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Bleeding Risk with Apixaban vs. Rivaroxaban in Acute Venous Thromboembolism

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ABSTRACT

BACKGROUND

Apixaban and rivaroxaban are the oral anticoagulants most frequently used to treat acute venous thromboembolism. However, uncertainty remains about the difference in bleeding risk between the two medications.

METHODS

In an international trial with a prospective, randomized, open-label, blinded endpoint design, we assigned, in a 1:1 ratio, eligible patients with acute symptomatic pulmonary embolism or proximal deep-vein thrombosis to receive apixaban or rivaroxaban for 3 months. Apixaban was given at a dose of 10 mg twice daily for 7 days followed by 5 mg twice daily, and rivaroxaban was given at a dose of 15 mg twice daily for 21 days followed by 20 mg daily. The primary outcome was clinically relevant bleeding, a composite of major bleeding or clinically relevant nonmajor bleeding, as defined according to the International Society on Thrombosis and Haemostasis, during the 3-month trial period. Secondary outcomes included death from any cause.

RESULTS

A total of 2760 patients underwent randomization: 1370 to the apixaban group and 1390 to the rivaroxaban group. A primary-outcome event occurred in 44 of 1345 patients (3.3%) in the apixaban group and 96 of 1355 patients (7.1%) in the rivaroxaban group (relative risk, 0.46; 95% confidence interval [CI], 0.33 to 0.65; P<0.001). Death from any cause occurred in 1 patient (0.1%) in the apixaban group and in 4 patients (0.3%) in the rivaroxaban group (relative risk, 0.25; 95% CI, 0.03 to 2.26). Serious adverse events unrelated to bleeding or venous thrombosis occurred in 36 patients (2.7%) in the apixaban group and in 30 patients (2.2%) in the rivaroxaban group.

CONCLUSIONS

Among patients with acute venous thromboembolism, the risk of clinically relevant bleeding was significantly lower with apixaban than with rivaroxaban during the 3-month treatment period. (Funded by the Canadian Institutes of Health Research and others; COBRRA ClinicalTrials.gov number, NCT03266783.)

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A complete list of the COBRRA trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

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CME

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Venous thromboembolism is a common treatable condition, yet it is the third most common cause of acute cardiovascular events and cardiovascular-related death worldwide.[1,2] The incidence of venous thromboembolism in the general population is 1 to 2 cases per 1000 persons,[3,4] and the incidence increases with age.[5,6] Anticoagulation therapy is needed for a minimum of 3 months after venous thromboembolism to prevent recurrent thrombotic events.[1,7]

Direct oral anticoagulants, including rivaroxaban and apixaban, are the most frequently prescribed treatments for acute venous thromboembolism. In randomized clinical trials, rivaroxaban at a dose of 15 mg twice daily for 21 days followed by 20 mg daily and apixaban at a dose of 10 mg twice daily for 7 days followed by 5 mg twice daily were noninferior to vitamin K antagonists regarding efficacy (risk of recurrent venous thromboembolism).[8,9] These trials showed that clinically relevant bleeding, a composite of major bleeding or clinically relevant nonmajor bleeding, occurred in 4.3% of the patients who received apixaban as compared with 9.7% of those who received vitamin K antagonists[9] and in 8.1% of patients who received rivaroxaban as compared with 8.1% of those who received vitamin K antagonists.[8] The difference between apixaban and rivaroxaban therapy regarding the risk of clinically relevant bleeding was hypothesized to be related to heterogeneity in the patient populations and differences in the trial designs.[8,9] Owing to a lack of trials that have compared rivaroxaban with apixaban regarding the risk of bleeding, clinical practice guidelines do not recommend one anticoagulant over the other.[1,7] We conducted the Comparison of Bleeding Risk between Rivaroxaban and Apixaban (COBRRA) trial to assess whether apixaban was superior to rivaroxaban with respect to safety in patients with acute venous thromboembolism.

