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Mortality after pulmonary embolism in patients with diabetes. Findings from the RIETE registry

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SUMMARY

Background: Among patients presenting with pulmonary embolism (PE), those with diabetes are at increased risk to die than those without diabetes. The reasons have not been identified. We used the RIETE (*Registro Informatizado Enfermedad Trombo Embólica*) database to compare the mortality rate and the causes of death during anticoagulation in patients with PE according to the presence or absence of diabetes.

Methods: A matched retrospective cohort study from consecutively enrolled patients in RIETE, from 179 hospitals in 24 countries. For each patient with diabetes we selected two patients with no diabetes matched by age, sex and year of diagnosis of the PE.

Results: As of September 2017, there were 2010 PE patients with diabetes and two age-and-gender matched controls. Mean age was 74 ± 11 years, 46% were men. Patients with diabetes were more likely to have comorbidities, to be using antiplatelets and to have more severe PE. During anticoagulation (median, 219 days), patients with diabetes had a higher mortality (hazard ratio [HR]: 1.45; 95% confidence intervals [CI]: 1.25–1.67) and a higher rate of arterial ischemic events (HR: 2.89; 95%CI: 1.71–4.94) than those without diabetes. On multivariable analysis, diabetes was not associated with an increased risk for death (HR: 1.26; 95%CI: 0.97–1.63). We also failed to find differences according to the use of antiplatelet drugs concomitantly.

Conclusions: In our cohort of patients with PE, diabetes was not an independent predictor for death. The influence of arterial events or antiplatelet drugs (if any) was low.

1. Background

The influence of diabetes on outcome in patients with venous thromboembolism (VTE) remains controversial [1–5]. Diabetes may facilitate thrombosis through activation of the coagulation system and impairing fibrinolysis, thus leading to a hypercoagulable state [6–9]. Other prothrombotic factors include chronic inflammation, enhanced oxidative stress, and decreased expression of protective endothelial factors [10]. Recently, it has been reported that patients with diabetes may have an increased risk to develop pulmonary embolism (PE) [11–14], and that diabetic patients presenting with PE may have a worse outcome than those without diabetes [15–18]. Even in PE patients without diabetes, raised serum levels of glucose have also been associated with worse outcomes [19–21].

Three recent studies reported diabetes as an independent predictor for death in patients with VTE [14, 22, 23], but the exact reasons have not been identified. In the Swiss cohort study, the hazard ratio (HR) for all-cause death in 991 VTE patients aged ≥65 years followed-up for a

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median of 30 months was 1.50 (95% confidence intervals [CI]: 1.02–2.22) [22]. In the Spanish Hospital Discharge Database, the HR for in-hospital mortality in 123,872 patients hospitalized for PE was 1.22 (95%CI: 1.12–1.32) [14]. In the Taiwan's National Health Insurance database, the HR for death in 2154 patients with unprovoked VTE during a 10-year period was 1.65 (95%CI: 1.37–1.99) [23]. None of these databases contained exhaustive data on treatment or on the causes of death.

In the current study, we hypothesized that diabetes might likely be associated with an increased mortality due to a higher rate of subsequent arterial ischemic events and/or of major bleeding complications, particularly in patients using antiplatelet drugs concomitantly. Thus, our aims were: 1) to confirm whether PE patients with diabetes are at increased risk to die compared with those without diabetes; and 2) to assess the influence of prior artery disease and concomitant use of antiplatelet drugs on mortality.

2. Methods

2.1. Patients

This study is an analysis of prospectively collected data in the RIETE (*Registro Informatizado de Enfermedad TromboEmbólica*) Registry. The RIETE Registry is an ongoing, multicenter, international registry of consecutive patients with objectively confirmed acute VTE (ClinicalTrials.gov identifier: NCT02832245) [24]. Data from this registry have been used to evaluate outcomes after acute VTE, such as the frequency of recurrent VTE, bleeding and mortality, and risk factors for these outcomes [25–30].

The RIETE registry included consecutive patients with acute objectively-confirmed deep vein thrombosis (DVT) or PE (compression ultrasonography or contrast venography for DVT; pulmonary angiography, ventilation-perfusion lung scan or helical computed tomography scan for PE). Exclusion criteria were a current enrollment in a therapeutic clinical trial with a blinded therapy. Informed consent was obtained from participants in accordance with local ethics committee requirements.

