 to 13.4% in 2014 (P <0.001 for trend). Local thrombolytic therapy use increased from 0.2% to 4.7% (P <0.001 for trend) and filter insertion increased from 1.5% to 2.5% (P <0.01 for trend) (**Figure 2**).

Temporal trends in mortality

The entire cohort had a 30-day all-cause mortality rate of 2.7% (736 of 26,695 patients). **Table 2** shows the causes of death for each of the three time periods. There was a significant trend toward decreased mortality during the study period for all study patients (**Figure 3, Table 3**). After adjustment for temporal trends in patient characteristics around the time of DVT diagnosis, overall mortality decreased from 3.9% in 2001-2005 to 2.7% in 2010-2014 (adjusted rate ratio per year, 0.84; 95% CI, 0.74 to 0.96; P <0.01 for trend). (**Tables 4 and 5**). The temporal trends in mortality were similar regardless of age group (≥65 years vs. <65 years) (P >0.10 for interaction), or location of treatment (inpatients

vs. outpatient) (P >0.10 for interaction). For analyses restricted to the 113 hospitals (24,624 patients) that participated in the RIETE registry for at least 5 years, the trends remained unchanged.

The entire cohort had a 7-day all-cause mortality rate of 0.6% (168 of 26,695 patients). Rates of 7-day all-cause mortality showed a non-statistically significant downward trend, with a risk-adjusted rate of 0.8% in 2001-2005 and 0.4% in 2010-2014 (adjusted rate ratio per year, 0.72; 95% CI, 0.47 to 1.10; P =0.13 for trend) (**Table 4**).

Secondary Outcomes

After adjustment, 30-day VTE-related mortality showed a non-statistically significant downward trend, from 0.2% in 2001-2005 to 0.1% in 2010-2014 (adjusted rate ratio per year, 0.70; 95% CI, 0.44 to 1.10; P =0.13 for trend), whereas 30-day bleeding-related mortality significantly decreased from 0.5% in 2001-2005 to 0.1% in 2010-2014 (adjusted rate ratio per year, 0.55; 95% CI, 0.40 to 0.77; P <0.01 for trend). In the subgroup of inpatients, 30-day bleeding-related mortality significantly decreased from 0.3% in 2001-2005 to 0.1% in 2010-2014. In the subgroup of outpatients, 30-day bleeding-related mortality significantly decreased from 0.1% in 2001-2005 to 0.05% in 2010-2014 (P >0.10 for interaction).

Rates of nonfatal 30-day VTE recurrence decreased over time, with a risk-adjusted rate of 1.2% in 2001-2005 and 0.8% in 2010-2014 (adjusted rate ratio per year, 0.80; 95% CI, 0.68 to 0.96; P =0.02 for trend) (**Table 4**). Nonfatal 30-day major bleeding decreased over time (risk-adjusted rate, 2.8% in 2001-2005 and 1.8% in 2010-2014; adjusted rate ratio per year, 0.80; 95% CI, 0.71 to 0.90; P <0.001 for trend).

DISCUSSION

This temporal analysis (2001 through 2014) of short-term outcomes in the largest multinational observational cohort study of patients with an acute DVT found a decreasing trend in the risk-adjusted 30-day all-cause and bleeding-associated mortality. The risk status of patients at presentation with DVT did not improve over the course of the present study, so temporal changes in practice may have influenced changes in clinical outcomes.

During the past few decades, major advances have occurred in treatment strategies for patients with DVT (6-9). The observed declining trends in short-term all-cause mortality, major bleeding, and recurrent VTE may be evidence of improved patient outcomes based on these advances. In fact, our study found substantial decreases in the length of hospital stay and changes in the treatment of acute DVT. The increased use of more effective therapies and interventions, that included direct oral anticoagulants, local thrombolysis, and inferior vena cava filter insertion, was accompanied by a statistically significant decrease in the rates of all-cause and bleeding-related death, nonfatal recurrences and nonfatal major bleeding. Although these data do not imply causality, the decrease of treatment-related (i.e., bleeding) complications may reflect the more widespread use of therapies shown in trials and meta-analyses to lower the risk of bleeding complications (25, 26).

