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Trends in the Management and Outcomes of Acute Pulmonary Embolism

Analysis From the RIETE Registry

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ABSTRACT

BACKGROUND Despite advances in hospital management in recent years, it is not clear whether mortality after acute pulmonary embolism (PE) has decreased over time.

OBJECTIVES This study describes the trends in the management and outcomes of acute symptomatic PE.

METHODS We identified adults with acute PE enrolled in the registry between 2001 and 2013. We assessed temporal trends in length of hospital stay and use of pharmacological and interventional therapies. Using multivariable regression, we examined temporal trends in risk-adjusted rates of all-cause and PE-related death to 30 days after diagnosis.

RESULTS Among 23,858 patients with PE, mean length of stay decreased from 13.6 to 9.3 days over time (32% relative reduction, $p < 0.001$). For initial treatment, use of low-molecular-weight heparin increased from 77% to 84%, whereas the use of unfractionated heparin decreased from 22% to 8.4% ($p < 0.001$ for trend for all comparisons). Thrombolytic therapy use increased from 0.7% to 1.0% ($p = 0.07$ for trend) and surgical embolectomy use doubled from 0.3% to 0.6% ($p < 0.01$ for trend). Risk-adjusted rates of all-cause mortality decreased from 6.6% in the first period (2001 to 2005) to 4.9% in the last period (2010 to 2013) ($p = 0.02$ for trend). Rates of PE-related mortality decreased over time, with a risk-adjusted rate of 3.3% in 2001 to 2005 and 1.8% in 2010 to 2013 ($p < 0.01$ for trend).

CONCLUSIONS In a large international registry of patients with PE, improvements in length of stay and changes in the initial treatment were accompanied by a reduction in short-term all-cause and PE-specific mortality.
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Pulmonary embolism (PE) remains a worldwide major health issue (1). PE is the most common cause of vascular death after myocardial infarction and stroke, and it is the leading preventable cause of death in hospital patients (2).

Randomized trials have provided robust evidence for the effect of pharmacological and interventional treatments in patients with acute symptomatic PE, and they have led to changes in practice guidelines (3–8). However, the extent and time course of recent changes in clinical practice for patients with acute PE are uncertain, and it is unknown whether such changes are associated with improved outcome. Previous studies have documented substantial gaps between guideline recommendations and clinical practice (9,10). Thus, there is a clinical priority to

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determine the extent to which evidence is applied in practice, whether this is changing over time, and whether such changes are associated with improved outcomes.

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The ongoing, multicenter, international, prospective RIETE (Registro Informatizado de la Enfermedad TromboEmbólica) Registry includes consecutive patients with symptomatic, objectively confirmed, acute venous thromboembolism (VTE) (11–13). Since its launch in 2001, investigators have enrolled a total of 50,782 patients in RIETE, which has a sufficiently large sample size (25,456 patients with PE) and study duration (13 years of recruitment) to define changes in management and outcome. We hypothesized that temporal changes in hospital management of patients with acute PE (i.e., length of hospital stay, use of evidence-based treatments) would be significantly associated with a reduction in mortality, independent of the risk status of the study population on presentation to hospital.

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 (14,15). Briefly, at each participating RIETE site, investigators aimed to enroll consecutive patients that had confirmed acute symptomatic or asymptomatic VTE (Online Appendix). Confirmatory testing consisted of high-probability ventilation-perfusion (V/Q) scintigraphy (16); positive contrast-enhanced, PE-protocol, helical chest computed tomography (CT) [single or multidetector CT] for PE (17); or lower limb venous compression ultrasonography positive for proximal deep vein thrombosis (18).

ABBREVIATIONS AND ACRONYMS

CT = computed tomography

PE = pulmonary embolism

sPESI = simplified Pulmonary Embolism Severity Index

V/Q = ventilation/perfusion

VTE = venous thromboembolism

DATA QUALITY CONTROL. To ensure the validity of the information entered into the database, 1 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 1.23 million 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 patients that enrolled in RIETE and had a diagnosis of acute symptomatic PE from January 1, 2001 through December 31, 2013. Because we were interested in examining trends in mortality over time, we excluded patients at hospitals with <3 years of data submission and patients at hospitals with low case volumes (<30 PE during the study period).

