

# Efficacy and Safety of Apixaban Compared With Warfarin in Patients With Atrial Fibrillation and Peripheral Artery Disease: Insights From the ARISTOTLE Trial

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**Background**—We studied (1) the rates of stroke or systemic embolism and bleeding in patients with atrial fibrillation and peripheral artery disease (PAD) and (2) the efficacy and safety of apixaban versus warfarin in patients with atrial fibrillation with and without PAD.

**Methods and Results**—The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial randomized 18 201 patients with atrial fibrillation to apixaban or warfarin for stroke/systemic embolism prevention; 884 (4.9%) patients had PAD at baseline. Patients with PAD had higher unadjusted rates of stroke and systemic embolism (hazard ratio [HR] 1.73, 95% CI 1.22–2.45;  $P=0.002$ ) and major bleeding (HR 1.34, 95% CI 1.00–1.81;  $P=0.05$ ), but after adjustment, no differences existed in rates of stroke and systemic embolism (HR 1.32, 95% CI 0.93–1.88;  $P=0.12$ ) and major bleeding (HR 1.03, 95% CI 0.76–1.40;  $P=0.83$ ) compared with patients without PAD. The risk of stroke or systemic embolism was similar in patients assigned to apixaban and warfarin with PAD (HR 0.63, 95% CI 0.32–1.25) and without PAD (HR 0.80, 95% CI 0.66–0.96; interaction  $P=0.52$ ). Patients with PAD did not have a statistically significant reduction in major or clinically relevant nonmajor bleeding with apixaban compared with warfarin (HR 1.05, 95% CI 0.69–1.58), whereas those without PAD had a statistically significant reduction (HR 0.65, 95% CI 0.58–0.73; interaction  $P=0.03$ ).

**Conclusions**—Patients with PAD in ARISTOTLE had a higher crude risk of stroke or systemic embolism compared with patients without PAD that was not present after adjustment. The benefits of apixaban versus warfarin for stroke and systemic embolism were similar in patients with and without PAD. These findings highlight the need to optimize the treatment of patients with atrial fibrillation and PAD.

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**Key Words:** apixaban • atrial fibrillation • bleeding • peripheral artery disease • stroke • systemic embolism

The rates of both peripheral artery disease (PAD) and atrial fibrillation (AF) are increasing, with an estimated 33.5 million people with AF and 202 million with PAD worldwide.<sup>1,2</sup> Patients with PAD and AF are at increased risk of stroke. Stroke risk scores have been developed for patients with AF and, with the exception of the recently created ABC risk score, are based on clinical variables.<sup>3</sup> The CHA<sub>2</sub>DS<sub>2</sub>-

VASc risk score for stroke and systemic embolism incorporates vascular disease, which includes myocardial infarction (MI), aortic plaque, and PAD. The inclusion of vascular disease in the CHA<sub>2</sub>DS<sub>2</sub>-VASc risk score emphasizes the importance of PAD as a risk factor in patients with AF.<sup>4,5</sup> Nevertheless, there are limitations to incorporating PAD into the CHA<sub>2</sub>DS<sub>2</sub>-VASc scoring system, including a small number (N=62 [5.7%])

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An accompanying Table S1 is available at <http://jaha.ahajournals.org/content/6/1/e004699/DC1/embed/inline-supplementary-material-1.pdf>

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of patients with PAD in the validation cohort and the exclusion of patients with PAD on oral anticoagulation at baseline.<sup>4,5</sup> Recent data from a large PAD cohort on oral anticoagulation at baseline found no statistically significant difference in risk of stroke or systemic embolism in patients with PAD but did find a treatment effect on bleeding risk with type of oral anticoagulant therapy.<sup>6</sup> The use of non-vitamin K antagonist oral anticoagulants in the treatment of AF is increasing; however, little is known about the effectiveness and safety of these newer agents in patients with PAD.<sup>7–9</sup>

In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial comparing apixaban and warfarin in patients with AF, apixaban was superior to warfarin in preventing stroke and systemic embolism and reducing major bleeding.<sup>10</sup> In this analysis of ARISTOTLE, we aimed to evaluate (1) the association of PAD with clinical outcomes (stroke, systemic embolism, and bleeding) and (2) the effectiveness and safety of apixaban and warfarin in patients with AF with and without PAD.

