Peripheral artery disease and clinical outcomes in patients with atrial fibrillation: A report from the FANTASIIA registry

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Abstract

Background. Atrial fibrillation (AF) and peripheral artery disease (PAD) are common conditions that increase cardiovascular risk. We determined the association between PAD and prognosis in a cohort of real-world patients receiving oral anticoagulant therapy for nonvalvular AF.

Methods. We prospectively included 1956 patients (mean age 73.8 ± 9.5 years, 44.0% women) receiving oral anticoagulant therapy for AF. Clinical characteristics were collected at baseline. Patients were followed for a period of 3 years. Survival analysis and multivariable regression analyses were performed to assess variables related to death, stroke, bleeding, myocardial infarction and major adverse cardiovascular events (MACE).

Results. Patients with PAD (n = 118; 6%) exhibited higher rates of cardiovascular risk factors and cardiovascular diseases. After 3 years of follow-up, there were a total of 255 deaths (no PAD 233, vs PAD 22), 45 strokes (43 vs 2), 146 major bleedings (136 vs 10) and 168 MACE (148 vs 20). On univariate analysis, there was a higher risk of cardiovascular mortality (2.02%/year no PAD vs 4.08%/year PAD, $P = .02$), myocardial infarction (0.99%/year no PAD vs 2.43%/year PAD, $P = .02$) and MACE (3.18%/year no PAD vs 6.99%/year PAD, $P < .01$). There was no statistically significant association with these events after multivariable adjustment.

Conclusions. In a large cohort of anticoagulated patients with AF, the presence of PAD represents a higher risk subgroup and is associated with worse crude outcomes. The exact contribution of the PAD independently of other cardiovascular diseases or risk factors requires further investigation.

Keywords

Atrial fibrillation, mortality, peripheral artery disease, prognosis, stroke

1 INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice, with an increasing prevalence and incidence particularly in the elderly.[1,2] Most patients with AF accumulate multiple risk factors and cardiovascular comorbidities.[3] The prognosis of patients with AF is mainly driven by the subsequent risk of stroke, and efforts are made to adequately assess the risk of stroke and to initiate anticoagulant therapy in high-risk patients.

Peripheral artery disease (PAD) is caused by the development of atherosclerotic lesions in the peripheral arteries, causing intermittent claudication and other complications such as necrosis, ulcers, infections and, eventually, limb loss.[4] PAD indicates the existence of atherosclerosis and is associated with higher rates of cardiovascular complications, such as death, myocardial infarction or stroke.[5]

Atrial fibrillation and PAD are two cardiovascular diseases that commonly coexist, with a strong bidirectional relationship between them. Patients with AF are at risk of developing PAD and *vice versa*.[6,7] The incidence of adverse events in patients with either of the two conditions is highly increased by the presence of the other. For stroke risk assessment, PAD is included within the CHA_2DS_2-VASc score.[8] However, not all studies have found a significant increase in the risk of thromboembolic events but, on the contrary, some have found a significant increase in the occurrence of bleeding episodes.[9] The aim of this study was to determine the association between PAD and prognosis in a cohort of real-world patients receiving oral anticoagulant therapy for nonvalvular AF.

2 METHODS

Full details of the FANTASIIA (Spanish acronym for "Atrial fibrillation: influence of the level and type of anticoagulation on the incidence of ischaemic and haemorrhagic stroke") registry rationale and design are described elsewhere.[10] In brief, it is an observational, prospective, national and multicenter study of clinical and demographic characteristics of Spanish patients with AF. Its main objective is to assess the incidence of thromboembolic and bleeding events in an unselected population of patients with AF, assessing the type of oral anticoagulant, that is vitamin K antagonists or direct oral anticoagulants used, and the quality of anticoagulation with vitamin K antagonists. The data that support the

findings of this study are available from the corresponding author upon reasonable request.

