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Rivaroxaban Versus Vitamin K Antagonist in Antiphospholipid Syndrome

A Randomized Noninferiority Trial

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Background: The potential role of new oral anticoagulants in antiphospholipid antibody syndrome (APS) remains uncertain.

Objective: To determine whether rivaroxaban is noninferior to dose-adjusted vitamin K antagonists (VKAs) for thrombotic APS.

Design: 3-year, open-label, randomized noninferiority trial. (EU Clinical Trials Register: EUDRA [European Union Drug Regulatory Authorities] code 2010-019764-36)

Setting: 6 university hospitals in Spain.

Participants: 190 adults (aged 18 to 75 years) with thrombotic APS.

Intervention: Rivaroxaban (20 mg/d or 15 mg/d, according to renal function) versus dose-adjusted VKAs (target international normalized ratio, 2.0 to 3.0, or 3.1 to 4.0 in patients with a history of recurrent thrombosis).

Measurements: The primary efficacy outcome was the proportion of patients with new thrombotic events; the primary safety outcome was major bleeding. The prespecified noninferiority margin for risk ratio (RR) was 1.40. Secondary outcomes included time to thrombosis, type of thrombosis, changes in biomarker levels, cardiovascular death, and nonmajor bleeding.

Results: After 3 years of follow-up, recurrent thrombosis occurred in 11 patients (11.6%) in the rivaroxaban group and 6 (6.3%) in the VKA group (RR in the rivaroxaban group, 1.83 [95% CI, 0.71 to 4.76]). Stroke occurred more commonly in patients receiving rivaroxaban (9 events) than in those receiving VKAs (0 events) (corrected RR, 19.00 [CI, 1.12 to 321.9]). Major bleeding occurred in 6 patients (6.3%) in the rivaroxaban group and 7 (7.4%) in the VKA group (RR, 0.86 [CI, 0.30 to 2.46]). Post hoc analysis suggested an increased risk for recurrent thrombosis in rivaroxaban-treated patients with previous arterial thrombosis, livedo racemosa, or APS-related cardiac valvular disease.

Limitation: Anticoagulation intensity was not measured in the rivaroxaban group.

Conclusion: Rivaroxaban did not show noninferiority to dose-adjusted VKAs for thrombotic APS and, in fact, showed a non–statistically significant near doubling of the risk for recurrent thrombosis.

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Antiphospholipid antibody syndrome (APS) is an acquired thrombophilic disorder in which vascular thrombosis (venous or arterial) and pregnancy losses may occur in the presence of persistent antiphospholipid antibodies (aPLs) (1–4). Although different pathogenic mechanisms have been described, long-term anticoagulation with vitamin K antagonists (VKAs), rather than immunosuppression, remains the standard treatment for secondary prevention of thrombosis.

Despite the use of dose-adjusted warfarin, the annual risk for recurrent thrombosis ranges from 2% to 5% (5–9), with half the cases occurring when the international normalized ratio (INR) is below the predetermined target range (5). In recent years, anticoagulation management has been a matter of debate, with arguments for and against high-intensity anticoagulation (INR, 3.1 to 4.0). Two randomized controlled trials demonstrated that standard-intensity anticoagulation (INR, 2.0 to 3.0) was noninferior to high-intensity treatment (5, 6). Maintaining optimized anticoagulation to prevent recurrent thrombosis and bleeding remains a therapeutic challenge.

Rivaroxaban is an orally active, direct factor Xa inhibitor that provides more consistent and predictable anticoagulation than warfarin. Currently, it is licensed for the treatment and secondary prevention of venous thromboembolism (10) and stroke prevention in patients with nonvalvular atrial fibrillation (11). So far, several case reports, case series, cross-sectional studies, and randomized controlled trials have provided conflicting data on the efficacy of rivaroxaban in APS (12–19).

Two randomized controlled trials comparing rivaroxaban with warfarin suggested that rivaroxaban may be efficacious in patients with previous venous thromboembolism who are receiving standard-intensity anticoagulation (INR, 2.0 to 3.0) (20) but showed an increased thrombotic risk in those with triple-positive aPLs (21). Results from these studies must be interpreted with caution in view of their limitations, which include the use of a laboratory surrogate marker as a

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primary outcome and premature termination due to an excess of study events (20, 21).

Thus, we conducted a randomized controlled comparative effectiveness trial to test whether rivaroxaban is noninferior to dose-adjusted VKAs for preventing thrombotic events in patients with APS.

METHODS

Design Overview

This multicenter, randomized, open-label, phase 3 noninferiority clinical trial was conducted at 6 university hospitals in Spain. The study recruited patients from March 2013 to December 2014. Follow-up was completed in December 2017. Vall d'Hebron Hospital (VHH) coordinated the trial, managed the database, and performed the primary analyses independently. The original research protocol and a summary of protocol changes are in **Supplement 1** (available at Annals.org). The local ethics committees approved the study, and all participants provided written informed consent before enrollment. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice principles. The full list of study investigators is shown in **Supplement 2, Appendix 1** (available at Annals.org).

Setting and Participants

Adult patients fulfilling the international consensus criteria for APS (3) were recruited from internal medicine and rheumatology clinics. Eligible patients included those with objectively confirmed arterial or venous thrombosis and a positive result on aPL testing on 2 occasions at least 3 months apart. Testing for aPL was performed locally and confirmed by the central laboratory (VHH). Acceptable candidates included those with lupus anticoagulant or moderate to high titers (≥40 GPL [IgG phospholipid] units) of IgG anticardiolipin, anti-β_2-glycoprotein I antibodies, or both, measured in accordance with international guidelines (3, 22). Patients with only IgM subtypes were not eligible. All patients with systemic lupus erythematosus were classified according to the revised criteria of the American College of Rheumatology (23).

