Extended Anticoagulation After Pulmonary Embolism

A Multicenter Observational Cohort Analysis

Chopard, Romain; Albertsen, Ida Ehlers; Ecarnot, Fiona; Guth, Sebastien; Besutti, Matthieu; Falvo, Nicolas; Piazza, Gregory; Meneveau, Nicolas

Published in:
Journal of the American Heart Association

DOI (link to publication from Publisher):
10.1161/JAHA.121.024425

Publication date:
2022

Document Version
Publisher's PDF, also known as Version of record

Journal of the American Heart Association

ORIGINAL RESEARCH

Extended Anticoagulation After Pulmonary Embolism: A Multicenter Observational Cohort Analysis

Romain Chopard, MD, PhD; Ida Ehlers Albertsen, MD, PhD; Fiona Ecarnot, PhD; Sebastien Guth, MD; Matthieu Besutti, MD; Nicolas Falvo, MD; Gregory Piazza, MD, MS*; Nicolas Meneveau, MD, PhD*

BACKGROUND: Pulmonary embolism (PE) has a long-term risk of adverse events, which can be prevented by extended anticoagulation. We compared clinical characteristics and outcomes between patients treated with 2-year extended anticoagulation and those who were not, in a population who had completed an initial phase of 3 to 6 months of anticoagulant therapy after acute PE.

METHODS AND RESULTS: Observational cohort analysis of patients with PE who survived an initial phase of 3 to 6 months anticoagulation. Primary efficacy outcome was all-cause death or recurrent venous thromboembolism. Primary safety outcome was major bleeding. In total, 858 (71.5%) patients were treated with and 341 (28.5%) were treated without extended anticoagulant therapy during the active study period. Age <65 years, intermediate-high or high-risk index PE, normal platelet count, and the absence of concomitant antiplatelet treatment were independently associated with the prescription of extended anticoagulation. The mean duration of the active phase was 2.1±0.3 years. The adjusted rate of the primary efficacy outcome was 2.1% in the extended group and 7.7% in the nonextended group (P<0.001) for patients treated with extended anticoagulant therapy. Rate of bleeding were similar between the extended anticoagulant group and the nonextended group.

CONCLUSIONS: Extended oral anticoagulation over 2 and a half years after index PE seems to provide a net clinical benefit compared with no anticoagulation in patients with PE selected to receive extended anticoagulation. Randomized clinical trials are warranted to explore the potential benefit of extended anticoagulation in patients with PE, especially those with transient provoking factors but residual risk.

Key Words: extended anticoagulation ■ outcomes ■ pulmonary embolism

Pulmonary embolism (PE) is becoming increasingly recognized as an important source of acute and chronic morbidity and mortality.[1] Patients with incident PE carry a long-lasting risk of recurrence, associated with long-term complications.[1,2] Patients with PE may develop chronic conditions including thromboembolic pulmonary hypertension, post-thrombotic syndrome if associated with deep vein thrombosis, post-PE syndrome, which impairs long-term clinical functional status, and acute arterial thrombotic events.[3–6]

Anticoagulation is the mainstay of PE treatment both in the in-hospital treatment phase and after hospital discharge. The purpose of anticoagulant therapy is initially to prevent extension of thrombus, but also to prevent recurrence of venous thromboembolism (VTE), and death.[7] Following the acute treatment period of a minimum of 3 months,[8,9] the aim of extended secondary anticoagulation is to prevent VTE recurrence over the long term. Overall, all direct oral anticoagulants (DOACs) effectively reduce recurrent VTE

Correspondence to: Romain Chopard, MD, PhD, Department of Cardiology, University Hospital Jean Minjoz, 3 Boulevard Fleming, 25000 Besancon, France. Email: chopardromain@yahoo.fr

*G. Piazza and N. Meneveau contributed equally.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.024425

For Sources of Funding and Disclosures, see page 11.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Extended oral anticoagulation over 2 and a half years after index pulmonary embolism provides a net clinical benefit compared with no anticoagulation in patients with pulmonary embolism selected to receive extended anticoagulation.

What Are the Clinical Implications?

- Our results seem to suggest that in patients with index pulmonary embolism who do not have an excess risk of bleeding, extended oral anticoagulation may be prescribed up to 2 years and beyond, regardless of the patient characteristics and clinical context.

Nonstandard Abbreviations and Acronyms

CRNMB	clinically relevant nonmajor bleeding
DOAC	direct oral anticoagulant
VKA	vitamin K antagonist

by about 80% to 90%, with a persisting 2.0% to 6.0% risk for clinically relevant nonmajor bleeding (CRNMB) in randomized clinical trials (RCTs).[10–14] The latest evidence-based guidelines recommend that extended oral anticoagulation of indefinite duration should be considered for patients with PE with no identifiable risk factors or with a minor transient or reversible risk factor.[9,15,16] Nevertheless, long-term follow-up data from unselected populations in daily clinical practice are needed to provide insights into the impact of extended anticoagulation after PE.[17]

Using data from a French multicenter prospective nonrandomized registry, we report a comparison of clinical characteristics and outcomes between patients treated with 2-year extended anticoagulation and those who were not, in a population who had completed 3 to 6 months of anticoagulant therapy after acute PE.

METHODS

Study Design

This is an analysis of a prospectively collected, nonrandomized, observational cohort recorded in the Burgundy Franche-Comté-France registry from January 2012 to December 2015.[18] The registry received approval from the national commission for data privacy and protection. This study was conducted in accordance with the amended Declaration of Helsinki. Our institutional review board approved the study. All patients provided written or oral consent for participation in the registry. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patient Selection

Patients were eligible for inclusion in the analysis if they were aged ≥18 years; if they had objectively confirmed, symptomatic PE (with or without deep vein thrombosis)[19,20]; and if they had survived an initial phase of 3 to 6 months of anticoagulant therapy (ie, initial phase).

Patients with a contraindication to anticoagulation who required implantation of inferior vena cava filter within 3 to 6 months after the index PE were excluded from the present analysis. Patients with a non-VTE related life-long indication for anticoagulation (eg, atrial fibrillation, mechanical heart valve, severe thrombophilia) were also excluded. Management was at the discretion of the physician-in-charge and was in accordance with the guidelines available at the time of the study.[21,22]

Data Collection

Research physicians (not involved in the care of the patients included) prospectively entered data into a dedicated database for deidentification of personal information and for data validation. Research physicians were also asked to ensure that recruitment was consecutive. Patients returned to the participating centers at 3 to 6 months (after the initial phase), and at least yearly after the index PE for a follow-up visit to record clinical status, anticoagulation treatments and outcomes. If the patients did not attend the hospital visit, physicians followed the sequential procedure hereafter: telephone interview with the patient (or family), consulted the hospitalization records, contacted the patient's general practitioner, and consulted the national death registry.

Study Outcomes and Definitions

Outcomes used were those recommended in regulatory guidelines for studies of extended treatment for VTE diseases.[23] The primary efficacy outcome was a composite of death from any cause or recurrent VTE. Secondary efficacy outcomes included: recurrent VTE or VTE-related death; non-VTE-related cardiovascular death, myocardial infarction, or stroke; and recurrent VTE, VTE-related death, myocardial infarction, stroke, or cardiovascular disease-related death. The primary safety outcome was major bleeding.[24] Secondary safety outcomes included CRNMB; major or CRNMB; and a composite of VTE, VTE-related death, myocardial infarction, stroke, cardiovascular death, or major bleeding. All suspected outcome events were classified by a central

adjudication committee (S. G. and R. C.). Disagreement was resolved by a third author (N.M.). The criteria for the diagnosis and adjudication of all outcomes and their components are described in Data S1.[24–26] Risk factors for PE were categorized as transient or reversible, persistent provoked, and no identifiable risk factor or unprovoked PE.[9,15,16,27] Associated cancer was defined as active or anti-tumor therapy within the last 6 months, or metastatic state.[28] Transient or reversible VTE factors included recent surgery (within 90 days), recent trauma (within 90 days), immobilization (3 days or more), recent hospitalization (within 90 days), pregnancy, postpartum, any infection within 30 days, exacerbation of inflammatory disease, oral contraceptive use, or hormone replacement therapy.[29] Persistent risk factors included active cancer, inflammatory disease, and antiphospholipid antibody syndrome. Unprovoked PE included factors which did not meet criteria for transient or persistent provoking factor.[9,15,16,27]

We also classified patients according to VTE-BLEED for subgroup analyses. The VTE-BLEED score includes active cancer (ie, cancer diagnosed within 6 months before diagnosis of VTE) (excluding basal-cell or squamous-cell carcinoma or any cancer that required anti-cancer treatment within 6 months before the VTE was diagnosed) (+2 points); male with uncontrolled hypertension (ie, defined by values of systolic blood pressure ≥140 mm Hg at baseline) (+1 point); anemia (ie, hemoglobin <13 g/dL in men or <12 g/dL in women) (+1.5 points); history of bleeding (ie, including major or nonmajor clinically relevant bleeding event, rectal bleeding, frequent nose bleeding, or hematuria) (+1.5 points); age >60 years (+1.5 points); and renal dysfunction (ie, estimated glomerular filtration rate <60 mL/min estimated with the Cockcroft-Gault formula) (+1.5 points). Patients with a VTE-BLEED score ≥2 were at high risk of bleeding.[30,31]

Statistical Analysis

We report the study methods and results in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines, based on the Recommendations for Statistical Reporting in Cardiovascular Medicine from the American Heart Association.[32,33]

Continuous variables are expressed as mean (SD). Categorical variables are expressed as number (percentage). Unadjusted differences between patients treated or not with extended anticoagulation were compared using the Chi-square test or Student *t*-test as appropriate. To investigate the independent associations of various characteristics with the prescription or nonprescription of extended anticoagulation in PE, we constructed a multivariable modified Poisson regression model.[34]

We compared clinical outcomes between patients treated with extended anticoagulation and those not

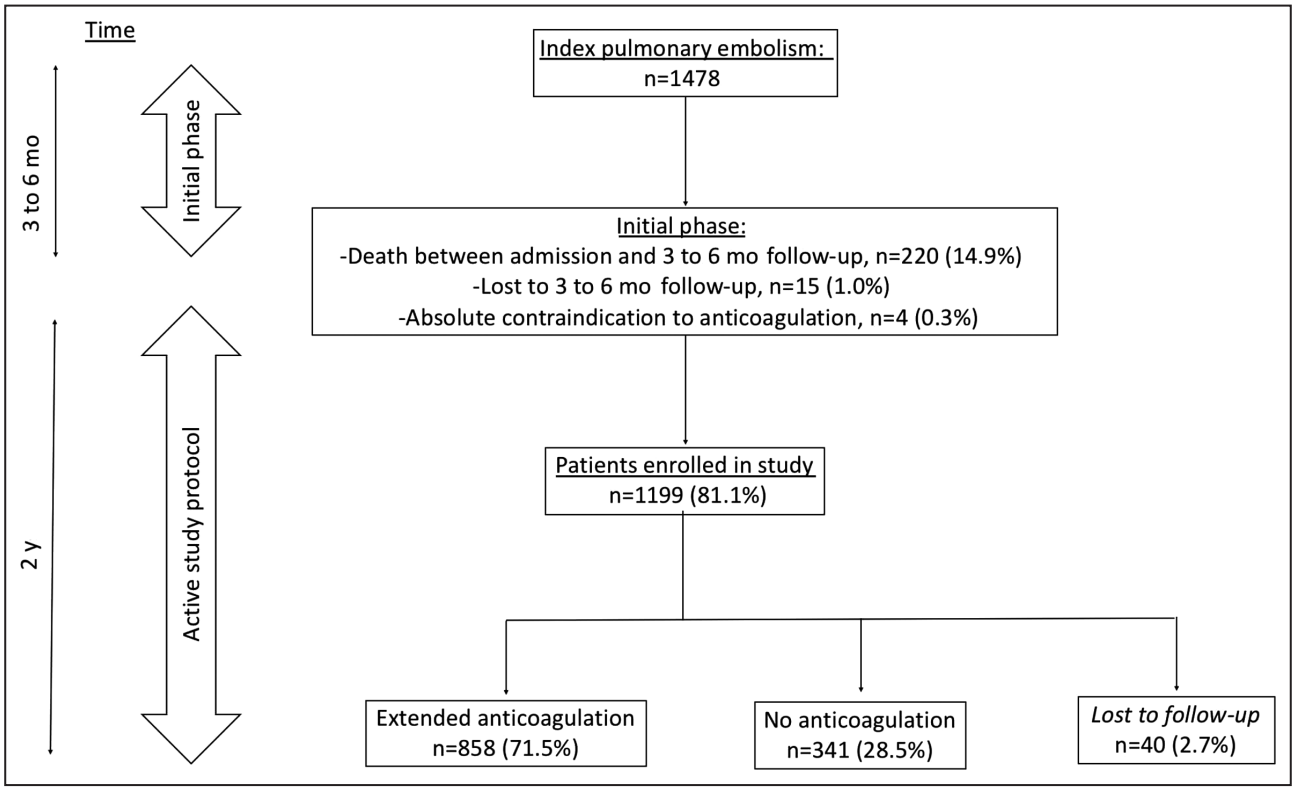


Figure 1. Study flowchart.