Spain (through an unrestricted educational grant) and Bayer Pharma AG. Bayer Pharma AG's support was limited to the part of the RIETE Registry outside of Spain, which accounts for 22.21% of the total patients included. Dr. Jiménez has served as an advisor or consultant for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Leo Pharma, Pfizer, ROVI, and Sanofi; has 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; and has received grants for clinical research from Sanofi and ROVI. Dr. Guijarro has served as an advisor or consultant for Bayer Health Care Pharmaceuticals, Boehringer Ingelheim, and Bristol-Myers Squibb; and has served as a speaker or a member of a speakers bureau for Bayer Health Care Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Leo Pharma, and Sanofi. Dr. Otero has served as an advisor or consultant for Bayer HealthCare Pharmaceuticals, Leo Pharma, Pfizer, ROVI, and Sanofi; has served as a speaker for Bayer HealthCare Pharmaceuticals, Leo Pharma, ROVI, and Sanofi; and has received grants for clinical research from Leo Pharma and ROVI. Dr. Meyer has received grants and nonfinancial support from Boehringer Ingelheim, Leo Pharma, and Bayer HealthCare; has received travel support from Leo Pharma, Bayer, and Daiichi-Sankyo; has performed uncompensated lectures for Bristol-Myers Squibb-Pfizer, Bayer, Leo Pharma, Daiichi-Sankyo, and Boehringer-Ingelheim; and is an uncompensated board member for Leo Pharma, Bayer, Bristol-Myers Squibb-Pfizer, and Daiichi-Sankyo. Dr. Yusen has received research funding from Bayer HealthCare Pharmaceuticals, Inc., Portola, Inc., Pfizer, Inc. and Bristol-Myers Squibb in the past 3 years; and has served as a consultant for Bayer HealthCare, Inc., Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Johnson & Johnson, Ortho Pharmaceuticals, Inc., Organon, Inc., Pfizer, Inc., Portola, Inc., Sanofi, and SCIOS, Inc. in the past 3 years. Dr. Monreal has served as an advisor or consultant for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Leo Pharma, Pfizer, and Sanofi; has served as a speaker or a member of a speakers bureau for Bayer HealthCare Pharmaceuticals, Daiichi-Sankyo, Leo Pharma, and Sanofi; and has received grants for clinical research from Sanofi and Bayer. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Jiménez and de Miguel-Díez contributed equally to this work.

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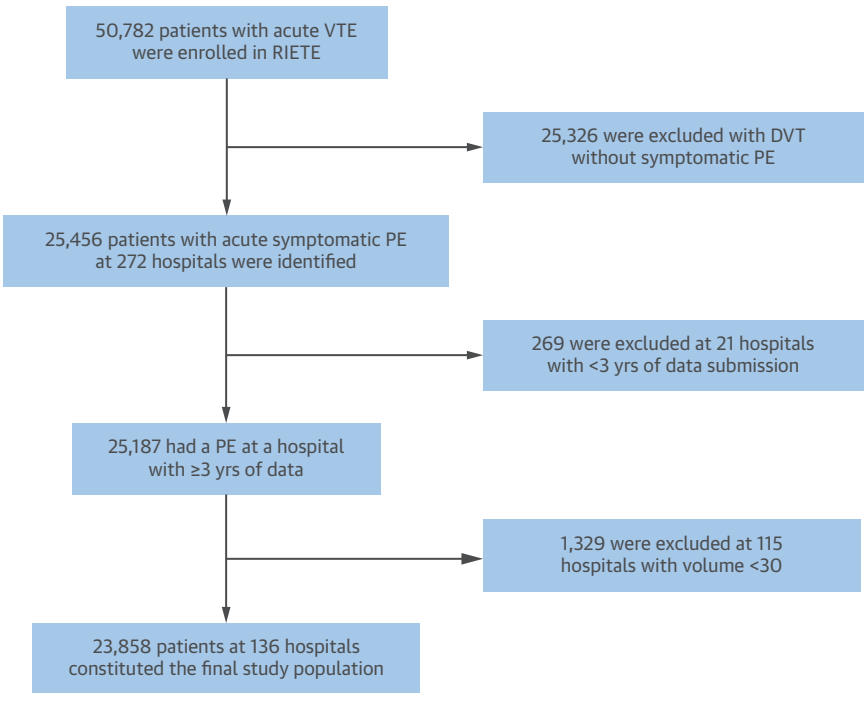
FIGURE 1 STROBE Study Cohort Flow Diagram



DVT = deep venous thrombosis; PE = pulmonary embolism; RIETE = Registro Informatizado de la Enfermedad TromboEmbólica; STROBE = STrengthening the Reporting of OBservational studies in Epidemiology; VTE = venous thromboembolism.

VARIABLES. Patients enrolled in RIETE had data collected from around the time of VTE diagnosis that included but were not limited to: age; sex; 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 nonsurgical 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, including heart rate, systolic blood pressure and arterial oxyhemoglobin saturation; and laboratory results at hospital admission that included hemoglobin, platelet count, and serum creatinine.

STUDY OUTCOMES. The primary outcome was 30-day all-cause mortality (defined as death from any cause 30 days after the diagnosis of PE). To better understand the association between specific phases of treatment and mortality, we examined rates of death from any cause within the 7 days following the diagnosis of PE. We also examined temporal trends in PE-related mortality through 7 and 30 days after diagnosis. The RIETE investigators used medical record review to assess vital status. For patients that died, further medical record review, and proxy interviews when necessary, assisted with determining date and cause of death. For deaths confirmed by autopsy or those following a clinically severe PE, either initially or shortly after an objectively confirmed recurrent event, in the absence of any alternative diagnosis, the investigators were instructed to judge death as due to fatal PE. We chose 7- and 30-day mortality assessment periods because they likely reflected variations related to changes in length of stay and evidence-based treatments and because they are standard measurements of quality of care (19). In addition, we examined rates of nonfatal VTE recurrences, and fatal and nonfatal bleeding events within 30 days following the diagnosis of PE.

