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ORIGINAL RESEARCH

# Association Between Preexisting Versus Newly Identified Atrial Fibrillation and Outcomes of Patients With Acute Pulmonary Embolism

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**BACKGROUND:** Atrial fibrillation (AF) may exist before or occur early in the course of pulmonary embolism (PE). We determined the PE outcomes based on the presence and timing of AF.

**METHODS AND RESULTS:** Using the data from a multicenter PE registry, we identified 3 groups: (1) those with preexisting AF, (2) patients with new AF within 2 days from acute PE (incident AF), and (3) patients without AF. We assessed the 90-day and 1-year risk of mortality and stroke in patients with AF, compared with those without AF (reference group). Among 16 497 patients with PE, 792 had preexisting AF. These patients had increased odds of 90-day all-cause (odds ratio [OR], 2.81; 95% CI, 2.33–3.38) and PE-related mortality (OR, 2.38; 95% CI, 1.37–4.14) and increased 1-year hazard for ischemic stroke (hazard ratio, 5.48; 95% CI, 3.10–9.69) compared with those without AF. After multivariable adjustment, preexisting AF was associated with significantly increased odds of all-cause mortality (OR, 1.91; 95% CI, 1.57–2.32) but not PE-related mortality (OR, 1.50; 95% CI, 0.85–2.66). Among 16 497 patients with PE, 445 developed new incident AF within 2 days of acute PE. Incident AF was associated with increased odds of 90-day all-cause (OR, 2.28; 95% CI, 1.75–2.97) and PE-related (OR, 3.64; 95% CI, 2.01–6.59) mortality but not stroke. Findings were similar in multivariable analyses.

**CONCLUSIONS:** In patients with acute symptomatic PE, both preexisting AF and incident AF predict adverse clinical outcomes. The type of adverse outcomes may differ depending on the timing of AF onset.

**Key Words:** atrial fibrillation ■ mortality ■ outcome ■ pulmonary embolism



Pulmonary embolism (PE) is a thromboembolic disease with potentially serious or fatal complications.[1–3] Understanding the risk profile for patients with acute PE is critical, because timely assessment may help with risk stratification.[4] Several tools exist for such risk assessment,[5,6] including the simplified Pulmonary Embolism Severity Index (sPESI).[7] Nevertheless, risk assessment remains suboptimal for several patient subgroups. Therefore, finding additional ways to predict adverse outcomes is crucial.

Atrial fibrillation (AF) is a common arrhythmia,[8] associated with increased rates of stroke, myocardial

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## CLINICAL PERSPECTIVE

### What Is New?

- This study demonstrated that atrial fibrillation (AF) may exist before or occur early in the course of acute pulmonary embolism and lead to worse clinical outcomes, which may be dependent on the timing of the AF: preexisting AF predicts all-cause mortality and 1-year risk of stroke whereas new (incident) AF predicts all-cause mortality and pulmonary embolism-related mortality.

### What Are the Clinical Implications?

- The presence of coexisting AF in patients with pulmonary embolism is indicative of higher risk for adverse events and should be assessed in future studies to determine whether it improves risk stratification and can direct more optimal use of treatment strategies.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **RIETE** | Registro Informatizado de Enfermedad TromboEmbólica |
| **sPESI** | simplified Pulmonary Embolism Severity Index |

infarction, and heart failure.[9,10] The presence of AF may affect the thromboembolic and hemorrhagic risk across a wide spectrum of cardiovascular conditions. For example, investigations related to coexisting AF and coronary disease have led to tailored strategies to address the thrombotic risk.[11–13]

The association between PE and AF has received recent attention.[14,15] Presentations of AF occurring before[15–17] or early in the course of[18] acute PE have been described. However, the majority of the prior studies of the AF-PE association has been based on a small number of patients or on administrative data.[15,19] Little is known about the comparative presentation and outcomes according to the time of AF onset with respect to PE. In addition, it remains unknown whether AF is merely a surrogate for cardiovascular risk, associated with increased all-cause mortality, or if it is associated with PE-related mortality. Further, it is unclear whether the associations, if present, are because of differences in baseline characteristics or whether they persist after multivariable adjustment.[15,20]

Using the data from the RIETE (Registro Informatizado de Enfermedad Tromboembólica) registry, we sought to identify patients with PE and coexisting AF and profile their PE presentation, coexisting characteristics, treatment patterns, and outcomes according to the time course of AF. We focused on (1) preexisting AF diagnosed before the index PE event, and (2) new AF diagnosed within the first 2 days of diagnosis of acute PE (incident AF). We considered patients with PE who did not have AF as referent.

## METHODS

The methods implemented for the current study are summarized. Further details about the study methodology or the underlying data will be made available to interested investigators, upon submitting a reasonable research request to the principal investigators (B.B., D.J., and M.M.) and approval of the RIETE advisory committee.

### Data Source

RIETE is a multicenter international registry of consecutive patients with objectively confirmed venous thromboembolism (VTE; deep vein thrombosis, PE, or splanchnic vein thrombosis). The methodology of the registry has been described previously.[21] The protocol for patient enrollment was approved by the participating centers. Data were stored and audited by the RIETE coordinating center (S&H Medical Sciences Services, Madrid, Spain). All study participants provided informed consent, in accordance with local institutional review board criteria. For the current study, we included patients with PE from April 2, 2014 to January 31, 2020. This choice was made to include patients for whom data elements related to AF were available, while avoiding the inclusion of patients with VTE in the setting of the COVID-19 pandemic.[22,23]

### Patients

Patients with acute symptomatic PE were considered for inclusion in this study. We excluded patients with asymptomatic PE. We hypothesized that patients with preexisting AF and patients with incident AF may each have different characteristics and outcomes compared with those without AF. However, because these differences may be epidemiologically and pathophysiologically distinct, we prespecified the analysis of these 2 subgroups of AF separately. For all analyses, patients without preexisting AF or incident AF were considered as referent.