Methods

Trial Design and Oversight

This trial was a pragmatic, international trial with a PROBE (prospective, randomized, open-label, blinded end-point) design that compared apixaban with rivaroxaban in patients with acute venous thromboembolism. The trial protocol is available with the full text of this article at NEJM.org. The first and last authors designed the trial. The members of the international steering committee had final responsibility for the design and oversight of the trial, clinical development and implementation of the protocol, writing of the manuscript, and decision to submit the manuscript for publication. Data analysis was performed at the Ottawa Methods Centre by two of the authors. An independent data and safety monitoring board and a statistician monitored the progress of the trial and the safety of the patients. The institutional review board or research ethics board at each of the participating sites approved the protocol. The investigators collected the data. The first author wrote the first draft of the manuscript. The authors vouch for the completeness and accuracy of the data and for the adherence of the trial to the protocol.

Patients provided integrated consent or written informed consent, depending on local requirements. With the integrated-consent approach, the treating physician used an approved script to provide all pertinent information about the trial to the patient during a clinical encounter. Patients were then asked to provide oral consent to undergo randomization and receive the assigned treatment for at least 3 months. Additional information about integrated consent is provided in the Supplementary Appendix, available at NEJM.org

The trial was coordinated and sponsored by the Ottawa Hospital Research Institute, the National Health and Medical Research Council Clinical Trials Centre, the University of Sydney, the Royal College of Surgeons in Ireland, and the University College Dublin Clinical Research Centre under the supervision of the steering committee. Data were collected at the trial sites and entered in an online database managed by staff at the Ottawa Methods Centre of the Ottawa Hospital Research Institute. An independent central adjudication committee whose members were unaware of the treatment assignments reviewed all suspected outcome events and causes of death with the use of an online platform (VERDICT).

The trial was funded by the Canadian Institutes of Health Research, the Medical Research Future Fund in Australia, the Royal College of Surgeons in Ireland, and the International Network of Venous Thromboembolism Clinical Research Networks. The funders had no role in the trial design, trial conduct, data collection and analysis, interpretation of data, or review or preparation of the

manuscript. The trial was endorsed by the International Network of Venous Thrombosis Networks, the CanVECTOR Network, and the Thrombosis and Haemostasis Society of Australia and New Zealand.

TRIAL POPULATION

Adults (≥18 years of age) with symptomatic acute venous thromboembolism were eligible for inclusion in the trial. Inclusion criteria were symptomatic acute proximal lower-limb deep-vein thrombosis or segmental or more proximal pulmonary embolism and the ability to provide informed consent. Patients were excluded if they had received therapeutic anticoagulation therapy for more than 72 hours immediately before the enrollment visit or had renal insufficiency with a creatinine clearance of less than 30 ml per minute according to the Cockcroft–Gault formula.[10] Among the other exclusion criteria were any contraindication to rivaroxaban or apixaban as determined by the local treating physician, including but not limited to active bleeding; active cancer[11]; a weight of more than 120 kg, owing to guidance recommendations at the time of the trial design[12]; known liver disease (Child–Pugh B or C disease); use of contraindicated interacting medications (according to information provided in the Supplementary Appendix); current pregnancy or breastfeeding; or another indication for long-term anticoagulation therapy, such as atrial fibrillation.

RANDOMIZATION AND TRIAL INTERVENTION

Eligible patients were randomly assigned in a 1:1 ratio to receive 3 months of treatment with rivaroxaban at a dose of 15 mg twice daily for 21 days followed by 20 mg daily or apixaban at a dose of 10 mg twice daily for 7 days followed by 5 mg twice daily. Randomization was conducted by means of a centralized Web-based system and a permuted block design with varying block sizes (4 and 6), with stratification according to renal insufficiency (creatinine clearance, <50 ml per minute vs. ≥50 ml per minute), planned continued use of antiplatelet therapy during the trial period (yes vs. no), and participating center. Treating clinicians and patients were aware of the treatment assignments. Patients received local prescriptions for the assigned medication that were to be filled at local commercial pharmacies. Members of the independent central adjudication committee and statisticians were unaware of the treatment assignments. Trial visits were scheduled to occur at enrollment and 2 weeks (with a window of ±1 week) and 3 months after randomization.