## Methods

ARISTOTLE was a randomized, double-blind, double-dummy trial comparing apixaban with dose-adjusted warfarin in 18 201 patients with AF and at least 1 risk factor for stroke. The study design was described previously.<sup>11</sup> Patients were randomly assigned to twice-daily dosing of apixaban 5 mg or dose-adjusted warfarin (target International Normalized Ratio 2.0–3.0). Key exclusion criteria were AF due to a reversible cause, moderate or severe mitral stenosis, conditions other than AF requiring anticoagulation, stroke within the previous 7 days, need for aspirin at a dose of >165 mg per day or both aspirin and clopidogrel, and severe renal insufficiency. The trial was designed and approved by a steering committee and approved by appropriate ethics committees at all sites. All patients provided written informed consent.

## Definition of PAD

The presence of PAD was designated by site investigators and reported on the case report form. Those with a history of PAD were included in the PAD cohort. The presence of carotid artery stenosis and aortic aneurysm was captured separately and did not constitute PAD.

## Outcomes

The primary efficacy outcome was ischemic or hemorrhagic stroke or systemic embolism. Secondary efficacy outcomes included death from any cause and rate of MI. The primary safety outcome was major bleeding, as defined by the

International Society on Thrombosis and Haemostasis (ISTH). Secondary safety outcomes included a composite of major bleeding and clinically relevant nonmajor bleeding. A clinical events committee, whose members were not aware of study group assignments, adjudicated the primary and secondary efficacy and safety outcomes.

## Statistical Analysis

The current analysis is a subgroup analysis of the ARISTOTLE population; however, it was not prespecified prior to the completion of the study. Cox proportional hazards regression models were used to assess (1) the association between PAD and efficacy and safety outcomes and (2) the treatment effect of apixaban versus warfarin within subgroups of patients with and without PAD.

All models were stratified by prior vitamin K antagonist use and region. Adjustment variables for each end point were determined by model selection in the full ARISTOTLE cohort. Adjustment variables for stroke or systemic embolism included age; weight; diabetes mellitus; hypertension; moderate valvular disease; prior stroke, transient ischemic attack, or systemic embolism; and type of AF. For the end points of all-cause and cardiovascular death, adjustment variables included age; sex; systolic blood pressure; diastolic blood pressure; weight; hypertension; moderate valvular disease; left bundle-branch block; prior MI; prior stroke, transient ischemic attack, or systemic embolism; anemia; smoking; New York Heart Association classification; CHADS<sub>2</sub> score; and renal function. Adjustment variables for MI included age, diabetes mellitus, coronary artery disease, prior MI, New York Heart Association classification, and renal function. Adjustment variables for all bleeding end points included age, sex, coronary artery disease, history of MI, prior bleeding, anemia, CHADS<sub>2</sub> score, and renal function.

Outcomes are presented as events per 100 patient-years of follow-up. Risk relationships are presented as adjusted hazard ratios (HRs) with 95% CIs derived from the adjusted Cox models. Categorical variables were compared for those with and without PAD using chi-square tests and are presented as count per number not missing (percentage). Continuous variables were compared by Wilcoxon rank sum tests and are presented as medians (25th, 75th percentiles).

## Results

### Study Population

A total of 18 201 patients were enrolled in the ARISTOTLE trial. PAD status was reported in 17 980 patients. Of those, 884 (4.9%) had PAD at baseline and were included in this analysis. Baseline demographics and patient characteristics