### Patient Characteristics

We assessed the demographics and comorbidities such as diabetes mellitus, hypertension, atherosclerotic vascular disease, chronic pulmonary disease, stroke, cancer, and recent surgery (ie, within 2 months before enrollment in RIETE). Treatment patterns for each group, including anticoagulant therapy and

advanced therapies (including fibrinolytic therapy and percutaneous or surgical thrombectomy) were evaluated. For patients who remained alive at follow-up, we explored within each group the proportion of patients who remained on anticoagulation at 90 days and at 1-year follow-up.

## Outcomes

The co-primary outcomes were PE-related mortality at 90 days from enrollment and all-cause mortality at 1-year follow-up. The prespecified secondary end points were the 1-year rate of ischemic stroke and the composite of thrombotic events (consisting of myocardial infarction, ischemic stroke, or subsequent VTE). Other study end points included 90-day all-cause mortality and 1-year PE-related mortality. Because we expected fewer short-term events, in order to minimize the type I error rate, we prespecified that we would assess stroke, recurrent VTE, and also composite thrombotic end points only at 1-year follow-up.

The main safety outcomes were major bleeding at 90-day and 1-year follow-up. Major bleeding was defined as events that required transfusion of ≥2 units of blood or were retroperitoneal, spinal, intracranial, intrapericardial, or fatal. This definition closely resembles that of the International Society on Thrombosis and Haemostasis.[24] In all analyses, patients without AF were considered as reference group.

## Statistical Analysis

Categorical variables were reported as percentages. Continuous variables were reported as mean and standard error of the mean (or median and interquartile range, where not normally distributed). To minimize type I error, it was prespecified to avoid unselected pairwise hypothesis testing for the baseline characteristics between groups.[25] We planned to report the relative frequencies for categorical variables with 99% CIs. Post hoc chi square tests were considered only if there were nonoverlapping 99% CIs of clinical relevance. For baseline numeric variables, to avoid inflation of the type I error, we prespecified to run tests of statistical comparisons only among the variables that reflected clinically meaningful differences (as decided by the study steering committee based on the magnitude of observed difference and expected difference based on clinical consensus), in addition to age and the sPESI, which were prespecified.[7] No a priori power calculation was made for this study.

In general, logistic regression models are more powerful and are less prone to statistical assumptions. As a unique strength of the registry, RIETE has complete 100% follow-up for all patients until 90 days from the index VTE event or until death. Accordingly, for assessment of 90-day outcomes, we used logistic regression models for adjustment and reported odds ratio (OR) as the effect measure.

For 1-year all-cause mortality, we used Cox proportional hazard models and reported hazard ratios (HR) as the effect measure. For outcomes other than all-cause mortality (ie, PE-related mortality, thrombosis composite outcome, and major bleeding), we used Fine-Gray hazard models that accounted for the competing risk of death from events other than the outcome of interest. Survival estimates were presented with Kaplan-Meier curves for all-cause mortality and competing risk regression (cumulative incidence function with Fine-Gray method) for PE-related mortality. Variables used for adjustment were prespecified and included age (continuous), sex, sPESI, and history of diabetes mellitus, heart failure, prior ischemic stroke, and arterial vascular disease (either coronary or peripheral artery disease). In all models, those without history of AF were the reference group.

For the assessment of the co-primary outcomes, because 90-day PE-related mortality rates are likely to affect 1-year mortality, we did not adjust the alpha level. However, it was planned to compare each of the patient subgroups with AF (ie, those with preexisting AF, as well as those with new incident AF) against those patients who did not have AF. Therefore, it was prespecified to set the significance level for the co-primary outcomes at $P<0.025$ (ie, reducing the alpha to half). All other comparisons were considered exploratory.

# RESULTS

Of 92 258 patients in RIETE, 48 554 had PE. Based on the inclusion and exclusion criteria, 16 497 patients with acute PE were included. Of those, 792 (4.8%) had known preexisting AF, whereas 445 (2.7%) were diagnosed with new incident AF within 48 hours of the diagnosis of acute PE (Figure 1).

## Baseline Characteristics and Presenting Features

Patients with preexisting AF had differing baseline characteristics compared with those without AF. Patients with preexisting AF were older (77.9±0.4 versus 65.7±0.1 years), more likely to have diabetes mellitus (25.3% versus 15.9%), hypertension (77.0% versus 50.2%), and history of heart failure (33.8% versus 6.7%), ($P<0.001$ for pairwise all comparisons). The proportion of patients with hypotension (3.6% versus 3.0, $P=0.29$) or syncope (12.8% versus 14.1%, $P=0.33$) at presentation was comparable between those with preexisting AF and patients without AF. Patients with preexisting AF had higher $CHA_2DS_2$-VASC and sPESI scores compared with those without AF ($P<0.001$ for both comparisons [Table 1]).