treated using multivariable Cox models. Models were adjusted for baseline characteristics, in-hospital and initial phase therapies, as well as clinical outcomes between index PE and 3 to 6 months that yielded a $P<0.10$ by univariable analysis. Results are reported as hazard ratios (HR) with associated 95% CI. A $P<0.05$ was considered significant. The full list of candidate covariates is given in Table S1. The results of the primary efficacy outcome between patients treated with extended anticoagulation and those not treated are displayed by Kaplan–Meier curves. The use of multiple imputation was not required, as the rate of missing data was <2% for all covariates (Table S1).[35]

To assess the robustness of the findings, we performed multiple sensitivity analyses for primary efficacy and safety outcomes across relevant subgroups[23] (including sex, age, weight, high bleeding risk according to the VTE-BLEED score [ie, ≥2], prior VTE, risk factors, cancer, and renal function impairment) with the use of Breslow-Day tests. We compared rates of primary outcomes between patients treated with DOAC, vitamin K antagonist (VKA) and those who did not receive any extended anticoagulation. Finally, we performed multiple subgroup analyses across unprovoked, prior VTE, and cancer-associated PE patients based on patients' bleeding-risk (ie, high versus low bleeding-risk). We used the family-wise error rate to control the overall false-positive rate for these comparisons by applying Bonferroni correction,[36] and we used the unadjusted time-dependent Log-rank test to compare outcomes.

All statistical analyses were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC).

Table 1. Baseline Characteristics and In-Hospital Management Outcomes Between Patients With Pulmonary Embolism Treated With and Without Extended Anticoagulant Therapy During the Active Study Period (n=1199)

	All study patients (n=1199)	Extended anticoagulation (n=858)	No anticoagulant therapy (n=341)	*P* value
Age, y	66.5±17.2	64.4±18.4	67.3±16.7	0.0.1
Female sex (%)	610 (50.1)	453 (52.8)	157 (46.0)	0.03
Weight, kg	78.9±16.9	78.4±18.6	80.2±18.8	0.13
ESC-defined risk stratification of index PE (%)				<0.001
Low-risk	253 (21.1)	165 (19.2)	88 (25.8)	
Intermediate-low risk	649 (54.1)	458 (53.4)	191 (56.0)	
Intermediate-high risk	247 (20.6)	201 (23.4)	46 (13.5)	
High-risk	50 (4.2)	34 (4.0)	16 (4.7)	
Comorbidities (%)				
Chronic pulmonary disease	105 (8.8)	75 (8.7)	30 (8.8)	0.97
Cancer	177 (14.8)	116 (31.5)	61 (17.9)	0.054
Prior VTE	306 (25.5)	270 (88.2)	36 (11.8)	<0.001
Transient or reversible risk factor	284 (23.7)	186 (21.7)	98 (28.7)	0. 009
Persistent risk factor	210 (17.5)	146 (17.0)	64 (18.8)	0.47
No identifiable risk factor (unprovoked PE)	705 (58.8)	526 (61.3)	179 (52.5)	0.005
Associated DVT	494 (41.2)	370 (43.1)	124 (36.4)	0.03
Biological data at inclusion				
Hemoglobin, g/dL	13.5±3.5	13.6±4.0	13.3±1.9	0.07
Platelet count, $\times 10^3/\mu L$	247.6±98.5	246.9±98.9	249.4±97.4	0.70
$eGRF_{MDRD}$, mmol/L	79.8±28.9	76.9±28.2	81.2±30.8	0.30
Concomitant antiplatelet therapy at inclusion (%)	75 (6.3)	30 (3.5)	45 (13.2)	<0.001
VTE BLEED score ≥2	919 (76.5)	671 (78.2)	248 (72.7)	0.12
Adverse outcomes between index PE and 3–6 mo follow-up (%)				
Any bleeding	90 (7.5)	58 (6.8)	32 (9.4)	0.11
Major bleeding	57 (4.7)	36 (4.2)	21 (6.2)	0.14
Acute heart failure	23 (1.9)	18 (2.1)	5 (1.5)	0.47
Acute myocardial infarction	8 (0.7)	7 (0.8)	1 (0.3)	0.31
Stroke	5 (0.4)	4 (0.5)	1 (0.3)	0.67

The statistics are shown as mean±SD or n (%). *P* values are for comparison between extended anticoagulation vs no anticoagulation groups. DVT indicates deep vein thrombosis; $eGRF_{MDRD}$, estimated glomerular function calculated with the Modification of Diet in Renal Disease equation; ESC, The European Society of Cardiology; and VTE, venous thromboembolism.

RESULTS

Study Population

A total of 1478 patients were admitted to the participating centers with a diagnosis of objectively confirmed PE between January 2012 and December 2015. The mean duration of the initial treatment phase was 3.8±0.7 months. Overall, 220 patients (14.9%) died during the initial phase, 4 patients (0.3%) suffered major bleeding that required implantation of an inferior vena cava filter with an absolute contraindication to pursuit of initial anticoagulation, and 15 patients (1.0%) were lost to follow-up. Among the remaining 1239 patients, 1199 patients (96.8%) had complete follow-up at 2 years after the 3- to 6-month initial phase and comprise the active study population (mean age, 66.5±17.2; 610 (50.1%) women) (Figure 1).

Patient Characteristics

In total, 858 (71.5%) patients were treated with and 341 (28.5%) were treated without extended anticoagulant therapy during the active study period after the initial phase of 3 to 6 months. Patients who were treated with extended anticoagulation received DOAC (n=637; 74.2%) or VKA (n=221; 25.8%) (Figure S1). A transient or reversible VTE risk factor was identified in 23.7% of patients, a persistent risk factor in 17.5%, and no identifiable risk factor was found in 58.8% (Table 1). Overall, patients with PE who received extended anticoagulation were younger, were more frequently women, and more frequently had PE with associated cancer and deep vein thrombosis, and more severe index PE. Patients with PE who received extended anticoagulation were less frequently treated with antiplatelet therapy. Rates of adverse events during the initial phase did not differ between 2 groups. The VTE BLEED score was similar between groups (Table 1). In total, 22.6% patients with a clear indication for extended anticoagulation as stipulated by the guidelines, including cancer (34.4%) and unprovoked PE (23.4%), did not receive anticoagulant therapy. At the end of the initial phase, 33.7% of patients with PE who had transient or reversible factors did not receive extended anticoagulation (Table 1). VTE-BLEED-defined high bleeding risk was not associated with the nonprescription of extended anticoagulation (OR, 0.90; 95% CI, 0.69–1.18).

Age <65 years, intermediate-high, or high-risk index PE, normal platelet count (ie, >150×10^3/μL), and the absence of concomitant antiplatelet treatment were independently associated with the prescription of extended anticoagulation (Figure 2).

Outcomes

The mean duration of study follow-up was 2.1±0.3 years after the initial phase of 3 to 6 months. During the study period, we observed 143 all-cause deaths (11.9%), as

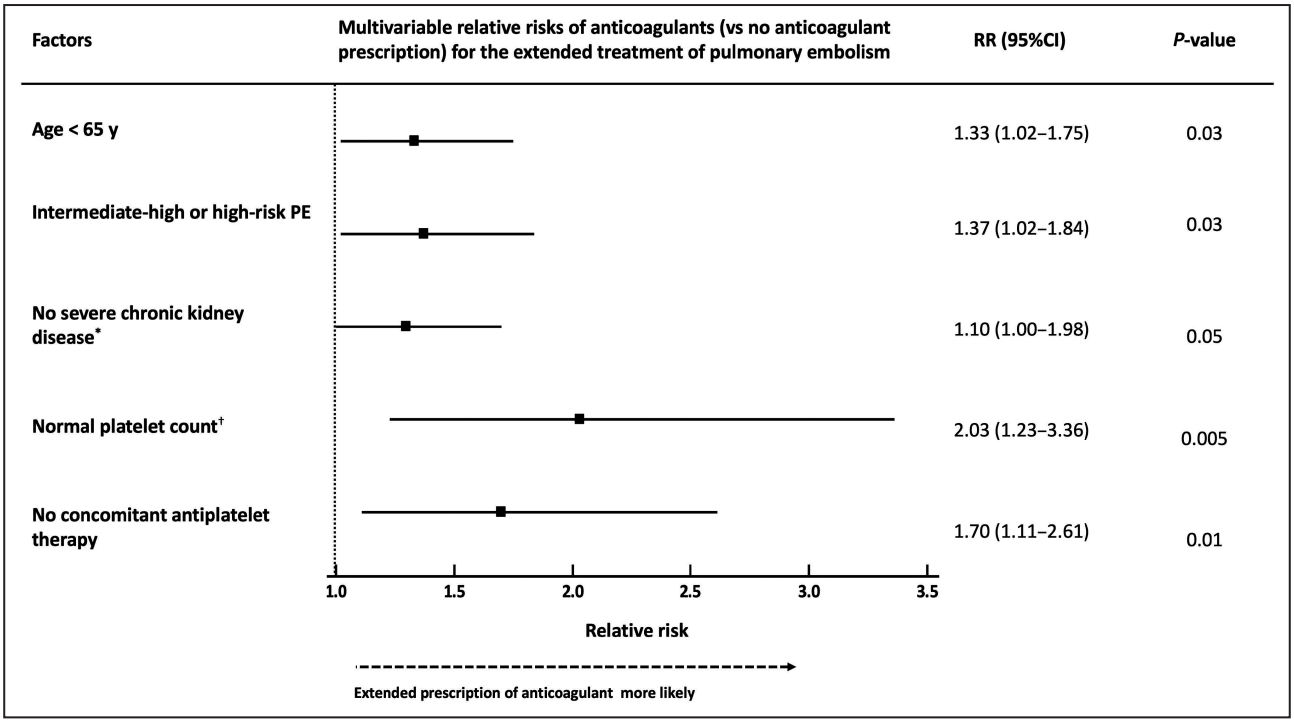


Figure 2. Factors independently associated with anticoagulant prescription vs nonprescription for the extended treatment of pulmonary embolism.