2.2. Study design

This is a matched retrospective cohort study from consecutively enrolled patients in RIETE, from 179 hospitals in 24 countries. For this study, only patients presenting with acute symptomatic, objectively proven PE were considered. Those with incidentally found PE were excluded. Diabetes is a variable included in RIETE only since April 2013. Hence, from 2001 to April 2013 this information was not documented. Patients were classified as having diabetes when there was a clinical history of diabetes or when they were taking insulin or oral anti-diabetic drugs. For each patient with diabetes we selected two patients with no diabetes matched by age, sex and year of diagnosis of the PE. If more than two patients were available for any patient with diabetes, the selection was done randomly.

The primary outcome was the mortality rate during the course of anticoagulant therapy. Secondary outcomes were the rates of PE recurrences, major bleeding and arterial ischemic events (i.e., myocardial infarction, ischemic stroke or lower limb amputation).

2.3. Treatment and follow-up

Patients were managed according to the clinical practice of each participating hospital (i.e., there was no standardization of treatment). Patients were followed-up for at least 3 months in the outpatient clinic. During each visit, any signs or symptoms suggesting symptomatic VTE recurrences, bleeding complications and/or arterial ischemic events were noted. All episodes of clinically suspected symptomatic PE recurrences during follow-up were investigated by repeat helical CT pulmonary angiography or pulmonary angiography at the discretion of the attending physicians. Bleeding complications were classified as 'major' if they were overt and required a transfusion of two units of blood or more, or were retroperitoneal, spinal or intracranial, or when they were fatal. Subsequent myocardial infarction was defined as the presence of typical chest pain in combination with a contemporaneoous increase of creatine kinase-MB or troponin beyond the reference local laboratory values and/or typical electrocardiogram signs (development of pathologic Q-waves or ST-segment elevation or depression). Ischemic stroke was diagnosed if the patient had an appropriate clinical event not resolving completely within 24 h, and had an acute cerebrovascular lesion on brain computed tomography or magnetic resonance imaging. Most outcomes were classified as reported by the clinical centers. However, if staff at the coordinating center were uncertain how to classify a reported outcome, that event was reviewed by a central adjudicating committee (< 10% of events).

2.4. Study variables

Characteristics of the incident PE episode and of participants (demographics, co-morbidities, severity of the PE event, concomitant medications, initial and long-term therapy) were recorded at baseline. PE was considered secondary to surgery if appearing within 2 months of the procedure and secondary to immobilization if within 2 months of confinement to bed with bathroom privileges for ≥ 4 days. Active cancer included cancer diagnosed within the 3 months prior to the incident PE, metastatic cancer or cancer with current therapy (i.e., surgery, chemotherapy, radiotherapy, hormonal or support therapy).

2.5. Statistical analysis

First, we compared the clinical characteristics and treatment strategies according to the presence or absence of diabetes. Then, we compared the rate of VTE recurrences, major bleeding, ischemic arterial events and death during the course of anticoagulant therapy. Finally, we compared the outcomes in patients with diabetes, according to the use of antiplatelet drugs concomitantly.

A descriptive statistical analysis was performed for all continuous and categorical variables by stratifying admissions for PE according to the presence or absence of diabetes. Variables were expressed as proportions and means with standard deviations (SD). We performed bivariate conditional logistic regression models to compare the prevalence or means of the study variables in patients with diabetes and in age-sex matched controls without diabetes. All analyses used time-to-event methods. Risks of fatal PE and all-cause death were assessed using proportional hazard Cox models. In the analysis, time

Table 1
Baseline clinical characteristics, risk factors for VTE and comorbidities, according to the presence or absence of diabetes.

