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CLINICAL RESEARCH

Adverse outcomes in patients with atrial fibrillation and peripheral arterial disease: a report from the EURObservational research programme pilot survey on atrial fibrillation

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Aims Peripheral arterial disease (PAD) is highly prevalent in general population. Data on the prevalence of symptomatic PAD in patients with atrial fibrillation (AF) are limited, and the impact of PAD on adverse outcomes in AF patients is controversial. Our aims were: (i) to define the prevalence of symptomatic PAD in European AF patients and describe its associated clinical risk factors and (ii) to establish the relationship of PAD to adverse events in AF, especially all-cause death.

Methods Atrial fibrillation patients enrolled in the EORP-AF Pilot study with data about PAD status were included in this analysis. Event rates were determined at 1-year follow-up.

Results Peripheral arterial disease was recorded in 328 (11%) patients. Age ($P < 0.0001$), hypertension ($P = 0.0059$), diabetes mellitus ($P = 0.0001$), chronic heart failure ($P < 0.0001$), previous stroke/transient ischaemic attack ($P = 0.0060$), and antiplatelet drug treatment ($P = 0.0001$) were associated with the presence of PAD, while female gender was inversely associated ($P = 0.0002$). Peripheral arterial disease patients had higher absolute rates of both cardiovascular (CV) and all-cause death (both $P < 0.0001$). On Kaplan–Meier analysis, risk of all-cause death was higher in PAD patients compared with those without PAD ($P < 0.0001$), but PAD did not emerge as an independent risk factor for mortality on Cox regression analysis. A lower risk of all-cause death was associated with the prescription of statins ($P = 0.0019$), angiotensin-converting enzyme inhibitors ($P = 0.0008$), and calcium-channel blockers ($P = 0.0071$).

Conclusion Peripheral arterial disease is prevalent in 11% of AF patients and related to various atherosclerotic risk factors. Even if PAD is associated with higher risk of all-cause death on univariate analysis, this risk was significantly lowered and was no longer evident after adjusting for the use of CV prevention drugs.

Keywords Peripheral arterial disease • Atrial fibrillation • Atherosclerosis • All-cause death

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What's new?

- In atrial fibrillation (AF), concomitant symptomatic peripheral arterial disease (PAD) is frequently reported. Its presence is associated with several common cardiovascular risk factors.
- The presence of PAD in AF patients is associated with a higher risk of all-cause death.
- Common cardiovascular prevention drugs are associated with a decreased mortality rate in AF patients with PAD.

Introduction

Peripheral arterial disease (PAD) is a highly prevalent cardiovascular (CV) condition,[1,2] with a prevalence of 8.3%,[3] being higher in males and increasing with age.[3] Being frequently asymptomatic, PAD is quite often underestimated and underdiagnosed.[2,4] The use of the ankle-brachial index to identify patients with asymptomatic PAD has been recommended.[4,5]

Peripheral arterial disease is an important independent risk factor for total mortality and incident CV events in the general population.[2] Large cohort studies have shown that PAD prevalence among AF patients is higher compared with non-AF subjects.[6,8] Moreover, the concomitant presence of AF and PAD confers a higher risk for both atherosclerotic and thromboembolic adverse events, when compared with that of AF without PAD.[6,9] Hence, PAD is part of the CHA_2DS_2-VASc score, which is used to assess thromboembolic risk in AF patients.[10] However, data on the impact of PAD on all-cause death in patients with AF have been controversial.[9] Nonetheless, several studies have shown that AF patients have a higher risk for atherosclerosis-related major adverse events[11–13] beyond thromboembolic risk, underlining how the links between AF and atherosclerosis may be even stronger than the mere epidemiological association.[14]

Data on the prevalence of PAD in AF have been reported with percentages ranging from 4 to 17%, according to the different clinical settings and definitions used.[15] Recent data from a large 'real world' Italian observational study of PAD prevalence in non-valvular AF patients showed a high prevalence of asymptomatic PAD (21%),[16] with a higher risk of vascular events in those AF patients with concomitant PAD diagnosis compared with those without PAD.[13] In contrast, an ancillary analysis from the 'Rivaroxaban Once daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation' (ROCKET-AF) study documented a lower prevalence (5.9%) of symptomatic PAD in this highly selected clinical trial population.[17]

The EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry is a prospective multi-national survey conducted by the European Society of Cardiology in nine European countries to determine clinical features, treatment patterns, and outcomes among patients with AF managed by cardiologists.[18] The objectives of this study were: (i) to assess the prevalence of symptomatic PAD among European AF patients seen by cardiologists, (ii) to establish clinical factors associated with the presence of PAD, (iii) to evaluate adverse events associated with PAD at 1-year follow-up, and (iv) to determine the impact of PAD on all-cause mortality in AF patients at 1-year follow-up, as well as the influence of CV prevention drug treatments.

Methods

Details on the EORP-AF study design, baseline, and 1-year prospective results have been previously described.[18,19] Briefly, EORP-AF was a prospective registry of consecutive AF patients managed by cardiologists, conducted by the European Society of Cardiology in the following European countries: Belgium, Denmark, Netherlands, Norway, Poland, Romania, Greece, Italy, and Portugal. Institutional review board for every institution approved the study protocol. All patients entered the study after signing a written informed consent. The study was performed according to the EU Note for Guidance on Good Clinical Practice CPMP/ECH/135/95 and the Declaration of Helsinki.

The study enrolled both in- and outpatients accessing to cardiology services (either hospital- or office-based centres) with AF as a primary or secondary diagnosis. The qualifying AF event was recorded by a 12-lead ECG, 24 h ECG Holter or other electrocardiographic documentation and should have been occurred within the 12 months before the enrolment. Follow-up data were recorded 1 year after the enrolment date according to the procedures previously described.[13] From February 2012 to March 2013, a total of 3119 AF patients were enrolled. All patients with available data about PAD status were included in the present analysis.

Peripheral arterial disease diagnosis was established by investigators at site level. The presence of PAD was defined by a positive history of any of the following: intermittent claudication, previous surgery, percutaneous intervention or thrombosis on abdominal or thoracic aorta, and lower extremity vessels. This assessment was performed by any physician during the clinical assessment and/or by searching through medical records, if available. Patients without positive clinical history of PAD were assigned to the 'non-PAD' group. The presence or absence of PAD was recorded in the electronic case report form of the registry, reporting the presence or absence of PAD, but with no further details on its clinical manifestations. Types of AF were defined as follows: (i) first detected AF, paroxysmal AF, and persistent AF were categorized as 'Non-Chronic AF'; and (ii) long-standing persistent AF and permanent AF were categorized 'Chronic AF'.

Thromboembolic risk was defined according to the CHA_2DS_2-VASc score.[10] 'Low-risk' patients were defined as males with a CHA_2DS_2-VASc 0 or females with a CHA_2DS_2-VASc equal to 1; 'moderate-risk' patients were defined as male patients with a CHA_2DS_2-VASc score 1; and 'high risk' was defined as CHA_2DS_2-VASc score ≥ 2.[20] Bleeding risk was assessed, as recommended by European Society of Cardiology guidelines,[21] based on the HAS-BLED bleeding score.[22]

During the pre-specified 1-year follow-up period, the occurrence of major adverse events was evaluated. Based on the study protocol, events recorded were as follows: CV death, all-cause death, and any thromboembolic event (TE) [defined as the occurrence of any stroke, transient ischaemic attack (TIA), acute coronary syndrome, coronary intervention, cardiac arrest, and peripheral or pulmonary embolism).

Statistical analysis

Continuous variables were reported as mean $\pm$ SD or as median and interquartile range. Between-group comparisons were made using a non-parametric test (Kruskal–Wallis test). Categorical variables were reported as percentages. Between-group comparisons were made using a χ^2 test or a Fisher's exact test if any expected cell count was <5. For

categorical variables with more than two possible values, exact *P*-values have been estimated according to the Monte Carlo method.