Patients were excluded if they had clinically significant bleeding diathesis (such as refractory thrombocytopenia with a platelet count $\leq 50 \times 10^9$ cells/L); had intracranial hemorrhage, stroke, or gastrointestinal bleeding within the previous 3 months; were pregnant or lactating; had severe renal impairment (creatinine clearance, calculated with the Cockcroft–Gault formula, ≤30 mL/min/1.73 m^2 [24]); had an alanine aminotransferase level more than twice the upper limit of normal; had Child–Pugh class B or C cirrhosis; were nonadherent to their warfarin regimen; or were receiving cytochrome P450 3A4 inducers. Complete eligibility criteria are shown in **Supplement 2, Appendix 2** (available at Annals.org).

Randomization and Interventions

The randomized list, stratified by center and presence of systemic lupus erythematosus, was created at VHH by using computer-generated random-number sequences (C4-Study design pack software [GlaxoSmithKline]) in blocks of 10. Sequentially numbered, concealed envelopes containing group assignments were provided to the investigators. After written informed consent was obtained, the envelopes were opened in sequence and patients were randomly assigned in a 1:1 ratio to receive rivaroxaban (20 mg/d, or 15 mg/d for patients with a creatinine clearance of 30 to 49 mL/min/1.73 m^2) (24) or to continue receiving the adjusted dosage of VKAs (target INR, 2.0 to 3.0, or 3.1 to 4.0 for those with a history of recurrent thrombosis).

The trial was open label to ensure optimum VKA dosing and monitoring, and because bleeding management differs between VKAs and rivaroxaban. The transition from VKAs to rivaroxaban involved an intermediate step to therapeutic low-molecular-weight heparin. In brief, VKA therapy was discontinued; then, heparin administration (1 mg/kg per 12 hours) began when the INR was 2 or less, and it was continued for 48 hours. Finally, rivaroxaban treatment was started (**Supplement 2, Appendix 3**, available at Annals.org).

During the study, the rivaroxaban dosage could be modified in relation to changes in creatinine clearance (24). Adherence in the rivaroxaban group was evaluated by self-reported questionnaire and residual pill count at each visit. Patients exiting the study were not considered in the adherence calculation.

The use of additional aspirin, antimalarial drugs, or immunosuppressive agents was allowed at the investigator's discretion (**Supplement 2, Appendix 3**).

Outcomes and Follow-up

The primary efficacy end point was the proportion of patients who had a new thrombotic event during the study, confirmed by adjudication. Diagnosis of venous and arterial thrombosis was based on objective imaging techniques. The primary safety end point was the proportion of patients with a major bleeding episode. Secondary efficacy end points included time to thrombosis, type of thrombotic event, cardiovascular death, and changes in levels of selected biomarkers (D-dimer, von Willebrand factor, and platelet factor 4) (25–27). Secondary safety end points included any adverse event and nonmajor bleeding.

An independent committee blinded to the clinical end points applied protocol definitions to adjudicate suspected cases of thrombosis, death, and bleeding events that contributed to the prespecified end points (see outcome definitions in **Supplement 2, Appendix 4**, available at Annals.org).

Patients were evaluated monthly for the first 3 months and every 3 months thereafter. Follow-up was 36 months, regardless of events. The study treatment could be discontinued early because of unacceptable serious adverse or thrombotic events, any change in the patient's condition that justified discontinuation, consent withdrawal, pregnancy, or lack of adherence to the protocol. In the VKA group, doses were monitored and INR was measured at local hematologic clinics. International normalized ratio was checked every 2 to 6

weeks as necessary, but every 4 weeks on average. Unscheduled INR measurements during a thrombotic episode were obtained from the patient's clinical record. If the INR was not measured on the day of the episode, the reported INR was the value at the last scheduled visit before diagnosis of the episode.

Patients were instructed to go to the local emergency department if they had recurrent thrombosis or major bleeding. Results of any objective diagnostic tests were forwarded to VHH. Temporary drug withdrawal due to bleeding, surgery, or invasive procedures was carried out according to established protocols. Reasons for premature discontinuation of treatment were recorded.

The following laboratory tests were performed at each visit: complete blood count; renal and liver function tests; standard coagulation tests; urinalysis; 24-hour protein collection; and tests for anti–double-stranded DNA antibodies, antinuclear antibodies, complement levels, lupus anticoagulant, IgG and IgM anticardiolipin, and anti-β_2-glycoprotein I antibodies. Additional samples were obtained at baseline and every 6 months for further measurement of thrombotic risk biomarkers (D-dimer, von Willebrand factor, and platelet factor 4). At randomization, Global Anti-Phospholipid Syndrome Score (28) also was assessed (see **Supplement 2, Appendix 5** [available at Annals.org] for study measures).