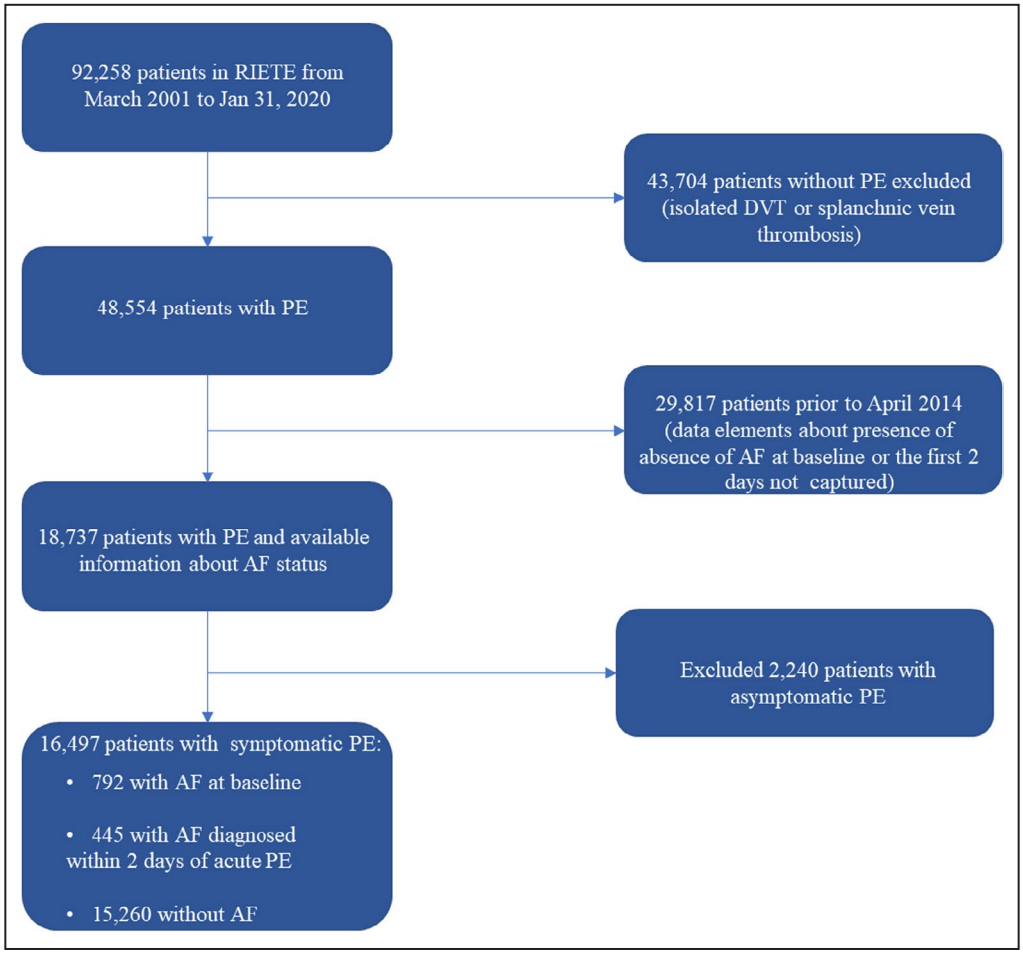



**Figure 1. Patient selection flow diagram.**
AF indicates atrial fibrillation; DVT, deep vein thrombosis; PE, pulmonary embolism; and RIETE, Registro Informatizado de Enfermedad Tromboembólica.

Patients with incident AF also had important differences in presenting features, compared with patients without AF. Comorbidities such as hypertension (63.9% versus 50.2%, $P<0.001$) and heart failure (10.8% versus 6.7%, $P=0.001$) were more frequently observed in patients with incident AF than those without AF. Further, patients with incident AF were more likely to present with hypotension (7.6% versus 3.0%, $P<0.001$) or syncope (18.0% versus 14.1%, $P=0.02$). As shown in Table 1, patients with incident AF had higher $CHA_2DS_2$-VASC and sPESI scores compared with those without AF ($P<0.001$ for both comparisons). The gradient of risk according to the European Society of Cardiology classification is summarized in Table S1.

## Treatment Patterns

Most patients in all 3 groups received initial anticoagulation. Use of percutaneous and surgical thrombectomy was rare (Table 2). Thrombolytic therapy was used in 1.1% of patients with preexisting AF, 4.3% of patients with incident AF, and 2.8% of patients without AF. At 1-year follow-up, a greater percentage of patients with preexisting AF were on anticoagulation than those who did not have a history of AF (75.2% versus 63.2%, $P<0.001$). Similarly, compared with those without AF, a greater proportion of patients with incident AF were on anticoagulation at 1-year follow-up (82.9% versus 63.2%, $P<0.001$).

## Outcomes at 90-Day Follow-Up

### *All-Cause Mortality*

In unadjusted analyses, patients with preexisting AF had higher odds of 90-day mortality compared with those without AF (16.0% versus 6.1%; OR, 2.81; 95% CI, 2.33–3.38). Findings were attenuated but consistent after multivariable adjustment (OR, 1.91; 95% CI, 1.57–2.32).

Patients with incident AF, compared with patients without AF, had higher odds of 90-day mortality in unadjusted analyses (13.0% versus 6.1%; OR, 2.28; 95% CI, 1.75–2.97). Results were similar after multivariable adjustment (OR, 1.61; 95% CI, 1.23–2.10) (Figure 2A).