STATISTICAL ANALYSIS. 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, and chronic heart disease), severity of PE (i.e., heart rate, systolic blood pressure, arterial oxyhemoglobin saturation, simplified Pulmonary Embolism Severity Index [sPESI]), 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 to 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 diagnostic test (CT vs. V/Q scan) and age group (≥65 years vs. <65 years) 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 ≥5 years of registry participation. Last, we repeated analyses for the subgroup of patients with acute PE that had hypotension (i.e., systolic blood pressure <90 mm Hg).

Data were complete for all covariates and outcomes except heart rate (3.0% missing), arterial oxyhemoglobin saturation (32% missing), and creatinine levels (2.0% missing) at the time of PE diagnosis. Missing patient-level covariates were assumed to be missing at random and were imputed using multiple imputation (20).

We conducted statistical analyses with STATA version 13.1 (STATA Corp, College Station, Texas). All hypothesis tests were 2-sided, with a significance level of 0.05.

The study's sponsor 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 25,456 adults at 272 hospitals participating in the RIETE registry that had a diagnosis of acute symptomatic PE during the time period of January 1, 2001, through December 31, 2013 (Figure 1). We excluded 269 patients at 21 hospitals with <3 years of data submission and 1,329 patients at 115 hospitals with low case volumes (<30 PEs). The final study sample included 23,858 patients from 136 hospitals.

PATIENT CHARACTERISTICS. There was initially an increase in number of sites participating in RIETE, from 92 sites providing 7,323 patients in the first period from 2001 to 2005 to a fairly stable number of

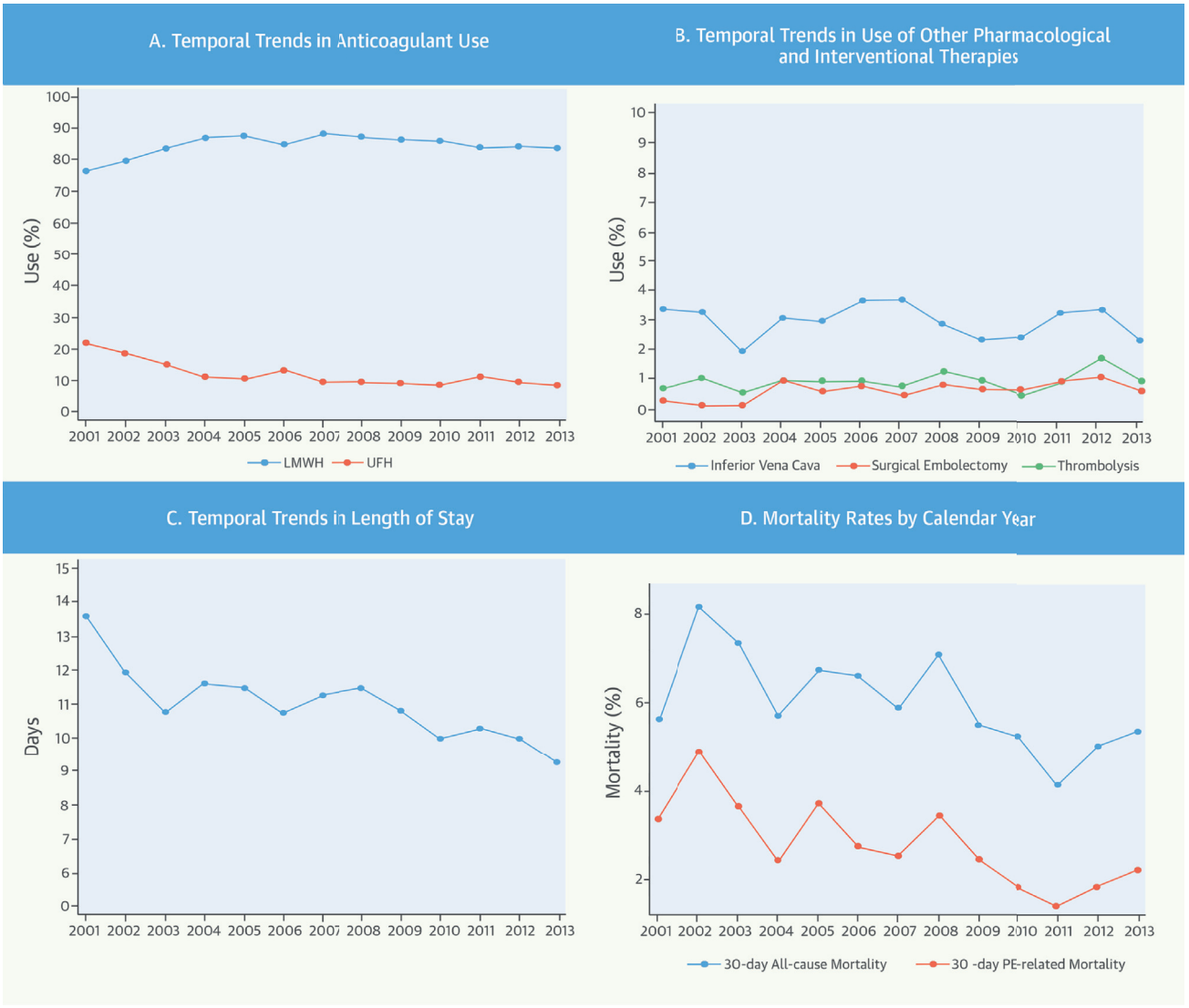
TABLE 1 Trends in Baseline Characteristics in Patients With Acute Pulmonary Embolism*