Despite current practice guidelines recommending initial outpatient treatment of most patients with acute DVT, we found that a significant number of patients underwent hospitalization for the acute phase of the disease. In a previous study by the RIETE registry, only 53.7% of DVT were entirely treated at home (27). In a post-hoc analysis of hospitalization and length of stay data conducted in the patients from the randomized open label EINSTEIN DVT trial (28), 52% of the patients were hospitalized for the initial event (1,711/3,434, 52%; 95% CI, 50 to 54%). For patients hospitalized, the median length of stay was 5.0 days (interquartile range, 3.0 to 9.0 days).

A smaller study of 1,369 DVT patients detected a nonsignificant decrease in 30-day all-cause mortality rates over a decade (13). However, this study might have lacked statistical power. In addition, the study's enrollment period (1999 to

2009) did not allow collecting information on the use of direct oral anticoagulants. In our analysis, the more contemporary period allowed for the assessment trends in the use of direct oral anticoagulants. Moreover, our study's large sample size, the adjustment for potential confounders, and the robustness of the findings provide strong evidence supporting a decreasing trend in adjusted death rates for acute DVT.

Several issues merit further critical review and discussion. The decreases in all-cause and bleeding-associated mortality may simply reflect a decrease in baseline risk over time. However, we found no evidence for this. Although patients in our study were younger by approximately 2 years at the end of the study period than those at the beginning, with less immobilization, they also had higher rates of cancer, chronic heart failure, hypotension, and laboratory abnormalities (renal failure). Moreover, the study showed consistent results even after adjustment for temporal changes in patient characteristics over time, including age. In addition, the analyses did not support that the study findings were due to enrollment of better-performing hospitals over time. We found results similar to the full data set when we restricted our analyses to hospitals that participated in the RIETE registry for 5 years or longer.

The findings of this study should be interpreted in light of the following potential limitations. First, although data in the RIETE registry allowed us to adjust for a number of key variables, the possibility of residual confounding still remains. Second, we did not have complete information on treatment details (INR control, concomitant medications), and quality-improvement initiatives at hospitals (e.g., adherence to guidelines) to better understand the reasons for decreased mortality. These are often difficult to document accurately, and further studies are required to examine the role of these factors in explaining the temporal decrease in mortality. Finally, although we found that improved survival trends were independent of the duration of hospital participation in the RIETE registry, our study cohort was probably composed of hospitals that were enthusiastic about evidence-based management of VTE, and the results may not be fully generalizable elsewhere.

In conclusion, contemporary multinational observational data from the RIETE registry showed significant temporal changes in the management of patients with DVT that were consistent with trial evidence and national and international guidelines. This study population demonstrated significant reductions in all-cause and bleeding-related mortality over time.

Acknowledgements

We express our gratitude to Sanofi Spain for supporting this Registry with an unrestricted educational grant. We also express our gratitude to Bayer Pharma AG for supporting this Registry. Bayer Pharma AG's support was limited to the part of RIETE outside Spain, which accounts for a 22,87% of the total patients included in the RIETE Registry. We also thank the RIETE Registry Coordinating Center, S & H Medical Science Service, for their quality control data, logistic and administrative support.

Declaration of interests

R.M. has nothing to disclose.

D.J. has served as an advisor or consultant for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Leo Pharma, Pfizer, ROVI and Sanofi; served as a speaker or a member of a speakers' bureau for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Leo Pharma, ROVI and Sanofi; received grants for clinical research from Sanofi and ROVI.

M.A.A. has nothing to disclose.

D.M. has nothing to disclose.

P.W. has served as an advisor or consultant for Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb and Daiichi Sankyo.

A.S. has nothing to disclose.

M.S.S. has nothing to disclose.