OUTCOMES

The primary outcome was clinically relevant bleeding, a composite of major bleeding or clinically relevant nonmajor bleeding, as defined by the International Society on Thrombosis and Haemostasis (ISTH). Major bleeding was defined as overt bleeding that occurred in a critical site, was associated with a decrease of at least 2 g per deciliter in the hemoglobin level, led to transfusion of 2 or more units of packed red cells, or contributed to death.[13] Clinically relevant nonmajor bleeding was defined as bleeding that did not meet the definition for major bleeding but met at least one of the following criteria: resulted in medical intervention by a health care professional, led to hospitalization or an increased level of care, or prompted face-to-face evaluation by a health care professional.[14]

Secondary outcomes included the individual components of the primary outcome and recurrent symptomatic venous thromboembolism (a composite of recurrent deep-vein thrombosis or recurrent pulmonary embolism).[15] Recurrent deep-vein thrombosis was defined by a noncompressible area in the popliteal vein or more proximal vein on compression ultrasonography that was not present at the time of diagnosis or by a constant intraluminal filling defect in the popliteal vein or more proximal veins on venography. Recurrent pulmonary embolism was defined by abnormalities on ventilation–perfusion scanning, including a new unmatched segmental or more proximal perfusion defect; an intraluminal filling defect in a segmental or more proximal vessel on computed tomographic pulmonary angiography that was previously free of thrombi; or a constant intraluminal filling defect or a cutoff of a vessel of more than 2.5 mm in diameter on pulmonary angiography. Other secondary outcomes included death from bleeding, death from recurrent venous thromboembolism (confirmed on the basis of a death certificate or autopsy findings), death from any cause, and medication adherence at each follow-up visit (see the Supplementary Appendix). All trial outcomes were adjudicated by an independent central adjudication committee

whose members were unaware of the treatment assignments.

STATISTICAL ANALYSIS

The current trial was designed to have 80% power to detect a 33% lower risk (minimum clinically meaningful reduction) of clinically relevant bleeding with apixaban than with rivaroxaban at a two-sided alpha level of 0.05. This design was based on the assumption that a primary-outcome event would occur in 5.4% of the patients in the apixaban group and in 8.1% of those in the rivaroxaban group. We calculated that a minimum of 1352 patients in each treatment group would be needed to detect such a difference in risk. Loss to follow-up was less than 1% in the EINSTEIN trials of rivaroxaban and the AMPLIFY (Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy) trial of apixaban.[8,9] Assuming a conservative loss to follow-up of 2% in the current trial, we planned to enroll 2760 participants (1380 participants per treatment group).

The primary outcome of adjudicated clinically relevant bleeding was analyzed in the intention-to-treat population, which included all the patients who had undergone randomization and completed follow-up, with data analyzed according to the patient s assigned treatment group. In the prespecified primary-outcome analysis, we used a chi-square test to calculate an unadjusted odds ratio and its corresponding 95% confidence interval. In a sensitivity analysis of the primary outcome, we used mixed-effects logistic regression with adjustment for the stratification variable of renal disease (creatinine clearance, <50 ml per minute vs. ≥50 ml per minute), continued antiplatelet use (yes vs. no), age (<75 years vs. ≥75 years), and sex (male vs. female) and a random effect for trial site to calculate an adjusted odds ratio and 95% confidence interval.

A time-to-event analysis of the primary outcome was conducted with the Kaplan Meier method. The secondary outcomes of major bleeding, clinically relevant nonmajor bleeding, recurrent venous thromboembolism, and death from any cause were analyzed with unadjusted odds ratios and their corresponding 95% confidence intervals.

At the request of the *Journal* editors, we calculated relative risks and their corresponding 95% confidence intervals for all primary and secondary outcomes and used a generalized linear mixed-effects model with a log link function to calculate the adjusted relative risk in the sensitivity analysis of the primary outcome. Relative risks are provided in the main text, and odds ratios, which were calculated as prespecified in the statistical analysis plan (available with the protocol), are provided in the Supplementary Appendix. Because the event of interest is rare (incidence, <10%), the odds ratios were expected to be similar to the relative risks.[16,17]

In the secondary-outcome analyses, the widths of the confidence intervals have not been adjusted for multiplicity, and the intervals should not be used in place of hypothesis testing. The main competing risk was death; however, because mortality was very low (<0.5% of the patients), we did not adjust for this competing risk in the analyses of the primary and secondary outcomes. The analyses of the primary and secondary outcomes and the mixed-effects logistic-regression analysis were conducted according to a complete-case approach because no data were missing among the baseline variables included in the analyses. In the prespecified subgroup analyses, unadjusted odds ratios and their corresponding 95% confidence intervals are provided. All the analyses were conducted in the intention-to-treat population.