	Year Group			
	2001-2005 (n = 7,323)	2006-2009 (n = 8,644)	2010-2013 (n = 7,891)	p Value for Trend
Clinical characteristics				
Age, yrs	68.5 ± 16.0	67.5 ± 17.1	67.3 ± 17.0	<0.001
Age >80 yrs	1,670 (22.8)	2,035 (23.5)	1,897 (24.0)	0.07
Male	3,374 (46.1)	3,969 (45.9)	3,655 (46.3)	0.59
Weight, kg	73.8 ± 14.5	74.9 ± 15.8	76.0 ± 16.1	<0.001
Risk factors for VTE				
History of VTE	1,139 (15.6)	1,236 (14.3)	1,188 (15.1)	0.10
Cancer†	1,552 (21.2)	2,030 (23.5)	1,785 (22.6)	<0.01
Recent surgery‡	953 (13.0)	1,015 (11.7)	899 (11.4)	<0.01
Immobilization for ≥4 days§	1,892 (25.8)	2,035 (23.5)	1,668 (21.1)	<0.001
Comorbid diseases				
Chronic lung disease	1,016 (13.9)	1,095 (12.7)	1,290 (16.3)	<0.001
Chronic heart disease	630 (8.6)	711 (8.2)	836 (10.6)	<0.001
Recent major bleeding	176 (2.4)	178 (2.1)	183 (2.3)	0.84
Clinical symptoms and signs at presentation				
Pulse, beats/min	94.1 ± 19.9	93.3 ± 19.9	91.5 ± 20.2	<0.001
Pulse ≥110 beats/min	1,629 (22.7)	1,763 (21.0)	1,475 (19.4)	<0.001
Systolic blood pressure, mm Hg	130.1 ± 24.9	129.3 ± 24.3	129.1 ± 23.9	<0.001
Systolic blood pressure <100 mm Hg	533 (7.3)	683 (7.9)	711 (9.0)	<0.001
Arterial oxyhemoglobin saturation (SaO_2) <90%	1,822 (31.1)	1,689 (29.0)	1,322 (29.9)	0.29
sPESI (21)				
Low risk	1,559 (27.1)	1,660 (28.8)	1,169 (26.8)	0.66
High risk	4,203 (72.9)	4,110 (71.2)	3,185 (73.2)	0.66
Laboratory findings				
Abnormal creatinine levels (>2 mg/dl)	1,283 (17.6)	1,541 (18.3)	1,519 (19.8)	<0.01
Hemoglobin, g/dl	13.04 ± 2.0	12.99 ± 2.0	12.97 ± 2.0	<0.01

Values are mean ± SD or n (%). *For illustrative purposes, trends in baseline characteristics are presented as 3 time periods: 2001–2005, 2006–2009, and 2010–2013. The p value for trend is for temporal changes in these characteristics by calendar year. †Active or under treatment in the last year. ‡In the previous month. §Immobilized patients were defined as nonsurgical patients who had been immobilized (i.e., total bed rest with bathroom privileges) for ≥4 days in the month prior to PE diagnosis.

sPESI = simplified Pulmonary Embolism Severity Index; VTE = venous thromboembolism.

CENTRAL ILLUSTRATION **Acute PE Mortality in the RIETE Registry: Significant Reductions in Mortality Over Time**



Jiménez, D. et al. J Am Coll Cardiol. 2016; 67(2):162–70.

The RIETE (Registro Informatizado de la Enfermedad TromboEmbólica) registry showed significant temporal changes in the management of patients with pulmonary embolism (PE) **(A and B)** that were consistent with trial evidence and national and international guidelines. Decreases in length of hospital stay **(C)** and in the rates of short-term all-cause and PE-specific mortality **(D)** accompanied these changes in practice. **(A)** Anticoagulant use (unadjusted $p < 0.001$ for trend for all comparisons). **(B)** The use of other pharmacological and interventional therapies (unadjusted $p = 0.07$ for trend for use of thrombolytics; unadjusted $p < 0.01$ for trend for use of surgical embolectomy; unadjusted $p = 0.90$ for trend for use of inferior vena cava filter). **(C)** Length of stay (unadjusted $p < 0.001$ for trend). **(D)** Unadjusted $p < 0.01$ for trend for 30-day all-cause mortality curve. Unadjusted $p < 0.01$ for trend for 30-day pulmonary embolism (PE)-related mortality curve. LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.

approximately 120 sites with 8,000 patients in the 2 subsequent 4-year periods.