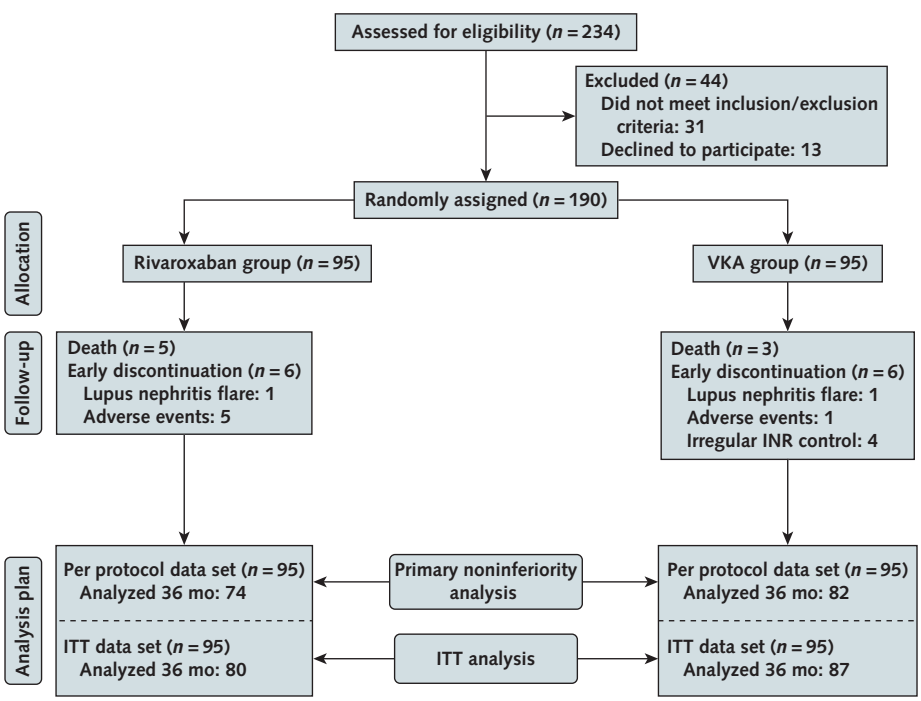
Reports of serious adverse events and serious adverse reactions were reviewed by external, independent, medically qualified staff and classified according to MedDRA (Medical Dictionary for Regulatory Activities), version 12 (available at www.meddra.org).

Statistical Analysis

The study was designed and powered to determine whether rivaroxaban was noninferior to VKAs by 36 weeks for the primary efficacy outcome. No clinical trials comparing rivaroxaban and warfarin in APS were available when the study was designed. Thus, to define the noninferiority margin, we considered meta-analysis data comparing warfarin with placebo with regard to stroke incidence in patients with atrial fibrillation (29), in whom the relative risk for stroke reduction was estimated as 0.36 (95% CI, 0.26 to 0.51). From this upper limit (0.51), the noninferiority margin was set to correspond to the preservation of 50% of the warfarin versus placebo effect, which corresponds to the square root of 0.51: 0.71. This corresponds to a relative risk for rivaroxaban versus warfarin of 0.71/0.51 = 1.40 as the noninferiority limit–that is, the limit of the upper 95% CI for rivaroxaban versus warfarin to declare noninferiority–with the 1-sided α-error at 2.5%. With these premises, 95 patients in each group would offer a statistical power of 80%.

Because this was a noninferiority study, the primary efficacy analysis was prespecified to be performed in the per protocol population, which included all patients receiving at least 1 dose of the study drug and being followed for events occurring while receiving treatment or within 7 days after discontinuation. An intention-to-treat (ITT) analysis was also performed. Follow-up in the ITT population continued until notification of study termination. The safety population comprised all patients receiving at least 1 dose of study medication. More detailed information is available in **Supplement 1**.

Figure 1. Study flow diagram.



INR = international normalized ratio; ITT = intention-to-treat; VKA = vitamin K antagonist.

Table 1. Characteristics of the Study Sample at Baseline

Characteristic	Rivaroxaban Group (n = 95)	VKA Group (n = 95)
Female sex, *n (%)*	61 (64.2)	60 (63.2)
Median age (IQR), *y*	47 (40–55)	51 (38–63)
Mean BMI (SD), *kg/m²*	28 (5.1)	29 (6.0)
Median duration of APS (IQR), *y*	7 (4–15)	6 (4–12)
APS category, *n (%)*		
Primary	64 (67.4)	68 (71.6)
Secondary	31 (32.6)	27 (28.4)
Clinical criteria for initial anticoagulation, *n (%)*		
Venous thrombosis	69 (72.6)	70 (73.7)
Arterial thrombosis	37 (38.9)	34 (35.8)
Both arterial and venous thrombosis	11 (11.6)	9 (9.5)
Obstetric medical history, *n (%)*	17 (17.9)	13 (13.7)
Recurrent thrombosis, *n (%)*	12 (12.6)	16 (16.8)
Other APS nonthrombotic manifestations, *n (%)*		
Valvular heart disease*	23 (24.2)	22 (23.2)
Renal thrombotic microangiopathy	6 (6.3)	9 (9.5)
Livedo reticularis†	37 (38.9)	26 (27.4)
Migraine†	33 (34.7)	21 (22.1)
Laboratory profile at inclusion, *n (%)*		
Lupus anticoagulant	93 (97.9)	90 (94.7)
Lupus anticoagulant alone	37 (38.9)	30 (31.6)
IgG/IgM antibodies		
aCL	62 (65.3)	65 (68.4)
Anti-β_2GPI	60 (63.2)	62 (65.3)
Anti-aPS/PT	31 (32.6)	33 (34.7)
Mean aCL/β_2GPI antibody level (SD)		
IgG aCL, *GPL units*	190.2 (6.5)	181.8 (275.5)
IgM aCL, *MPL units*	21.8 (30.4)	16.5 (20.3)
IgG anti-β_2GPI, *GPL units*	141.4 (241.9)	137.4 (262.8)
IgM anti-β_2GPI, *MPL units*	24.8 (31.9)	19.1 (31.6)
Lupus anticoagulant and IgG aCL and IgG anti-β_2GPI antibodies, *n (%)*	58 (61.1)	57 (60.0)
GAPSS risk for thrombosis‡		
Mean score (SD)	13.8 (2.7)	13.5 (2.7)
Score, *n (%)*		
<10	10 (10.5)	10 (10.5)
10 to <15	63 (66.3)	68 (71.6)
≥15	22 (23.2)	17 (17.9)
Aspirin use, *n (%)*	13 (13.7)	11 (11.6)
Rivaroxaban dose, *n (%)*		
20 mg once daily	90 (94.7)	NA
15 mg once daily§	5 (5.2)	NA
Coexisting cardiovascular risk factors, *n (%)*		
Smoking‖	28 (29.5)	38 (40.0)
Dyslipidemia	40 (42.1)	34 (35.8)
Diabetes mellitus	8 (8.4)	4 (4.2)
Hypertension	39 (41.1)	38 (40.0)
Mean biomarker levels		
D-dimer (SD), *nmol/L*	0.72 (0.76)	0.49 (0.45)
von Willebrand factor (SD), *ng/mL*	7221.3 (7458.9)	6381.7 (3381.9)
PF4 (SD), *ng/mL*	475.4 (237.1)	468.9 (4123)