RESULTS

PATIENTS

From December 13, 2017, to January 23, 2025, a total of 2760 patients underwent randomization at 32 centers in Canada, Australia, and Ireland (Fig. 1). We assigned 1370 patients to receive apixaban and 1390 to receive rivaroxaban. After the exclusion of 60 patients (2.2%) who had undergone randomization, 1345 patients in the apixaban group and 1355 in the rivaroxaban group were assessed in the intention-to-treat analysis (Fig. 1 and Table S1 in the Supplementary Appendix).

Baseline demographic and clinical characteristics appeared to be well balanced between the treatment groups (Table 1). The mean age was 58.3 years, and 1175 patients (43.5%) were female. Approximately 10% of the patients reported non-White race (Table S2). Most of the patients (2087; 77.3%) had an unprovoked venous thromboem-

bolism event; 1409 patients (52.2%) had deep-vein thrombosis alone, and 1291 (47.8%) had pulmonary embolism with or without deep-vein thrombosis. Overall, 429 patients (15.9%) had a history of venous thromboembolism.

PRIMARY OUTCOME AND KEY SECONDARY OUTCOMES

In the intention-to-treat analysis, clinically relevant bleeding during the 3-month trial period occurred in 44 of 1345 patients (3.3%) in the apixaban group and in 96 of 1355 (7.1%) in the rivaroxaban group (relative risk, 0.46; 95% confidence interval [CI], 0.33 to 0.65; P<0.001) (Table 2 and Fig. 2). Findings appeared to be consistent across prespecified subgroups (Fig. S1). In the sensitivity analysis conducted with a generalized linear mixed-effects model, the adjusted marginal relative risk was 0.45 (95% CI, 0.32 to 0.64).

Major bleeding occurred in 5 patients (0.4%) in the apixaban group and in 32 patients (2.4%) in the rivaroxaban group (relative risk, 0.16; 95% CI, 0.06 to 0.40). Major bleeding resulted in a decrease in the hemoglobin level or a blood transfusion in all 5 patients in the apixaban group. In the rivaroxaban group, major bleeding led to a decrease in the hemoglobin level or a blood transfusion in 28 patients and to bleeding in a critical area or organ in 4 patients (Table S3). No deaths due to bleeding occurred in the treatment groups.

Clinically relevant nonmajor bleeding occurred in 39 patients (2.9%) treated with apixaban and in 67 patients (4.9%) treated with rivaroxaban (relative risk, 0.59; 95% CI, 0.40 to 0.86). The most common types of clinically relevant nonmajor bleeding were vaginal bleeding (in 2.7% of the patients) and gastrointestinal bleeding (in 0.6%) in the apixaban group and vaginal bleeding (in 3.8%), hematuria (in 1.3%), and gastrointestinal bleeding (in 1.0%) in the rivaroxaban group (Table S4). Recurrent symptomatic venous thromboembolism occurred in 15 patients (1.1%) in the apixaban group and in 14 patients (1.0%) in the rivaroxaban group (relative risk, 1.08; 95% CI, 0.52 to 2.23) (Fig. 3). Death from any cause occurred in 1 patient (0.1%) in the apixaban group and in 4 patients (0.3%) in the rivaroxaban group (relative risk, 0.25; 95% CI, 0.03 to 2.26). No deaths attributed to recurrent venous thromboembolism occurred in the treatment groups. Odds ratios for the primary and secondary outcomes are provided in Table S5.