*Estimated glomerular function rate >30 mL/min; †platelet count >150×10^3/μL. PE indicates pulmonary embolism; and RR, relative risk.

well as 74 recurrent VTE (6.2%), 10 myocardial infarctions (0.8%), 19 strokes (1.6%), 24 major bleeding (2.0%), and 20 CRNMB (2.5%) (Tables S2 and S3). The absolute rate of the primary outcome was 9.1% in the group of patients who received extended anticoagulation and 34.0% in the group who did not (*P* Log-rank test <0.001) (Figure 3). Table S4 displays covariates associated with the occurrence of the primary end point of all-cause death or recurrent VTE in univariable and multivariable analyses. The adjusted rate of all-cause death or recurrent VTE was 2.1% (95% CI, 1.2–3.5) in the extended group and 7.7% (95% CI, 4.8–12.1) in the nonextended group, yielding a hazard ratio of 0.23 (95% CI, 0.17–0.31; *P*<0.001) (Figure 3). The adjusted rates of all-cause mortality and recurrent VTE were 3.7% (95% CI, 2.1–6.5) and 0.07% (95% CI, 0.02–0.23), respectively, in the extended anticoagulation group, and 8.0% (95% CI, 4.5–14.2) and 1.0% (95% CI, 0.4–2.3) in the nonextended group (*P*<0.001, and *P*<0.001, respectively). Unadjusted rates of the composite outcome of all-cause death or recurrent VTE were lower regardless of the drug (ie, DOAC or VKA) or DOAC dose used, compared with those observed in the nonextended group (Figure S2).

Adjusted rates of major or CRNMB were similar between the extended anticoagulant group and the no-anticoagulant group (5.1% versus 5.0%, and 4.6% versus 3.0%, respectively) (Table 2). Unadjusted rates of the major bleeding were lower whatever the drug (ie, DOAC or VKA) or DOAC dose used, compared with those observed in the no-anticoagulant group (Figure S2).

Sensitivity Analyses

We consistently observed a lower rate of the composite end point of all-cause death or recurrent VTE (Figure 4) and similar rates of major bleeding (Figure 5) with extended anticoagulant therapy in all relevant subgroups. Results were unchanged, regardless of whether VKA or DOAC were prescribed for extended anticoagulant therapy (Figures 5 and 6). The unadjusted impact of extended anticoagulant therapy on the primary efficacy and safety outcomes was constant in patients with unprovoked PE, prior VTE, and associated cancer, whatever their bleeding risk (Figure S3 and Table S5).

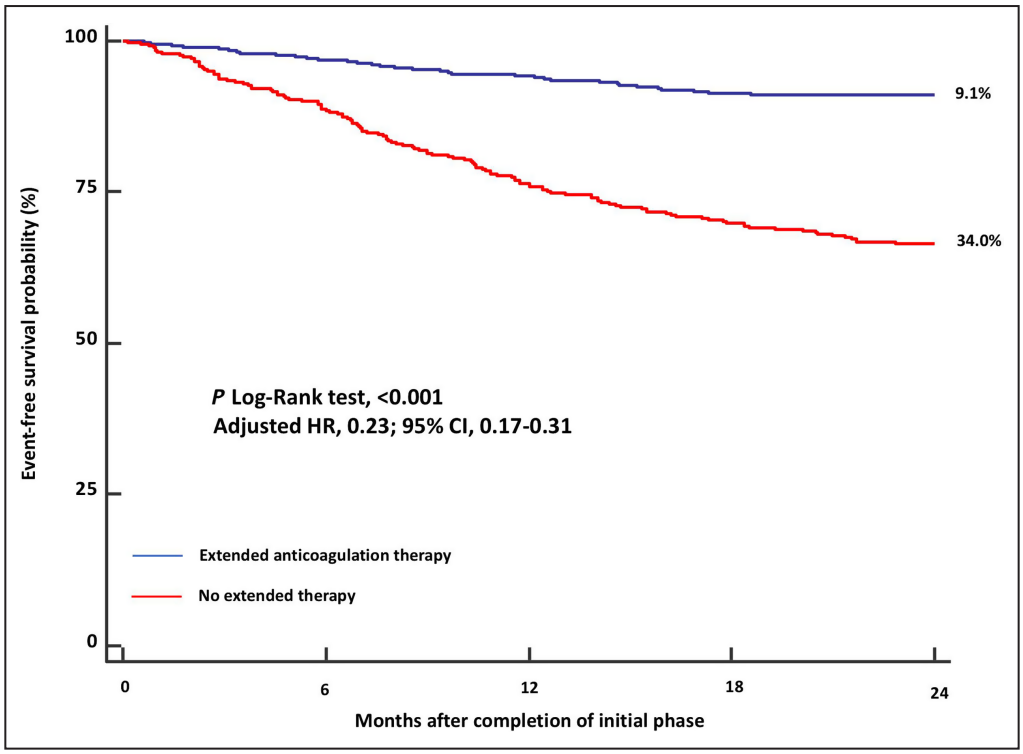


Figure 3. Kaplan–Meier curves for the composite end point, all-cause death, or recurrent venous thromboembolism, between patients treated with vs without extended anticoagulation.
The primary efficacy rates between patients treated with extended vs without extended anticoagulation were adjusted for age (per 10 years), weight <60 kg, prior arterial hypertension, prior coronary artery disease, chronic lung disease, active cancer, systolic blood pressure <100 mm Hg at admission, anemia at admission (ie, hemoglobin <12 g/dL), thrombocythemia at admission (ie, platelet count <150×10^3/μL), renal dysfunction at admission (ie, estimated glomerular function calculated with the Modification of Diet in Renal Disease equation <60 mL/min), and major bleeding events between index pulmonary embolism and 3 to 6 months (ie, initial phase) (see Table S4). HR indicates hazard ratio.

Table 2. Clinical Outcomes Between Patients With Pulmonary Embolism Treated With and Without Extended Anticoagulant Therapy During the Active Study Period (n=1199)

Outcomes	Adjusted rates (%, 95% CI)*		Hazard ratio (95% CI)	*P* value
	Extended anticoagulation (n=858)	No anticoagulation (n=341)		
Efficacy outcomes				
Recurrent VTE or death from any cause—primary efficacy outcome	2.1% (95% CI, 1.2–3.5)	7.7% (95% CI, 4.8–12.1)	0.23 (0.17–0.31)	<0.001
Recurrent VTE or VTE-related death	0.3% (95% CI, 0.1–0.7)	2.0% (95% CI, 0.9–4.3)	0.12 (0.07–0.21)	<0.001
Non-VTE–related cardiovascular death, myocardial infarction, or stroke	2.1% (95% CI, 1.2–3.5)	8.4% (95% CI, 4.9–14.4)	0.40 (0.29–0.56)	<0.001
Recurrent VTE, VTE-related death, myocardial infarction, stroke, or cardiovascular disease-related death	5.0% (95% CI, 2.5–7.2)	16.8% (95% CI, 8.9–23.0)	0.47 (0.29–0.56)	<0.001
Safety outcomes				
Major bleeding—primary safety outcome	5.1% (95% CI, 2.1–11.9)	5.0% (95% CI, 1.6–13.9)	1.0 (0.57–1.76)	0.98
Clinically relevant nonmajor bleeding	4.6% (95% CI, 1.2–16.8)	3.0% (95% CI, 0.4–15.5)	1.65 (0.67–4.07)	0.27
Major or clinically relevant nonmajor bleeding	5.3% (95% CI, 2.1–13.2)	4.6% (95% CI, 1.4–14.3)	1.14 (0.61–2.11)	0.67
VTE, VTE-related death, myocardial infarction, stroke, cardiovascular death, or major bleeding	2.2% (95% CI, 1.0–4.5)	10.3% (95% CI, 5.5–19.1)	0.45 (0.30–0.69)	<0.001

VTE indicates venous thromboembolism.
*Rates of outcomes were adjusted with covariates that yielded a $P<0.10$ by univariable analysis (see Table 1 and Table S4).

DISCUSSION

Our analysis suggests that extended oral anticoagulation over 2 and a half years after index PE, whether by VKA or DOAC, provides a net clinical benefit compared with no anticoagulation in patients selected by providers to receive extended anticoagulation, likely based on their bleeding risk profile, including factors such as age, renal function, presence of thrombocytopenia or antiplatelet therapy. We observed lower rates of death and recurrent VTE, and an associated similar rate of bleeding in the group of patients treated with long-term anticoagulant therapy. Results were consistent across the high-thrombotic-risk subgroup (ie, cancer, unprovoked PE, and prior history of VTE) as well as in populations at risk of bleeding (ie, women, elderly patients, renal function impairment, low body weight, and VTE-BLEED score defined high bleeding risk patients). These findings underscore the crucial role of anticoagulant therapy for extended secondary prevention of PE. They provide additional evidence that may help to clarify the persisting zones of uncertainty in evidence-based guidelines for the long-term management of PE.[9,15,16]

Existing guidelines were principally derived from 5 RCTs that included selected patients with strict inclusion and exclusion criteria, which may not entirely reflect the risks and benefits of anticoagulation in the less controlled setting of everyday clinical practice.[10–14] It was reported that almost one quarter of patients with VTE have at least 1 exclusion criterion, making them ineligible for RCTs.[37] Moreover, most available RCTs had only an additional 6 or 12 months treatment/placebo duration in patients who had completed initial therapy for VTE.[10–14] The RE-MEDY/active-control study (Secondary Prevention of Venous Thrombo Embolism [VTE]) was the sole trial that randomized patients to receive dabigatran 150 mg twice daily or warfarin with a follow-up of 36 months.[10]

Similar to our study, other reports have raised the question of extended anticoagulation duration in PE. First, a nationwide cohort study including 74 000 patients suggested that when extending follow-up to 10 years, risk of recurrence of unprovoked and cancer-related VTE was almost the same, with an absolute risk of 20% for both types of VTE. Above all, the absolute risk of recurrence for patients with provoked PE remains non-negligible, >15% at 10 years.[2] Second, in the PADIS-PE trial (Extended Duration of Oral Anticoagulant Therapy After a First Episode of Idiopathic Pulmonary Embolism: a Randomized Controlled Trial), 371 patients with unprovoked PE were initially treated with warfarin for 6 months. After this period, patients were randomized to either an additional 18 months of warfarin treatment or to placebo.[38] During the additional 18-month treatment period, warfarin was associated with higher risk of bleeding compared with placebo (2.2% versus 0.5%; HR, 3.96; 95% CI, 0.44–35.89), but also a lower risk of recurrent VTE (1.7% versus 13.5%; HR, 0.15; 95% CI, 0.05–0.43). However, the benefit of anticoagulation in reducing recurrence abated after anticoagulation was discontinued at 18 months, with a continuous increase in the rate of recurrent VTE in the warfarin group over the subsequent 2-year follow-up