	Diabetes	No diabetes	Odds ratio
	(n = 2010)	(n = 4017)	(95%CI)
Clinical characteristics			
Male gender	932 (46%)	1864 (46%)	1.00 (0.90–1.11)
Mean age (years)	74 ± 11	74 ± 11	0.987
Body weight (kg)	78 ± 17	75 ± 14	< 0.0001
Risk factors for VTE			
Recent surgery	187 (9.3%)	385 (9.6%)	0.97 (0.81–1.16)
Immobility ≥4 days	522 (26%)	859 (21%)	1.29 (1.14–1.46)
Cancer	546 (27%)	948 (24%)	1.21 (1.07–1.36)
Hormonal use	54 (2.7%)	96 (2.4%)	1.13 (0.80–1.58)
Prior VTE	262 (13%)	529 (13%)	0.99 (0.84–1.16)
Comorbidities			
Current smoking	180 (9.2%)	348 (8.8%)	1.06 (0.88–1.28)
Chronic lung disease	392 (20%)	687 (17%)	1.17 (1.02–1.35)
Chronic heart failure	331 (16%)	369 (9.2%)	1.95 (1.66–2.29)
Arterial hypertension	1598 (80%)	2311 (58%)	2.86 (2.53–3.24)
Atrial fibrillation	98 (4.8%)	130 (3.2%)	1.53 (1.17–2.01)
Prior myocardial infarction	311 (15%)	324 (8.1%)	2.09 (1.77–2.46)
Prior ischemic stroke	242 (12%)	356 (8.9%)	1.41 (1.18–1.67)
Peripheral arterial disease	144 (7.2%)	130 (3.2%)	2.31 (1.81–2.94)
Prior artery disease	584 (29%)	718 (18%)	1.88 (1.66–2.13)
Recent major bleeding	46 (2.3%)	90 (2.2%)	1.02 (0.71–1.46)
Anemia	864 (43%)	1240 (31%)	1.69 (1.51–1.89)
CrCl levels < 60 ml/min	1005 (50%)	1832 (46%)	1.19 (1.07–1.33)
Concomitant medications			
Antiplatelets	710 (35%)	814 (20%)	2.15 (1.91–2.42)
Antiplatelets discontinued (N = 936)	275 (63%)	295 (59%)	1.14 (0.87–1.48)
Severity signs			
SBP levels < 100 mmHg	219 (11%)	333 (8.3%)	1.35 (1.13–1.62)
Sat O2 levels < 90%	457 (36%)	769 (30%)	1.27 (1.10–1.47)
Heart rate > 110 bpm	379 (19%)	592 (15%)	1.36 (1.18–1.57)
Respiratory rate ≥ 20/min	473 (44%)	850 (39%)	1.22 (1.05–1.42)
Initial therapy			
Low-molecular-weight heparin	1858 (92%)	3758 (94%)	0.84 (0.68–1.04)
Unfractionated heparin	70 (3.5%)	135 (3.4%)	1.04 (0.77–1.39)
Thrombolytics	60 (3.0%)	82 (2.0%)	1.48 (1.05–2.07)
Inferior vena cava filter	59 (2.9%)	106 (2.6%)	1.12 (0.81–1.54)
Long-term therapy			
Vitamin K antagonists	1297 (65%)	2739 (68%)	0.85 (0.76–0.95)
Low-molecular-weight heparin	587 (29%)	1073 (27%)	1.13 (1.00–1.27)

Abbreviations: VTE: venous thromboembolism; CrCl, creatinine clearance; SBP, systolic blood pressure; CI, confidence intervals.

zero was the date of PE diagnosis and participants were censored at the time of discontinuation of anticoagulation, at the time of death or at the last date for which outcome data were available. The variables included in the multivariable models were those showing a significant association on bivariate analysis. Matching of cases with control and all statistical analyses were performed using Stata version 13.1 (Stata, College Station, Texas, USA). Statistical significance was set at $p < 0.05$ (2-tailed).

2.6. Ethical aspects

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. All patients provided written or oral informed consent for participation in the registry in accordance with local ethics committee requirements.

3. Results

As of September 2017, 12,293 patients with acute PE fulfilled the inclusion criteria. Of these, 2023 (16%) had diabetes. We found 2010 patients with diabetes to have two age-and-gender matched controls without diabetes. Thus, the study sample included 6027 patients. Mean age was 74 ± 11 years and 46% were men. Patients with diabetes weighed more than those without diabetes and were more likely to have recent immobility, cancer, chronic lung or heart failure, hypertension, prior myocardial infarction, ischemic stroke or peripheral artery disease, and more likely presented with anemia or renal insufficiency at baseline (Table 1).

As can be seen in Table 1 the prevalence of atrial fibrillation was 4.8% and 3.2% among patients with and without diabetes (OR 1.53 95%CI 1.17–2.01; $p = 0.002$).

Moreover, they were more likely to be using antiplatelets at baseline, and more likely presented with severity signs of PE (i.e., hypotension, tachycardia, tachypnea or hypoxemia) than patients without diabetes. Most patients in both subgroups (92% and 94%, respectively) received low-molecular-weight heparin (LMWH) therapy initially, but a slightly higher proportion of patients with diabetes received thrombolytics (3.0% vs. 2.0%, respectively). Then, 65% and 68% of patients respectively switched to long-term vitamin K antagonists.