**Table 1.** Baseline Demographics and Patient Characteristics by History of PAD

Variable	PAD (n=884)	No PAD (n=17 096)	P Value
Age, y, median (25th, 75th)	73 (66.5, 79)	70 (62, 76)	<0.0001
Female sex	251/884 (28.4)	6090/17 096 (35.6)	<0.0001
Region			<0.0001
North America	307/884 (34.7)	4133/17 096 (24.2)	
Latin America	138/884 (15.6)	3299/17 096 (19.3)	
Europe	368/884 (41.6)	6893/17 096 (40.3)	
Asia Pacific	71/884 (8.0)	2771/17 096 (16.2)	
CHADS <sub>2</sub> score, mean±SD	2.66±1.25	2.09±1.09	<0.0001
≤1	164/884 (18.6)	5929/17 096 (34.7)	
2	284/884 (32.1)	6152/17 096 (36.0)	
≥3	436/884 (49.3)	5015/17 096 (29.3)	
Presenting characteristics			
Systolic BP, mm Hg, median (25th, 75th)	130 (120, 140)	130 (120, 140)	0.2785
Weight, kg, median (25th, 75th)	83.0 (71.5, 95.8)	82.0 (70.0, 95.5)	0.1417
Moderate or severe renal impairment	228/884 (25.8)	2745/17 021 (16.1)	<0.0001
Baseline comorbidities			
History of stroke, TIA, or systemic embolism	295/884 (33.4)	3189/17 096 (18.7)	<0.0001
Carotid disease (bruit, stent, stenosis, endarterectomy)	169/884 (19.1)	441/17 096 (2.6)	<0.0001
Nonparoxysmal AF type	745/884 (84.3)	14 470/17 093 (84.7)	0.7609
Prior warfarin/VKA	553/884 (62.6)	9721/17 096 (56.9)	0.0008
Coronary artery disease	523/884 (59.2)	5469/17 092 (32.0)	<0.0001
Myocardial infarction	257/884 (29.1)	2297/17 094 (13.4)	<0.0001
CHF within 3 months or LVEF ≤40%	363/884 (41.1)	6000/17 096 (35.1)	0.0003
Diabetes mellitus	325/884 (36.8)	4172/17 096 (24.4)	<0.0001
Hypertension	813/884 (92.0)	14 991/17 096 (87.7)	0.0001
Current smoking	89/884 (10.1)	1378/17 079 (8.1)	0.0343
Moderate or worse valvular heart disease	239/884 (27.0)	2953/17 094 (17.3)	<0.0001
History of bleeding	213/884 (24.1)	2794/17 093 (16.3)	<0.0001
History of fall within previous year	77/828 (9.3)	669/15 451 (4.3)	<0.0001
Medications			
ACEI or ARB	668/877 (76.2)	12 053/16 817 (71.7)	0.0039
Beta blocker	603/877 (68.8)	10 767/16 817 (64.0)	0.0044
Aspirin	345/884 (39.0)	5231/17 096 (30.6)	<0.0001
Clopidogrel	33/884 (3.7)	300/17 096 (1.8)	<0.0001

ACEI indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BP, blood pressure; CHF, congestive heart failure; LVEF, left ventricular ejection fraction; PAD, peripheral artery disease; TIA, transient ischemic attack; VKA, vitamin K antagonist.

according to the presence or absence of PAD are shown in Table 1.

Participants with PAD were more likely to be older, male, and current smokers. They were more likely to have a history of diabetes mellitus, MI, coronary artery disease, carotid artery disease, or moderate or worse valvular heart

disease and to have been on warfarin previously and had a higher risk of bleeding and fall within the previous year. Patients with PAD were more likely to be on aspirin, clopidogrel, or any aspirin or thienopyridine at baseline, at 1 year of follow-up, and at the time of study drug discontinuation (Table 2).

**Table 2.** Antiplatelet Use at Baseline and During Follow-up

	PAD (All)	No PAD (All)	PAD (Apixaban)	PAD (Warfarin)	No PAD (Apixaban)	No PAD (Warfarin)
<b>Baseline</b>						
Patients, n	884	17 096	442	442	8564	8532
ASA	345 (39.0)	5231 (30.6)	160 (36.2)	185 (41.9)	2668 (31.2)	2563 (30.0)
Clopidogrel	33 (3.7)	300 (1.8)	21 (4.8)	12 (2.7)	146 (1.7)	154 (1.8)
Any ASA or thienopyridine	376 (42.5)	5477 (32.0)	179 (40.5)	197 (44.6)	2786 (32.5)	2691 (31.5)
<b>At 1 year</b>						
Patients, n	793	15 976	398	395	8037	7939
ASA	222 (28.0)	3311 (20.7)	95 (23.9)	127 (32.2)	1713 (21.3)	1598 (20.1)
Clopidogrel	34 (4.3)	238 (1.5)	18 (4.5)	16 (4.1)	124 (1.5)	114 (1.4)
Any ASA or thienopyridine	247 (31.1)	3484 (21.8)	110 (27.6)	137 (34.7)	1800 (22.4)	1684 (21.2)
<b>At time of study drug discontinuation*</b>						
Patients, n	884	17 096	442	442	8564	8532
ASA	263 (29.8)	3559 (20.8)	115 (26.0)	148 (33.5)	1828 (21.3)	1731 (20.3)
Clopidogrel	31 (3.5)	244 (1.4)	18 (4.1)	13 (2.9)	113 (1.3)	131 (1.5)
Any ASA or thienopyridine	289 (32.7)	3742 (21.9)	130 (29.4)	159 (36.0)	1914 (22.3)	1828 (21.4)

ASA indicates aspirin; PAD, peripheral artery disease.