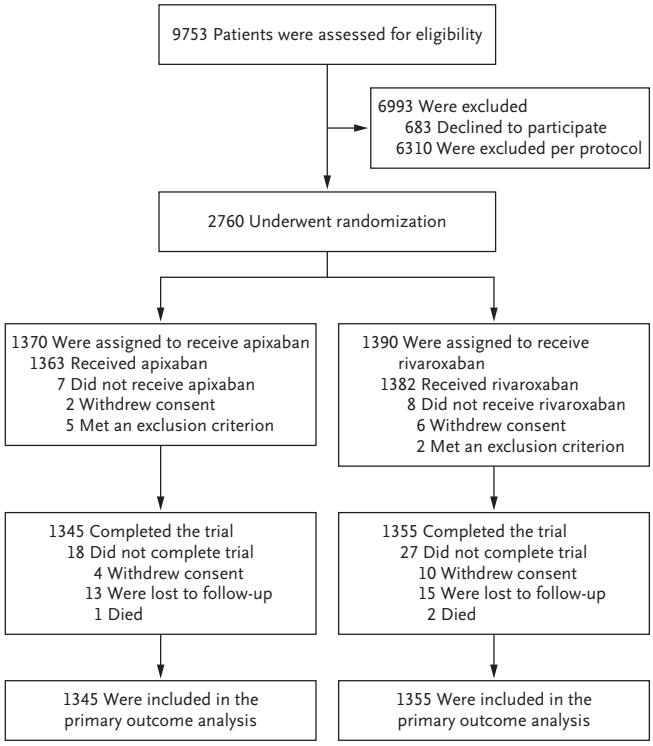

Figure 1. Randomization and Follow-up.

Eligible patients were randomly assigned in a 1:1 ratio to receive 3 months of rivaroxaban at a dose of 15 mg twice daily for 21 days followed by 20 mg daily or apixaban at a dose of 10 mg twice daily for 7 days followed by 5 mg twice daily. Seven participants met exclusion criteria after randomization and were not assessed in the primary analysis; five patients in the apixaban group were excluded owing to a weight of more than 120 kg (in 1 patient) or the absence of a qualifying venous thromboembolism (in 4), and two patients in the rivaroxaban group were excluded owing to the absence of a qualifying venous thromboembolism. Qualifying venous thromboembolism events were proximal deep-vein thrombosis or segmental or more proximal pulmonary embolism. Nonqualifying venous thromboembolism events are described in Table S1 in the Supplementary Appendix.

MEDICATION ADHERENCE

At each follow-up visit, medication adherence as reported by the patient was recorded with the use of a series of questions that were designed to assess adherence in different ways. Complete adherence was reported by 65.7% of the patients in the apixaban group and by 75.1% of those in the rivaroxaban group (Table S6).

SAFETY

Serious adverse events that were not related to bleeding or venous thrombosis occurred in 36 pa-

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Apixaban (N=1345)	Rivaroxaban (N=1355)
Age yr	58.0±16.3	58.5±15.8
Female sex no. (%)	597 (44.4)	578 (42.7)
Race or ethnic group no. (%)		
White	1182 (87.9)	1218 (89.9)
Black	51 (3.8)	44 (3.2)
Asian	36 (2.7)	31 (2.3)
Hispanic or Latino	21 (1.6)	13 (1.0)
Indigenous or Aboriginal	8 (0.6)	4 (0.3)
Other	38 (2.8)	35 (2.6)
Country no. (%)		
Canada	1244 (92.5)	1254 (92.5)
Australia	100 (7.4)	98 (7.2)
Ireland	1 (0.1)	3 (0.2)
Body weight kg	85.9±16.4	85.2±15.8
Body-mass index	29.1±5.2	28.9±5.1
Creatinine clearance		
Overall ml/min	107.1±38.8	105.6±38.3
<50 ml/min no. (%)	60 (4.5)	63 (4.6)
Continued antiplatelet use no. (%)	36 (2.7)	35 (2.6)
Qualifying venous thromboembolism diagnosis no. (%)		
Deep-vein thrombosis alone	691 (51.4)	718 (53.0)
Pulmonary embolism with or without deep-vein thrombosis	654 (48.6)	637 (47.0)
Provoked venous thromboembolism	322 (23.9)	290 (21.4)
Unprovoked venous thromboembolism	1022 (76.0)	1065 (78.6)
History of venous thromboembolism no. (%)‖	210 (15.6)	219 (16.2)

* Eligible patients were randomly assigned in a 1:1 ratio to receive 3 months of rivaroxaban at a dose of 15 mg twice daily for 21 days followed by 20 mg daily or apixaban at a dose of 10 mg twice daily for 7 days followed by 5 mg twice daily.
Plus minus values are means ±SD. Percentages may not sum to 100 because of rounding.
Race and ethnic group were reported by the patient.
Body-mass index is the weight in kilograms divided by the height in square meters.
Qualifying venous thromboembolism diagnosis indicates the diagnosis that led to enrollment and participation in the trial.
Provoked venous thromboembolism was defined as venous thromboembolism related to surgery, hospitalization, trauma, leg fracture or lower-limb cast, immobilization for at least 3 days, estrogen therapy, pregnancy, or postpartum status.
‖ History of venous thromboembolism indicates a medical history of venous thromboembolism before the qualifying thrombosis event.

tients (2.7%) in the apixaban group and in 30 patients (2.2%) in the rivaroxaban group (Table S7).