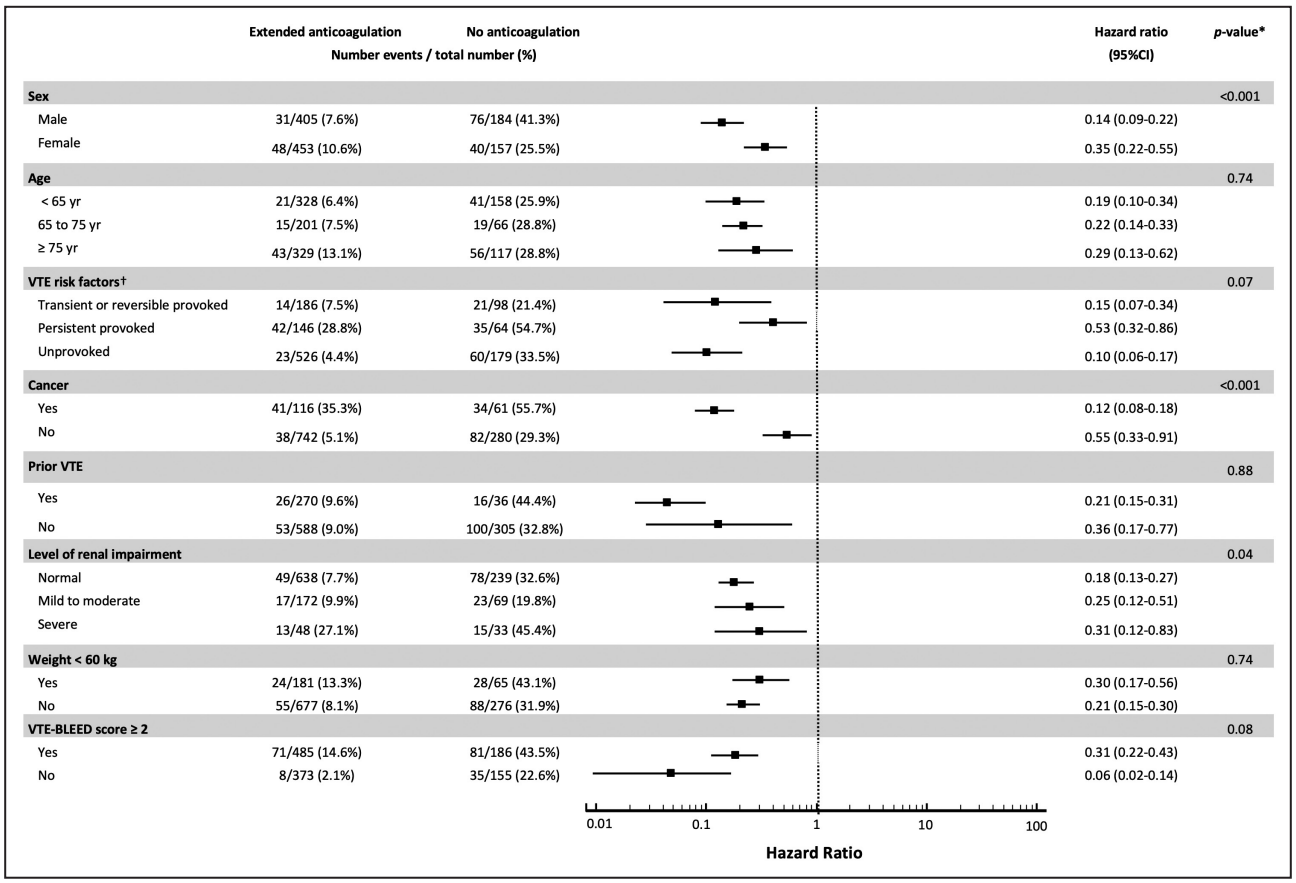


Figure 4. Sensitivity analyses of the composite end point, all-cause death or recurrent venous thromboembolism, across relevant subgroups.
VTE indicates venous thromboembolism. **P* value for interaction; †according to Kearon et al.[27]

period. Accordingly, at 42 months (18 months treatment period plus 24 months follow-up), the risk in the warfarin group resembled the risk of the placebo group (17.9% versus 22.1%; HR, 0.69; 95% CI, 0.42–1.12).

The COMMAND VTE (Contemporary Management and Outcomes in Patients with Venous Thromboembolism) multicenter "real-world" registry evaluated long-term recurrent VTE and bleeding risks between cancer-related, unprovoked, and provoked VTE. In the landmark analysis, the cumulative 3-year incidence of recurrent VTE was lower in patients on anticoagulation than in patients off anticoagulation beyond 1 year in the unprovoked group (on [3.7%] versus off [12.2%], $P<0.001$), but not in the transient risk and cancer groups (respectively, 1.6% versus 2.5%, $P=0.30$; 5.6% versus 8.6%, $P=0.44$).[39] Conversely, in our analysis, we observed a clinical benefit of anticoagulation across all subgroups, including cancer-associated PE. The numerically higher rates of extended anticoagulation among patients with PE with associated transient or reversible factors and cancer observed in our study might explain these differences (33.7% versus 37.3% for PE with transient or reversible factors not receiving extended anticoagulation, and 34.4% versus 43.5% for cancer-associated PE, respectively).

The choice to introduce extended oral anticoagulation should balance the benefits of preventing recurrent VTE against the potential harms of bleeding.[8,9,15,16] In the present analysis, it seems that providers may have chosen not to prescribe extended anticoagulant therapy based on clinical factors known to increase bleeding risk in the stable anticoagulation setting (ie older age, coagulation disturbance with thrombocytopenia, and concomitant anti-platelet treatment).[40–42] In addition to individual decision-making, the VTE-BLEED score has been developed to identify patients with PE at high risk of bleeding under chronic anticoagulation.[41] The VTE BLEED score demonstrated good performances in identifying patients with PE at high-risk of major bleeding in external analyses from randomized and cohort studies (C-index, 0.66 [95% CI, 0.61–0.72], and 0.63 [95% CI, 0.58–0.68], respectively).[30,31] In our analysis, the VTE-BLEED score was not associated with the nonprescription of extended anticoagulation. Individual decision-making may have played a major role in the choice of the long-term strategy. Conversely,

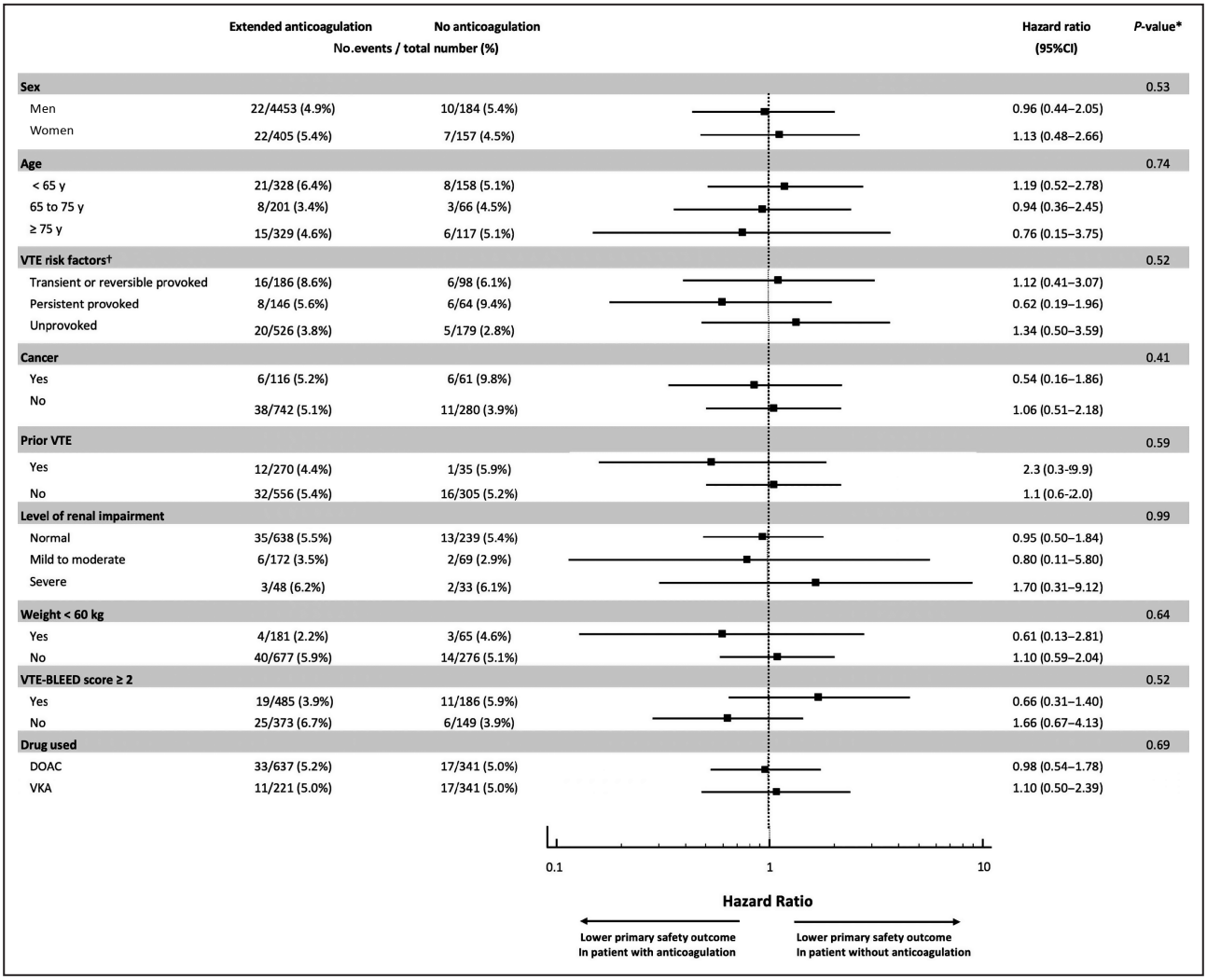


Figure 5. Sensitivity analyses of major bleeding across relevant subgroups.
DOAC indicates direct oral anticoagulation; VKA, vitamin K antagonist; and VTE, venous thromboembolism. **P* value for interaction; †according to Kearon et al.[27]

several prediction models, either during or after anticoagulation, have tried to identify selected patients at high risk of recurrent VTE who might benefit from extended anticoagulation.[2,9,43–47] For instance, a scoring system developed from a nationwide database including 11 519 patients showed good calibration and modest discrimination. Nevertheless, external analyses are lacking to expand the use of these scoring systems in individual patients with PE.[9]

Finally, our results showing the favourable impact of extended anticoagulation were consistent, whichever drug was used (ie, VKA or DOAC). Evidence-based clinical practice guidelines recommend DOACs as the preferred choice for most patients with VTE, except those with severe kidney disease and antiphospholipid syndrome, who may be best treated with VKA.[8,9,48] In a network analysis of 18 221 patients from RCTs, standard-dose VKA and low/standard-dose DOAC shared similar effects on VTE recurrence and major bleeding.[49] In addition, DOACs have a rapid onset of action, more predictable pharmacokinetics, and avoid the need for routine laboratory monitoring and dose adjustments.

Additional important information on the relationship between extended anticoagulation and clinical outcomes will be provided by 2 ongoing RCTs. The single center, randomized trial (HI-PRO [Extended-duration Low-intensity Apixaban to Prevent Recurrence in High-risk Patients with Provoked VTE]) is recruiting 600 patients to compare low-dose apixaban versus placebo for 12-month prevention of recurrence after provoked VTE in patients with persistent provoking factors (NCT04168203). The RENOVE (Reduced Dose Versus Full-Dose of Direct Oral Anticoagulant After Unprovoked Venous Thromboembolism) study is designed to include 2200 participants to demonstrate

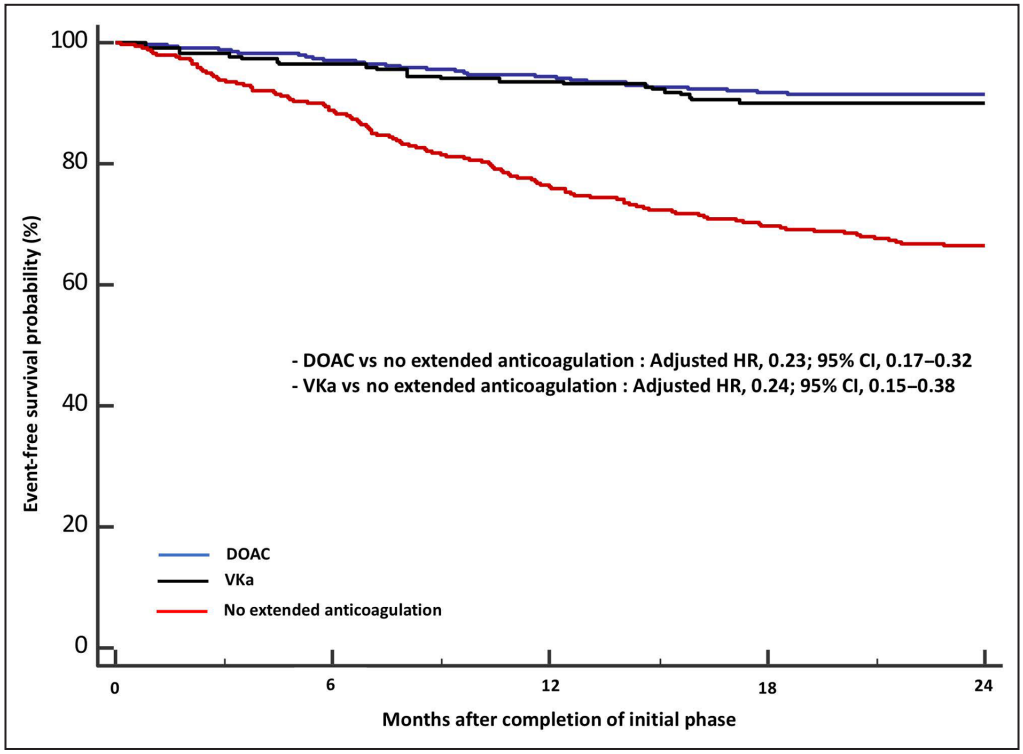


Figure 6. Kaplan–Meier curves for the composite end point, all-cause death or recurrent venous thromboembolism, between patients treated with extended vitamin K antagonist, direct oral anticoagulant, or no treated with extended vs without extended anticoagulation.
DOAC indicates direct oral anticoagulant; HR, hazard ratio; and VKA, vitamin K antagonist. The primary efficacy rates between patients treated with extended vs without extended anticoagulation were adjusted by age (per 10 years), weight <60 kg, prior arterial hypertension, prior coronary artery disease, chronic lung disease, active cancer, systolic blood pressure <100 mm Hg at admission, anemia at admission (ie, hemoglobin <12 g/dL), thrombocythemia at admission (ie, platelet count <150×10^3/μL), renal dysfunction at admission (ie, estimated glomerular function calculated with the Modification of Diet in Renal Disease equation <60 mL/min), and major bleeding events between index pulmonary embolism and 3 to 6 months (ie, initial phase) (see Table S4).

the noninferiority of reduced doses of rivaroxaban and apixaban for extended treatment with a mean follow-up period of 24 months (range, 12 to 48 months) (NCT03285438).