aCL = anticardiolipin; APS = antiphospholipid antibody syndrome; aPS/PT = antiphosphatidylserine/prothrombin; β_2GPI = β_2-glycoprotein I; BMI = body mass index; GAPSS = Global Anti-Phospholipid Syndrome Score; GPL = IgG phospholipid; IQR = interquartile range; MPL = IgM phospholipid; NA = not applicable; PF4 = platelet chemokine platelet factor 4; VKA = vitamin K antagonist.

* Defined as echocardiographic detection of lesions, regurgitation, or stenosis of the mitral or aortic valve, according to the actual definition of APS-associated cardiac valve disease (3).

† $P < 0.050$ for the between-group comparison.

‡ GAPSS (33) is a categorical score derived from combining independent risk factors for thrombosis and pregnancy loss, considering the antiphospholipid antibody profile, conventional cardiovascular risk factors, and the autoimmune antibody profile. It was developed and validated in a cohort of patients with systemic lupus erythematosus. The GAPSS ranges from 1 to 20, with higher scores indicating increased risk.

§ Given only to patients with creatinine clearance of 30 to 49 mL/min/1.73 m^2.

‖ Including a history of smoking.

For the sample description, continuous variables are presented as mean and range or SD or as median and interquartile range; categorical variables are presented as frequencies and percentages. To estimate the main results, risks for thrombotic events and their ratio were calculated with 95% confidence limits. When a zero count was present, a corrected RR was computed, adding 0.5 in each table cell. A noninferiority contrast test against the noninferiority limit of 1.40 was applied.

Time to thrombotic event was analyzed with Cox proportional hazard models. If the number of events was too small to obtain a direct estimator of the hazard ratio, the Firth correction was applied. As secondary analyses, efficacy end points were also estimated, adjusting for potential confounder variables that substantially modify (>10%) the raw estimates: age, recurrent thrombosis, livedo racemosa, and migraine. Poisson regression was used to calculate the adjusted RRs. The estimates for bleeding events were not adjusted for other variables. Adverse events were compared by using the Fisher exact test. For the graphic representation, the product limit method was used. The estimators for potential interest subgroups were calculated with an exploratory aim. The statistical significance limit was set at $P < 0.050$. Statistical analyses were performed by using Stata 13.1 (StataCorp) and SAS 9.4 (SAS Institute).

Biomarker values were presented as continuous variables. Comparisons between groups were performed by *t* test, or Mann–Whitney U test for continuous values. Statistical analyses were performed by using GraphPad Prism, version 6.

Role of the Funding Source

Bayer Hispania had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

RESULTS

Recruitment and Follow-up

A total of 190 patients were randomly assigned to treatment groups (Figure 1). In each group, 6.3% of patients permanently stopped their assigned therapy before a thrombotic event and before the end date. Mean length of treatment was 33.1 months (range, 2 to 36 months) in the rivaroxaban group and 34.1 months (range, 6 to 36 months) in the VKA group; overall mean follow-up was 35.4 months (range, 18 to 36 months).

Patient Characteristics and Treatments

Table 1 shows the baseline clinical characteristics of the study participants. Migraine and livedo racemosa were more prevalent in the rivaroxaban group. A third of the patients had concomitant cardiovascular risk factors, such as smoking history, hypertension, or hyperlipidemia. Overall, APS-related valvular heart disease was present on echocardiography in 45 patients. Among these patients, mild to moderate mitral thickening was the most common finding (21 patients [22.1%] in the rivaroxaban group and 14 [14.7%] in the VKA group). Mean duration of valvular disease before randomization was 7.15 years (range, 1 to 15 years) in the rivaroxaban group and 8.4 years (range, 1 to 16 years) in the VKA group. Global Anti-Phospholipid Syndrome Score was similar between groups. Twenty-eight patients (14.7%) were receiving high-intensity VKA therapy. At baseline, 13 patients (13.7%) in the rivaroxaban group and 11 (11.6%) in the VKA group were receiving concomitant aspirin. Likewise, hydroxychloroquine and corticosteroids were being used by 29 patients (30.5%) and 26 patients (27.4%) in the rivaroxaban group and 26 (27.4%) and 23 (24.2%) in the VKA group, respectively (Supplement Table 1, available at Annals.org).