During the course of anticoagulant therapy (median, 219 days), 116 patients presented VTE recurrences (recurrent PE 80, DVT 36), 227 had major bleeding, 57 arterial ischemic events (ischemic stroke 37, myocardial infarction 18, lower limb amputation 3) and 781 died. Patients with diabetes had a higher rate of all-cause death (HR: 1.45; 95% CI: 1.25–1.67) or arterial ischemic events (HR: 2.89; 95% CI: 1.71–4.94), a non-significantly higher rate of fatal PE (HR: 1.63; 95% CI: 0.96–2.75) and similar rate of VTE recurrences (HR: 1.05; 95% CI: 0.71–1.55) or major bleeding (HR: 1.06; 95% CI: 0.80–1.39) than those without diabetes (Table 2). The most common causes of death were: disseminated cancer (262 deaths, 34%), respiratory insufficiency (11%), pulmonary embolism (7.3%), infection (6.9%), bleeding (5.9%) and heart insufficiency (5.8%). On multivariable analysis, body weight, cancer, transient risk factors for VTE, chronic heart or lung failure, anemia, systolic blood pressure levels < 100 mmHg and tachypnea were found to independently predict the risk for death (Table 3). Diabetes was not associated with an increased risk for all-cause death (HR: 1.26; 95%CI: 0.97–1.63).

Among 710 patients with diabetes that were receiving antiplatelets at PE diagnosis, these drugs were discontinued in 275, continued in 165, and there is no information for the remaining 270 patients (Table 4). We failed to find differences between subgroups in the rate of DVT recurrences, major bleeding or death, but patients that continued to use antiplatelets concomitantly with anticoagulant therapy had a higher rate of PE recurrences (HR: 4.16; 95%CI: 1.69–8.65) or arterial ischemic events (HR: 3.97; 95%CI: 1.61–8.26) than those not using antiplatelets (Table 5).

Table 2
Clinical outcomes during the course of anticoagulation, according to the presence or absence of diabetes.

	Diabetes		No diabetes		Hazard ratio (95%CI)
	N	Events per 100 patient-years	N	Events per 100 patient-years	
Patients, N	*2010*		*4017*		
Duration of therapy					
Mean days ± SD	324 ± 344		338 ± 362		0.151
Median days (IQR)	213 (110–390)		223 (130–398)		0.113
Outcomes					
Recurrent PE	26	1.48 (0.99–2.13)	54	1.48 (1.12–1.92)	1.00 (0.62–1.58)
Recurrent DVT	14	0.79 (0.45–1.30)	22	0.60 (0.38–0.89)	1.33 (0.66–2.59)
Major bleeding	76	4.36 (3.46–5.43)	151	4.13 (3.51–4.83)	1.06 (0.80–1.39)
Myocardial infarction	14	0.79 (0.45–1.30)	4	0.11 (0.03–0.26)	7.32 (2.52–25.8)
Ischemic stroke	17	0.96 (0.58–1.51)	20	0.54 (0.34–0.82)	1.78 (0.92–3.42)
Limb amputation	2	0.11 (0.02–0.37)	1	0.03 (0.00–0.13)	4.17 (0.32–123)
Any arterial ischemic event	33	1.88 (1.31–2.61)	24	0.65 (0.43–0.95)	2.89 (1.71–4.94)
Death	320	18.0 (16.1–20.1)	461	12.4 (11.3–13.6)	1.45 (1.25–1.67)
Causes of death					
Pulmonary embolism	25	1.41 (0.93–2.05)	32	0.86 (0.60–1.21)	1.63 (0.96–2.75)
Initial PE	20	1.13 (0.71–1.71)	25	0.68 (0.45–0.98)	1.67 (0.91–3.01)
Recurrent PE	5	0.28 (0.10–0.62)	7	0.19 (0.08–0.37)	1.49 (0.43–4.81)
Bleeding	14	0.79 (0.45–1.29)	32	0.86 (0.60–1.21)	0.91 (0.47–1.69)
Sudden, unexpected	7	0.39 (0.17–0.78)	21	0.57 (0.36–0.85)	0.69 (0.27–1.59)
Ischemic stroke	5	0.28 (0.10–0.62)	5	0.14 (0.05–0.30)	2.08 (0.56–7.74)
Myocardial infarction	4	0.23 (0.07–0.54)	3	0.08 (0.02–0.22)	2.78 (0.57–14.9)

Abbreviations: SD, standard deviation; IQR, interquartile range; PE, pulmonary embolism; DVT, deep vein thrombosis; CI, confidence intervals.