Our study has some limitations. The main limitation is the potential for selection bias in the orientation of patients towards extended anticoagulation therapy by providers, likely based on a more favorable risk-benefit profile. Despite the use of multivariable Poisson regression including several covariates, we did not directly record specific reasons that drove providers to prescribe extended anticoagulation or not. Our results should therefore be interpreted as a pilot study derived from a multicenter cohort population, which should be evaluated in RCT. Finally, we were unable to distinguish between major and minor transient risk factors of VTE as recently defined by the international guidelines.[9,15,16] The strengths of our analysis include the multicenter design and prospective inclusion of our cohort population, the high rate of complete follow-up among survivors of the initial phase (96.8%), independent adjudication of clinical outcomes between the index PE and extended follow-up, as well as the 2-year follow-up after initial treatment of PE.

CONCLUSIONS

Our analysis suggests that extended oral anticoagulation over 2 and a half years after index PE, whether by VKA or DOAC, provides a net clinical benefit compared with no anticoagulation in patients selected by providers to receive extended anticoagulation, likely based on their bleeding risk profile. Sensitivity analyses yielded consistent results across all relevant subgroups, including high bleeding and thrombotic risk groups. Randomized clinical trials are warranted to explore the potential benefit of extended anticoagulation in patients with PE, especially those with transient provoking factors but residual risk.

ARTICLE INFORMATION

Received October 21, 2021; accepted March 28, 2022.

Affiliations

Department of Cardiology, University Hospital Jean Minjoz, Besançon, France (R.C., F.E., S.G., M.B., N.M.); EA3920, University of Burgundy Franche-Comté, Besançon, France (R.C., F.E., N.M.); F-CRIN, INNOVTE Network, Saint-Etienne, France (R.C., N.M.); Aalborg Thrombosis Research Unit, Aalborg University Hospital, Aalborg, Denmark (I.E.A.); Department of Internal Medicine, University Hospital Dijon-Bourgogne, Dijon, France (N.F.); and Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (G.P.).

Sources of Funding

The study was supported by grants from Bayer Healthcare SAS (Loos, France). Bayer Healthcare SAS had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclosures

Dr Albertsen has received speaking fees from Pfizer and Bayer AG. Dr Piazza reports research grants from BMS/Pfizer, BSC, Amgen, Bayer, Janssen, Portola; and Participation on a Data Safety Monitoring Board or Advisory Board for Pfizer, Amgen, Prairie Education Research Cooperative, Agile; Dr Meneveau reports personal fees from Abbott, personal fees from BMS-Pfizer, personal fees from Bayer Healthcare, personal fees from Edwards Lifesciences, personal fees from Terumo, outside the submitted work. The remaining authors have no disclosures to report.

Supplemental Material

Data S1
Tables S1–S5
Figures S1–S3

REFERENCES

1. Sogaard KK, Schmidt M, Pedersen L, Horvath-Puho E, Sorensen HT. 30-year mortality after venous thromboembolism: a population-based cohort study. *Circulation*. 2014;130:829–836. doi: 10.1161/CIRCULATIONAHA.114.009107
2. Albertsen IE, Nielsen PB, Sogaard M, Goldhaber SZ, Overvad TF, Rasmussen LH, Larsen TB. Risk of recurrent venous thromboembolism: a Danish Nationwide Cohort Study. *Am J Med*. 2018;131:1067–1074.e4. doi: 10.1016/j.amjmed.2018.04.042
3. Piazza G, Goldhaber SZ. Chronic thromboembolic pulmonary hypertension. *N Engl J Med*. 2011;364:351–360. doi: 10.1056/NEJMra0910203
4. Galanaud JP, Monreal M, Kahn SR. Epidemiology of the post-thrombotic syndrome. *Thromb Res*. 2018;164:100–109. doi: 10.1016/j.thromres.2017.07.026
5. Kahn SR, Akaberi A, Granton JT, Anderson DR, Wells PS, Rodger MA, Solymoss S, Kovacs MJ, Rudski L, Shimony A, et al. Quality of life, dyspnea, and functional exercise capacity following a first episode of pulmonary embolism: results of the ELOPE cohort study. *Am J Med*. 2017;130:990.e9–990.e21. doi: 10.1016/j.amjmed.2017.03.033
6. Lind C, Flinterman LE, Enga KF, Severinsen MT, Kristensen SR, Brækkan SK, Mathiesen EB, Njølstad I, Cannegieter SC, Overvad K, et al. Impact of incident venous thromboembolism on risk of arterial thrombotic diseases. *Circulation*. 2014;129:855–863. doi: 10.1161/CIRCULATIONAHA.113.004168
7. Becattini C, Agnelli G. Acute treatment of venous thromboembolism. *Blood*. 2020;135:305–316. doi: 10.1182/blood.2019001881
8. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, Huisman M, King CS, Morris TA, Sood N, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest*. 2016;149:315–352. doi: 10.1016/j.chest.2015.11.026
9. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing G-J, Harjola V-P, Huisman MV, Humbert M, Jennings CS, Jiménez D, et al. 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J*. 2020;41:543–603. doi: 10.1093/eurheartj/ehz405
10. Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D, Kvamme AM, Friedman J, Mismetti P, Goldhaber SZ, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *N Engl J Med*. 2013;368:709–718. doi: 10.1056/NEJMoa1113697
11. EINSTEIN Investigators, Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, Lensing AW, Misselwitz F, Prins MH, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363:2499–2510. doi: 10.1056/NEJMoa1007903
12. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Porcari A, Raskob GE, Weitz JI; Investigators A-E. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med*. 2013;368:699–708. doi: 10.1056/NEJMoa1207541
13. Weitz JI, Lensing AWA, Prins MH, Bauersachs R, Beyer-Westendorf J, Bounameaux H, Brighton TA, Cohen AT, Davidson BL, Decousus H, et al. Rivaroxaban or aspirin for extended treatment of venous thromboembolism. *N Engl J Med*. 2017;376:1211–1222. doi: 10.1056/NEJMoa1700518
14. Raskob G, Ageno W, Cohen AT, Brekelmans MPA, Grosso MA, Segers A, Meyer G, Verhamme P, Wells PS, Lin M, et al. Extended duration of anticoagulation with edoxaban in patients with venous thromboembolism: a post-hoc analysis of the Hokusai-VTE study. *Lancet Haematol*. 2016;3:e228–236. doi: 10.1016/S2352-3026(16)00023-5
15. Ortel TL, Neumann I, Ageno W, Beyth R, Clark NP, Cuker A, Hutten BA, Jaff MR, Manja V, Schulman S, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv*. 2020;4:4693–4738. doi: 10.1182/bloodadvances.2020001830
16. Stevens SM, Woller SC, Kreuziger LB, Bounameaux H, Doerschug K, Geersing G-J, Huisman MV, Kearon C, King CS, Knighton AJ, et al. Antithrombotic therapy for VTE disease: second update of the CHEST guideline and expert panel report. *Chest*. 2021;160:e545–e608. doi: 10.1016/j.chest.2021.07.055
17. Albertsen IE, Piazza G, Sogaard M, Nielsen PB, Larsen TB. Extended oral anticoagulation after incident venous thromboembolism—a paradigm shift? *Expert Rev Cardiovasc Ther*. 2020;18:201–208. doi: 10.1080/14779072.2020.1755260
18. Chopard R, Piazza G, Falvo N, Ecarnot F, Besutti M, Capellier G, Schiele F, Badoz M, Meneveau N. An original risk score to predict early major bleeding in acute pulmonary embolism: the Syncope, Anemia, Renal Dysfunction (PE-SARD) bleeding score. *Chest*. 2021;160:1832–1843. doi: 10.1093/eurheartj/ehab724.1926
19. Investigators P. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). *JAMA*. 1990;263:2753–2759.
20. 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;185:381–387. doi: 10.1148/radiology.185.2.1410342
21. Jaff MR, McMurtry MS, Archer SL, Cushman M, Goldenberg N, Goldhaber SZ, Jenkins JS, Kline JA, Michaels AD, Thistlethwaite P, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation*. 2011;123:1788–1830. doi: 10.1161/CIR.0b013e318214914f
22. Konstantinides S, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galiè N, Gibbs JSR, Huisman M, Humbert M, Kucher N, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2014;35:3145–3146. doi: 10.5603/KP.2014.0211
23. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical investigation of medicinal products for the treatment of venous thromboembolic disease. Document reference: Ema/chmp/41230/2015. 2016. Available at: https://www.Ema.Europa.Eu/en/documents/regulatory-procedural-guideline/guideline-clinical-investigation-medicinal-products-treatment-venous-thromboembolic-disease_en.Pdf. Accessed September 24, 2021.
24. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the S, Standardization Committee of the International Society on T, Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3:692–694. doi: 10.1111/j.1538-7836.2005.01204.x

25. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, Elkind MSV, George MG, Hamdan AD, Higashida RT, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44:2064–2089. doi: 10.1161/STR.0b013e318296aeca
26. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD. Fourth universal definition of myocardial infarction (2018). *Circulation*. 2018;138:e618–e651. doi: 10.1161/CIR.0000000000000617
27. Kearon C, Ageno W, Cannegieter SC, Cosmi B, Geersing GJ, Kyrle PA; Subcommittees on Control of A, Predictive, Diagnostic Variables in Thrombotic D. Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH. *J Thromb Haemost*. 2016;14:1480–1483. doi: 10.1111/jth.13336
28. Farge D, Frere C, Connors JM, Ay C, Khorana AA, Munoz A, Brenner B, Kakkar A, Rafii H, Solymoss S, et al. 2019 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. *Lancet Oncol*. 2019;20:e566–e581. doi: 10.1016/S1470-2045(19)30336-5
29. Rogers MA, Levine DA, Blumberg N, Flanders SA, Chopra V, Langa KM. Triggers of hospitalization for venous thromboembolism. *Circulation*. 2012;125:2092–2099. doi: 10.1161/CIRCULATIONAHA.111.084467
30. Klok FA, Barco S, Konstantinides SV. External validation of the VTE-BLEED score for predicting major bleeding in stable anticoagulated patients with venous thromboembolism. *Thromb Haemost*. 2017;117:1164–1170. doi: 10.1160/TH16-10-0810
31. Nishimoto Y, Yamashita Y, Morimoto T, Saga S, Amano H, Takase T, Hiramori S, Kim K, Oi M, Akao M, et al. Validation of the VTE-BLEED score's long-term performance for major bleeding in patients with venous thromboembolisms: from the COMMAND VTE registry. *J Thromb Haemost*. 2020;18:624–632. doi: 10.1111/jth.14691
32. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP; Initiative S. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Epidemiology*. 2007;18:800–804. doi: 10.1097/EDE.0b013e3181577654
33. Althouse AD, Below JE, Claggett BL, Cox NJ, de Lemos JA, Deo RC, Duval S, Hachamovitch R, Kaul S, Keith SW, et al. Recommendations for statistical reporting in cardiovascular medicine: a special report from the American Heart Association. *Circulation*. 2021;144:e70–e91. doi: 10.1161/CIRCULATIONAHA.121.055393
34. Zou G. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159:702–706. doi: 10.1093/aje/kwh090
35. Barnard J, Meng XL. Applications of multiple imputation in medical studies: from AIDS to NHANES. *Stat Methods Med Res*. 1999;8:17–36. doi: 10.1177/096228029900800103
36. Cabral HJ. Multiple comparisons procedures. *Circulation*. 2008;117:698–701. doi: 10.1161/CIRCULATIONAHA.107.700971
37. Monreal M, Suarez C, Fajardo JA, Barba R, Uresandi F, Valle R, Rondon P; Investigators R. Management of patients with acute venous thromboembolism: findings from the RIETE registry. *Pathophysiol Haemost Thromb*. 2003;33:330–334. doi: 10.1159/000083823
38. Couturaud F, Sanchez O, Pernod G, Mismetti P, Jego P, Duhamel E, Provost K, dit Sollier CB, Presles E, Castellant P, et al. Six months vs extended oral anticoagulation after a first episode of pulmonary embolism: the PADIS-PE randomized clinical trial. *JAMA*. 2015;314:31–40. doi: 10.1001/jama.2015.7046
39. Yamashita Y, Morimoto T, Amano H, Takase T, Hiramori S, Kim K, Konishi T, Akao M, Kobayashi Y, Inoue T, et al. Anticoagulation therapy for venous thromboembolism in the real world- from the COMMAND VTE Registry. *Circ J*. 2018;82:1262–1270. doi: 10.1253/circj.CJ-17-1128
40. Gage BF, Yan Y, Milligan PE, Waterman AD, Culverhouse R, Rich MW, Radford MJ. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). *Am Heart J*. 2006;151:713–719. doi: 10.1016/j.ahj.2005.04.017
41. Klok FA, Hosel V, Clemens A, Yollo WD, Tilke C, Schulman S, Lankeit M, Konstantinides SV. Prediction of bleeding events in patients with venous thromboembolism on stable anticoagulation treatment. *Eur Respir J*. 2016;48:1369–1376. doi: 10.1183/13993003.00280-2016
42. O'Brien EC, Simon DN, Thomas LE, Hylek EM, Gersh BJ, Ansell JE, Kowey PR, Mahaffey KW, Chang P, Fonarow GC, et al. The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation. *Eur Heart J*. 2015;36:3258–3264. doi: 10.1093/eurheartj/ehv476
43. Timp JF, Braekkan SK, Lijfering WM, van Hylckama VA, Hansen JB, Rosendaal FR, le Cessie S, Cannegieter SC. Prediction of recurrent venous thrombosis in all patients with a first venous thrombotic event: the Leiden Thrombosis Recurrence Risk Prediction model (L-TRRIP). *PLoS Medicine*. 2019;16:e1002883. doi: 10.1371/journal.pmed.1002883
44. Rodger MA, Kahn SR, Wells PS, Anderson DA, Chagnon I, Le Gal G, Solymoss S, Crowther M, Perrier A, White R, et al. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. *CMAJ*. 2008;179:417–426. doi: 10.1503/cmaj.080493
45. Tosetto A, Iorio A, Marcucci M, Baglin T, Cushman M, Eichinger S, Palareti G, Poli D, Tait RC, Douketis J. Predicting disease recurrence in patients with previous unprovoked venous thromboembolism: a proposed prediction score (DASH). *J Thromb Haemost*. 2012;10:1019–1025. doi: 10.1111/j.1538-7836.2012.04735.x
46. Eichinger S, Heinze G, Jandeck LM, Kyrle PA. Risk assessment of recurrence in patients with unprovoked deep vein thrombosis or pulmonary embolism: the Vienna prediction model. *Circulation*. 2010;121:1630–1636. doi: 10.1161/CIRCULATIONAHA.109.925214
47. Franco Moreno AI, García Navarro MJ, Ortiz Sánchez J, Martín Díaz RM, Madroñal Cerezo E, de Ancos Aracil CL, Cabello Clotet N, Perales Fraile I, Gimeno García S, Montero Hernández C, et al. A risk score for prediction of recurrence in patients with unprovoked venous thromboembolism (DAMOVES). *Eur J Intern Med*. 2016;29:59–64. doi: 10.1016/j.ejim.2015.12.010
48. Pengo V, Denas G, Zoppellaro G, Jose SP, Hoxha A, Ruffatti A, Andreoli L, Tincani A, Cenci C, Prisco D, et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. *Blood*. 2018;132:1365–1371. doi: 10.1182/blood-2018-04-848333
49. Mai V, Bertoletti L, Cucherat M, Jardel S, Grange C, Provencher S, Lega JC. Extended anticoagulation for the secondary prevention of venous thromboembolic events: an updated network meta-analysis. *PLoS One*. 2019;14:e0214134. doi: 10.1371/journal.pone.0214134

Supplemental Material

Data S1.

Supplemental Methods

Definition of outcomes:

- Death was classified as related to VTE, related to cardiovascular disease, related to cancer, related to bleeding, or related to non-cancer, non-cardiovascular causes. VTE was considered as the cause of death if there was objective documentation or if death could not be attributed to another documented cause and PE could not be ruled out.
- Recurrent venous thromboembolism included fatal and nonfatal pulmonary embolism and deep-vein thrombosis. Recurrent VTE was defined as presence of (1) symptoms suggesting pulmonary embolism, and new defects seen on computed tomography pulmonary angiogram or ventilation-perfusion scan; or (2) diagnosis of deep vein thrombosis on compression ultrasonography.
- Any bleeding included clinically relevant non-major (CRNM) bleeding and major bleeding.
- Major bleeding was defined according to the International Society on Thrombosis and Haemostasis (ISTH) criteria, namely: (1) fatal bleeding and/or (2) symptomatic bleeding in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome), and/or (3) bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.[24]

- Clinically relevant non-major bleeding was acute clinically overt bleeding that consists of: any bleeding compromising hemodynamics; any bleeding leading to hospitalization; subcutaneous hematoma larger than 25 cm^2, or 100 cm^2 if there was a traumatic cause; intramuscular hematoma documented by ultrasonography; epistaxis that lasted for more than 5 minutes, was repetitive (i.e., two or more episodes of bleeding more extensive than spots on a handkerchief within 24 hours), or led to an intervention (e.g., packing or electrocoagulation); gingival bleeding occurring spontaneously (i.e., unrelated to eating or tooth brushing) or lasting for more than 5 minutes; hematuria that was macroscopic and was spontaneous or lasted for more than 24 hours after instrumentation (e.g., catheter placement or surgery) of the urogenital tract; macroscopic gastrointestinal hemorrhage, including at least one episode of rectal blood loss, if more than a few spots on toilet paper; hemoptysis, if more than a few speckles in the sputum and not occurring within the context of PE; or any other bleeding type considered to have clinical consequences for a patient such as medical intervention, the need for unscheduled contact (visit or telephone call) with a physician, or temporary cessation of a study drug, or associated with pain or impairment of activities of daily life. [24]

- Acute myocardial infarction was defined as the presence of at least two of the three following conditions: (1) An appropriate clinical situation suggestive of an MI (e.g., abnormal history, physical examination, or new electrocardiogram changes); (2) troponin T or I ≥2 × upper limit of normal (ULN); (3) New, significant (≥0.04 seconds) Q waves in ≥2 contiguous leads. [25]

- Acute stroke was defined as a new, focal neurologic deficit of sudden onset, lasting at least 24 hours, not due to a readily identifiable nonvascular cause (i.e., brain tumor, trauma). [26]

Table S1. List of candidate covariates for the multivariable models performed in the present analysis after acute pulmonary embolism.

Covariates	Missing data (%)	Unvariate analysis Extended anticoagulation group vs No anticoagulation group	
		p-value for the primary efficacy outcome	p-value for the primary safety outcome
Age, year	0	-	-
Age > 65 years		0.004	0.26
Age > 70 years		0.001	0.67
Age > 75 years		<0.001	0.65
Age > 80 years		<0.001	0.26
Female sex	0	0.11	0.57
Weight, kg	0.1	-	-
Weight < 50 kg		0.24	0.34
Weight < 60 kg		0.04	0.21
BMI, kg/m^2	0	-	-
BMI > 25 kg/m^2		0.67	0.87

BMI > 30 kg/m^2		0.56	0.69
BMI > 35 kg/m^2		0.30	0.43
BMI < 18 kg/m^2		0.21	0.32
Comorbidities			
Current smoker	0	0.39	0.24
Hypertension	0	0.05	0.98
Diabetes mellitus	0	0.28	0.43
Dyslipidemia	0	0.54	
Chronic pulmonary disease	0	0.006	
Coronary artery disease	0	0.08	0.04
Cancer	0	<0.001	0.25
Prior stroke	0	0.88	<0.001
Prior bleeding	1.2	0.40	0.98
Prior VTE	0	0.14	0.78
Neurocognitive disorders	0.3	0.36	0.88
Liver disease	0	0.77	0.28
Excessive Fall Risk	0.4	0.88	0.38
Ethanol abuse	0	0.69	0.08

Recent surgery	0	0.34	0.65
Recent hospitalization	0	0.25	0.24
Thrombophilia	0	0.87	0.15
Pregnancy	0	0.99	0.98
Post-partum period	0	0.99	0.99
Immobility due to sitting (e.g. prolonged car or air travel)	0	0.78	0.65
Bed rest > 3 days	0	0.25	0.67
Varicose veins	0	0.24	0.87
Associated DVT	0	0.11	0.29
Clinical presentation and management of the acute PE event			
Syncope	0	0.20	0.82
Arterial oxyhaemoglobin saturation <90% at admission	0	0.25	0. 98
SBP < 90 mmHg at admission	0	0.06	0.01
SBP < 100 mmHg	0	0.001	0.98
Heart rate > 110 b.p.m at admission	0	0.22	0.40
RV dysfunction at admission	0	0.17	0.36
Advanced therapy[a]	0	0.81	0.33
Concomitant anti-thrombotic therapy at admission			

Antiplatelet therapy	0	0.19	0.06
Anticoagulation	0	0.32	0.25
Concomitant antiplatelet therapy between index PE and 3 to 6 months	0	0.38	0.23
Adverse outcomes between index PE and 3 to 6 months			
Any bleeding	0	0.16	0.007
Major bleeding	0	0.03	0.19
Acute heart failure	0	0.014	0.09
Acute myocardial infarction	0	0.14	0.98
Stroke	0	0.97	0.99
Biological data at inclusion			
Hemoglobin (g/dL)	0.6	-	-
Anemia with hemoglobin < 10 gl/dL		<0.001	0.31
Anemia with hemoglobin < 12 gl/dL		<0.001	0.55
Anemia with hemoglobin < 13 g/dL in men and ,12 g/dL in women		0.01	0.68
Anemia with hemoglobin <13 g/dL in men and < 12 g/dL in women) and hematocrit < 40% in men and < 36% in women		0.02	0.72

Platelet count (x 10^3/microliter)	0.7	-	-
Thrombocytopenia with platelet count < 50 10^3/microliter		0.01	0.87
Thrombocytopenia with platelet count < 100 10^3/microliter		<0.001	0.93
Thrombocytopenia with platelet count < 150 10^3/microliter		<0.001	0.98
eGFR	0		
$eGRF_{CKD-EPI,}$ mmol/L		-	-
$eGRF_{MDRD4,}$ mmol/L		-	-
$eGRF_{CG-BSA,}$ mmol/L		-	-
$eGRF_{CKD-EPI}$ < 60 mL/min		0.007	0.35
$eGRF_{MDRD4}$ < 60 mL/min		0.01	0.32
$eGRF_{CG-BSA}$ < 60 mL/min		0.02	0.70
$eGRF_{CKD-EPI}$ < 30 mL/min		<0.001	0.88
$eGRF_{MDRD4}$ < 30 mL/min		<0.001	0.65
$eGRF_{CG-BSA}$ < 30 mL/min (%)		0.004	0.65

BMI, body mass index; VTE, venous thromboembolic; DVT, deep vein thrombosis; SBP, systolic blood pressure; eGFR, estimated glomerular function; CKD-EPI, The Chronic Kidney Disease Epidemiology Collaboration equation; MDRD4, the four variables the Modification of Diet in Renal Disease equation; CG-BSA, the body surface area-adjusted Cockcroft-Gault equation. [a] Advanced therapy included systemic thrombolysis, surgical embolectomy, or extra-corporeal membrane oxygenation.