\*Or at the time of last contact.

## Outcomes in Patients With and Without PAD

Rates of efficacy end points and corresponding HRs for patients with PAD compared with patients without PAD are shown in Table 3. The overall unadjusted rate of stroke or systemic embolism was higher in patients with versus without PAD (HR 1.73, 95% CI 1.22–2.45;  $P=0.002$ ), but after adjustment for differences in patient characteristics, no difference was present in rates of stroke or systemic embolism (HR 1.32, 95% CI 0.93–1.88;  $P=0.12$ ). Those with PAD had an increased risk of all-cause death (HR 1.36, 95% CI 1.11–1.67;  $P=0.003$ ) and cardiovascular death (HR 1.44, 95% CI 1.08–1.90;  $P=0.01$ ) compared with those without PAD.

Rates of bleeding end points and corresponding HRs for patients with PAD compared with those without PAD are also shown in Table 3. Crude rates of ISTH major bleeding were higher in patients with versus without PAD (HR 1.34, 95% CI 1.00–1.81;  $P=0.05$ ), but no difference in event rates was present after adjustment (HR 1.03, 95% CI 0.76–1.40;  $P=0.83$ ) between patients with and without PAD. Clinically overt bleeding was more common in patients with PAD compared with those without PAD (HR 1.61, 95% CI 1.13–2.30;  $P=0.008$ ), and patients with PAD were more likely to have mucosal bleeding (HR 1.58, 95% CI 1.07–2.33;  $P=0.02$ ) and gastrointestinal bleeding (HR 1.72, 95% CI 1.11–2.67;  $P=0.02$ ) compared with those without PAD. There was no statistically significant difference in intracranial bleeding (HR

1.19, 95% CI 0.60–2.35;  $P=0.63$ ) in patients with PAD compared with those without PAD.

## Apixaban Versus Warfarin in Patients With and Without PAD

The effect of apixaban versus warfarin for the prevention of stroke or systemic embolism was similar in patients with PAD (HR 0.63, 95% CI 0.32–1.25) and without PAD (HR 0.80, 95% CI 0.66–0.96; interaction  $P=0.52$ ) (Figures 1 and 2). The effect of apixaban versus warfarin on all-cause death was also similar in patients with PAD (HR 1.03, 95% CI 0.71–1.51) and without PAD (HR 0.88, 95% CI 0.78–0.99; interaction  $P=0.42$ ).

Patients with PAD appeared to have no difference in ISTH major bleeding with apixaban compared with warfarin (HR 0.81, 95% CI 0.46–1.44) versus those without PAD (HR 0.68, 95% CI 0.59–0.79; interaction  $P=0.58$ ) (Figure 1). Patients with PAD had no statistically significant reduction in major or clinically relevant nonmajor bleeding (HR 1.05, 95% CI 0.69–1.58) with apixaban compared with warfarin, whereas those without PAD had a statistically significant reduction in major or clinically relevant nonmajor bleeding (HR 0.65, 95% CI 0.58–0.73; interaction  $P=0.03$ ) with apixaban compared with warfarin. Similar results were seen for the outcome of clinically relevant nonmajor bleeding alone (apixaban versus warfarin: HR 1.39, 95% CI 0.77–2.50; patients with versus without PAD: HR 0.65, 95% CI 0.56–0.75; interaction  $P=0.01$ ) (Figure 3, Table S1).