A.M. has nothing to disclose.

R.Y. has received research funding from Bayer HealthCare Pharmaceuticals, Inc., Portola, Inc., Pfizer, Inc. and Bristol-Meyers Squibb in the past 3 years. He has served as a consultant for Bayer HealthCare, Inc., Bristol-Meyers Squibb Glaxo-Smithkline, Janssen, Johnson & Johnson, Ortho Pharmaceuticals, Inc., Organon, Inc., Pfizer, Inc., Portola, Inc., Sanofi-aventis, SCIOS, Inc. in the past 3 years.

M.M. has served as an advisor or consultant for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Leo Pharma, Pfizer and Sanofi; served as a speaker or a member of a speakers' bureau for Bayer HealthCare Pharmaceuticals, Daiichi Sankyo, Leo Pharma and Sanofi; received grants for clinical research from Sanofi and Bayer.

Author contributions

Study concept and design: Jimenez, Wells, Yusen, Monreal

Acquisition of data; analysis and interpretation of data; statistical analysis: Morillo, Jiménez, Aibar, Mastroiacovo, Wells, Sampériz, Saraiva de Sousa, Muriel, Yusen, Monreal

Drafting of the manuscript: Morillo, Jimenez, Wells, Yusen, Monreal

Critical revision of the manuscript for important intellectual content: Morillo, Jiménez, Aibar, Mastroiacovo, Wells, Sampériz, Saraiva de Sousa, Muriel, Yusen, Monreal

Study supervision: Jimenez, Monreal

The corresponding author, David Jiménez, had full access to all the data in the study and had final responsibility for the decision to submit for publication. The manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; and any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Figure 1. STROBE study cohort flow diagram

Figure 2. Temporal trends in a) length of stay, b) anticoagulant use, and c) use of other pharmacological and interventional therapies

Figure 3. Unadjusted mortality rates, by calendar year

Table 1. Trends in baseline characteristics in patients with acute deep vein thrombosis

Characteristic	*Year Group*			*P value for trend*
	2001-2005 (N = 8,780)	*2006-2009 (N = 8,626)*	*2010-2014 (N = 9,289)*	
Clinical characteristics,				
Age, years (mean ± SD)	64.4 ± 17.2	63.4 ± 18.2	62.5 ± 18.5	<0.01
Age > 80 years, n (%)	1,391 (15.8)	1,583 (18.4)	1,683 (18.1)	<0.001
Male gender, n (%)	4,618 (52.6)	4,470 (51.8)	4,685 (50.4)	0.63
Weight, kilograms (mean ± SD)	73.7 ± 14.2	74.5 ± 15.2	75.8 ± 16.4	<0.01
Risk factors for VTE,				
History of VTE, n (%)	1,457 (16.6)	1,397 (16.2)	1,488 (16.0)	0.60
Cancer, n (%) †	1,889 (21.5)	1,856 (21.5)	2,165 (23.3)	<0.001
Recent surgery, n (%) ‡	993 (11.3)	859 (10.0)	944 (10.2)	0.28
Immobilization for ≥ 4 days, n (%) §	2,322 (26.4)	2,058 (23.9)	2,062 (22.2)	<0.001
Comorbid diseases,				
Chronic lung disease, n (%)	779 (8.9)	672 (7.8)	809 (8.7)	0.46
Chronic heart disease, n (%)	352 (4.0)	369 (4.3)	448 (4.8)	<0.001
Recent major bleeding, n (%)	187 (2.1)	164 (1.9)	166 (1.8)	0.26
Clinical symptoms and signs at presentation,				
Pulse, beats (mean ± SD)	81.2 ± 14.5	80.8 ± 14.5	80.9 ± 15.1	0.48
Pulse ≥ 110 beats/min, n (%)	293 (3.3)	263 (3.0)	308 (3.3)	0.54
Systolic blood pressure, mmHg (mean ± SD)	132.7 ± 20.9	132.7 ± 21.1	132.0 ± 20.7	0.17
Systolic blood pressure < 100 mm Hg, n (%)	533 (7.3)	683 (7.9)	711 (9.0)	<0.01
Laboratory findings,				
Abnormal creatinine levels (> 2 mg/dL)	982 (11.3)	1210 (14.6)	1410 (15.9)	<0.001
Hemoglobin, g/dL (mean ± SD)	12.95 ± 2.04	12.89 ± 2.09	12.94 ± 3.68	0.83
Length of hospital stay,				
Inpatients, days (mean ± SD)	8.98 ± 6.73	8.30 ± 9.28	7.56 ± 7.87	<0.01