2.1 Study population

Between June 2013 and March 2014, outpatients with confirmed diagnosis of paroxysmal, persistent or permanent AF were prospectively enrolled. All patients included had been receiving oral anticoagulation for at least 6 months at the time of recruitment. By design, each investigator included 16 patients taking vitamin K antagonists and four patients who were taking direct oral anticoagulants. Eighty investigators, working in 50 outpatient clinics, performed the study. Exclusion criteria were patients with valvular heart disease (rheumatic valve disease, moderate-severe valve disease and prosthesis or valve repair surgery), younger than 18 years or with recent hospital admission. The study aimed to assess the influence of the anticoagulant treatment in prognosis; thus, patients admitted or with an admission in the prior three months were excluded. All patients provided signed informed consent.

The study complied with the ethical principles of the Declaration of Helsinki and Good Clinical Practice Guidelines. It was approved by the Spanish Agency of Medicine and Health Products as a prospective follow-up postauthorization study (approval number SEC-ACO-2012-01) and by the Ethics Committee of the Hospital Universitario San Juan de Alicante. Reporting of the study conforms to broad EQUATOR guidelines.[11]

2.2 Study variables and data collection

Clinical and demographic data for all AF patients were collected in a detailed medical history. We defined previous heart disease as the composite of coronary artery disease, heart failure and other structural cardiomyopathies (such as hypertrophic cardiomyopathy, chronic pericardial disease or congenital diseases). In patients under vitamin k antagonists, coagulation status was determined by the international normalized ratio values at six months prior to study entry and at one year of follow-up. The estimated time spent in the therapeutic range was assessed by the Rosendaal method. Stroke risk was calculated using the $CHADS_2$ and CHA_2DS_2-VASc scores,[8,12] bleeding risk using the HAS-BLED score[13] and comorbidity according to the Charlson index. Serum

creatinine levels were collected at baseline, and the estimated glomerular filtration rate was calculated using the Cockcroft-Gault formula: [(140 − age) × (weight in kg) × (0.85 if female)/(72 × creatinine)].

At 3 years, we assessed the incidence of stroke, major bleeding, all-cause mortality, cardiovascular mortality, myocardial infarction and major adverse cardiovascular events (MACE, defined as the composite of ischaemic stroke, myocardial infarction and cardiovascular mortality). Thromboembolic events were defined as stroke or transient ischaemic attack and peripheral artery embolism. All strokes were evaluated by computed tomography or magnetic resonance imaging according to the neurologist's criteria. Bleeding events were assessed according to the 2005 International Society of Thrombosis and Haemostasis criteria.[14] All-cause and cardiovascular mortalities were also recorded. Death was classified as cardiovascular when caused by acute coronary syndrome, heart failure, lethal arrhythmia or sudden death, artery aneurysm rupture or stroke. An external event assignment committee evaluated all adverse events.

2.3 Statistical analyses

The Kolmogorov-Smirnov method was employed to test the normality of continuous variables, which were reported as mean ± standard deviation (SD) or median (interquartile range, IQR), as appropriate. Categorical variables were expressed as relative frequencies (%). Qualitative variables were compared using the chi-square test. Cox regression analyses were used to test the associations between PAD and mortality, bleeding and cardiovascular events. The independent effect of clinical variables on adverse clinical outcomes was calculated using a Cox proportional hazards regression; the multivariable model included variables yielding a *P* value of <.15 on univariable analysis. The models included PAD, age, sex, hypertension, dyslipidemia, diabetes, coronary artery disease, heart failure, aortic disease, chronic kidney disease, Charlson index, history of stroke, CHA_2DS_2-VASc and HAS-BLED scores. Differences in event-free survival were examined with the log-rank test, and Kaplan-Meier curves were drafted accordingly. *P* values of <.05 were considered statistically significant. All statistical analyses were performed with Stata version 12 (Stata Corporation, College Station).

3 RESULTS

The final study sample was comprised by 1956 patients. The mean age was 73.8 ± 9.5 years, 44.0% were women, and 118 (6%) had PAD.