Primary Efficacy Outcome

In the per protocol analysis, recurrent thrombosis occurred in 11 patients (11.6%) in the rivaroxaban

Table 2. Efficacy End Points of Recurrent Thrombotic Events*

Study Population	Events, *n* (%)		Risk Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)‡	*P* Value
	Rivaroxaban Group (*n* = 95)	VKA Group (*n* = 95)†				
Per protocol, as treated						
All events	11 (11.6)	6 (6.3)	1.83 (0.71–4.76)	0.21	1.94 (0.72–5.24)	0.190
Arterial events§	10 (10.5)	3 (3.2)	3.33 (0.95–11.73)	0.060	3.52 (0.97–12.79)	0.060
Venous events§	2 (2.1)	3 (3.2)	0.67 (0.11–3.90)	0.65	0.70 (0.12–4.21)	0.70
Stroke	9 (9.5)	0 (0)	19.00 (1.12–321.9)	<0.001	19.97 (1.00–400.0)	0.050
Intention to treat						
All events	12 (12.6)	6 (6.3)	2.00 (0.78–5.11)	0.150	2.10 (0.79–5.59)	0.140
Arterial events	11 (11.6)	3 (3.2)	3.67 (1.06–12.73)	0.040	3.84 (1.07–13.76)	0.040
Venous events	2 (2.1)	3 (3.2)	0.67 (0.11–3.90)	0.65	0.70 (0.12–4.18)	0.69
Stroke	10 (10.5)	0 (0)	21.00 (1.25–353.3)	0.001	20.01 (1.12–431.8)	0.040

VKA = vitamin K antagonist.
* All analyses of thrombotic events were based on the first event in the safety population during treatment. Among patients who had a thrombotic event, 3 (50%) in the VKA group and 6 (54.5%) in the rivaroxaban group had additional conventional cardiovascular risk factors, and they were adherent to their treatment.
† Four thrombotic events in the VKA group occurred in patients with an international normalized ratio below target.
‡ Hazard ratios are for the rivaroxaban group compared with the VKA group.
§ One patient with catastrophic antiphospholipid antibody syndrome presented with arterial and venous events simultaneously.

Table 3. Safety End Points of Bleeding Events*

Variable	Events, *n* (%)		Risk Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)†	*P* Value
	Rivaroxaban Group (*n* = 95)	VKA Group (*n* = 95)				
Major bleeding						
Any	6 (6.3)	7 (7.4)	0.86 (0.30–2.46)	0.77	0.88 (0.30–2.63)	0.82
Decrease in hemoglobin level >2 g/dL	6 (6.3)	5 (5.3)	1.20 (0.38–3.80)	0.76	1.03 (0.30–3.54)	0.97
Transfusion	5 (5.3)	5 (5.3)	1.00 (0.30–3.34)	1.00	1.03 (0.30–3.57)	0.96
Critical bleeding‡	0	4 (4.2)	0.00 (0.00–1.51)	0.060	0.12 (0.00–3.03)	0.190
Fatal bleeding	0	0	–	–	–	–
Intracranial hemorrhage	0	2 (2.1)	0.00 (0.00–5.32)	0.25	0.21 (0.01–8.48)	0.41
Any bleeding	31 (32.6)	26 (27.4)	1.19 (0.77–1.85)	0.43	1.27 (0.75–2.15)	0.37
Nonmajor clinically relevant bleeding	9 (9.5)	5 (5.3)	1.80 (0.63–5.17)	0.28	2.35 (0.72–7.61)	0.160
Minor bleeding	16 (16.8)	14 (14.7)	1.14 (0.59–2.21)	0.69	1.16 (0.57–2.37)	0.69

VKA = vitamin K antagonist.
* All analyses of bleeding rates were based on the first event in the safety population during treatment.
† Hazard ratios are for the rivaroxaban group compared with the VKA group.
‡ Bleeding events were considered critical if they occurred in intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular (with compartment syndrome), or retroperitoneal sites.

group and 6 (6.3%) in the VKA group (RR, 1.83 [CI, 0.71 to 4.76]; *P* for noninferiority = 0.29, *P* for VKA superiority = 0.20). These results (upper CI, 4.76) clearly exceed the defined noninferiority margin of 1.40. Among all randomly assigned patients in the ITT analysis, primary events occurred in 12 (12.6%) in the rivaroxaban group and 6 (6.3%) in the VKA group (RR, 2.0 [CI, 0.78 to 5.11]; *P* for noninferiority = 0.57; *P* for VKA superiority = 0.13). Table 2 shows results of the unadjusted analyses, because those of the adjusted analyses were similar.

Bleeding Outcomes

In the as-treated safety population, major bleeding occurred in 6 patients (6.3%) in the rivaroxaban group and 7 (7.4%) in the VKA group (corrected RR, 0.86 [CI, 0.30 to 2.46]). Overall bleeding occurred in 31 patients (32.6%) in the rivaroxaban group and 26 (27.4%) in the VKA group (RR, 1.19 [CI, 0.77 to 1.85]) (Table 3). Bleeding at critical anatomical sites (such as intracranial, intraspinal, retroperitoneal, or pericardial sites) occurred in 4 patients in the VKA group, 2 of which were intracranial. No fatal bleeding episodes were observed. Rates of major bleeding from gastrointestinal sites were low in both groups (1.1% in the rivaroxaban vs. 2.1% in the VKA group). Menorrhagia was more common in patients receiving rivaroxaban (21 [22.1%] vs. 10 [10.5%]).