DISCUSSION

The current trial compared the direct oral anticoagulants apixaban and rivaroxaban with respect to the risk of bleeding among patients with acute pulmonary embolism or proximal deep-vein thrombosis. The trial showed that apixaban (at a dose of 10 mg twice daily for 7 days followed by 5 mg twice daily) was superior to rivaroxaban (at a dose of 15 mg twice daily for 21 days followed by 20 mg daily) regarding the primary outcome of clinically relevant bleeding, a composite of major bleeding or clinically relevant nonmajor bleeding,

Table 2. Clinical Outcomes during the Trial Period.

Outcome	Apixaban (N=1345)	Rivaroxaban (N=1355)	Relative Risk (95% CI)*
Primary outcome			
Clinically relevant bleeding	44 (3.3)	96 (7.1)	0.46 (0.33 0.65)
Secondary outcomes			
Major bleeding	5 (0.4)	32 (2.4)	0.16 (0.06 0.40)
Clinically relevant nonmajor bleeding	39 (2.9)	67 (4.9)	0.59 (0.40 0.86)
Death from bleeding	0	0	
Recurrent symptomatic venous thromboembolism	15 (1.1)	14 (1.0)	1.08 (0.52 2.23)
Death from recurrent venous thromboembolism	0	0	
Death from any cause	1 (0.1)	4 (0.3)	0.25 (0.03 2.26)

* Analyses of secondary outcomes were not adjusted for multiplicity, and the widths of the confidence intervals should not be used in place of hypothesis testing.
Clinically relevant bleeding was defined as a composite of major bleeding or clinically relevant nonmajor bleeding.
P<0.001 for the comparison of the apixaban group with the rivaroxaban group.

during the 3-month trial period. There was no apparent difference in the risk of the secondary outcome of recurrent venous thromboembolism between the two groups.

Clinical practice guidelines recommend direct oral anticoagulants as first-line therapy for acute venous thromboembolism because these agents have a better safety profile than vitamin K antagonists.[1,7,18] Prospective direct comparison trials have been lacking, which has limited recommendations for the preference of apixaban or rivaroxaban. Minimizing bleeding complications during treatment is an important consideration in the management of acute venous thromboembolism.[19] In the pivotal registration trials for apixaban and rivaroxaban, differences in the risk of clinically relevant bleeding were noted between the two direct oral anticoagulants and vitamin K antagonists, whereas the risk of recurrent thrombosis was similar.[8,9] These findings prompted deeper consideration of the differences in bleeding risks with respect to the trial design and participant characteristics.[20,21] Our trial confirms the lower risk of clinically relevant bleeding with apixaban than with vitamin K antagonists that was seen in the AMPLIFY trial.[9] In the present trial, the 3-month incidence of clinically relevant bleeding was significantly lower in the apixaban group than in the rivaroxaban group. The most common types of bleeding in the apixaban group were vaginal bleeding (in 2.7% of the patients) and gastrointestinal bleeding (in 0.6%), with a lower incidence of vaginal bleeding than in the AMPLIFY trial (5.4%).[9,22] In the rivaroxaban group, the most common types of bleeding were vaginal bleeding (in 3.8% of the patients), hematuria (in 1.3%), and gastrointestinal bleeding (in 1.0%). The incidence of vaginal bleeding in the rivaroxaban group was lower in our trial than in the EINSTEIN trials (9.5%).[8,22]

Our trial does not explain the difference in bleeding risk between patients treated with apixaban and those treated with rivaroxaban. Anticoagulant adherence at 3 months was lower in the apixaban group than in the rivaroxaban group (65.7% vs. 75.1%). However, the percentage of patients with recurrent venous thromboembolism during the 3-month trial period was approximately 1% in each group. Nonetheless, emphasizing anticoagulation adherence and discussing barriers to adherence with patients are critical to the management of acute venous thromboembolism. In our trial, the difference in the risk of clinically relevant bleeding may be related to the dose of rivaroxaban, given that most of the difference seems to have occurred during the first 3 weeks of treatment, a period when rivaroxaban was given at a dose that was 50% higher than the maintenance dose (Fig. 2). Despite this factor, the risk of recurrent venous thromboembolism appeared to be similar in each treatment group. Further evaluation in clinical trials is needed to confirm whether