Abbreviations: SD, standard deviation; VTE, venous thromboembolism.

† Active or under treatment in the last year.

‡ In the previous month.

§ Immobilized patients defined as non-surgical patients who had been immobilized (i.e., total bed rest with bathroom privileges) for ≥4 days in the month prior to PE diagnosis.

Table 2. Causes of death by calendar period

Causes of death	Year Group		
	2001-2005	**2006-2009**	**2010-2014**
Total	**280/8,780 (3.2%)**	**238/8,626 (2.8%)**	**218/9,289 (2.3%)**
VTE	15/8,780 (0.2%)	17/8,626 (0.2%)	8/9,289 (0.1%)
Bleeding	35/8,780 (0.4%)	26/8,626 (0.3%)	12/9,289 (0.1%)
Cancer	76/8,780 (0.9%)	79/8,626 (0.9%)	89/9,289 (1.0%)
Infection	25/8,780 (0.3%)	39/8,626 (0.5%)	24/9,289 (0.3%)
Respiratory failure	20/8,780 (0.2%)	28/8,626 (0.3%)	27/9,289 (0.3%)
Cardiovascular	8/8,780 (0.1%)	4/8,626 (0.05%)	3/9,289 (0.03%)
Unknown	79/8,780 (0.9%)	18/8,626 (0.2%)	15/9,289 (0.2%)
Others	22/8,780 (0.3%)	27/8,626 (0.3%)	40/9,289 (0.4%)

Abbreviations: VTE, venous thromboembolism.

Table 3. Observed rates of mortality and nonfatal outcomes by calendar period

Overall-no./total no. (%)	2001-2005	2006-2009	2010-2014
30-day all-cause mortality	280/8,780	238/8,626	218/9,289
	(3.2)	(2.8)	(2.3)
7-day all-cause mortality	70/8,780	53/8,626	45/9,289
	(0.8)	(0.6)	(0.5)
30-day VTE-related mortality	15/8,780	17/8,626	8/9,289
	(0.2)	(0.2)	(0.1)
30-day bleeding-related mortality	35/8,780	26/8,626	12/9,289
	(0.4)	(0.3)	(0.1)
Nonfatal complications			
30-day major bleeding	235/8,780	195/8,626	167/9,289
	(2.7)	(2.3)	(1.8)
30-day VTE recurrences	107/8,780	90/8,626	75/9,289
	(1.2)	(1.0)	(0.8)

Abbreviations: VTE, venous thromboembolism.

Table 4. Trends in mortality and nonfatal outcomes

Outcome	Risk-adjusted rates †			Adjusted rate ratio per period (95% CI) ‡	P value for trend ‡
	2001-2005	2006-2009	2010-2014		
		Percent			
30-day all-cause mortality	3.9	3.5	2.7	0.84 (0.74-0.96)	<0.01
7-day all-cause mortality	0.8	0.7	0.4	0.72 (0.47-1.10)	0.13
30-day VTE-related mortality	0.2	0.2	0.1	0.70 (0.44-1.10)	0.13
30-day bleeding-related mortality	0.5	0.3	0.1	0.55 (0.40-0.77)	<0.01
Nonfatal complications					
30-day VTE recurrences	1.2	1.1	0.8	0.80 (0.68-0.96)	0.02
30-day major bleeding	2.8	2.3	1.8	0.80 (0.71-0.90)	<0.001

Abbreviations: VTE, venous thromboembolism; CI, confidence interval

† Risk-adjusted rates of all-cause mortality, VTE-related mortality, and nonfatal complications for each calendar period are reported for the overall cohort. Rates were adjusted for temporal changes in patient and hospital characteristics (see **Table 4** for all model covariates).