Secondary Efficacy Outcomes

Recurrent thrombotic events in the rivaroxaban group were predominantly arterial, with a high rate of stroke: 9 events compared with none in the VKA group (RR, 19.00 [CI, 1.12 to 321.9]). The hazard ratio for time to the primary event was 1.94 (CI, 0.72 to 5.24) (*P* = 0.19) (Figure 2). Results for the ITT analyses were effectively the same (Table 2). Catastrophic APS developed in 1 patient receiving rivaroxaban. Thrombotic events are reported in Supplement Table 2 (available at Annals.org); none occurred during the anticoagulation therapy–substitution transition. Adherence to rivaroxaban treatment was 97%. Among the patients who had a thrombotic event, rivaroxaban was withdrawn in 5 and aspirin was added for the rest. Among patients receiving VKAs, INR values were within therapeutic range a mean of 56% of the time (median, 58% [interquartile range, 46 to 70]). Four thrombotic events in the VKA group occurred in patients with an INR below target; aspirin was added to treatment for 2 patients.

Five deaths occurred in the rivaroxaban group (5.3%) and 3 in the VKA group (3.2%) (RR, 1.67 [CI, 0.41 to 6.78]; *P* = 0.47). Most were cancer related. Data on causes of death and nonhemorrhagic adverse events are shown in Supplement Table 3 and Table 4 (available at Annals.org).

No significant differences were observed in comparative biomarker levels at baseline or during follow-up (Supplement Figure 1 and Figure 2, available at Annals.org).

Exploratory Subgroup Analyses in Patients With Recurrent Thrombotic Events

Although the subgroups were too small to draw firm conclusions, recurrent thrombotic episodes tended to develop more frequently in the rivaroxaban than the VKA group among patients with livedo racemosa (21.6% vs. 7.7%), valvular heart disease (39.1% vs. 4.5%), and previous arterial episodes (18.9% vs. 8.8%) (Figure 3). In the rivaroxaban group, patients with recurrent thrombosis had a higher prevalence of livedo racemosa (72.7% vs. 34.5%; *P* = 0.02) and mitral valve disease (72.7% vs. 14.3%; *P* < 0.001) than those without it (Supplement Table 5, available at Annals.org).