**Table 3.** Association Between PAD and Outcomes

Outcomes	PAD Events (Rate)	No PAD Events (Rate)	Unadjusted HR (95% CI)	Unadjusted P Value	Adjusted HR (95% CI)	Adjusted P Value
<b>Efficacy end points</b>						
Stroke or systemic embolism	34 (2.17)	440 (1.40)	1.73 (1.22–2.45)	0.0022	1.32 (0.93–1.88)	0.1227
All-cause death	108 (6.71)	1151 (3.58)	1.97 (1.61–2.40)	<0.0001	1.36 (1.11–1.67)	0.0033
Cardiovascular death	58 (3.60)	586 (1.82)	2.13 (1.62–2.79)	<0.0001	1.44 (1.08–1.90)	0.0117
MI	19 (1.20)	171 (0.54)	2.02 (1.26–3.26)	0.0037	1.25 (0.77–2.03)	0.3722
<b>Safety end points</b>						
ISTH major bleeding	47 (3.42)	731 (2.56)	1.34 (1.00–1.81)	0.0504	1.03 (0.76–1.40)	0.8256
ISTH major or clinically relevant nonmajor bleeding	92 (6.85)	1380 (4.93)	1.38 (1.12–1.71)	0.0027	1.12 (0.90–1.39)	0.3114
Clinically relevant nonmajor bleeding	45 (3.30)	710 (2.50)	1.29 (0.96–1.75)	0.0957	1.10 (0.81–1.50)	0.5416
GUSTO moderate or severe bleed	36 (2.61)	486 (1.69)	1.57 (1.12–2.21)	0.0089	1.22 (0.86–1.72)	0.2709
TIMI major or minor bleed	41 (2.98)	560 (1.95)	1.56 (1.13–2.14)	0.0063	1.22 (0.88–1.70)	0.2226
<b>ISTH major bleeding type</b>						
Required transfusion	27 (1.96)	294 (1.02)	1.80 (1.21–2.68)	0.0036	1.32 (0.88–1.98)	0.1840
Required a medical or surgical intervention to stop bleeding	12 (0.86)	218 (0.76)	1.15 (0.64–2.06)	0.6383	0.97 (0.54–1.76)	0.9242
Required changes in antithrombotic therapy	33 (2.39)	360 (1.25)	1.86 (1.30–2.66)	0.0007	1.41 (0.98–2.04)	0.0665
Required hospitalization	29 (2.10)	338 (1.17)	1.76 (1.21–2.58)	0.0035	1.28 (0.86–1.89)	0.2178
Fatal bleeding	2 (0.14)	17 (0.06)	2.87 (0.65–12.62)	0.1624	1.94 (0.42–8.94)	0.3960
<b>ISTH major bleeding site</b>						
Intracranial	9 (0.65)	165 (0.57)	1.35 (0.69–2.64)	0.3869	1.19 (0.60–2.35)	0.6250

GUSTO indicates Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis; MI, myocardial infarction; PAD, peripheral artery disease; TIMI, Thrombolysis in Myocardial Infarction.