**Table 1. Cohort Characteristics of Patients With PE According to Presence and Time-Course of AF**

| | Known preexisting AF | Incident AF (diagnosed within 2 d after PE) | No AF at all |
|---|---|---|---|
| Number of patients (total N=16 497) | N=792 | N=445 | N=15 260 |
| Demographics | | | |
| Female sex, % | 56.1% (99% CI, 51.4–60.6) | 52.8% (99% CI, 46.5–58.9%) | 51.3% (99% CI, 50.3–52.3%) |
| Age, y±SEM | 77.9±0.4 | 75.2±0.6 | 65.7±0.1 |
| Age, y, median±IQR | 80 (72–86) | 78 (68–84) | 69 (55–79) |
| Prior history | | | |
| Current smoker | 7.1% (99% CI, 4.9–9.8%) | 9.3% (99% CI, 6.0–13.4%) | 14.1% (99% CI, 13.4–14.9%) |
| Diabetes mellitus | 25.3% (99% CI, 21.4–29.5%) | 18.1% (99% CI, 13.5–23.2%) | 15.9% (99% CI, 15.1–16.7%) |
| Hypertension | 77.0% (99% CI, 72.9–80.1%) | 63.9% (99% CI, 57.7–69.8%) | 50.2% (99% CI, 4.9.1–51.2%) |
| Coronary artery disease | 15.7% (99% CI, 12.5–19.4%) | 9.1% (99% CI, 6.0%–13.3%) | 6.7% (99% CI, 6.1–7.2%) |
| Peripheral arterial disease | 8.5% (99% CI, 6.1–114%) | 4.2% (99% CI, 2.1–7.3%) | 3.5% (99% CI, 3.1–3.9%) |
| Coronary or peripheral arterial disease | 22.0% (99% CI, 18.1–26.1%) | 12.5% (99% CI, 8.7–17.1%) | 9.4% (99% CI, 8.8–10.0%) |
| Heart failure | 33.8% (99% CI, 29.6–38.3%) | 10.8% (99% CI, 7.3–15.1%) | 6.7% (99% CI, 6.1–7.2%) |
| Ischemic stroke | 16.1% (99% CI, 12.9–19.8%) | 11.7% (99% CI, 8.1–16.2%) | 6.3% (99% CI, 5.8–6.9) |
| Prior (old) venous thromboembolism | 13.4% (99% CI, 10.4–16.8%) | 9.0% (99% CI, 5.8–13.0%) | 14.1% (99% CI, 13.4–14.8%) |
| Coexisting deep vein thrombosis diagnosed with the index PE event | 23.7% (99% CI, 19.9–27.8%) | 26.1% (99% CI, 20.1–31.8%) | 29.5% (99% CI, 28.6–30.5%) |
| Chronic lung disease | 20.7% (99% CI, 17.1–24.7%) | 12.4% (99% CI, 8.7–16.9%) | 13.5% (99% CI, 12.8–14.3%) |
| Active cancer | 17.3% (99% CI, 14.0–21.0%) | 16.9% (99% CI, 12.5–21.9%) | 16.7% (99% CI, 15.9–17.5%) |
| Anemia | 39.3% (99% CI, 34.8–43.9%) | 33.0% (99% CI, 27.4–39.1%) | 30.9% (99% CI, 29.9–31.9) |
| Creatinine clearance levels, mL/min | 73.3±247.3 | 66.4±31.5 | 87.1±64.3 |
| Clinical factors | | | |
| Median (IQR) heart rate | 90 (75–110) | 101 (85–126) | 90 (77–103) |
| Systolic blood pressure <90 mm Hg | 3.6% (99% CI, 2.1–5.7%) | 7.6% (99% CI, 4.8–11.5%) | 3.0% (99% CI, 2.7–3.4%) |
| Syncope | 12.8% (99% CI, 9.9–16.2%) | 18.0% (99% CI, 13.5–23.1%) | 14.1% (99% CI, 13.4–14.8) |
| Simplified Pulmonary Embolism Severity Index score, median±IQR | 2 (1–2) | 1 (1–2) | 1 (0–2) |
| $CHA_2DS_2VASC$ Score, median±IQR | 4 (3–5) | 3 (2–4) | 2 (1–4) |
| Use of echocardiography within the first 3 d of PE diagnosis | 56.6 (99% CI, 51.7–61.5%) | 69.7% (99% CI, 63.7–75.3%) | 58.5% (99% CI, 57.4–59.6%) |
| Aspirin use at baseline | 35.7% | 26.2% | 18.9% |

Categorical variables have been reported with their respective 99% CIs. Pairwise statistical comparisons were intentionally avoided to minimize type I error. AF indicates atrial fibrillation; IQR, interquartile range; and PE, pulmonary embolism.

## Thrombotic Outcomes

Patients with preexisting AF had higher odds of 90-day PE-related mortality compared with those without AF (1.8% versus 0.76%; OR, 2.38; 95% CI, 1.37–4.14, *P*=0.002). However, the results were not significant after multivariable adjustment (OR, 1.50; 95% CI, 0.85–2.66).

When compared with patients without AF, patients with incident AF had higher odds of 90-day PE-related mortality both in unadjusted (2.7% versus 0.76%; OR,

**Table 2. Treatment Patterns**

| | Known preexisting AF | Incident AF (diagnosed within 2 d after PE) | No AF at all |
|---|---|---|---|
| | N=792 | N=445 | N=15 260 |
| Initial therapy | | | |
| Any anticoagulant therapy N=16 440 | N=787 | N=444 | N=15 209 |
| Low-molecular-weight heparin | 676 (86%) | 397 (89%) | 12 696 (83%) |
| Unfractionated heparin | 42 (5.3%) | 18 (4.1%) | 879 (5.8%) |
| Fondaparinux | 14 (1.8%) | 2 (0.45%) | 227 (1.5%) |
| Direct oral anticoagulants | 23 (2.9%) | 4 (0.90%) | 902 (5.9%) |
| Thrombolytic therapy | 9 (1.1%) | 19 (4.3%) | 420 (2.8%) |
| Surgical or percutaneous thrombectomy N=14 762 | N=674<br>4 (0.59%) | N=400<br>3 (0.75%) | N=13 688<br>169 (1.2%) |
| Vena cava filter use | 18 (2.3%) | 20 (4.5%) | 377 (2.5%) |
| No anticoagulant therapy | 2 (0.25%) | 1 (0.22%) | 16 (0.10%) |
| Long-term treatment (among survivors with valid follow-up information) | | | |
| Vitamin K antagonists | 274 (35%) | 201 (45%) | 6942 (47%) |
| Low-molecular-weight heparin | 235 (30%) | 128 (29%) | 4214 (28%) |
| Direct oral anticoagulants | 210 (27%) | 83 (19%) | 3504 (24%) |
| Fondaparinux | 4 (0.51%) | 3 (0.67%) | 78 (0.53%) |
| Unfractionated heparin | 4 (0.51%) | 0 | 32 (0.22%) |
| Others | 5 (0.63%) | 2 (0.45%) | 30 (0.20%) |
| Anticoagulation at 90 d | | | |
| Patients alive and followed | 664 | 386 | 14 306 |
| Patients alive and still on anticoagulation | 620 (93.4%) | 372 (96.4%) | 13 801 (96.5%) |
| Anticoagulation at 180 d | | | |
| Patients alive and followed | 434 | 252 | 9250 |
| Patients alive and still on anticoagulation | 369 (85.0%) | 226 (89.7%) | 7941 (85.8%) |
| Anticoagulation at 365 d | | | |
| Patients alive and followed | 258 | 164 | 5607 |
| Patients alive and still on anticoagulation | 194 (75.2%) | 136 (82.9%) | 3541 (63.2%) |

AF indicates atrial fibrillation; and PE, pulmonary embolism.

3.64; 95% CI, 2.01–6.59, $P<0.001$) and multivariable adjusted analyses (OR, 2.29; 95% CI, 1.25–4.18). (Figure 2B).