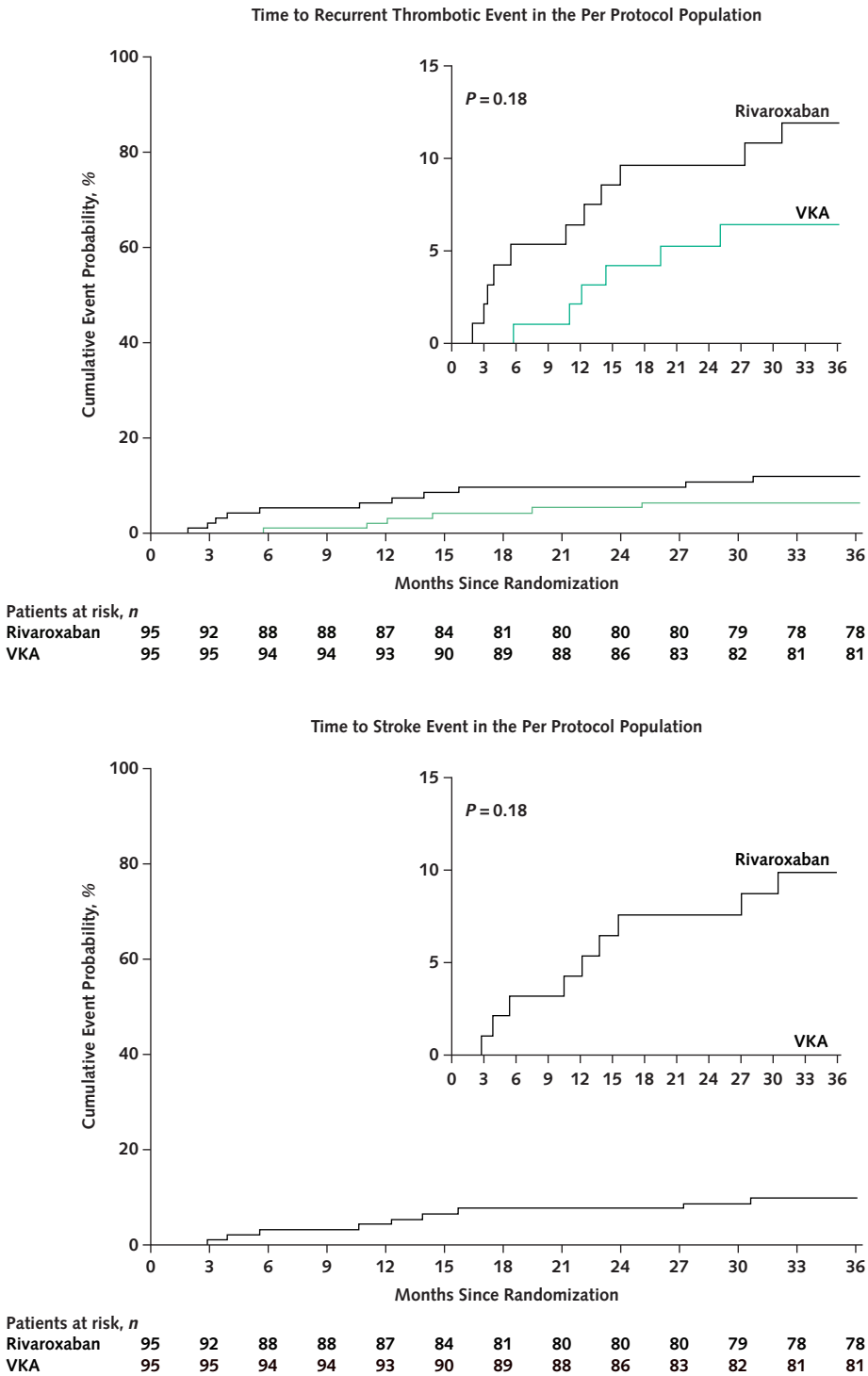
DISCUSSION

Long-term anticoagulation with VKAs is the mainstay of therapy for thrombotic APS, but its use may be problematic because of food and drug interactions, bleeding complications, and the need for frequent monitoring. Because newly available anticoagulation therapies may overcome some of these drawbacks, comparing them with VKAs is necessary.

In this randomized noninferiority trial, we compared rivaroxaban with VKA for secondary thromboprophylaxis in patients with APS. Baseline variables were evenly distributed, except for a higher proportion

of patients with migraine, livedo racemosa, recurrent thrombosis, and older age in the rivaroxaban group. This imbalance occurred by chance, and our analysis adjusted for these factors. The primary efficacy analyses could not demonstrate rivaroxaban noninferiority to dose-adjusted VKAs. In fact, although inconclusive, we found an increased risk for recurrent thrombosis in the rivaroxaban group, with a predominance of arterial thrombotic events and stroke in particular. Recurrent thrombosis in the VKA group occurred mainly while INR

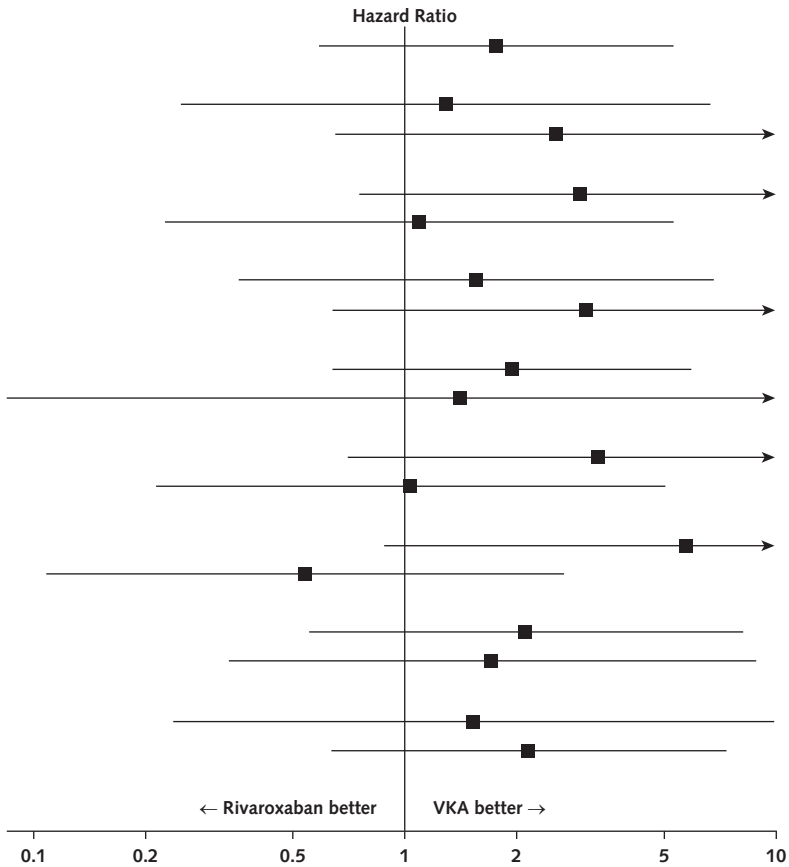
Figure 2. Time to recurrent thrombotic and stroke events in the per protocol population.



Intention-to-treat data do not differ perceptibly from those of the per protocol analyses. *P* values are from a log-rank test. VKA = vitamin K antagonist.

Figure 3. Exploratory subgroup analysis: Risk ratios of thrombosis in patient subgroups, according to clinically relevant characteristics.

Subgroup	Patients, *n*/*N* (%)	
	Rivaroxaban	VKA
All patients	11/95 (11.6)	6/95 (6.3)
Recurrent thrombosis		
Yes	3/12 (25.0)	3/16 (18.8)
No	8/83 (9.6)	3/79 (3.8)
Previous arterial thrombosis		
Yes	7/37 (18.9)	3/34 (8.8)
No	4/58 (6.9)	3/61 (4.9)
Previous venous thrombosis		
Yes	6/69 (8.7)	3/70 (4.3)
No	5/26 (19.2)	3/25 (12.0)
aPL triple positivity		
Yes	10/58 (17.2)	5/57 (8.8)
No	1/37 (2.7)	1/38 (2.6)
Livedo racemosa		
Yes	8/37 (21.6)	2/26 (7.7)
No	3/58 (5.2)	4/69 (5.8)
APS-related valvular disease		
Yes	9/23 (39.1)	1/22 (4.5)
No	2/72 (2.8)	5/73 (6.8)
Migraine		
Yes	8/33 (24.2)	3/21 (14.3)
No	3/62 (4.8)	3/71 (4.2)
SLE		
Yes	3/31 (9.7)	2/27 (7.4)
No	8/64 (12.5)	4/68 (5.9)



Cardiac valvular disease related to APS was defined as echocardiographic detection of mitral or aortic valve lesions, regurgitation, or stenosis according to the APS-associated cardiac valvular disease definition (3). aPL = antiphospholipid antibody; APS = antiphospholipid antibody syndrome; SLE = systemic lupus erythematosus; VKA = vitamin K antagonist.

values were below the desired range. In the primary safety analysis, no differences were observed in major bleeding rates.