‡ Adjusted risk ratios and P values for trend were determined with a model evaluating calendar period as a continuous variable

Table 5. Multivariable model of predictors of 30-day mortality*

Variable	*Adjusted Odds ratio*	*95% CI*	*P value*
Calendar year (per 1 year)	0.97	0.95-0.99	0.042
Age (per 1 year)	1.02	1.01-1.02	< 0.001
Sex (female vs. male)	1.41	1.16-1.71	< 0.001
Weight (per 1 kilogram)	0.98	0.97-0.99	< 0.001
History of VTE	0.80	0.59-1.08	0.139
Cancer †	3.10	2.57-3.74	< 0.001
Recent surgery ‡	0.72	0.52-0.99	0.048
Immobilization for ≥ 4 days §	1.92	1.54-2.41	< 0.001
Chronic lung disease	1.04	0.75-1.44	0.80
Chronic heart disease	1.35	1.01-1.80	0.04
Recent major bleeding	1.29	0.94-1.77	0.12
Pulse (per 1 beat/min)	1.02	1.01-1.02	< 0.001
Systolic blood pressure (per mmHg)	0.99	0.98-0.99	< 0.001
Abnormal creatinine levels (> 2 mg/dL)	1.75	1.45-2.11	< 0.001
Hemoglobin (per 1 g/dL)	0.89	0.86-0.93	< 0.001

* Adjusted odds ratio, 95% confidence intervals and P values are provided for all model covariates included in the multivariable model for 30-day mortality in the overall cohort.

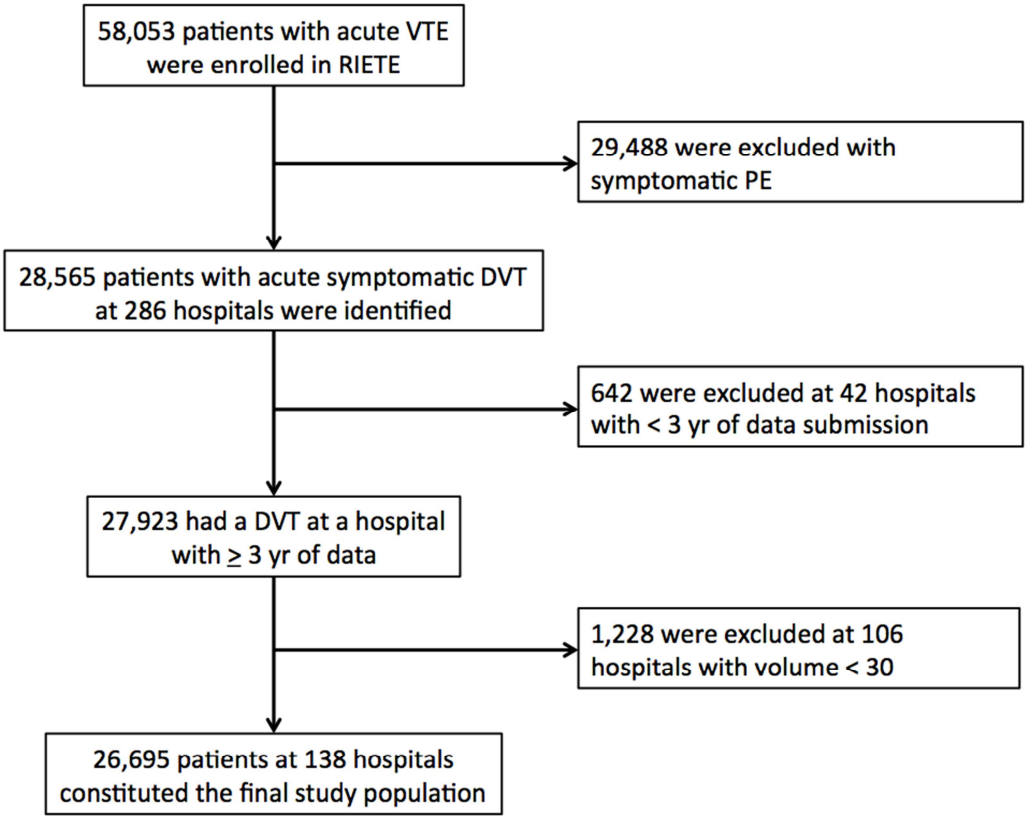
Abbreviations: VTE, venous thromboembolism.