During the study period, the proportion of patients who had PE assessment with CT increased from 47% to 90%, whereas the proportion of patients who were assessed with V/Q scan decreased from 58% to 11% ($p < 0.001$ for trends). **Table 1** shows temporal trends in patient characteristics, grouped into 3 time periods. During the study period, there was a calendar-year trend for younger age (68 to 66 years), whereas the proportion of women did not vary (53% in 2001 to 50% in 2013; $p = 0.59$). The prevalence of cancer, chronic

lung disease, and chronic heart failure increased over time. Alternatively, the study showed decreases in a history of immobility (27% to 21%) and a history of surgery (14% to 12%) over time. A history of recent bleeding did not significantly change over time (2.6% in 2001 to 3.1% in 2013; p = 0.84 for trends).

During the study period, the proportion of high-risk patients according to the sPESI (21) did not vary (72% in 2001 to 74% in 2013; p = 0.66 for trends) (Table 1), although the sPESI mean scores increased from 1.26 in 2001 to 1.31 in 2013 (p < 0.001 for trends). Regarding time trends for signs of clinical PE severity, mean heart rate and systolic blood pressure significantly decreased (p < 0.001 for trend for all comparisons), but arterial oxyhemoglobin saturation did not vary (91%). The proportion of patients with elevated creatinine levels (i.e., creatinine >2 mg/dl) increased from 18% (95% confidence interval [CI]: 16% to 21%) to 20% (95% CI: 17% to 22%) (p < 0.01), whereas mean hemoglobin levels significantly decreased over time (p < 0.01 for trends) (Table 1).

TEMPORAL TRENDS IN LENGTH OF HOSPITAL STAY AND PHARMACOLOGICAL MANAGEMENT. During the 13-year study period, mean length of hospital stay decreased from 13.6 days (95% CI: 11.2 to 15.9 days) to 9.3 days (95% CI: 8.8 to 9.7 days) (32% relative reduction; p < 0.001) (Central Illustration). A total of 0.03% (2 of 7,323; 0.03%; 95% CI: 0.0% to 0.1%) of patients were managed as outpatients between 2001 and 2005; 0.6% (52 of 8,644; 0.6%; 95% CI: 0.4% to 0.8%) between 2006 and 2009; and 1.7% (134 of 7,891; 95% CI: 1.4% to 2.0%) between 2010 and 2013. Regarding in-hospital treatments known to influence outcomes, the use of low-molecular-weight heparins (77% in 2001 to 84% in 2013) and direct oral anticoagulants (0% in 2001 to 2.2% in 2013) showed an increase, whereas the use of unfractionated heparin decreased from 22% to 8.4% over the study period (p < 0.001 for trend for all comparisons). Thrombolysis showed an increase from 0.7% to 1.0% (p = 0.07 for trends), and surgical embolectomy increased from 0.3% to 0.6% (p < 0.01 for trends), whereas filter insertion showed a nonstatistically significant downward trend (3.4% in 2001 to 2.3% in 2013; p = 0.90) (Central Illustration).

TEMPORAL TRENDS IN MORTALITY. The entire cohort had a 30-day all-cause mortality rate of 5.9% (n = 1,418 of 23,858). There was a significant trend toward decreased mortality during the study period for all study patients (Central Illustration, Table 2). After adjustment for temporal trends in patient characteristics around the time of PE diagnosis, overall mortality decreased from 6.6% from 2001 to 2005 to 4.9% from 2010 to 2013 (adjusted rate ratio per period: 0.84; 95% CI: 0.73 to 0.97; p = 0.02 for trend) (Tables 3 and 4). The temporal trends in mortality were similar according to diagnostic procedure (CT vs. V/Q scan) and age group (≥65 years vs. <65 years) (p > 0.10 for all interactions). For analyses restricted to the 110 hospitals (21,947 patients) that participated in the RIETE Registry for at least 5 years, the trends remained unchanged (Table 5). Only 778 of 23,858 (3.3%; 95% CI: 3.0% to 3.5%) patients with acute PE had hypotension. Among hypotensive patients, the 30-day all-cause mortality decreased from 15.4% in the first period of 2001 to 2005 to 13.4% in 2006 to 2009 and 12.1% in the last period of 2010 to 2013 (p = 0.30 for trend).

The entire cohort had a 7-day all-cause mortality rate of 2.6% (609 of 23,858 patients). Rates of 7-day all-cause mortality decreased over time, with a risk-adjusted rate of 2.9% in 2001 to 2005 and 1.9% in 2010 to 2013 (adjusted rate ratio per period: 0.81; 95% CI: 0.67 to 0.98; p = 0.03 for trend) (Table 3). Among hypotensive patients, the 7-day all-cause mortality decreased from 26 of 234 (11.1%) in 2001 to 2005 to 16 of 239 (6.7%) in 2010 to 2013 (p = 0.08 for trend).

SECONDARY OUTCOMES. After adjustment, 30-day PE-related mortality significantly decreased from 3.3% in 2001 to 2005 to 1.8% in 2010 to 2013 (adjusted rate ratio per period: 0.73; 95% CI: 0.60 to 0.89; p < 0.01 for trend), whereas 7-day PE-related mortality decreased from 2.2% in 2001 to 2005 to 1.1% in 2010 to 2013 (adjusted rate ratio per period: 0.72; 95% CI: 0.58 to 0.90; p < 0.01 for trend).