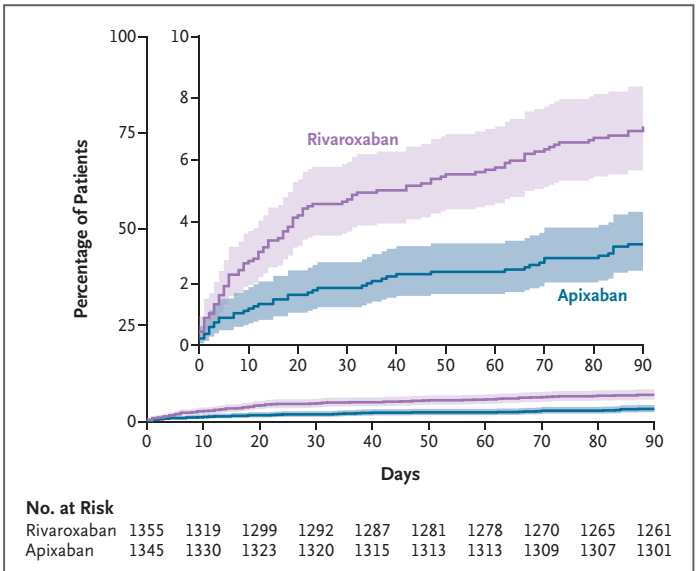

Figure 2. Clinically Relevant Bleeding.

Shown are Kaplan Meier curves for the first episode of clinically relevant bleeding, a composite of major bleeding or clinically relevant nonmajor bleeding, during the 3-month treatment period (primary outcome). The inset shows the same data on an enlarged y-axis. Shading indicates 95% confidence intervals.

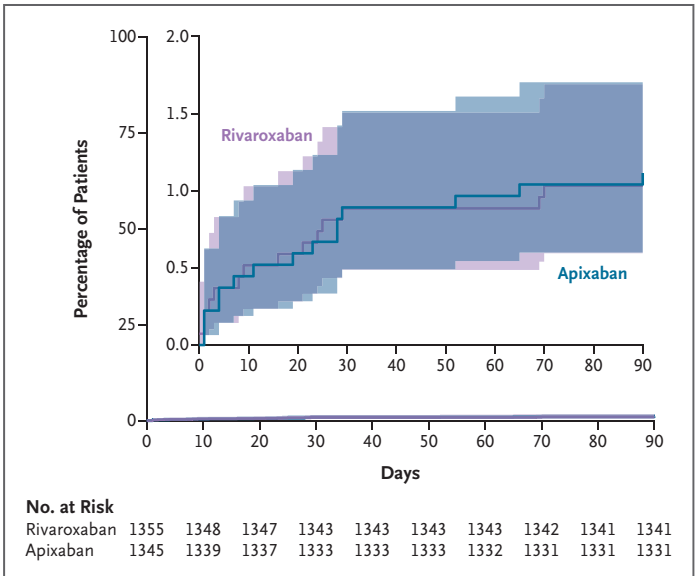

Figure 3. Recurrent Venous Thromboembolism.

Shown are Kaplan Meier curves for the first episode of recurrent symptomatic venous thromboembolism, a composite of recurrent deep-vein thrombosis or recurrent pulmonary embolism, during the 3-month treatment period (secondary outcome). The inset shows the same data on an enlarged y-axis. Shading indicates 95% confidence intervals.

the rivaroxaban dosing regimen contributed to the observed bleeding risks. Findings regarding the primary outcome were consistent across prespecified subgroups (Fig. S1). The 3-month mortality was low in each treatment group, a finding that is also consistent with published data.[23]

Our trial has limitations. The open-label design could have introduced ascertainment bias. Emerging data during the trial may have influenced physician perceptions about the bleeding risk with apixaban and rivaroxaban. However, ascertainment bias is unlikely because the bleeding events that were assessed in the trial are by definition overt and require a visit to a medical facility. Also, it is unlikely that knowledge of the anticoagulant received would have influenced the decision to transfuse or proceed with an intervention. We collected data only during the first 3 months of anticoagulation therapy; whether the differences in bleeding risk persist beyond this time period is unknown. The bleeding definitions used in the current trial do not incorporate the use of health care resources for the management of bleeding, nor do they consider patient perceptions about clinical severity and the effects of bleeding on quality of life.