3.1 Baseline characteristics across PAD status

Table **1** shows the patient's characteristics of the study sample stratified by the presence of PAD. Patients with PAD exhibited a higher risk, based on a higher proportion of prior dyslipidemia (51.5% no PAD vs 63.6% PAD, $P = .01$), diabetes (28.5% no PAD vs 42.4% PAD, $P < .01$), smoking habit (4.8% no PAD vs 8.5% PAD, $P = .08$), higher proportion of cardiovascular diseases and comorbidities, like kidney (18.5% no PAD vs 31.4% PAD, $P < .01$) or liver disease (1.1% no PAD vs 3.4% PAD, $P = .03$), cancer (8.3% no PAD vs 13.6% PAD, $P = .04$), alcohol abuse (3.4% no PAD vs 8.5% PAD, $P < .01$) and Charlson index (1.05 ± 1.07 no PAD vs 2.61 ± 1.39 PAD, $P < .01$).
1532 patients (78.3%) did not have PAD nor coronary artery disease, 68 (3.5%) had PAD without coronary artery disease, 306 (15.6%) had coronary artery disease without PAD, and 50 (2.6%) had concomitant PAD and coronary artery disease.
Patients with PAD received more statins (54.1% no PAD vs 69.5% PAD, <0.01) and antiplatelet therapies (9.9% no PAD vs 21.2% PAD, <0.01), while no differences were found in the prescription of diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers or antiarrhythmic drugs (Table **2**). In patients under vitamin k antagonists, the time in therapeutic range (TTR) was lower among patients with PAD (Table **1**).
No differences were found in the history of previous episodes of stroke, systemic embolism or major bleeding, although patients with PAD showed higher values of $CHADS_2$ (2.23 ± 1.24 no PAD vs 2.58 ± 1.34 PAD, $P < .01$), CHA_2DS_2-VASc (3.65 ± 1.57 no PAD vs 4.66 ± 1.50 PAD, $P < .01$) and HAS-BLED scores (1.98 ± 1.03 no PAD vs 2.39 ± 1.24 PAD, $P < .01$).

3.2 Events during follow-up

After a median follow-up of 1078 days (IQR 766-1113), a total of 255 deaths (107 of cardiovascular causes), 45 strokes, 146 major bleedings, 46 myocardial infarctions and 168 MACE were observed (Tables **3** and **4**).

A trend towards higher all-cause mortality was found among patients with PAD (4.95%/year patients without PAD vs 7.48%/year patients with PAD, $P = .06$), and these differences were statistically significant for cardiovascular mortality (2.02%/year no PAD vs 4.08%/year PAD, $P = .02$), myocardial infarction (0.99%/year no PAD vs 2.43%/year PAD, $P = .02$) and MACE (3.18%/year no PAD vs 6.99%/year PAD, $P < .01$).

3.3 Multivariate analysis

After adjusting for confounding variables, PAD was not independently associated with any of the major cardiovascular outcomes, that is total and cardiovascular mortality, stroke, major bleeding, myocardial infarction and MACE (Table **5**).

4 DISCUSSION

In a large cohort of anticoagulated patients with AF, those with PAD were associated with a higher prevalence of various risk factors and developed more adverse events in the follow-up. However, we did not find an independent association with poor prognosis.

Patients with PAD have a higher incidence of AF, and this incidence further increases with the severity of PAD.[15,16] This trend is similarly seen in the opposite direction, and AF is independently associated with incident PAD.[17] In a large population cohort with a long follow-up, the bidirectional association was confirmed, and an increased risk both for incident AF in PAD patients and for incident PAD in AF patients was found.[18]