Table S2. Observed rates of clinical outcomes between pulmonary embolism patients treated with extended vs without extended anticoagulant therapy during the active study period (n = 1,199).

	Extended anticoagulation (n = 858)	No anticoagulation (n = 341)
Death from any cause	76 (8.8%; 95% CI, 6.7-10.9)	67 (19.6%; 95% CI, 15.5-24.2)
Recurrent VTE	11 (1.3%; 95% CI, 0.6-2.3)	63 (18.5%; 95% CI, 14.5-23.0)
Myocardial infarction	2 (0.2%; 95% CI, 0.02-0.8)	8 (2.3%; 95% CI, 1.0-4.5)
Stroke	14 (1.6; 95% CI, 0.9-2.7)	5 (1.5%; 95% CI, 0.5-3.4)
Major bleeding	16 (1.9%; 95% CI, 1.1-3.0)	8 (2.3%; 95% CI, 1.0-4.5)
Clinically relevant non-major bleeding	24 (2.8%; 95% CI, 1.8-4.1)	6 (1.8%; 95% CI, 0.7-3.8)

VTE, venous thromboembolism; CI, confidence interval.

The statistics are shown as mean ± standard deviation (SD) or N (%, 95% CI)

Table S3. Observed causes of death between pulmonary embolism patients treated with extended vs without extended anticoagulant therapy during the active study period (n = 1,199).

Cause of death	Extended anticoagulation (n = 858)	No anticoagulation (n = 341)
VTE-related	4 (0.5%; 95% CI, 0.1-1.2)	6 (1.8%; 95% CI, 0.7-3.8)
Cardiovascular disease-related	2 (0.2%; 95% CI, 0.02-0.8)	2 (0.6%; 95% CI, 0.08-2.1)
Cancer-related	35 (4.1%; 95% CI, 2.8-5.6)	35 (10.3%; 95% CI, 7.3-14.0)
Bleeding-related	3 (0.34%; 95% CI, 0.07-1.0)	1 (0.29%; 95% CI, 0.01-1.6
Non-cancer, non cardiovascular-related	35 (4.1%; 95% Ci, 2.9-5.6)	24 (7.0%; 95% CI, 4.5-10.2)

VTE, venous thromboembolism.

Table S4. Univariable and multivariate predictors of the primary efficacy and safety outcomes (i.e. recurrent venous thromboembolism or all-cause death) at 2 years in pulmonary embolism patients treated with vs without extended anticoagulant therapy during the study period (n = 1,199).

Variable	**HR (95% CI)**	**p value**	**HR (95% CI)**	**p value**
	Univariate analysis		**Multivariate analysis**	
Primary efficacy outcome: **All-cause death or recurrent VTE**				
Age, per 10 years	1.09 (1.01-1.16)	0.01	**1.26 (1.13-1.41)**	**<0.001**
Weight < 60 kg	1.36 (0.99-1.87)	0.051	-	-
Prior arterial hypertension	1.33 (1.00-1.77)	0.05	**-**	**-**
Prior CAD	1.40 (0.95-2.04)	0.08	**-**	**-**
Chronic lung disease	1.73 (1.15-2.62)	0.008	**-**	**-**
Cancer	1.39 (0.99-1.95)	0.055	**3.45 (2.51-4.73)**	**<0.001**
SBP < 100 mmHg at admission	2.14 (1.30-3.52)	0.002	-	-
Anemia[a] at admission	2.36 (1.76-3.17)	<0.001	**1.40 (1.01-1.96)**	**0.04**
Thrombocytopenia[b] at admission	2.0 (1.41-2.80)	< 0.001	-	-
Renal dysfunction[c] at admission	1.48 (1.11-1.99)	0.007	-	-
Extended anticoagulation	1.5 (1.04-2.1)	0.03	**0.23 (0.17-0.31)**	**<0.001**
Major bleeding between index PE	1.82 (1.07-3.09)	0.02	**-**	**-**

and 3 to 6 months follow-up				
Primary safety outcome: **Major bleeding**				
Prior CAD	1.86 (1.01-3.44)	0.04	-	-
Prior stroke	3.37 (1.71-6.65)	<0.001	**2.88 (1.43-5.79)**	**0.002**
Alcohol use	2.21 (0.88-5.51)	0.08	**-**	**-**
Major transient or reversible risk factors	1.80 (1.07-3.3)	0.02	-	-
High-risk PE	2.16 (0.86-5.39)	0.09	-	-
Extended anticoagulation	1.03 (0.58-1.80)	0.91	**1.0 (0.57-1.76)**	**0.98**
Major bleeding or CNRM bleeding between index PE and 3 to 6 months follow-up	2.55 (1.29-5.03)	0.006	**-**	**-**
Acute heart failure between index PE and 3 to 6 months follow-up	2.70 (0.84-8.62)	0.09	**-**	**-**

CAD, coronary artery disease; SBP, systolic blood pressure; PE, pulmonary embolism; CNRM Clinically relevant non-major bleeding.

[a] Defined as a hemoglobin level < 12 g/dL; [b] Defined as platelet count < 150 x10^3/microliter; [c] Defined as estimated glomerular function calculated with the Modification of Diet in Renal Disease equation < 60 mL/min.

Table S5. Sub-groups analyses of the unadjusted primary safety outcome rates, major bleeding, across unprovoked, prior VTE, and cancer-associated PE patients based on patients bleeding-risk (high and low bleeding-risk).

	Extended anticoagulation n, % (95% CI)	No anticoagulation n, % (95% CI)	p log-rank
High bleeding-risk (n=671)*			
Unprovoked PE (n= 532)	14 (3.6% [2.2-5.6])	8 (5.6% [3.8-7.9])	0.29
Prior VTE (n=174)	7 (4.8% [2.1-9.1])	1 (3.6% [1.4-7.6])	0.78
Cancer-associated PE (n=171)	6 (5.2% [2.4-9.7])	6 (9.8% [5.8-15.3])	0.22
Low bleeding-risk (n=671)**			
Unprovoked PE (n= 532)	14 (3.9% [2.4-5.9])	2 (2.1% [1.1-3.7])	0.20
Prior VTE (n=174)	5 (4.0% [1.6-8.1])	0 (0)	0.56
Cancer-associated PE (n=171)	-	-	-

PE, pulmonary embolism; VTE, venous thrombo-embolism. *defined by a VTE-BLEED score ≥ 2; **defined by a VTE-BLEED score < 2. The statistics are shown as mean ± standard deviation (SD) or N (%, 95% CI)

Figure S1. Type of drugs and doses used for anticoagulant therapy in pulmonary embolism patients eligible for extended treatment (n = 858). The statistics are shown as a frequency (%)

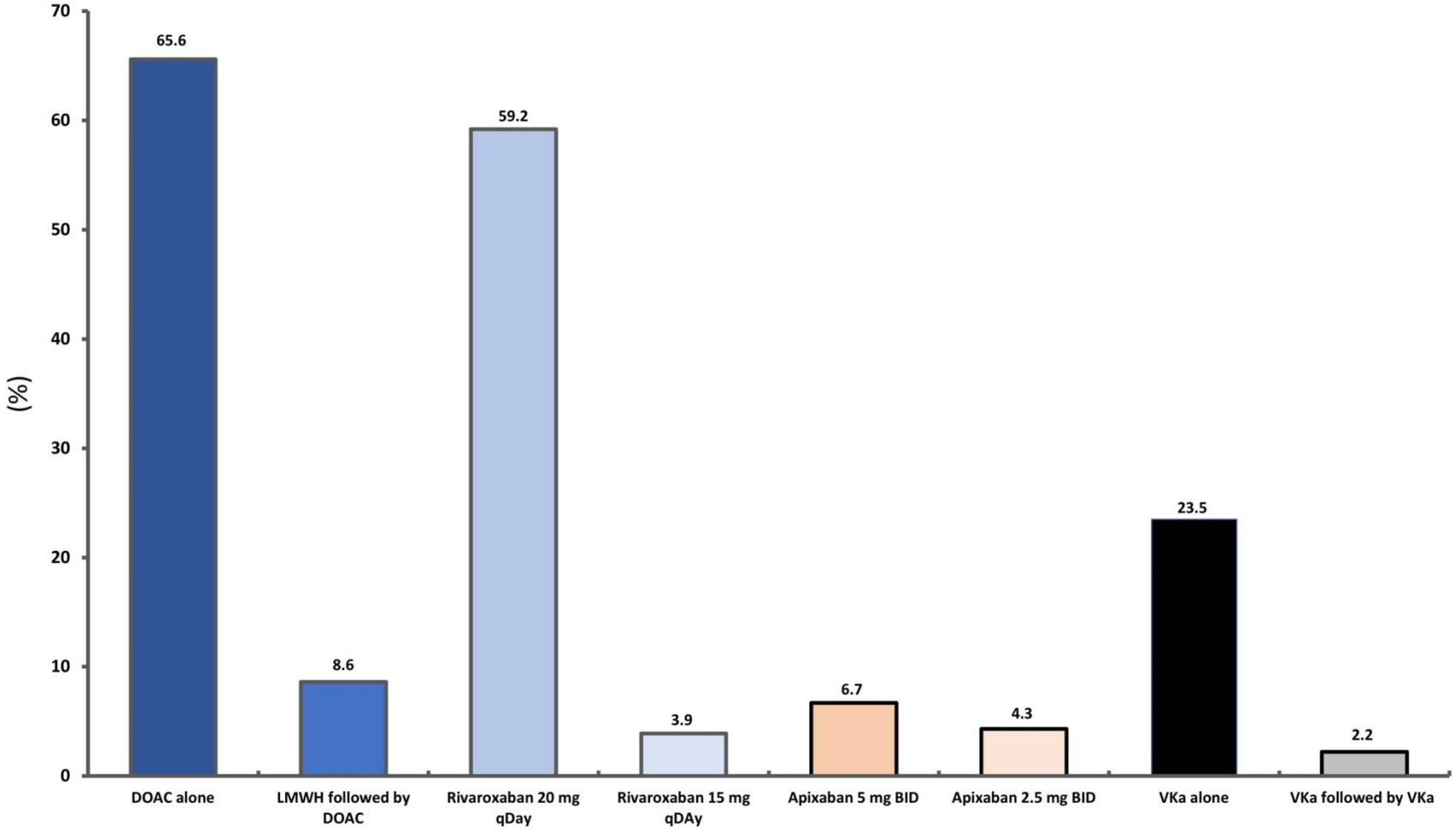
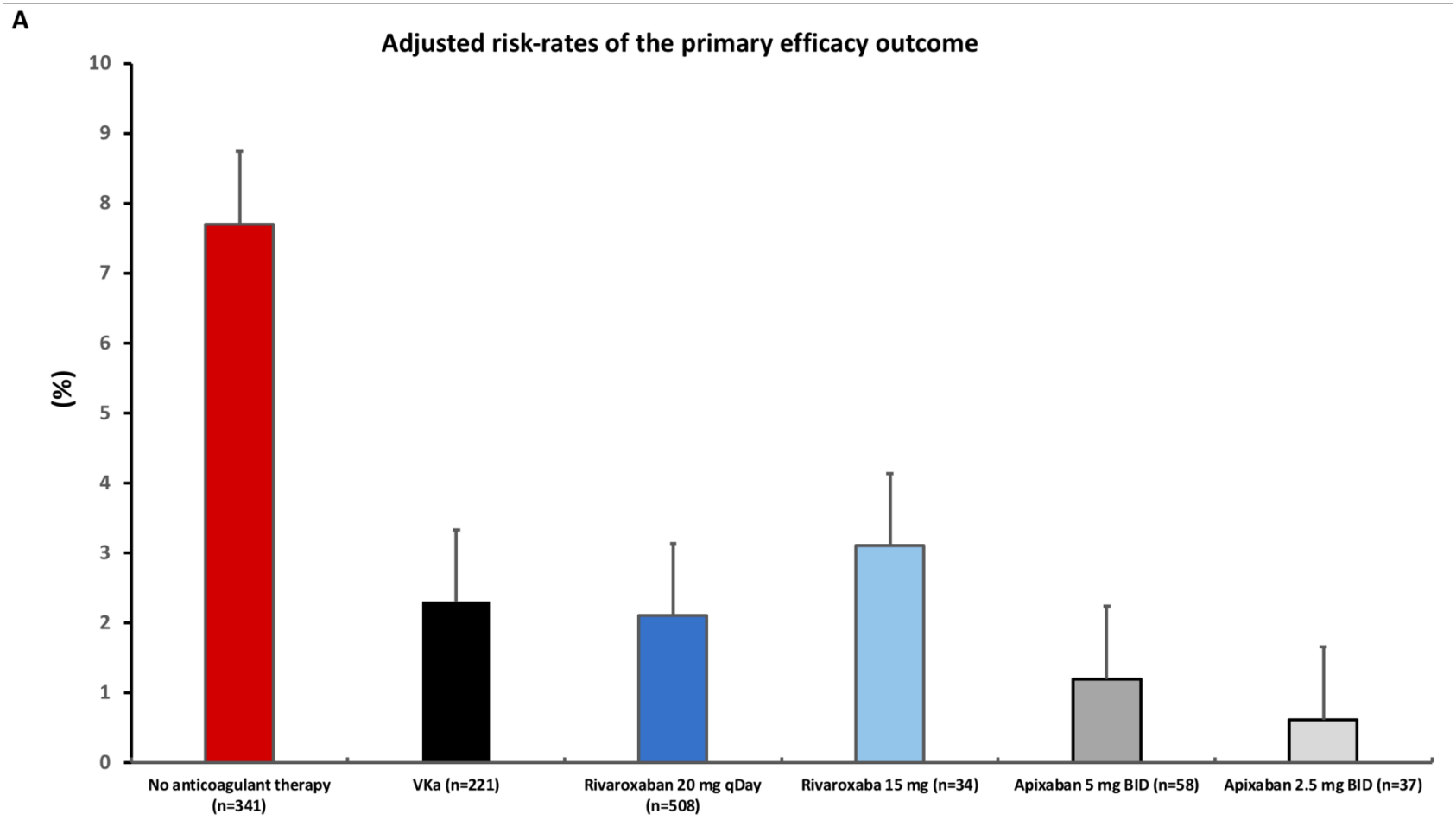