† Active or under treatment in the last year.

‡ In the previous month.

§ Immobilized patients defined as non-surgical patients who had been immobilized (i.e., total bed rest with bathroom privileges) for ≥4 days in the month prior to PE diagnosis.

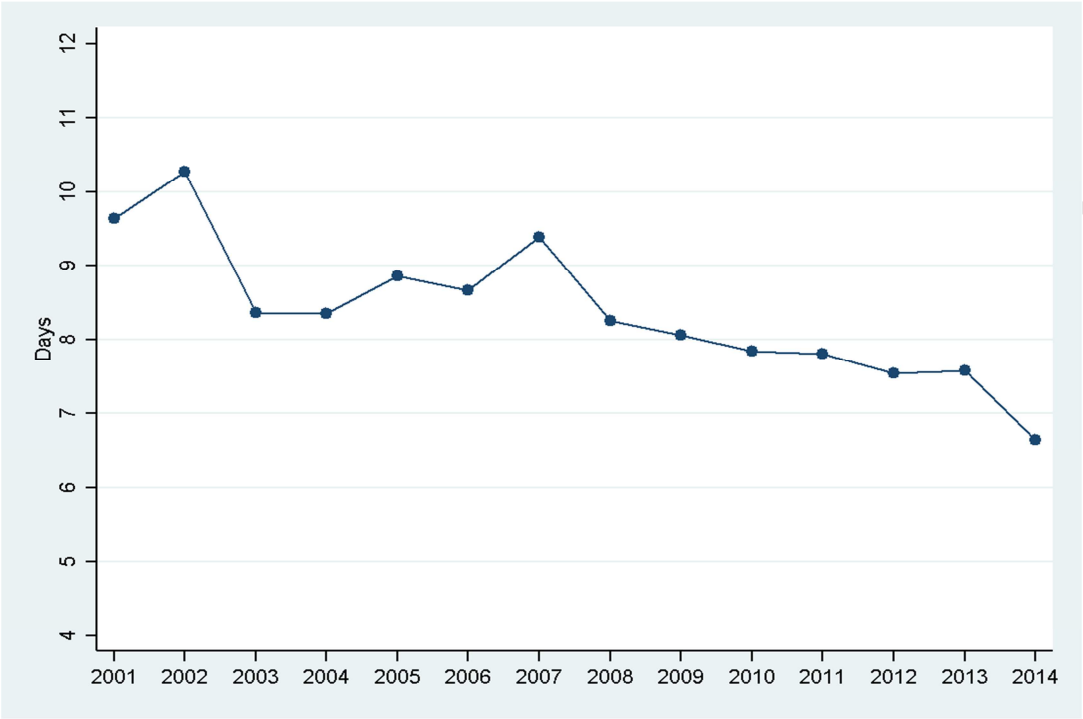
Figure 1.



Abbreviations: VTE, venous thromboembolism; RIETE, Registro Informatizado de la Enfermedad TromboEmbólica; PE, pulmonary embolism; DVT, deep venous thrombosis.