Rates of nonfatal PE recurrence decreased over time, with a risk-adjusted rate of 1.1% in 2001 to 2005 and 0.6% in 2010 to 2013 (adjusted rate ratio per period: 0.72; 95% CI: 0.58 to 0.91; p < 0.01 for trend) (Table 3). Nonfatal major bleeding decreased over time (risk-adjusted rate: 4.0% in 2001 to 2005 and 3.1% in 2010 to 2013; adjusted rate ratio per year: 0.89; 95% CI: 0.77 to 1.03; p = 0.11 for trend). For

TABLE 2 Observed Rates of Mortality and Nonfatal Outcomes by Year Group

	2001-2005	2006-2009	2010-2013
30-day all-cause mortality	489/7,323 (6.7)	541/8,644 (6.2)	388/7,891 (4.9)
7-day all-cause mortality	220/7,323 (3.0)	244/8,644 (2.8)	145/7,891 (1.8)
30-day PE-related mortality	258/7,323 (3.5)	244/8,644 (2.8)	143/7,891 (1.8)
7-day PE-related mortality	176/7,323 (2.4)	173/8,644 (2.0)	89/7,891 (1.1)
Nonfatal complications			
30-day VTE recurrences	82/7,323 (1.1)	52/8,644 (0.6)	52/7,891 (0.6)
30-day major bleeding	299/7,323 (4.1)	225/8,644 (2.6)	250/7,891 (3.2)
30-day fatal bleeding	30/7,323 (0.4)	33/8,644 (0.4)	19/7,891 (0.2)

Values are n/N (%).
PE = pulmonary embolism; VTE = venous thromboembolism.

TABLE 3 Trends in Mortality and Nonfatal Outcomes

	Risk-Adjusted Rates (%)*			Adjusted Rate Ratio Per Period (95% CI)†	p Value for Trend†
	2001-2005	2006-2009	2010-2013		
30-day all-cause mortality	6.6	6.1	4.9	0.84 (0.73-0.97)	0.02
7-day all-cause mortality	2.9	2.7	1.9	0.81 (0.67-0.98)	0.03
30-day PE-related mortality	3.3	2.7	1.8	0.73 (0.60-0.89)	<0.01
7-day PE-related mortality	2.2	1.9	1.1	0.72 (0.58-0.90)	<0.01
Nonfatal complications					
30-day VTE recurrences	1.1	0.6	0.6	0.72 (0.58-0.91)	<0.01
30-day major bleeding	4.0	2.7	3.1	0.89 (0.77-1.03)	0.11

*Risk-adjusted rates of all-cause mortality, PE-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.

CI = confidence interval; other abbreviations as in Table 2.

30-day fatal bleeding, data were too sparse to show trends (Table 2).

DISCUSSION

These data, from the largest multinational, observational cohort study of patients with an acute PE, demonstrated evidence of a recent temporal change in practice for both length of hospital stay and pharmacological and interventional treatments of acute PE. Decreases in the rates of short-term all-cause and PE-specific mortality accompanied these changes in practice. The risk status of patients at presentation with PE did not improve over the course of the present study, so it may be plausible that the changes in clinical outcomes were a consequence of changes in practice.

TABLE 5 Trends in Mortality and Nonfatal Outcomes by Calendar Period Among Patients at Hospitals Participating for at Least 5 Years in the RIETE Registry

	Risk-Adjusted Rates (%)*			Adjusted Rate Ratio Per Period (95% CI)†	p Value for Trend†
	2001-2005	2006-2009	2010-2013		
30-day all-cause mortality	6.7	6.1	4.8	0.84 (0.72-0.98)	0.03
7-day all-cause mortality	2.9	2.7	1.9	0.82 (0.67-1.0)	0.05
30-day PE-related mortality	3.4	2.7	1.8	0.74 (0.60-0.91)	<0.01
7-day PE-related mortality	2.2	1.9	1.2	0.74 (0.59-0.93)	<0.01
Nonfatal complications					
30-day VTE recurrences	1.1	0.6	0.6	0.70 (0.56-0.87)	<0.01
30-day major bleeding	4.0	2.6	2.8	0.84 (0.72-0.96)	0.01

*Risk-adjusted rates of all-cause mortality, PE-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.

RIETE = Registro Informatizado de la Enfermedad TromboEmbólica; other abbreviations as in Tables 2 and 3.

TABLE 4 Multivariable Model of Predictors of 30-Day Mortality*

	Adjusted Odds Ratio	95% CI	p Value
Calendar year (per 1 yr)	0.96	0.93-0.99	0.02
Age (per 1 yr)	1.03	1.02-1.04	<0.001
Sex (female vs. male)	0.74	0.65-0.85	<0.001
Weight (per 1 kg)	0.98	0.97-0.98	<0.001
History of VTE	0.62	0.51-0.75	<0.001
Cancer†	3.33	2.85-3.88	<0.001
Recent surgery‡	0.56	0.44-0.71	<0.001
Immobilization for ≥4 days§	2.09	1.81-2.41	<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)	1.01	1.01-1.02	<0.001
Systolic blood pressure (per mm Hg)	0.99	0.985-0.993	<0.001
Arterial oxyhemoglobin saturation (SaO_2) (per 1%)	0.97	0.96-0.97	<0.001
Abnormal creatinine levels (>2 mg/dl)	1.57	1.35-1.83	<0.001
Hemoglobin (per 1 g/dl)	0.87	0.84-0.91	<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. †Active or under treatment in the last year. ‡In the previous month. §Immobilized patients were defined as nonsurgical patients who had been immobilized (i.e., total bed rest with bathroom privileges) for ≥4 days in the month prior to PE diagnosis.