### *Bleeding*

Patients with preexisting AF had higher odds of 90-day major bleeding compared with those without AF (3.5% versus 2.0%; OR, 1.87; 95% CI, 1.27–2.75). The association was no longer significant after multivariable adjustment (OR, 1.40; 95% CI, 0.93–2.10). Similarly, patients with incident AF, compared with patients without AF, had higher odds of 90-day major bleeding (OR, 2.02; 95% CI, 1.24–3.29), which was not significant after multivariable adjustment (OR, 1.48; 95% CI, 0.89–2.45) (Figure 2C).

## Outcomes at 1-Year Follow-Up

### *All-Cause Mortality*

Patients with preexisting AF were at higher risk for 1-year all-cause mortality compared with those without AF (HR, 2.62; 95% CI, 2.23–3.07; $P<0.001$). Findings were attenuated but consistent after multivariable adjustment (HR, 1.77; 95% CI, 1.50–2.10) (Figure 3A).
Patients with incident AF, compared with patients without AF, had higher risk of 1-year all-cause mortality in unadjusted analyses (HR, 1.86; 95% CI, 1.46–2.36; $P<0.001$). Results were attenuated but consistent in multivariable adjustment (HR, 1.34; 95% CI, 1.05–1.71) (Figure 3A and 3B).

### *Thrombotic Outcomes*

Considering the competing risk of non-PE death, patients with preexisting AF had a higher risk of PE death at 1-year follow-up (HR, 2.27; 95% CI, 1.33–3.86). However, the results were no longer significant after multivariable adjustment (HR, 1.50; 95% CI, 0.88–2.60).

Compared with those without AF, patients with incident AF had an increased hazard for 1-year PE-related mortality in analyses accounting for the competing

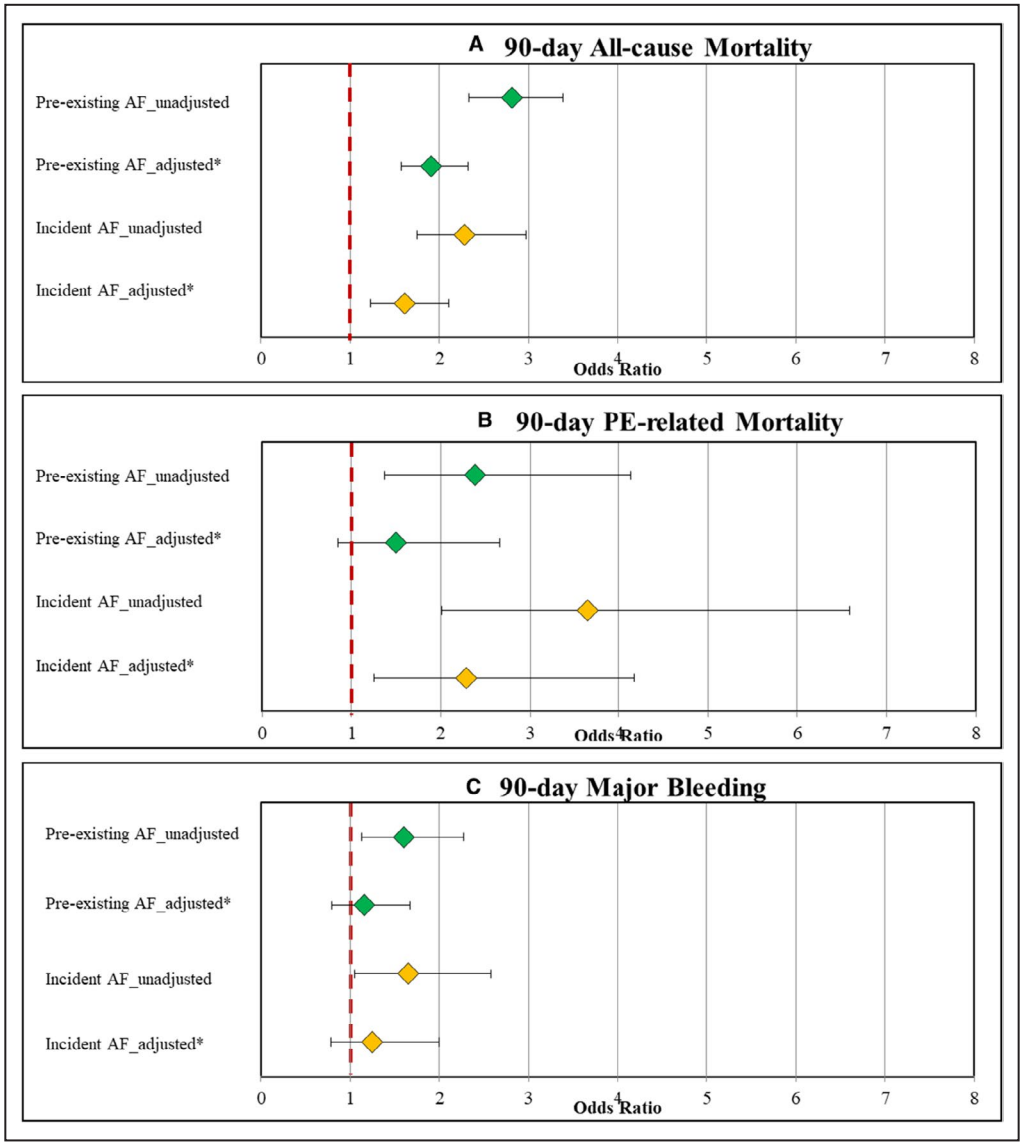
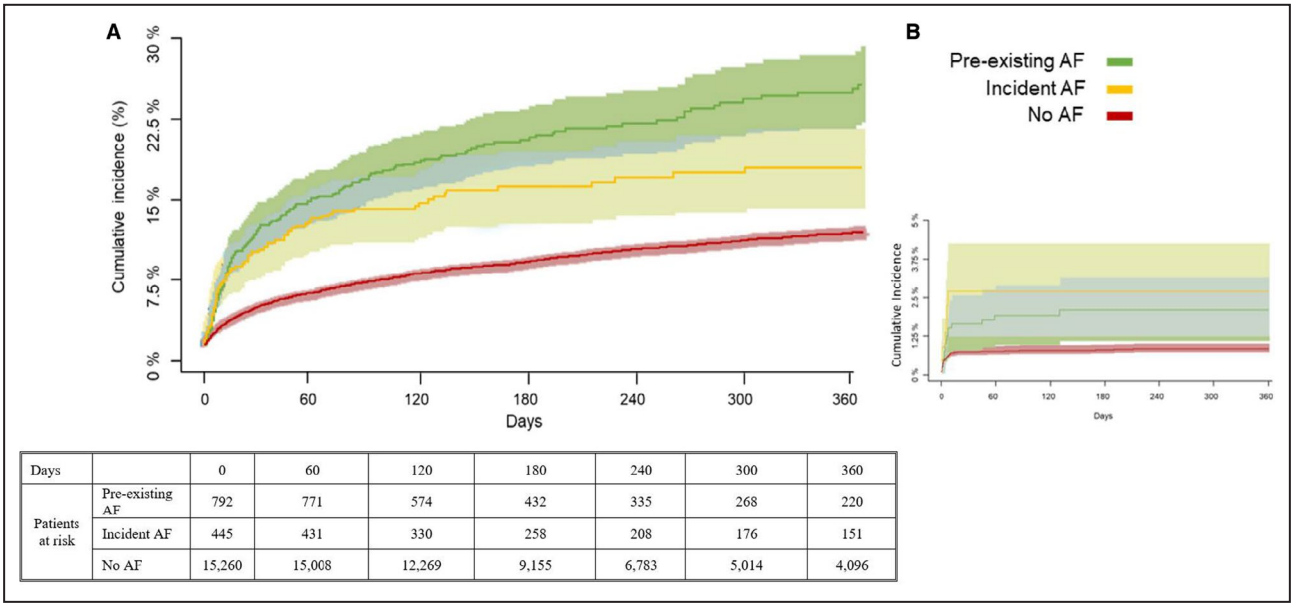