The coexistence of AF and PAD in the same patient increases the risk of stroke, heart failure and mortality.[7, 19-21] In our study, this association seems to be limited to the higher incidence of myocardial infarction, cardiovascular mortality and MACE found on univariable analysis; however, we were not able to find an independent association with these events after multivariable adjustment (Table **4**). This may be related to the modest cohort size and the fact that all the patients were under anticoagulant therapy, of note the

rate of bleeding events tripled that of thrombotic events. Similar findings have been described in observational studies of anticoagulated patients.[22] In our population, the anticoagulation was performed with direct oral anticoagulants and with vitamin k antagonists in a 1:4 ratio, per protocol. Recent studies have shown that the protection conferred by direct oral anticoagulants is at least similar in the prevention of death[21,23] and superior in the prevention of limb adverse events compared to vitamin k antagonists,[24] the differences being more pronounced in diabetic patients.[25] The association between the coexistence of PAD and coronary artery disease and adverse outcomes has been also demonstrated in the setting of AF.[26,27] In our patients, this association was significant for all-cause mortality, cardiovascular mortality, acute myocardial infarction and MACE (Table **4**).

The main studies demonstrating the association between PAD and stroke in AF patients have been developed in nonanticoagulated cohorts,[8,20] while other studies performed in patients taking anticoagulants have shown the lack of independent association (as with the present study).[9,15,28] Chronic oral anticoagulation is an effective therapy for stroke prevention in this setting, and the low stroke rates found in cohorts of patients, while under anticoagulant therapy explains the lack of association of variables without a strong association with the development of stroke. When asymptomatic patients with PAD have been included in the analyses through a systematic search for PAD by means of ankle-brachial index, evidence suggests that PAD is also associated with higher incidence of myocardial infarction or vascular death, but is not associated with stroke or total mortality.[18,29,30]

A recent metanalysis has shown that statin therapy may prevent limb events in patients with PAD.[31] In our study, patients with PAD were more prone to receive statin therapy; however, in the light of this recent publication statin therapy should be more widely implemented.

Patients with PAD tend to accumulate many cardiovascular risk factors and comorbidities.[32] We could hypothesize that PAD might represent a cluster of other conditions that finally increase the risk of developing a stroke, which may explain why crude rates of cardiovascular events are a constant in most studies, but this effect is lost after multivariate adjustment. The number of patients with PAD in most cohorts of AF patients is low, which reduces the statistical power to detect independent associations.

But the higher proportion of cardiovascular risk factors and cardiovascular disease and the high incidence of cardiovascular events in the follow-up is a constant in all studies. Further data are still needed to elucidate the exact contribution of each of these variables to prognosis among patients with AF.

4.1 Limitations

Firstly, given the observational nature of our study, the effects of residual confounding cannot be fully excluded. PAD was assessed only based on symptomatic status or for being recorded in the clinical history, but no routine ankle-brachial index was performed in our patients. When systematic ankle-brachial index has been used for diagnosis of PAD in patients with AF, the prevalence of PAD has increased by two-fold.[29] Finally, as happens with most negative studies, a larger sample size could increase statistical power and yield significant results. Nonetheless, our results suggest that the contribution of PAD to the risk of patients receiving anticoagulant therapy for AF modest.

5 CONCLUSIONS

In a large cohort of anticoagulated patients with AF, the presence of PAD represents a higher risk subgroup and is associated with worse crude outcomes. The exact contribution of the PAD independently of other cardiovascular diseases or risk factors requires further investigation.

CONFLICT OF INTEREST

None.

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TABLE 1. Baseline characteristics stratified by PAD