Our findings differ from those of Cohen and colleagues (20), who observed no thrombotic events after 6 months of rivaroxaban or standard-intensity warfarin in patients with APS. However, the primary outcome of that trial was a laboratory surrogate measure: the difference in endogenous thrombin potential. In addition, patients with arterial events and recurrent thrombosis were excluded, only 28% of patients had a high-risk antibody profile, and the follow-up was short (20).

Our results are consistent with those of observational studies showing recurrent thrombosis in patients with APS after switching from warfarin to direct oral anticoagulants (12–19), as well as with the findings of TRAPS (Trial on Rivaroxaban in Antiphospholipid Syndrome) (21). The TRAPS study aimed to demonstrate that rivaroxaban is noninferior to warfarin for preventing thromboembolic events in patients with high-risk triple-positive APS. In contrast to our study, the primary outcome was a composite of thromboembolic events, major bleeding, and vascular death. The trial was interrupted prematurely because of an imbalance in the composite end point. As in our study, a higher rate of thrombotic events was observed in the rivaroxaban groups, all occurring in the arterial circulation. Seven (12%) occurred in patients randomly assigned to rivaroxaban (4 ischemic strokes and 3 myocardial infarctions), whereas none occurred in the warfarin group (21).

Although our study was not powered for subgroup analysis, we identified livedo racemosa, valvular heart disease, and previous arterial thrombosis as risk factors for recurrent thrombosis in patients receiving rivaroxaban. These are already known risk factors for arterial thrombosis in APS (30–33). Although aPL triple positivity has been associated with recurrent thrombosis during direct oral anticoagulant treatment (12, 21), we did not find this association. Conventional cardiovascular risk factors were found concomitantly in 30% to 40% of the patients, similar to other reported cohorts (21), but no association with thrombotic risk was found.

A strong association between widespread livedo racemosa and cerebrovascular events has been de-

scribed for more than a decade (34). Livedo reticularis also has been strongly associated with lupus anticoagulant, hypertension, and heart valve abnormalities, especially mitral valve regurgitation. Its low prevalence in patients with only venous events makes it a good marker for the "arterial–arteriolar" APS subset (32, 33).

Whether additional therapy with aspirin is effective in APS remains unknown (27). Although the proportion of patients receiving aspirin in our study was small, no statistical differences in arterial thrombotic rates were observed between recipients and nonrecipients. Likewise, conclusions could not be drawn regarding additional therapy with hydroxychloroquine, a drug suggested to play a role in lowering aPL titers and preventing thrombotic recurrence (35).

The reasons rivaroxaban failed to prevent arterial thrombotic events in patients with APS are uncertain. One explanation may be a suboptimal drug concentration related to interindividual variability; however, in previous trials of direct oral anticoagulation in which variable drug concentration was measured, no association between thrombosis and bleeding risk was demonstrated (36, 37). Another reason may be higher anti-Xa activity requirements to prevent arterial events, as described in experimental models (38). A third explanation may be poor treatment adherence, because routine coagulation monitoring is not required; however, the adequate adherence rate in our study, despite premature withdrawal in 6% of patients, does not explain the failure of treatment. Finally, whereas warfarin targets factors II, VII, IX, and X; protein S; and protein C, and pharmacokinetically has a longer half-life than rivaroxaban, rivaroxaban targets only 1 coagulation factor (Xa). Whether inhibition of only 1 factor rather than several might explain treatment failure is uncertain.

Our aim was to evaluate whether the new therapy had an efficacy at least similar to that of the standard treatment. The acceptable noninferiority margin was defined from information available when the study was designed. At that time, the anticipated rate of recurrent thrombosis in patients with APS receiving warfarin was estimated to be 14% over 3 years (5–7). However, the outcome risk in our study's control group was lower than expected (6.3% vs. 14%), but the potential problems that this could cause were limited by the poor results in the rivaroxaban group.

The study had several limitations: Anticoagulation intensity was not measured, the study was underpowered to detect differences in patient subgroups, and the exploratory nature of post hoc analyses did not allow conclusions to be drawn. Therefore, caution must be used in interpreting results related to livedo racemosa, migraine, and previous arterial episodes.

In conclusion, rivaroxaban did not demonstrate noninferiority to dose-adjusted VKAs for secondary thromboprophylaxis in patients with thrombotic APS. Instead, our results indicate a recurrent thrombotic rate that is nearly double, albeit without statistical significance.

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Data Sharing Statement: The following data will be made available with publication: deidentified participant data (available from Dr. Josefina Cortés-Hernández; e-mail, fina.cortes@vhir.org). The following supporting documents will be made available with publication: informed consent form (available from Dr. Josefina Cortés-Hernández; e-mail, fina.cortes@vhir.org). These data will be made available to researchers whose proposed use of the data has been approved for a specified purpose, with investigator support, and with a signed data access agreement (no restrictions).

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