Table 3
Multivariate analysis for all-cause death during anticoagulation.

	Crude OR	Adjusted OR
	(95% CI)	(95% CI)
Clinical characteristics		
Male gender	1.27 (1.10–1.46)	–
Age > 65 years	1.23 (1.03–1.48)	–
Body weight < 75 kg	1.87 (1.62–2.16)	1.64 (1.25–2.15)
Risk factors for VTE		
Unprovoked	Ref.	Ref.
Cancer	6.39 (5.33–7.66)	5.58 (4.00–7.78)
Transient risk factors	2.38 (1.93–2.94)	1.99 (1.37–2.89)
Prior VTE	0.58 (0.45–0.75)	0.61 (0.38–0.98)
Comorbidities		
Diabetes mellitus	1.43 (1.24–1.84)	1.26 (0.97–1.63)
Chronic lung disease	1.39 (1.18–1.65)	1.52 (1.16–1.99)
Chronic heart failure	2.02 (1.69–2.41)	1.47 (1.04–2.07)
Prior myocardial infarction	1.31 (1.06–1.61)	–
Prior ischemic stroke	1.80 (1.48–2.18)	–
Peripheral arterial disease	1.93 (1.49–2.51)	
Anemia	1.94 (1.68–2.23)	1.42 (1.10–1.84)
CrCl levels < 60 ml/min	1.60 (1.39–1.84)	–
Concomitant medications		
Antiplatelets	1.37 (1.18–1.60)	–
Severity signs		
SBP levels < 100 mmHg	1.99 (1.64–2.41)	1.55 (1.11–2.16)
Sat O2 levels < 90%	1.61 (1.35–1.92)	–
Heart rate > 110 bpm	1.50 (1.26–1.78)	–
Respiratory rate ≥ 20/min	2.24 (1.84–2.73)	1.47 (1.13–1.91)

Abbreviations: VTE, venous thromboembolism; CrCl, creatinine clearance; SBP, systolic blood pressure; bpm, beats per minute; OR, odds ratio; CI, confidence intervals.

4. Discussion

Consistent with data from other studies [14, 22, 31], the proportion of patients with diabetes at the time of presentation in our investigation was 16%. In addition, as found by Piazza et al. [15], the presence of VTE in patients with clinical history of diabetes was associated with a higher probability to have a complicated clinical course. Despite this, the prognostic role of diabetes is not well established in PE patients, contrary to what happens in patients with ischemic heart disease or cerebrovascular disease [32, 33].

A number of observational studies reported that VTE patients with diabetes had a higher mortality rate than those without diabetes [14, 22, 23]. However, there were a number of differences between patients with vs. without diabetes (including patient's age, presence of co-morbidities and treatment details) that made it difficult to adjust for potentially confounding variables. This is the reason why we designed a case-control study, adjusting for gender and age. Our data confirm that PE patients with diabetes were more likely to have comorbidities (cancer, chronic lung or heart failure, hypertension or prior artery disease) and to use antiplatelets at baseline than those without diabetes. They were also more likely to suffer a severe PE (in terms of hypotension, tachycardia, tachypnea or hypoxemia) and received similar therapy (anticoagulant drugs, doses, duration). During the course of anticoagulant therapy, patients with diabetes had a higher mortality rate, a higher rate of arterial ischemic events and a similar rate of VTE recurrences or major bleeding than those without diabetes. On multivariable analysis however, the increased risk to die was not confirmed.

As in our cohort, patients with diabetes in the population-based Worcester VTE Study, the Spanish Hospital Discharge Database and in the Taiwan's National Health Insurance Database were more likely

Table 4
Baseline clinical characteristics, risk factors for VTE and comorbidities in patients with diabetes, according to use of antiplatelets.