A regression analysis was performed to establish the clinical factors significantly associated with the presence of PAD. All variables considered of clinical relevance underwent a univariate analysis and those predictors with a level significance of $P < 0.10$ were inserted into a forward multivariate logistic model. Kaplan–Meier analysis was used to establish the relation of PAD to all-cause death and differences in survival were analysed using the log-rank test.

Evaluation of factors significantly associated with all-cause death used a Cox proportional hazards analysis. All demographic variables underwent a univariate analysis. All variables with a *P*-value of <0.10 for the association to all-cause death at the univariate analysis were inserted in the stepwise multivariate model along with PAD. Additional stepwise models were then performed inserting in any model a specific class of drugs with a known role in CV prevention (i.e. influencing atherosclerosis progression and/or reducing CV events) such as antiplatelets, statins, angiotensin-converting enzyme (ACE) inhibitors, and calcium-channel blockers. A Hosmer and Lemeshow goodness-of-fit test was used to verify that the models were optimal. A two-sided *P*-value of <0.05 was considered statistically significant. All analyses were performed using SAS statistical software version 9.3 (SAS Institute, Inc., Cary, NC, USA).

Results

Of the original EORP-AF cohort, data on PAD status were available for 2975 patients (40.7% female) (*Figure 1*). Chronic AF was recorded in 650 (22.3%) patients. A high thromboembolic risk, with CHA_2DS_2-VASc ≥ 2, was recorded in 82.2%, while a high risk for bleeding (HAS-BLED ≥ 3) was documented in 14.5%. At baseline, 31.6% were treated at least with one antiplatelet drug, while anticoagulant therapy was used in 1764 (59.9%) AF patients. Overall, 1154 (39.3%) patients were treated with a statin at enrolment.

Peripheral arterial disease was recorded in 11% ($n = 328$). Clinical characteristics in patients with and without PAD are summarized in *Table 1*. Patients with PAD were more frequently male ($P = 0.0070$) and older ($P < 0.0001$) compared with patients without PAD. Peripheral arterial disease patients had a higher prevalence of hypertension, diabetes mellitus, hypercholesterolaemia, prior stroke/TIA, ischaemic thromboembolic complications, coronary artery disease or chronic heart failure (CHF), and chronic kidney disease (all $P < 0.0001$). Prior bleeding events were more reported in PAD patients ($P = 0.0006$).

As expected, patients with PAD had higher CHA_2DS_2-VASc than patients without PAD; a high thromboembolic risk was recorded in 98.2% ($P < 0.0001$). HAS-BLED score was higher in patients with PAD ($P < 0.0001$).

Pharmacological therapies distribution

At enrolment, PAD patients were more commonly treated with antiplatelet drugs, usually acetylsalicylic acid, than those without ($P < 0.0001$). Similarly, clopidogrel ($P = 0.0007$), ticlopidine ($P = 0.0020$), non-dihydropyridine (DHP) calcium-channel blockers ($P = 0.0261$), and statins ($P = 0.0001$) were more used in PAD patients.

After discharge, PAD patients were more frequently started on an oral anticoagulant drug ($P = 0.0186$), whether a vitamin K antagonist ($P = 0.0069$) or non-vitamin K antagonist oral anticoagulant ($P = 0.009$). Statin therapy use was higher at discharge in in patients taking anticoagulants, more commonly among PAD patients ($P < 0.0001$). A higher proportion of PAD patients were treated with antiplatelet drugs ($P < 0.0001$), non-DHP calcium-channel blockers ($P = 0.0064$), and ACE inhibitors ($P = 0.0417$).