Among additional limitations are the exclusion of patients with a body weight of more than 120 kg in accordance with the ISTH guidance at the time of the trial design,[12] which limits data on patients with overweight or obesity. Patients with cancer-associated thrombosis were also excluded from the trial because low-molecular-weight heparin was standard care at the time of the trial design. Pivotal registration trials of apixaban and rivaroxaban in that population were completed after our trial began. Diversity according to race and ethnic group was limited in the trial population. Finally, the trial was not powered to detect differences in the risk of recurrent venous thromboembolism. Findings from our trial should not be extrapolated to other indications, including extended secondary prevention of venous thromboembolism with a full or reduced dose of direct oral anticoagulants, cancer-associated acute venous thromboembolism, and atrial fibrillation; a clinical trial assessing bleeding risk with rivaroxaban and apixaban in patients with atrial fibrillation is ongoing (ClinicalTrials.gov number, NCT04642430).

Among patients with acute venous thromboembolism, the risk of clinically relevant bleeding

at 3 months was significantly lower with apixaban than with rivaroxaban.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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REFERENCES

1. Konstantinides SV, Meyer G, Becattini C, 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.
2. Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. Lancet 2012;379:1835-46.
3. White RH. The epidemiology of venous thromboembolism. Circulation 2003; 107:Suppl 1:I-4 I-8.
4. Cohen AT, Agnelli G, Anderson FA, et al. Venous thromboembolism (VTE) in Europe: the number of VTE events and associated morbidity and mortality. Thromb Haemost 2007;98:756-64.
5. Delluc A, Tromeur C, Le Ven F, et al. Current incidence of venous thromboembolism and comparison with 1998: a community-based study in Western France. Thromb Haemost 2016;116:967-74.
6. Heit JA. The epidemiology of venous thromboembolism in the community. Arterioscler Thromb Vasc Biol 2008;28:370-2.
7. Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic therapy for VTE disease: second update of the CHEST guideline and expert panel report. Chest 2021; 160(6):e545-e608.
8. The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363:2499-510.
9. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med 2013;369:799-808.
10. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.
11. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med 2018;378:615-24.
12. Martin K, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. J Thromb Haemost 2016;14: 1308-13.
13. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005; 3:692-4.
14. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost 2015;13:2119-26.

15. Le Gal G, Carrier M, Castellucci LA, et al. Development and implementation of common data elements for venous thromboembolism research: on behalf of SSC subcommittee on official communication from the SSC of the ISTH. J Thromb Haemost 2021;19:297-303.
16. Ranganathan P, Aggarwal R, Pramesh CS. Common pitfalls in statistical analysis: odds versus risk. Perspect Clin Res 2015;6:222-4.
17. McNutt L-A, Wu C, Xue X, Hafner JP. Estimating the relative risk in cohort studies and clinical trials of common outcomes. Am J Epidemiol 2003;157:940-3.
18. Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. Blood Adv 2020;4:4693-738.
19. Chai-Adisaksopha C, Hillis C, Isayama T, Lim W, Iorio A, Crowther M. Mortality outcomes in patients receiving direct oral anticoagulants: a systematic review and meta-analysis of randomized controlled trials. J Thromb Haemost 2015;13:2012-20.
20. Tritschler T, Castellucci LA. It s time for head-to-head trials with direct oral anticoagulants. Thromb Res 2019;180:64-9.
21. Beyer-Westendorf J, Lensing AWA, Arya R, et al. Choosing wisely: the impact of patient selection on efficacy and safety outcomes in the EINSTEIN-DVT/PE and AMPLIFY trials. Thromb Res 2017;149:29-37.
22. Godin R, Marcoux V, Tagalakis V. Abnormal uterine bleeding in women receiving direct oral anticoagulants for the treatment of venous thromboembolism. Vascul Pharmacol 2017;93-95:1-5.
23. van Es N, Coppens M, Schulman S, Middeldorp S, B ller HR. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. Blood 2014;124:1968-75.

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