	No antiplatelets	Antiplatelets discontinued	Antiplatelets continued
Clinical characteristics	*1300*	*275*	*165*
Male gender	588 (45%)	121 (44%)	99 (60%)‡
Mean age (years)	73 ± 12	78 ± 9.3‡	76 ± 9.1‡
Body weight (kg)	79 ± 18	77 ± 15	77 ± 14
Risk factors for VTE			
Recent surgery	126 (9.7%)	17 (6.2%)	17 (10%)
Immobility ≥4 days	307 (24%)	84 (31%)*	52 (32%)*
Cancer	374 (29%)	63 (23%)	48 (29%)
Hormonal use	39 (3.0%)	5 (1.8%)	7 (4.2%)
Prior VTE	168 (13%)	36 (13%)	19 (12%)
Comorbidities			
Current smoking	128 (10%)	25 (9.3%)	12 (7.4%)
Chronic heart failure	134 (10%)	65 (24%)‡	49 (30%)‡
Arterial hypertension	981 (75%)	237 (86%)‡	143 (87%)†
Prior myocardial infarction	81 (6.2%)	60 (22%)‡	74 (45%)‡
Prior ischemic stroke	70 (5.4%)	60 (22%)‡	40 (24%)‡
Prior peripheral arterial disease	50 (3.8%)	31 (11%)‡	27 (16%)‡
Prior artery disease	179 (14%)	126 (46%)‡	117 (71%)‡
Recent major bleeding	27 (2.1%)	6 (2.2%)	7 (4.2%)
Anemia	531 (41%)	123 (45%)	94 (57%)‡
CrCl levels < 60 ml/min	609 (47%)	156 (57%)†	87 (53%)
Severity signs			
SBP levels < 100 mmHg	144 (11%)	29 (11%)	19 (12%)
Sat O2 levels < 90%	281 (35%)	63 (37%)	47 (41%)
Heart rate > 110 bpm	267 (21%)	54 (20%)	27 (17%)
Respiratory rate ≥ 20/min	317 (46%)	51 (39%)	38 (39%)
Initial therapy			
Low-molecular-weight heparin	1205 (93%)	249 (91%)	155 (94%)
Unfractionated heparin	40 (3.1%)	10 (3.6%)	5 (3.0%)
Thrombolytics	40 (3.1%)	14 (5.1%)	2 (1.2%)
Inferior vena cava filter	42 (3.2%)	4 (1.5%)	3 (1.8%)
Long-term therapy			
Vitamin K antagonists	818 (63%)	184 (67%)	97 (59%)
Low-molecular-weight heparin	405 (31%)	71 (26%)	55 (33%)

Comparisons between patients with antiplatelet drugs at baseline and those without: *$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$.
Abbreviations: VTE: venous thromboembolism; CrCl, creatinina clearance; SBP, systolic blood pressure; bpm, beats per minute.

to have co-morbidities (hypertension, chronic heart or lung failure, recent immobility, prior myocardial infarction, ischemic stroke or peripheral artery disease, or renal insufficiency) and to receive aspirin at the time of VTE diagnosis and at discharge [14, 22, 23]. On multivariable analysis, patients with diabetes were at increased risk for death, but the causes of death were not analyzed. They also were at increased risk for myocardial infarction or ischemic stroke, and patients with diabetes receiving aspirin at discharge were at increased risk for major bleeding. Unfortunately however, we failed to demonstrate that the increased mortality in patients with diabetes might be attributed to a higher rate of fatal myocardial infarction or stroke. We also failed to find different mortality rates in patients with diabetes according to the use of antiplatelet drugs concomitantly. In any case, the comparison of our study with those previously published is difficult to perform, because there are relevant differences between them, including study design, number of patients, objectives, main outcome variable, co-variables and results obtained. In other to facilitate the comparison and discussion with these previous investigation their main characteristics of are shown in Supplementary Table 1.

Although in our study we did not find major differences in anticoagulant therapy, other authors reported that patients with diabetes were more likely to discontinue anticoagulation, mostly because of emerging medical issues, such as deterioration of renal function, arterial ischemic events and for safety considerations because of initiation of antiplatelet medication [34].

Our results have both clinical and research implications. From a clinical point of view, PE patients who have diabetes carry a higher risk of mortality than those without diabetes and, therefore, they may potentially benefit from more intensive surveillance both in the hospital and after discharge.