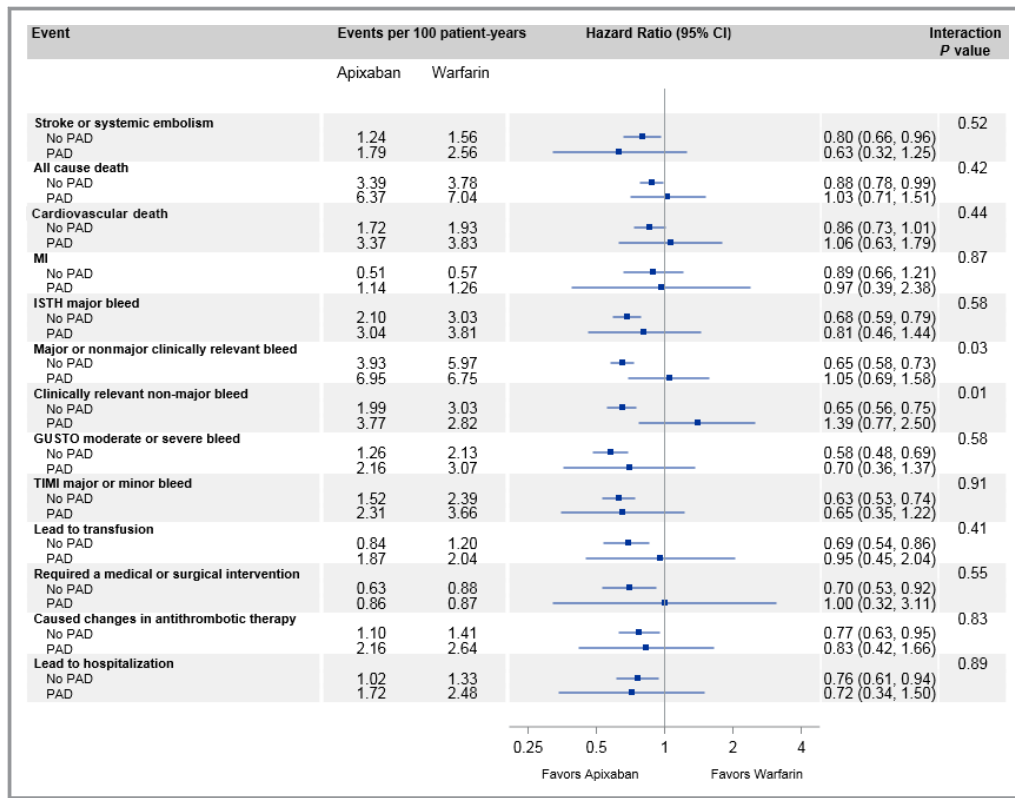
## Discussion

As new therapies are introduced and utilized in the treatment of AF, it is imperative to understand the impact of comorbidities such as PAD on clinical outcomes. This analysis of patients with PAD in ARISTOTLE had 4 major findings. First, crude rates of stroke and bleeding were higher among those with PAD, but after adjustment for differences in patient characteristics, there was no difference in rate of stroke or systemic embolism and bleeding in patients with versus without PAD. Second, patients with PAD had an increased risk of all-cause death and cardiovascular death compared with those without PAD. Third, the effect of apixaban versus warfarin for the prevention of stroke or systemic embolism was consistent in patients with and without PAD. Fourth, the reduction in bleeding with apixaban in the whole trial cohort was not observed in this relatively small subgroup with PAD.

Our first major finding, that the presence of PAD was not statistically significantly associated with stroke or systemic embolism, was not entirely surprising. A simple explanation for this is the low number of stroke or systemic embolic events in patients with PAD (N=32) thus limiting the power to detect a difference. The current results are similar to a post

hoc analysis of patients with PAD in ROCKET AF (Rivaroxaban Once daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation). In ROCKET AF, patients with PAD compared with those without PAD did not have a statistically significant increase in stroke or systemic embolism (HR 1.04, 95% CI 0.72, 1.50;  $P=0.84$ ).<sup>6</sup> Our results are congruent with this prior analysis and suggest that in patients with AF and at least 1 additional risk factor for stroke who are on oral anticoagulant therapy, the presence of PAD is not independently associated with a substantial increase in risk of stroke. For patients not on anticoagulation, whether the presence of PAD (including as a sole factor) is associated with risk of stroke cannot be addressed with our study.

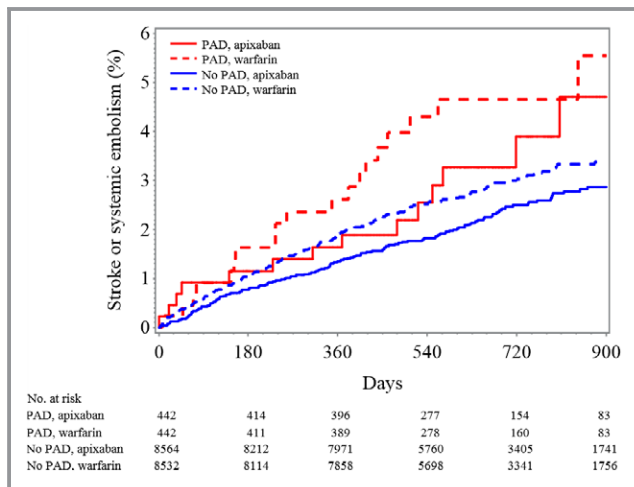
Our second finding, that PAD was associated with a higher risk of all-cause death and cardiovascular death in patients with PAD compared with those without PAD, is consistent with prior studies and has been seen across many different cardiovascular trials and registries.<sup>12</sup> PAD alone has been shown to be a powerful independent predictor of coronary and cerebrovascular disease. In addition, worsening PAD severity has been associated with increased mortality in