	All patients	No PAD	PAD	*P* value
N	1956	1838	118	
Demographic data				
Age (y, mean ± SD)	73.8 ± 9.5	73.8 ± 9.6	73.6 ± 8.2	.57
Women (%)	44.0	45.4	22.0	<.01
Comorbidities and cardiovascular risk factors				
Arterial hypertension (%)	80.4	80.3	82.2	.61
Dyslipidemia (%)	52.2	51.5	63.6	.01
Diabetes mellitus (%)	29.4	28.5	42.4	<.01
Smoking habit (%)	5.1	4.8	8.5	.08
CODP/OSAS (%)	17.5	17.0	26.3	.01
Chronic kidney failure (%)	19.3	18.5	31.4	<.01
Liver dysfunction (%)	1.2	1.1	3.4	.03
Cancer	8.6	8.3	13.6	.04
Charlson index	1.14 ± 1.16	1.05 ± 1.07	2.61 ± 1.39	<.01
Previous cardiac disease				
Heart failure (%)	28.9	28.0	42.4	<.01
Coronary artery diseases (%)	18.2	16.7	42.4	<.01
Acute coronary syndrome (%)	13.8	12.6	33.1	<.01
Coronary revascularization (%)	11.5	10.5	26.3	<.01
Dilated cardiomyopathy or LVEF <45% (%)	11.7	11.3	17.8	.03
Bleeding episodes in the last 6 mo				
Major bleeding episodes (%)	4.1	3.9	6.8	.13
Thrombotic and bleeding risk				
History of stroke	17.0	16.8	20.3	.32
History of systemic embolism	2.2	2.1	3.4	.36
$CHADS_2$ (mean ± SD)	2.25 ± 1.24	2.23 ± 1.24	2.58 ± 1.34	<.01
CHA_2DS_2-VASc (mean ± SD)	3.71 ± 1.59	3.65 ± 1.57	4.66 ± 1.50	<.01
HAS-BLED (mean ± SD)	2.01 ± 1.05	1.98 ± 1.03	2.39 ± 1.24	<.01
TTR <70%	59.1	58.3	71.3	.02
Complementary examinations				
Haemoglobin (g/dL, mean ± SD)	13.7 ± 1.7	13.7 ± 1.7	13.7 ± 1.9	.52
Serum creatinine (mg/dL, mean ± SD)	1.1 ± 0.5	1.1 ± 0.5	1.2 ± 0.4	<.01
Glomerular filtration rate (mL/min/1.73 m^2, mean ± SD)	66.2 ± 22.9	66.5 ± 23.1	60.9 ± 20.8	<.01
Total cholesterol (mg/dL, mean ± SD)	177.1 ± 38.6	178.0 ± 38.5	163.1 ± 37.7	<.01

Glucose (mg/dL, mean ± SD)	108.6 ± 31.6	108.3 ± 30.8	118.3 ± 40.5	<.01
HbA1c (%, mean ± SD)	6.2 ± 1.3	6.1 ± 1.3	6.5 ± 1.4	<.01

Abbreviations: AF, atrial fibrillation; AV, atrioventricular; COPD, chronic obstructive pulmonary disorder; ECG, electrocardiogram; HbA1c, haemoglobin A1c; LVEF, left ventricular ejection fraction; OSAS, obstructive sleep apnoea syndrome; PAD, peripheral artery disease; SD, standard deviation; TTR, time in the therapeutic range

TABLE 2. Pharmacological treatment at baseline stratified by PAD

	All patients	No PAD	PAD	*P* value
N	1956	1838	118	
Diuretics (%)	57.1	57.0	64.4	.11
Aldosterone antagonists (%)	14.0	14.0	14.4	.88
ACE inhibitors (%)	30.8	30.6	34.8	.34
Angiotensin receptor blockers (%)	40.7	40.8	39.8	.84
Statins (%)	55.0	54.1	69.5	<.01
Antiplatelets (%)	10.6	9.9	21.2	<.01
Beta-blockers (%)	60.3	60.3	61.0	.87
Digoxin (%)	18.2	18.4	13.6	.18
Antiarrhythmic drugs (%)	24.6	25.0	19.5	.18
Vitamin K antagonists (%)	75.8	75.9	73.7	.59
Direct oral anticoagulants (%)	24.2	24.1	26.3	.59

Abbreviations: ACE, angiotensin-converting-enzyme; PAD, peripheral artery disease.