**Figure 2. Ninety-day clinical outcomes based on presence of preexisting or incident AF.**
Patients with no AF were the reference group in all analyses. *Adjusted for age, sex, simplified Pulmonary Embolism Severity Index, and history of diabetes mellitus, heart failure, prior ischemic stroke, and arterial vascular disease (either coronary or peripheral artery disease). AF indicates atrial fibrillation; and PE, pulmonary embolism.

risk of non-PE death (HR, 3.24; 95% CI, 1.80–5.85). Findings persisted after multivariable adjustment (HR, 2.18; 95% CI, 1.18–4.04) (Figure 4B).

Accounting for the competing risk of nonthrombotic death, patients with preexisting AF had a nonsignificant increase in the risk of recurrent VTE (HR, 1.54; 95% CI, 0.96–2.45) and a 5-fold increased risk of stroke (HR, 5.48; 95% CI, 3.10–9.69) (Figure 4C). Patients with preexisting AF had a higher risk of the composite thrombotic outcome compared with those who did not have AF, both in unadjusted analyses (HR, 2.31; 95% CI, 1.63–3.26) as well as in multivariable adjusted analyses (HR, 1.86; 95% CI, 1.29–2.70, Figure 4E).

Among patients with PE and incident AF, the composite thrombotic outcome was rare at 1-year follow up, with only 6 thrombotic events, including 5 recurrent nonfatal VTEs but no ischemic strokes. As such, in models accounting for nonthrombotic death as the competing risk, patients with incident AF—compared with patients without AF—did not have an increased risk for recurrent VTE (HR, 0.68; 95% CI, 0.27–1.65) or the composite thrombotic outcome (HR, 0.61; 95%




| Days | | 0 | 60 | 120 | 180 | 240 | 300 | 360 |
|---|---|---|---|---|---|---|---|---|
| Patients at risk | Pre-existing AF | 792 | 771 | 574 | 432 | 335 | 268 | 220 |
| | Incident AF | 445 | 431 | 330 | 258 | 208 | 176 | 151 |
| | No AF | 15,260 | 15,008 | 12,269 | 9,155 | 6,783 | 5,014 | 4,096 |

**Figure 3. Kaplan Meier curve for all-cause death (A) and competing risk regression (Fine and Grey) for PE-related death (B).**
AF indicates atrial fibrillation; and PE, pulmonary embolism.

CI, 0.27–1.38) (Figure 4E). Given the paucity of events, multivariable analysis was not performed.

### *Bleeding*

Patients with preexisting AF had increased 1-year risk of major bleeding in unadjusted analyses compared with those without AF (Fine-Gray HR, 1.60; 95% CI, 1.13–2.27), but the findings were no longer significant after multivariable adjustment (HR, 1.16; 95% CI, 0.79–1.67).

Compared with patients without AF, patients with incident AF had increased unadjusted 1-year risk of major bleeding accounting for the competing risk of nonhemorrhagic death (HR, 1.65; 95% CI, 1.05–2.58). The results were no longer significant after multivariable adjustment.