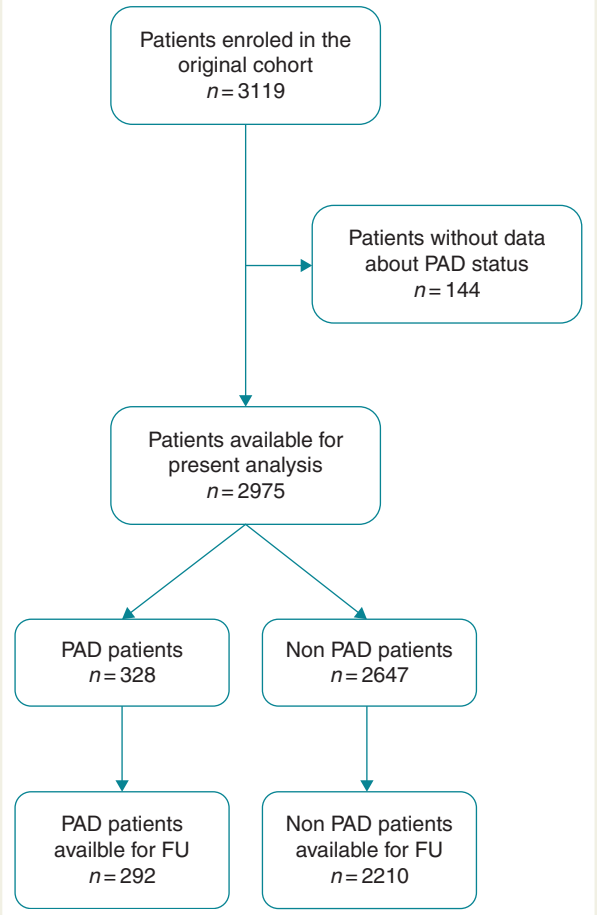

Figure 1 Study patients' flow chart.

Clinical determinants of peripheral arterial disease

On the basis of the univariate logistic analysis (Supplementary material online, *Table S1*), a multivariate model was constructed (see *Table 2*). On multivariate logistic analysis, age ($P < 0.0001$), hypertension ($P = 0.0059$), diabetes mellitus ($P = 0.0001$), CHF ($P < 0.0001$), previous stroke/TIA ($P = 0.0060$), and antiplatelet therapy ($P = 0.0001$) were significantly associated with the presence of PAD, while female gender ($P = 0.0002$) was inversely associated (*Table 2*). Of note, coronary artery disease was associated with PAD on univariate but not multivariate analysis (Supplementary material online, *Table S1*).

Major adverse events and survival analysis

Follow-up data were available for a total of 2502 (84.1%) patients. Of the whole cohort available at the pre-specified 1-year follow-up,

Table 1 Clinical characteristics of the population according to the presence of PAD