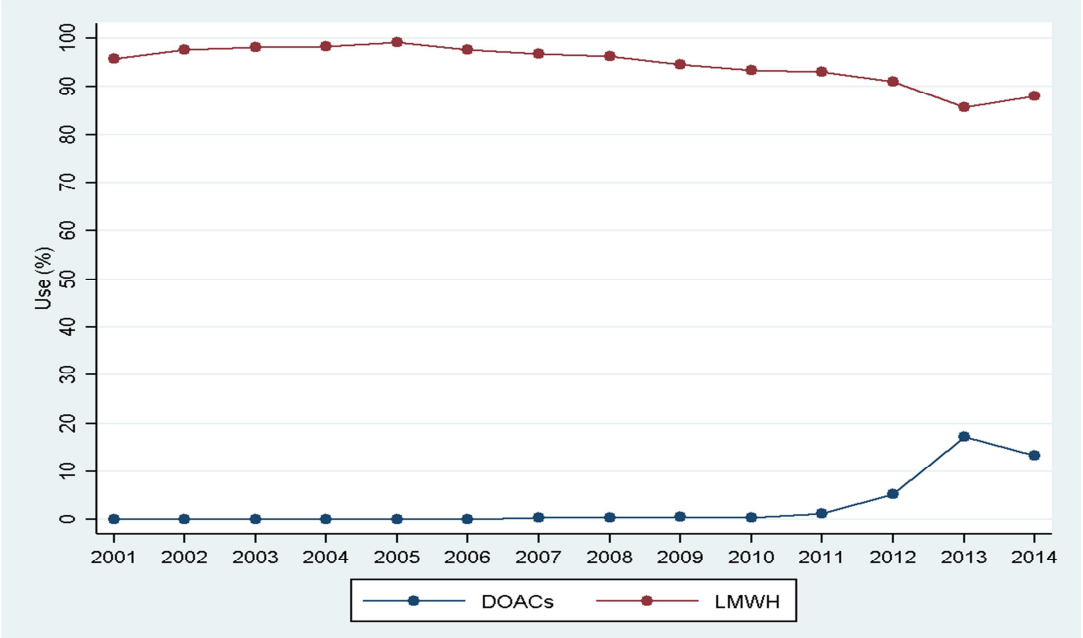
Figure 2.

a)



P < 0.01 for trend.

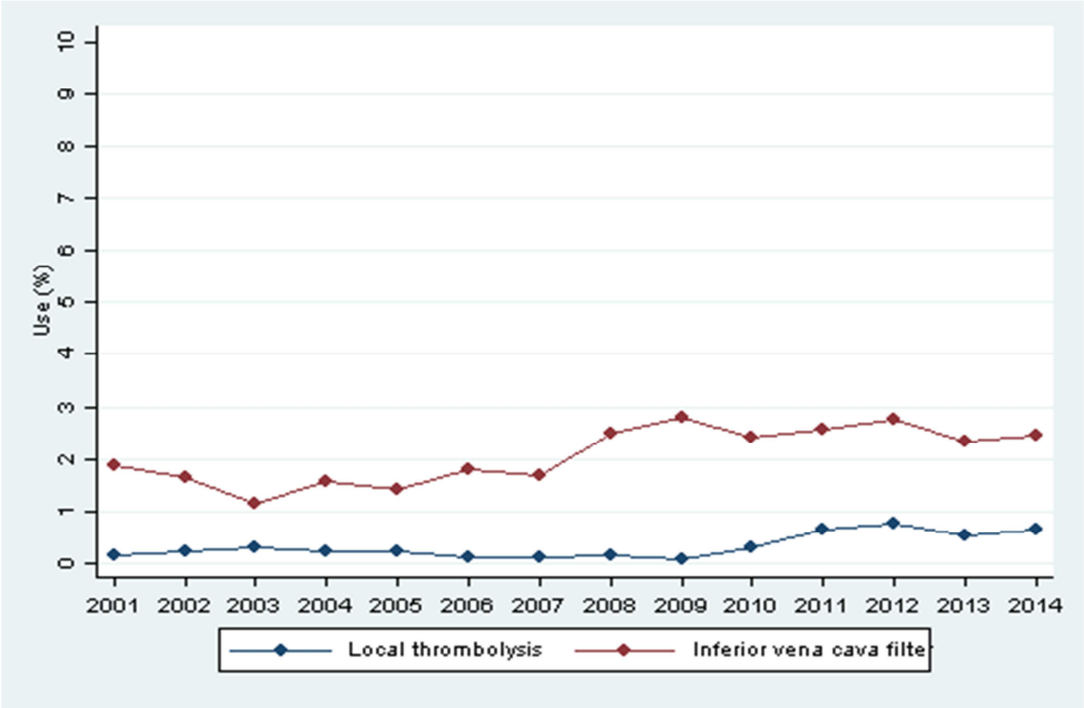
b)