## Sensitivity Analysis

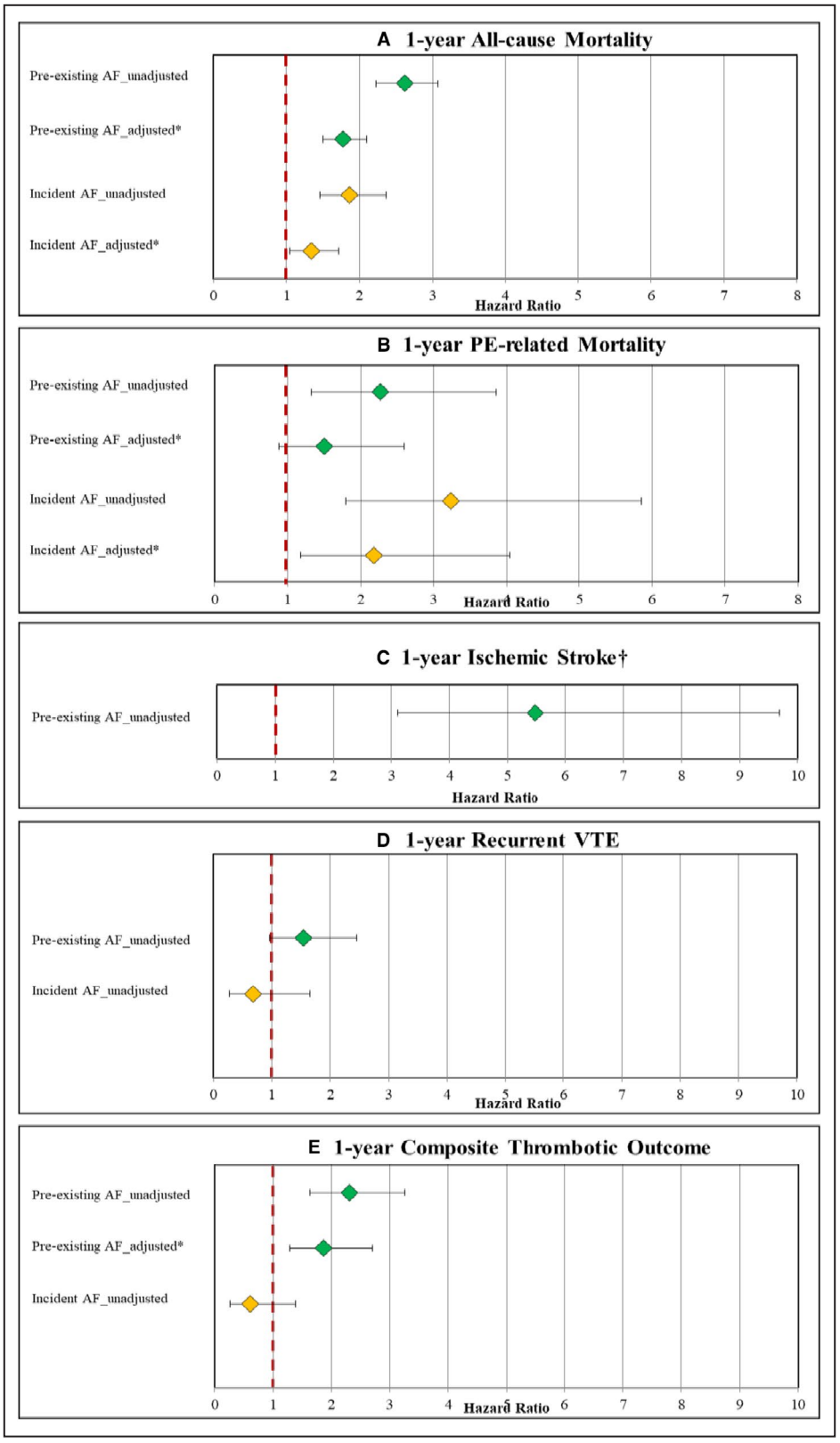
Owing to clinicians' discretionary decisions for hospital discharge, in-hospital outcomes were not prespecified for the main analyses. Sensitivity analyses showed that in-hospital outcomes were broadly similar to 30-day results (data not shown).

# DISCUSSION

Among patients with acute symptomatic PE, both preexisting and newly incident AF were associated with greater frequency of cardiovascular risk factors, and higher $CHA_2DS_2VASC$ and sPESI scores, compared with patients without AF. Both forms of AF were associated with adverse outcomes, including all-cause mortality, although the pattern of risk had distinct features based on the timing of AF onset. Preexisting AF was associated with increased risk of subsequent thrombotic events, including stroke, but not a significantly increased risk for PE-related mortality, once adjusted for sPESI and comorbid conditions. In contrast, incident AF was associated with increased risk of PE-related mortality but not with long-term risk of stroke or the composite thrombosis end point. Although some findings were partially attributable to underlying risk factors, others persisted even in multivariable adjusted analyses.

Findings from this study add novel information to complement prior studies about concomitant AF in patients with PE. The proportion of patients with preexisting AF and incident AF reported in this study are in range with prior reports.[15,19] Some prior studies,[26,27] including a meta-analysis,[28] indicated an increased

**Figure 4. One-year outcomes based on presence of preexisting or incident AF.**
Patients with no AF were the reference group in all analyses. **(A)** all-cause mortality (**(B)**) PE-related mortality, **(C)** ischemic stroke, **(D)** recurrent VTE **(E)** composite thrombotic outcome. In all models other than all-cause mortality, competing risk of death was considered; see text for details. In models where the number of events were very few, multivariable adjustment was not pursued. *Adjusted for age, sex, simplified Pulmonary Embolism Severity Index, and history of diabetes mellitus, heart failure, prior ischemic stroke, and arterial vascular disease (either coronary or peripheral artery disease). †No patient with incident AF developed ischemic stroke during follow-up. AF indicates atrial fibrillation; PE, pulmonary embolism; and VTE, venous thromboembolism.




risk for shock and mortality in patients with PE who had coexisting AF, whereas others did not show a significant association.[19,29] Our investigation, based on a large patient population showed a clinically meaningful and statistically significant association between AF and clinical outcomes. Further, we were able to conduct multivariable analyses, without concern for small number of events.

We noted an increased risk of mortality and thrombotic events in patients with preexisting AF. In this sense, preexisting AF may be a thrombosis risk factor or an indicator of poor cardiopulmonary reserve, which increases the risk of death. The sPESI was higher in patients with preexisting AF compared with patients without AF. However, the association between preexisting AF and PE-related mortality was no longer significant after adjustment for sPESI and other comorbidities.