TABLE 3. Events during follow-up, stratified by PAD

	All patients		No PAD		PAD		*P* value
	n	Annual rate (%/y)	n	Annual rate (%/y)	n	Annual rate (%/y)	
All-cause mortality	255	5.09	233	4.95	22	7.48	.06
Cardiovascular mortality	107	2.14	95	2.02	12	4.08	.02
Stroke	45	0.91	43	0.92	2	0.68	.68
Major bleeding	146	2.99	136	2.96	10	3.50	.61
Acute myocardial infarction	53	1.07	46	0.99	7	2.43	.02
MACE	168	3.41	148	3.18	20	6.99	<.01

Abbreviations: MACE, major adverse cardiovascular event (composite of ischaemic stroke, myocardial infarction and cardiovascular mortality); PAD, peripheral artery disease.

TABLE 4. Events during follow-up, stratified by PAD and COAD

	No PAD or CAD		PAD and no CAD		CAD and no PAD		PAD and CAD		*P* value
	n	Annual rate (%/y)	n	Annual rate (%/y)	n	Annual rate (%/y)	n	Annual rate (%/y)	
All-cause mortality	176	4.45	9	5.09	57	7.56	13	11.07	<.01
Cardiovascular mortality	65	1.64	6	3.39	30	3.98	6	5.11	<.01
Stroke	31	0.79	1	0.57	12	1.61	1	0.86	.93
Major bleeding	108	2.79	6	3.55	28	3.87	4	3.41	.69
Acute myocardial infarction	24	0.61	2	1.14	22	2.99	5	4.41	<.01
MACE	98	2.50	9	5.16	50	6.85	11	9.85	<.01

Abbreviations: CAD, coronary artery disease; MACE, major adverse cardiovascular event (composite of ischaemic stroke, myocardial infarction and cardiovascular mortality); PAD, peripheral artery disease.