Figure S2. Unadjusted rates of the primary efficacy (i.e. all-cause death or recurrent venous thromboembolism) (A) and safety (i.e. major bleeding) (B) outcomes in the no-anticoagulant group, in patients treated with vitamin K antagonist or direct anticoagulant (DOAC), and according to DOAC dosing. The statistics are shown as a frequency (%).



B

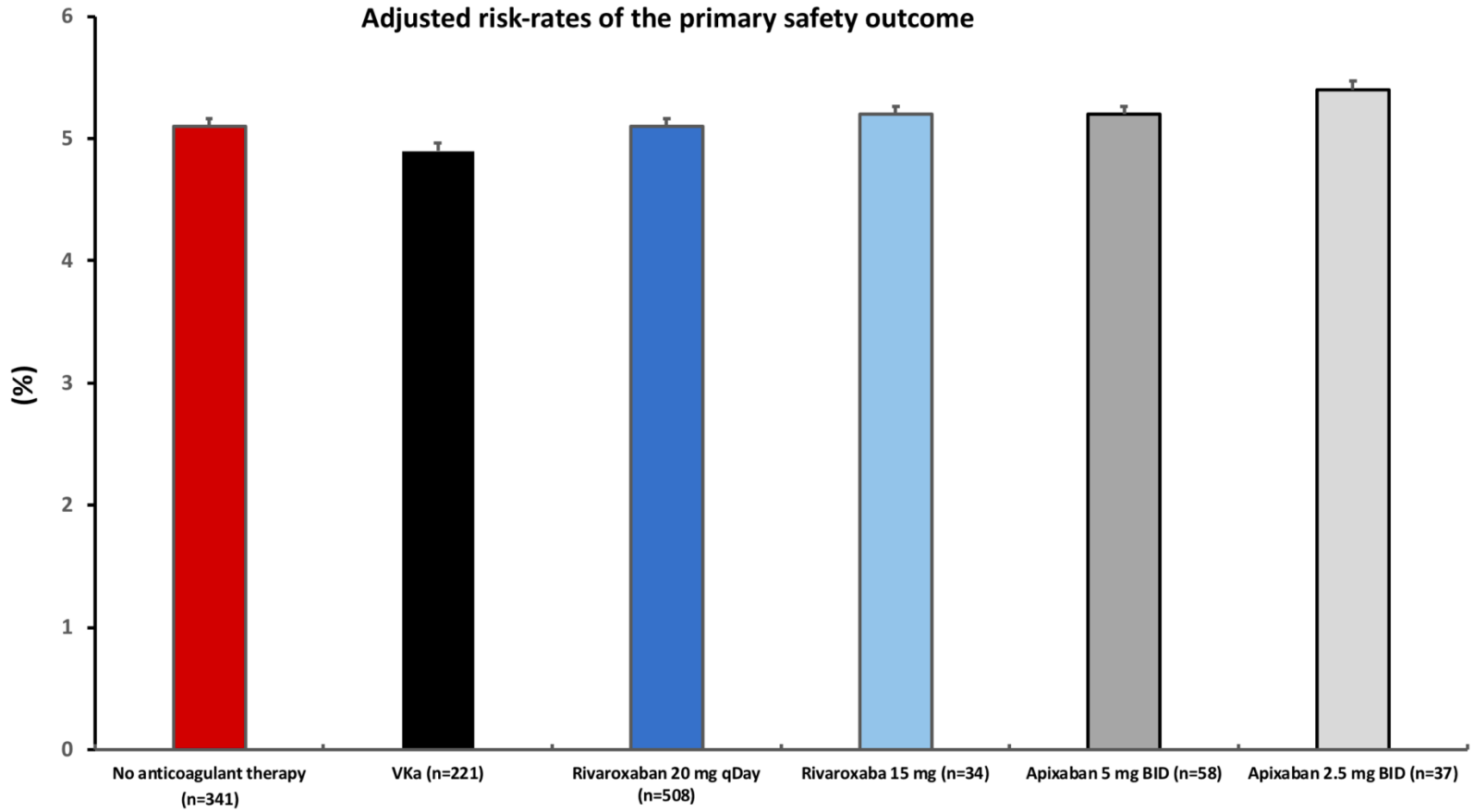
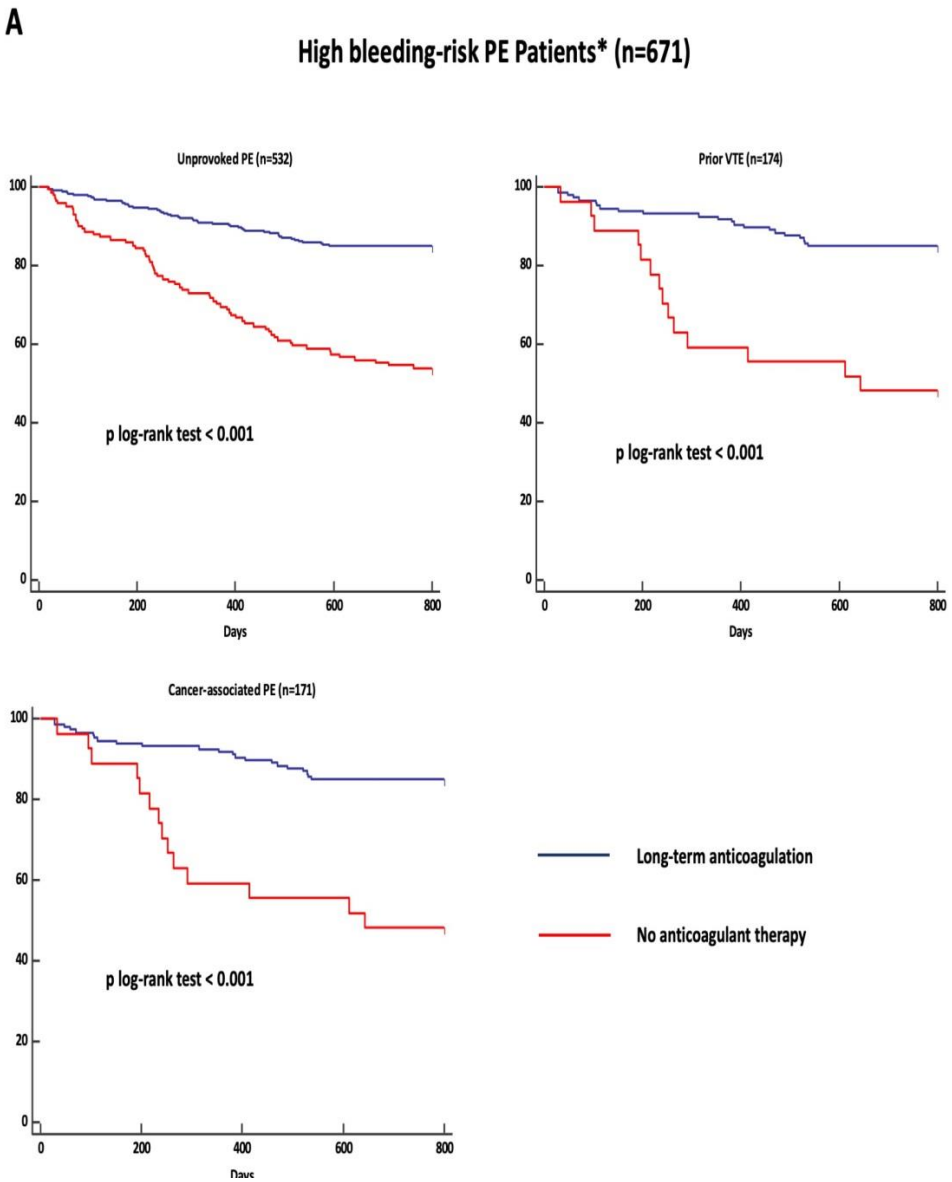


Figure S3. Sub-groups analyses of the unadjusted primary efficacy outcome rates, all-cause mortality, or recurrent venous thrombo-embolism across unprovoked, prior VTE, and cancer-associated PE patients based on patients bleeding-risk (high [A] and low [B] bleeding-risk). High bleeding-risk defined by a VTE-BLEED score ≥ 2; Low bleeding-risk defined by a VTE-BLEED score < 2.



B