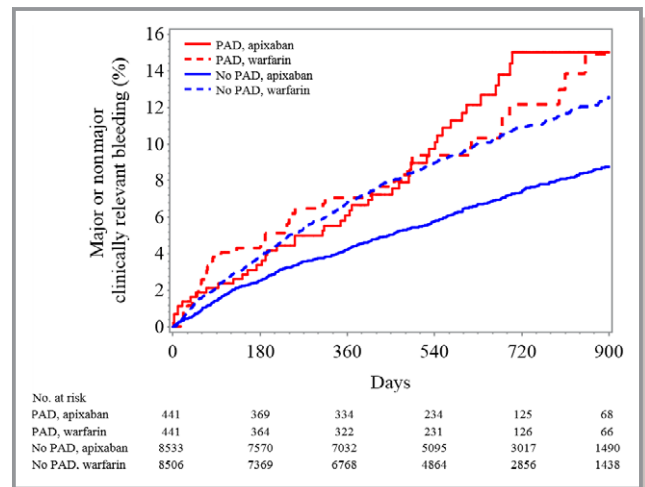
**Figure 1.** Treatment effects according to PAD. GUSTO indicates Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; ISTH, International Society on Thrombosis and Haemostasis; MI, myocardial infarction; PAD indicates peripheral artery disease; TIMI, thrombolysis in myocardial infarction.

patients with multiple disease states.<sup>13,14</sup> We were unable to validate this finding in the present analysis because of limited information regarding severity of PAD in the ARISTOTLE data set.

Our third major finding is that the benefit of apixaban versus warfarin for the prevention of stroke or systemic embolism was similar in patients with and without PAD. These results are consistent with the main trial results from



**Figure 2.** Kaplan–Meier plot for cumulative rate of stroke or systemic embolism in patients classified by PAD and treatment assignment. PAD indicates peripheral artery disease.



**Figure 3.** Kaplan–Meier plot for major or clinically relevant nonmajor bleeding classified by PAD status and treatment assignment. PAD indicates peripheral artery disease.

ARISTOTLE, which found that apixaban was superior to warfarin in preventing stroke or systemic embolism in the entire study population.<sup>10</sup> This helps provide confidence that apixaban can be used effectively to prevent stroke or systemic embolism in patients with AF with and without PAD.

In terms of bleeding risk, patients with PAD did not have a significantly increased risk of major bleeding compared with patients without PAD. In those who had overt bleeding, patients with PAD were more likely than those without PAD to have mucosal or gastrointestinal bleeding, but the overall event rates were low in both groups. This can be explained, at least in part, by the greater use of antiplatelet agents among patients with PAD (Table 2). Patients with PAD, compared with those without PAD, were more likely to be on aspirin, clopidogrel, or any aspirin or thienopyridine at baseline, at 1-year follow-up, and at the time of study drug discontinuation. In addition to antiplatelet therapy, the impact of PAD itself (related to something inherent about the disease, the need for invasive procedures, or other factors) may also contribute to an increased bleeding risk.

Interestingly, our study found a treatment interaction with apixaban compared with warfarin in patients with PAD. Patients with PAD had no statistically significant reduction in major or clinically relevant nonmajor bleeding with apixaban compared with warfarin, whereas those without PAD had a statistically significant reduction in major or clinically relevant nonmajor bleeding. Prior analysis of the ARISTOTLE trial found a similar interaction in patients with diabetes mellitus, which is of interest because PAD and diabetes mellitus are often comorbid conditions.<sup>15</sup> Our current results are consistent with a similarly sized post hoc analysis of patients with AF with PAD enrolled in ROCKET AF, in which patients with PAD had a higher risk of major bleeding or clinically relevant nonmajor bleeding with rivaroxaban compared with warfarin.<sup>6</sup> Although the use of antiplatelet agents at baseline and during the study may have contributed to this effect, patients with PAD on warfarin were more likely to be on concomitant antiplatelet therapy compared with patients with PAD on apixaban. These findings may not fully represent and explain the impact of antiplatelet agents on bleeding with warfarin and apixaban because patients may have been started on aspirin and/or a thienopyridine after year 1 and before study drug discontinuation. Furthermore, a prior analysis of the ARISTOTLE trial regarding concomitant aspirin use found that apixaban actually caused significantly less bleeding among both aspirin and nonaspirin users compared with warfarin.<sup>16</sup> This makes it less likely that concomitant aspirin use alone is driving this interaction. Finally, one should always consider the play of chance when analyzing results from small subgroups like patients with AF and PAD in the ARISTOTLE trial.