Abbreviations as in Tables 2 and 3.

Few studies have addressed the temporal trends of various aspects related to the care and outcomes of patients with PE, such as duration of hospital stay, therapy, and all-cause and PE-related mortality (22,23). Previous studies have suggested that the length of stay and the case-fatality rate of PE have not changed over time (24–26). Alternatively, we found substantial improvements in the length of hospital stay, similar to other studies for patients admitted with cardiovascular diseases other than PE (e.g., heart failure) (27). Although some health systems have provided an incentive for shortening length of stay, the generalized use of anticoagulant agents (e.g., low-molecular-weight heparin) that combine greater convenience with similar or better efficacy and safety profiles compared with the previous standard approaches (e.g. unfractionated heparin) might explain this finding.

In our study, the increased use of more effective therapies and interventions, including low-molecular-weight heparins, direct oral anticoagulants, thrombolysis, and surgical embolectomy, was accompanied by a statistically significant decrease in the rates of death, nonfatal recurrences, and nonfatal major bleeding. Although this study does not imply causality, the decrease of PE-specific (i.e., recurrent VTE) and treatment-related (i.e., bleeding) complications and

PE-related mortality may reflect the more widespread use of therapies shown in trials and meta-analyses to lower the risk of recurrent VTE and bleeding complications (28). Treatment pattern changes likely played a larger role in affecting outcomes than any changes in patients' baseline characteristics.

Several issues merit further critical review and discussion. First, the decreases in all-cause and PE-associated mortality may simply reflect a decrease in baseline risk over time. However, we found little evidence that this occurred. 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 and a lower heart rate, they also had higher rates of cancer, chronic lung disease, chronic heart failure, hypotension, and laboratory abnormalities (e.g., renal failure, anemia). Moreover, the study showed consistent results even after adjustment for temporal changes in patient characteristics over time, including age. Second, increasing use of the CT scan for PE diagnosis could have introduced selection bias into the registry over time (29). The observed decrease in length of stay may reflect an increase in the detection of minor PE, which could account for the lower 30-day mortality. The observed temporal increase in severity markers (e.g., mean sPESI) suggests otherwise. Furthermore, mortality trends did not differ by diagnostic test (CT vs. V/Q scan). Finally, the analyses did not support that the study findings were due to enrollment of better-performing hospitals over time, because we found similar results when we restricted our analyses to hospitals that participated in the RIETE registry for 5 years or longer.

STUDY 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 specific hospital-based risk-stratification protocols (e.g., troponin, echocardiogram), treatment details (e.g., international normalized ratio 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. Third, the low mortality rate for patients diagnosed with PE might suggest that RIETE enrolled a less ill population. However, the study cohort showed a 30-day mortality rate of 5.9% that was similar to the 5.4% mortality rate in the EMPEROR (Emergency Medicine Pulmonary Embolism in the Real World Registry) registry (30). Furthermore, our data are consistent with the 2007 National ED Survey, which reported a 3.3% in-hospital mortality rate for 121,026 emergency department patients diagnosed with PE (31). Another limitation of the study was the lack of data evaluating catheter-directed interventions, and we could not assess the effect of these therapies on clinical outcomes. 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 PE, and the results may not be fully generalizable elsewhere. However, the RIETE registry is the only large-scale, multinational, observational study of the spectrum of patients diagnosed with a PE with continuous recruitment of patients for more than 10 years, and it offers a unique opportunity to look at a large number of patients in various treatment settings over a long period of time.

CONCLUSIONS

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

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PERSPECTIVES

COMPETENCY IN PRACTICE-BASED LEARNING: Improvements in the initial treatment of PE have been accompanied by reductions in length of hospital stay, as well as short-term all-cause and PE-specific mortality.

TRANSLATIONAL OUTLOOK: Future studies should evaluate the relative effect of pharmacological therapy and catheter-directed interventions on clinical outcomes across a variety of treatment settings over a long period of time.

REFERENCES

1. Bělohlávek J, Dytrych V, Linhart A. Pulmonary embolism, part I: epidemiology, risk factors and risk stratification, pathophysiology, clinical presentation, diagnosis and nonthrombotic pulmonary embolism. Exp Clin Cardiol 2013;18:129–38.

2. Heit JA. The epidemiology of venous thromboembolism in the community. Arterioscler Thromb Vasc Biol 2008;28:370–2.

3. Simonneau G, Sors H, Charbonnier B, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. N Engl J Med 1997;337:663–9.

4. The Columbus Investigators. Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. N Engl J Med 1997; 337:657–62.

5. The Matisse Investigators. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. N Engl J Med 2003;349:1695–702 [Erratum in N Engl J Med 2004;350:423].