Abbreviations: DOACs, direct oral anticoagulants; LMWH, low-molecular-weight heparin.

P < 0.001 for trend for all comparisons.

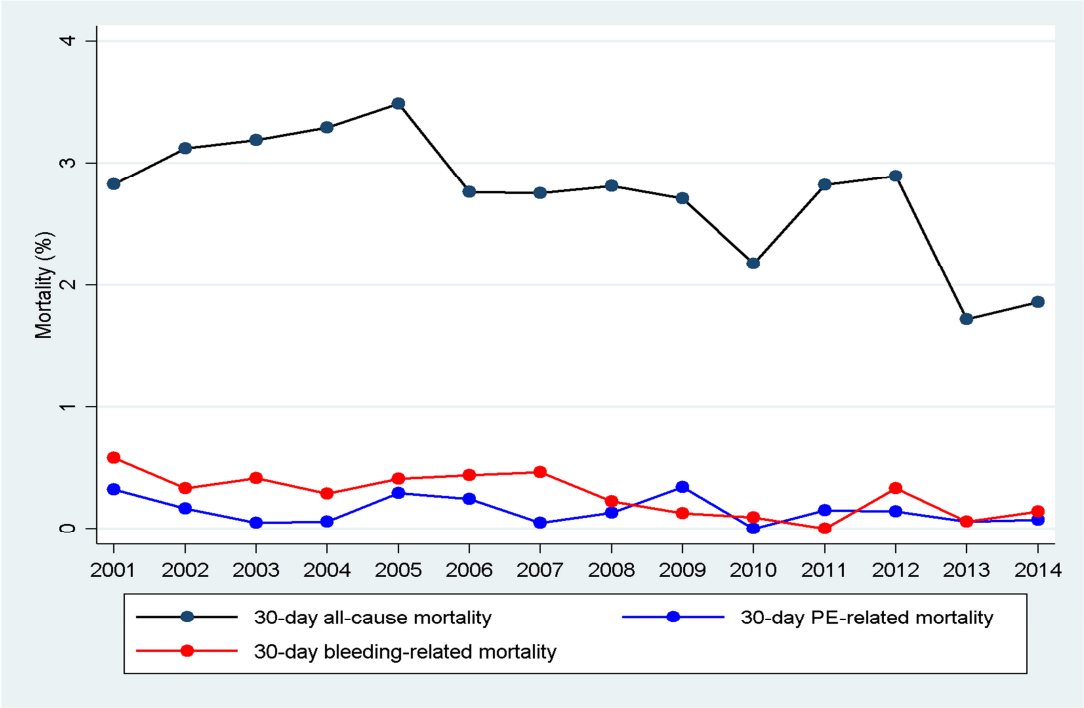
c)



P = 0.02 for trend for use of thrombolytics.

P < 0.01 for trend for use of inferior vena cava filter.

Figure 3.



P < 0.01 for trend for 30-day all-cause mortality curve.

P = 0.29 for trend for 30-day PE-related mortality curve.

P < 0.001 for trend for 30-day bleeding-related mortality curve.