## Limitations

This analysis has several limitations. First, given its post hoc nature, our results should be interpreted as hypothesis generating rather than definitive. The multivariable model attempts to account for known confounders between the PAD and no PAD cohorts but is unable to account for unmeasured confounders. In addition, this study included a relatively small sample of patients with PAD compared with those without PAD because only 4.9% of patients included in this study had PAD. The power to detect similarities and differences in patient characteristics and baseline demographics is limited. Moreover, the results of our findings may not be generalizable to other non-clinical trial populations. In addition, patients with PAD in our study were identified as determined by site investigators. The severity of PAD in our subgroup is not known. Finally, although cerebrovascular disease was distinguished from PAD on the case report form, the disease burden and symptom status (eg, asymptomatic PAD, intermittent claudication, or critical limb ischemia) of PAD patients were not measured or recorded by site investigators. Because these factors influence morbidity and mortality with PAD, they could lead to imprecise findings in this small group of patients with PAD in ARISTOTLE.

## Conclusions

Patients with AF and PAD had higher rates of death and trends toward higher rates of stroke or systemic embolism and bleeding than patients without PAD. The benefits of apixaban compared with warfarin for stroke and death were similar in patients with and without PAD. In the relatively small subgroup of patients with PAD in ARISTOTLE, no statistically significant reduction in major or clinically relevant nonmajor bleeding was observed in the larger population of patients without PAD. These findings highlight the need to optimize the treatment of patients with AF and PAD.

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# **SUPPLEMENTAL MATERIAL**

**Table S1.** Proportional hazards regression models for PAD-by-treatment interactions on ISTH bleeding endpoints

Variable	No PAD, apixaban	No PAD, warfarin	No PAD unadjusted HR (95% CI)	No PAD adjusted HR (95% CI)	PAD, apixaban	PAD, warfarin	PAD unadjusted HR (95% CI)	PAD adjusted HR (95% CI)	Unadjusted interaction p-value	Adjusted interaction p-value
Clinically relevant non-major bleeding	1.99 (287)	3.03 (423)	0.66 (0.57, 0.77)	0.65 (0.56, 0.75)	3.77 (26)	2.82 (19)	1.36 (0.75, 2.46)	1.39 (0.77, 2.50)	0.0201	0.0149
Major bleeding	2.10 (303)	3.03 (428)	0.69 (0.60, 0.80)	0.68 (0.59, 0.79)	3.04 (21)	3.81 (26)	0.81 (0.45, 1.44)	0.81 (0.46, 1.44)	0.6176	0.5772
Major bleeding type										
Required transfusion	0.84 (123)	1.20 (171)	0.71 (0.56, 0.89)	0.69 (0.54, 0.86)	1.87 (13)	2.04 (14)	0.97 (0.45, 2.06)	0.95 (0.45, 2.04)	0.4399	0.4125
Required a medical or surgical intervention to stop bleeding	0.63 (92)	0.88 (126)	0.72 (0.55, 0.94)	0.70 (0.53, 0.92)	0.86 (6)	0.87 (6)	0.98 (0.32, 3.05)	1.00 (0.32, 3.11)	0.5952	0.5495
Required changes in antithrombotic therapy	1.10 (160)	1.41 (200)	0.79 (0.64, 0.97)	0.77 (0.63, 0.95)	2.16 (15)	2.64 (18)	0.84 (0.42, 1.66)	0.83 (0.42, 1.66)	0.8614	0.8282
Required hospitalization	1.02 (149)	1.33 (189)	0.77 (0.62, 0.96)	0.76 (0.61, 0.94)	1.72 (12)	2.48 (17)	0.72 (0.34, 1.50)	0.72 (0.34, 1.50)	0.8472	0.8921
Major bleeding site										
Intracranial	0.34 (50)	0.80 (115)	0.43 (0.31, 0.60)	0.42 (0.30, 0.59)	0.28 (2)	1.02 (7)	0.26 (0.05, 1.25)	0.26 (0.05, 1.24)	0.5353	0.5444

PAD=peripheral artery disease

HR=hazard ratio

CI=confidence interval

ISTH=International Society on Thrombosis and Haemostasis