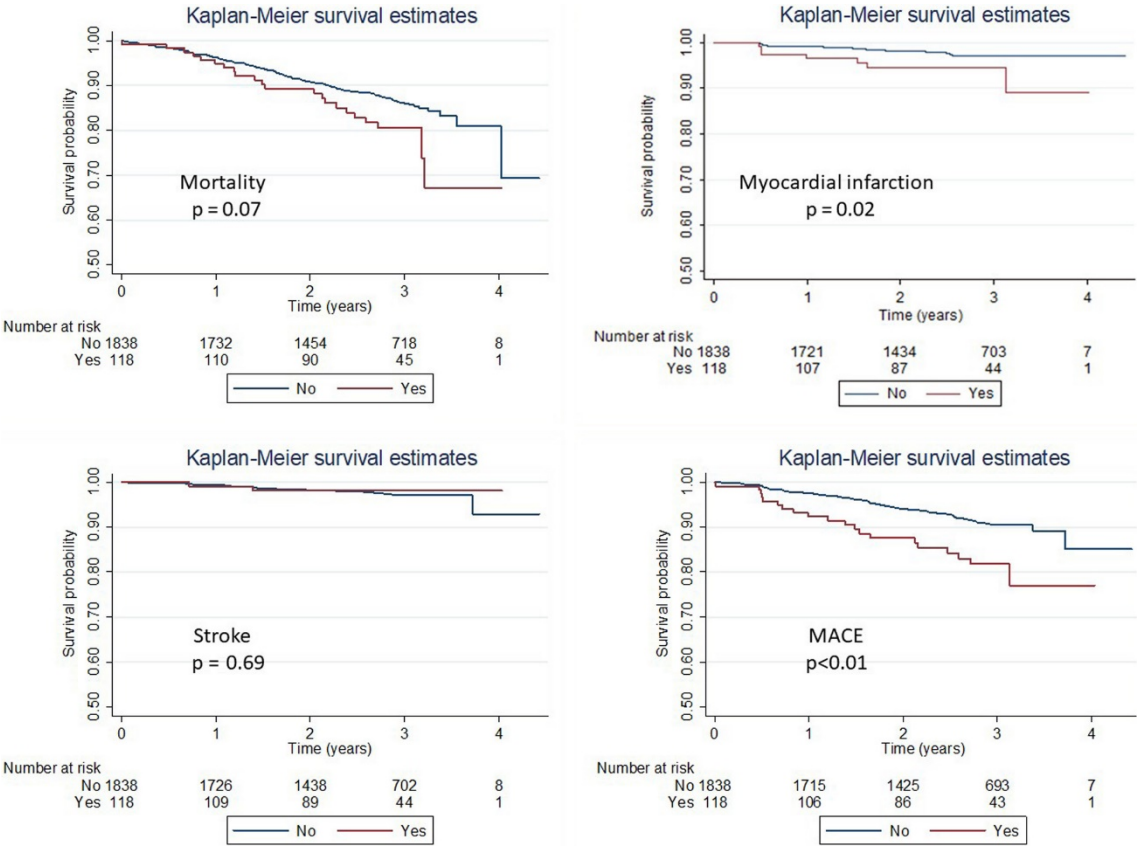

FIGURE 1. Event-free survival curves for total mortality, stroke, myocardial infarction and MACE stratified by PAD

TABLE 5. Multivariate Cox regression

	HR	95% CI	*P* value
Total mortality			
PAD	1.23	0.79-1.94	.36
Sex, female	0.59	0.45-0.77	<.01
Age, per year	1.08	1.06-1.10	<.01
Hypertension	1.48	1.02-2.14	.04
Diabetes	1.36	1.05-1.77	.02
Heart failure	1.97	1.52-2.55	<.01
Chronic kidney failure	1.50	1.13-2.01	<.01
Cardiovascular mortality			
PAD	1.65	0.86-3.18	.13
Age, per year	1.08	1.04-1.11	<.01
Diabetes mellitus	2.01	1.31-3.09	<.01
Coronary artery disease	1.66	1.05-2.63	.03
Heart failure	2.28	1.48-3.52	<.01
Chronic kidney failure	1.81	1.11-2.96	.02
Stroke			
PAD	0.57	0.13-2.40	.44
Heart failure	1.88	1.02-3.47	.04
Chronic kidney failure	2.01	1.11-3.64	.02
Major bleeding			
PAD	1.11	0.58-2.12	.75
Diabetes	1.45	1.03-2.05	.03
Dyslipidemia	0.60	0.43-0.84	.03
Heart failure	1.45	1.03-2.05	.03
Chronic kidney failure	1.70	1.17-2.48	<.01
Myocardial infarction			
PAD	1.47	0.65-3.34	.36
Age, per year	1.05	1.02-1.09	<.01
Coronary artery disease	3.98	2.23-7.12	<.01
MACE			
PAD	1.55	0.96-2.52	.08
Age, per year	1.05	1.03-1.07	<.01
Diabetes	1.59	1.16-2.19	<.01
Coronary artery disease	1.92	1.36-2.71	<.01

Heart failure	2.02	1.47-2.78	<.01
Chronic kidney failure	1.44	1.02-2.04	.04

Note. Model adjustment: Mortality: PAD, sex, age, hypertension, diabetes, coronary artery disease, heart failure and chronic kidney disease; Cardiovascular mortality: PAD, age, diabetes, dyslipidemia, coronary artery disease, heart failure chronic kidney disease and TTR <70%; Stroke: PAD, coronary artery disease, heart failure and chronic kidney failure; Major bleeding: PAD, age, diabetes, dyslipidemia, heart failure and chronic kidney failure; Myocardial infarction: PAD, age, diabetes, dyslipidemia, coronary artery disease and heart failure. Myocardial infarction: PAD, age, diabetes, dyslipidemia, coronary artery disease and heart failure; MACE: PAD, age, hypertension, diabetes, dyslipidemia, coronary artery disease, heart failure and chronic kidney disease.

Abbreviations: CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events; PAD, peripheral artery disease; TTR, time in the therapeutic range.