The main strength of this study was the large number of patients with PE that were enrolled and followed during a period of at least 3 months after discharge, representing a real-life scenario. In addition, all cases met strict criteria for acute PE and diabetes mellitus was identified by clinical diagnosis. However, it is also important to address potential limitations of our study. We were unable to assess the influence of glucose level on admission or severity and disease control over long-term outcomes. In this way, other measures of hyperglycemia, rather than diabetes itself, could be influence more in outcomes of PE. Thus, for example, the risk of arterial disease and all-cause mortality have been shown to increase across levels of hemoglobin A1c, independently of the presence of diabetes [35]. Also, Bell et al. found that both diabetes and raised levels of hemoglobin A1c tended to be associated with higher VTE risk [36]. This association remained after adjusting for diabetes medication, thus suggesting that use of diabetes medications were not the explanation. By constrast, Lerstad et al. failed to find an association between HbA1c levels and the risk of VTE [37]. Unfortunately, this variable was not available in the RIETE registry. On the other hand, the method used for the assessment of glomerular filtration was not homogeneous in all patients, with variations found in the different participating centers, so there could be some bias in this regard [38]. Moreover, information on diabetes treatment neither was available in our study. Thus, we cannot address the question whether treatment for diabetes may reduce mortality associated with this disease. We do not value hypoglycemia either. Although causality is unproven, hypoglycemia may cause adverse cardiovascular outcomes and death in diabetic patients [39].

In conclusion, in this large sample of patients with PE, diabetes was associated with increased rates for all-cause death, myocardial infarction or ischemic stroke. On multivariable analysis, the higher mortality rate could not be attributed to diabetes itself, but rather to the most common presence of cancer, chronic heart or lung failure, anemia, or the more severe presentation of the index PE event in patients with diabetes. Future studies should investigate if an appropriate control of diabetes has any impact on survival in these patients.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejim.2018.08.001.

Competing interests

The authors declare that they have no competing interests.

Table 5
Clinical outcomes during the course of anticoagulation in patients with diabetes, according to the use of antiplatelets.

	No antiplatelets		Antiplatelets discontinued		Antiplatelets continued	
	N	Events per 100 patient-years	N	Events per 100 patient-years	N	Events per 100 patient-years
Patients, N	*1300*		*275*		*165*	
Duration of therapy						
Mean days ± SD	323 ± 352		345 ± 339		338 ± 335	
Median days (IQR)	211 (110–388)		240 (110–448)		228 (101–416)	
Outcomes						
Recurrent PE	14	1.23 (0.70–2.01)	3	1.17 (0.30–3.19)	6	4.16 (1.69–8.65)*
Recurrent DVT	9	0.79 (0.38–1.45)	3	1.17 (0.30–3.19)	1	0.66 (0.03–3.26)
Major bleeding	53	4.69 (3.55–6.09)	10	3.95 (2.01–7.04)	4	2.74 (0.87–6.60)
Myocardial infarction	5	0.44 (0.16–0.97)	3	1.16 (0.30–3.16)	3	1.98 (0.50–5.39)
Ischemic stroke	9	0.79 (0.38–1.44)	4	1.60 (0.51–3.85)	3	1.98 (0.50–5.40)
Limb amputation	1	0.09 (0.00–0.43)	0	–	0	–
Any arterial ischemic event	15	1.32 (0.77–2.13)	7	2.81 (1.23–5.55)	6	3.97 (1.61–8.26)*
Death	197	17.2 (14.9–19.7)	46	17.7 (13.1–23.4)	29	19.1 (13.0–27.1)
Causes of death						
Pulmonary embolism	16	1.39 (0.83–2.22)	4	1.54 (0.49–3.71)	2	1.32 (0.22–4.36)
Initial PE	14	1.22 (0.69–2.00)	3	1.15 (0.29–3.14)	1	0.66 (0.03–3.25)
Recurrent PE	2	0.17 (0.03–0.58)	1	0.38 (0.02–1.90)	1	0.66 (0.03–3.25)
Sudden, unexpected	2	0.17 (0.03–0.58)	4	1.54 (0.49–3.71)*	0	–
Ischemic stroke	4	0.35 (0.11–0.84)	0	–	0	–
Myocardial infarction	1	0.09 (0.00–0.43)	0	–	1	0.66 (0.03–3.25)
Any arterial ischemic event	5	0.44 (0.16–0.97)	0	–	1	0.66 (0.03–3.25)
Bleeding	10	0.87 (0.44–1.55)	2	0.77 (0.13–2.54)	1	0.66 (0.03–3.25)

Comparisons between patients with antiplatelet drugs at baseline and those without: $^{*}p < 0.05$; $^{\dagger}p < 0.01$; $^{\ddagger}p < 0.001$.
Abbreviations: SD, standard deviation; IQR, interquartile range; PE, pulmonary embolism; DVT, deep vein thrombosis.

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Appendix A. Appendix

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