6. Hull RD, Raskob GE, Brant RF, et al. Low-molecular-weight heparin vs heparin in the treatment of patients with pulmonary embolism. Arch Intern Med 2000;160:229–36.

7. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians. Evidence-Based Clinical Practice Guidelines. Chest 2012;141:419S–94S.

8. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Eur Heart J 2014;35:3033–73.

9. Witty LA, Krichman A, Tapson VF. Thrombolytic therapy for venous thromboembolism. Utilization by practicing pulmonologists. Arch Intern Med 1994;154:1601–4.

10. Egermayer P, Town GI. Compliance with guidelines for the investigation and management of patients with suspected pulmonary embolism at Christchurch Hospital. N Z Med J 1998; 111:70–3.

11. Laporte S, Mismetti P, Décousus H, et al. Clinical predictors for fatal pulmonary embolism in 15,520 patients with venous thromboembolism: findings from the RIETE registry. Circulation 2008; 117:1711–6.

12. Muriel A, Jiménez D, Aujesky D, et al. Survival effects of inferior vena cava filter in patients with acute symptomatic venous thromboembolism and a significant bleeding risk. J Am Coll Cardiol 2014; 63:1675–83.

13. Monreal M, Kakkar AK, Caprini JA, et al. The outcome after treatment of venous thromboembolism is different in surgical and acutely ill medical patients. Findings from the RIETE registry. J Thromb Haemost 2004;2:1892–8.

14. Riera-Mestre, Jiménez D, Muriel A, et al. Thrombolytic therapy and outcome of patients with an acute symptomatic pulmonary embolism. J Thromb Haemost 2012;10:751–9.

15. Nieto JA, Tuesta AD, Marchena PJ, et al. Clinical outcome of patients with venous thromboembolism and recent major bleeding: findings of a prospective registry (RIETE). J Thromb Haemost 2005;3:703–9.

16. Remy-Jardin M, Remy J, Wattinne L, Giraud F. Central pulmonary thromboembolism: diagnosis with spiral volumetric CT with the single-breath-hold-technique-comparison with pulmonary angiography. Radiology 1992;185:381–7.

17. PIOPED Investigators. Value of ventilation/perfusion scan in acute pulmonary embolism: results of the prospective investigation of the pulmonary embolism diagnosis (PIOPED). JAMA 1990;263:2753–9.

18. Kearon C, Ginsberg JS, Hirsh J. The role of venous ultrasonography in the diagnosis of suspected deep venous thrombosis and pulmonary embolism. Ann Intern Med 1998;129:1044–9.

19. Krumholz HM, Keenan PS, Brush JE Jr., et al. Standards for measures used for public reporting of efficiency in health care: a scientific statement from the American Heart Association Interdisciplinary Council on Quality of Care and Outcomes Research and the American College of Cardiology Foundation. Circulation 2008;118: 1885–93.

20. Raghunathan T, Solenberger P, Van Hoeyk J. IVEware: Imputation and Variance Estimation Software—User's Guide. Ann Arbor, MI: University of Michigan Survey Research Center, Institute for Social Research, 2002.

21. Jiménez D, Aujesky D, Moores L, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med 2010;170:1383–9.

22. Park B, Messina L, Dargon P, et al. Recent trends in clinical outcomes and resource utilization for pulmonary embolism in the United States. Chest 2009;136:983–90.

23. Shiraev TP, Omari A, Rushworth RL. Trends in pulmonary embolism morbidity and mortality in Australia. Thromb Res 2013;132:19–25.

24. Anderson FA Jr., Wheeler HB, Goldberg RJ, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism: the Worcester DVT study. Arch Intern Med 1991;151:933–8.

25. Lilienfeld DE, Godbold JH, Burke GL, et al. Hospitalization and case fatality for pulmonary embolism in the Twin Cities: 1979–1984. Am Heart J 1990;120:392–5.

26. Stein PD, Kayali F, Olson RE. Estimated case-fatality rate of pulmonary embolism, 1979 to 1998. Am J Cardiol 2004;93:1197–9.

27. Bueno H, Ross JS, Wang Y, et al. Trends in length of stay and short-term outcomes among Medicare patients hospitalized for heart failure, 1993–2006. JAMA 2010;303:2141–7.

28. Castellucci LA, Cameron C, Le Gal G, et al. Clinical and safety outcomes associated with treatment of acute venous thromboembolism: a systematic review and meta-analysis. JAMA 2014; 312:1122–35.

29. Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. Arch Intern Med 2011;171:831–7.

30. Pollack CV, Schreiber D, Goldhaber SZ, et al. Clinical characteristics, management, and outcomes of patients diagnosed with acute pulmonary embolism in the emergency department. J Am Coll Cardiol 2011;57:700–6.

31. Healthcare Cost and Utilization Project (HCUP). National (Nationwide) Inpatient Sample (NIS). Available at: http://www.hcup-us.ahrq.gov/nisoverview.jsp. Accessed December 1, 2010.

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APPENDIX For a list of RIETE Registry members, please see the online version of this article.