In turn, newly incident AF may have been triggered by catecholamines or serotonin release in the setting of acute PE or comorbidities such as thyrotoxicosis.[15,19] Worse outcomes in patients with PE and incident AF may be attributable to comorbidities, or the acute effect of AF on right ventricular preload,[15] as suggested by higher relative frequency of syncope and hypotension in these patients. The association between incident AF and PE-related mortality attenuated but persisted, even after adjustment for sPESI and other clinical factors. Among survivors of acute PE, we did not identify an increased risk of stroke in patients with PE and incident AF. We hypothesize that in many such patients AF may have resolved after stabilization of acute PE. In others, thrombotic risk may have been mitigated by anticoagulant therapy.[15]

Excess bleeding in patients with preexisting AF, or those with incident AF, compared with patients without AF, is a clinical challenge. This excess risk is likely attributable to comorbidities that increase the risk of not only thrombosis but also bleeding.[30] More intensive antithrombotic therapy (eg, combination of anticoagulants and antiplatelet agents) may aggravate this risk. For example, in post hoc assessment, we noted that a larger proportion of patients with preexisting AF were receiving aspirin at baseline, compared with patients with AF (35.7% versus 18.9%). Therefore, the search continues for antithrombotic regimens that may safely mitigate the residual thrombotic risk.[31]

Findings of this study may have implications for risk stratification and management. To our knowledge, this is the largest investigation to address the presentation and outcomes according to the timing of occurrence of AF. With respect to patients with preexisting AF, subsequent investigations are needed to understand the long-term treatment adherence and to find effective strategies to mitigate the excess thrombotic risk. In addition, dedicated studies are needed to assess whether incorporation of AF (particularly incident AF) can improve clinical risk stratification for patients with acute PE, above and beyond sPESI and markers of right ventricular function. In addition, it should be determined whether acute management strategies, including level of care and use of advanced therapies, need to be modified in patients with acute PE and incident AF.

This study has several limitations. First, RIETE does not include all patients with PE in the enrolling countries. However, it does include consecutive patients in large and small regional and referral centers from 25 countries. Data from RIETE closely correlate with that of large administrative databases.[32] Second, this study was not designed to test to test the comparative effectiveness of a more prolonged or more intensive antithrombotic regimen in patients with PE and coexisting AF. More prolonged use of anticoagulation in each subgroup may indicate regional practices, residual confounding, or mediation effect and is outside the scope of the current study. Rather, our goal was to determine the impact of preexisting versus incident AF as risk markers for patients with acute PE. Of note, we identified an association with outcomes, even in short-term adjusted models, in which most patients received anticoagulation. Third, newly identified AF in a minority of patients may have been, indeed, preexisting but clinically silent and not otherwise perceived by the patient or captured by clinicians before the index PE event. True ascertainment of such cases of silent AF would be possible only with long-term population-based rhythm monitoring, which is cumbersome and outside the scope of this study. Lack of any ischemic stroke events during short-term and 1-year follow-up support the hypotheses that the vast majority of newly identified AF events were, incident AF rather than preexisting silent AF (which has a noticeable risk for stroke).[33] Fourth, although we present the results in unadjusted and multivariable adjusted analyses that account for several of the comorbidities and markers of disease severity, we cannot exclude the possibility of residual confounding. Fifth, although RIETE is the largest ongoing VTE registry in the world, we cannot exclude the possibility of type II error because no *a priori* power calculation was performed. Finally, we are unable to verify the termination or persistence of AF among patients with PE and incident AF during long-term follow-up. This issue deservers further investigation.

## CONCLUSIONS

In conclusion, AF is a relatively common and clinically relevant coexisting condition in patients with acute symptomatic PE. Both preexisting AF and incident AF predict an adverse clinical course. The type of adverse outcomes may differ, depending on the timing of AF onset. The clinical challenge will be to identify optimal strategies to mitigate the long-term adverse outcomes in patients with PE and preexisting AF. In addition, future research may lead to more sophisticated risk stratification algorithms that incorporate the presence of incident AF.

## APPENDIX

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Author contributions: Study design: Bikdeli, Jiménez, Piazza, Lip, Goldhaber, Monreal; Data acquisition: Jiménez, Monreal; Statistical analyses: Muriel, Jiménez, Bikdeli, Monreal; Critical revision of the article: all authors. Drs Bikdeli, Jimenez, and Monreal take responsibility for the integrity of the work as a whole, from inception to published article.

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## Disclosures

Dr Bikdeli reports that he is a consulting expert, on behalf of the plaintiff, for litigation related to 2 specific brand models of inferior vena cava filters. Dr Jimenez 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; and received grants for clinical research from Daiichi Sankyo, Sanofi, and ROVI. Dr Piazza has received significant research grant support from BTG International, Bristol Myers Squibb, Daiichi-Sankyo, Bayer, Portola, and Janssen and modest consulting fees from Pfizer and Thrombolex. Dr Lip reports that he is a consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo and a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally. Dr Goldhaber reports grants from Bayer, Boehringer-Ingelheim, BMS, BTG EKOS, Daiichi Sankyo, Janssen, US National Heart Lung and Blood Institute, and Thrombosis Research Institute; and personal fees from Bayer and Boehringer-Ingelheim, outside the submitted work. Dr Monreal has served as an advisor or consultant for Sanofi, Leo Pharma, and Daiichi-Sankyo and has received a nonrestricted educational grant by Sanofi and Bayer to sponsor the RIETE registry.

## Supplementary Material

Table S1

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# SUPPLEMENTAL MATERIAL

**Table S1. ESC Classification Risk Among the Study Participants***

| | Known Pre-existing AF | Incident AF (diagnosed within 2 days after PE) | No AF at all |
|---|---|---|---|
| Number of patients (total N=16,497) | N=792 | N=445 | N=15,260 |
| Low Risk | 102 (12.9%) | 64 (14.4%) | 6,030 (39.5%) |
| Intermediate-low risk PE | 639 (80.7%) | 322 (72.4 %) | 8093 (53.0 %) |
| Intermediate-high risk PE | 22 (2.7 %) | 25 (5.6 %) | 681 (4.4 %) |
| High Risk | 2 (3.7%) | 34 (7.4%) | 458 (3.0%) |

* Cardiac biomarkers (or echocardiographic features of right ventricular dysfunction) are available in many RIETE participants, but are not mandatory fields in RIETE, with missing values in some participants. AF: Atrial fibrillation, ESC: European Society of cardiology, PE: pulmonary embolism.