	PAD (n = 328)	Non-PAD (n = 2647)	P-value
Age (years)			
N	328	2647	
Mean ± SD	72.9 ± 10.5	68.5 ± 11.6	<0.0001
Female gender	111/328 (33.8%)	1101/2647 (41.6%)	0.0070
Type of AF			0.1375
Non-chronic AF	242/325 (74.5%)	2022/2589 (78.1%)	
Chronic AF	83/325 (25.5%)	567/2589 (21.9%)	
Hypertension	270/326 (82.8%)	1820/2633 (69.1%)	<0.0001
Coronary artery disease	167/299 (55.9%)	795/2377 (33.4%)	<0.0001
Diabetes mellitus	112/325 (34.5%)	508/2634 (19.3%)	<0.0001
Hypercholesterolaemia	196/322 (60.9%)	1219/2586 (47.1%)	<0.0001
Current smoker	32/324 (9.9%)	287/2562 (11.2%)	0.4734
Previous stroke/TIA	51/316 (16.1%)	236/2632 (9.0%)	<0.0001
Chronic heart failure	225/325 (69.2%)	1147/2628 (43.6%)	<0.0001
LVEF (%)			
N	257	2073	
Median (IQR)	50.0 (39.0–60.0)	55.0 (45.0–60.0)	0.0001
Chronic kidney disease	91/325 (28.0%)	304/2642 (11.5%)	<0.0001
Bleeding events	33/317 (10.4%)	146/2639 (5.5%)	0.0006
Ischaemic thromboembolic complications	89/316 (28.2%)	302/2640 (11.4%)	<0.0001
CHA_2DS_2-VASc			
N	328	2647	
Median (IQR)	5.0 (4.0–6.0)	3.0 (2.0–4.0)	<0.0001
Low risk	0/328 (0.0%)	235/2647 (8.9%)	
Intermediate risk	6/328 (1.8%)	287/2647 (10.8%)	
High risk	322/328 (98.2%)	2125/2647 (80.3%)	
HAS-BLED			
N	328	2647	
Median (IQR)	2.0 (1.0–3.0)	1.0 (1.0–2.0)	<0.0001
0–2	236/328 (72.0%)	2309/2647 (87.2%)	
≥3	92/328 (28.0%)	338/2647 (12.8%)	
Treatments before hospital admission/consultation			
No antithrombotic agent	47/326 (14.4%)	579/2630 (22.0%)	0.0015
Any antiplatelet	151/326 (46.3%)	783/2630 (29.8%)	<0.0001
ASA	134/326 (41.1%)	728/2630 (27.7%)	<0.0001
Clopidogrel	29/325 (8.9%)	120/2634 (4.6%)	0.0007
Prasugrel	(0.0%)	(0.0%)	NA
Ticagrelor	(0.0%)	6/2634 (0.2%)	>0.999[a]
Ticlopidine	7/326 (2.1%)	11/2633 (0.4%)	0.0020[a]
Indobufen	2/326 (0.6%)	4/2633 (0.2%)	0.1347[a]
Any anticoagulant	200/324 (61.7%)	1564/2623 (59.6%)	0.4665
Vitamin K Antagonists	184/324 (56.8%)	1397/2625 (53.2%)	0.2240
NOACs	8/326 (2.5%)	128/2634 (4.9%)	0.0504
Heparin	11/326 (3.4%)	57/2631 (2.2%)	0.1700
Other antithrombotic Agents	(0.0%)	15/2633 (0.6%)	0.3970[a]
Statins	159/324 (49.1%)	995/2615 (38.0%)	0.0001
DHP calcium-channel blockers	51/324 (15.7%)	317/2619 (12.1%)	0.0619
Non-DHP calciumchannel blockers	24/324 (7.4%)	120/2619 (4.6%)	0.0261
ACE inhibitors	130/323 (40.2%)	990/2618 (37.8%)	0.3956
Treatments at discharge			
No antithrombotic agent	4/328 (1.2%)	135/2641 (5.1%)	0.0016

Continued

Table 1 ***Continued***

	PAD (n = 328)	Non-PAD (n = 2647)	P-value
Any antiplatelet	168/327 (51.4%)	878/2641 (33.2%)	<0.0001
ASA	149/327 (45.6%)	789/2641 (29.9%)	<0.0001
Clopidogrel	54/328 (16.5%)	250/2642 (9.5%)	<0.0001
Prasugrel	2/328 (0.6%)	2/2642 (0.1%)	0.0627[a]
Ticagrelor	(0.0%)	6/2642 (0.2%)	>0.999[a]
Ticlopidine	3/328 (0.9%)	6/2641 (0.2%)	0.0677[a]
Indobufen	3/328 (0.9%)	8/2641 (0.3%)	0.1128[a]
Any anticoagulant	284/328 (86.6%)	2144/2638 (81.3%)	0.0186
Vitamin K Antagonists	256/328 (78.0%)	1871/2638 (70.9%)	0.0069
NOACs	14/328 (4.3%)	222/2641 (8.4%)	0.0090
Heparin	27/328 (8.2%)	130/2641 (4.9%)	0.0115
Other antithrombotic Agents	(0.0%)	10/2642 (0.4%)	0.6142[a]
Statins	198/328 (60.4%)	1276/2635 (48.4%)	<0.0001
DHP calcium-channel blockers	47/328 (14.3%)	342/2639 (13.0%)	0.4882
Non-DHP calcium-channel blockers	32/328 (9.8%)	155/2639 (5.9%)	0.0064
ACE inhibitors	159/328 (48.5%)	1123/2638 (42.6%)	0.0417

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ASA, acetylsalicylic acid; DHP, dihydropyridine; IQR, interquartile range; LVEF, left ventricular ejection fraction; NOACs, non-vitamin K antagonists oral anticoagulants; SD, standard deviation; TIA, transient ischaemic attack.
[a]Fisher's exact test.

Table 2 Multivariate logistic analysis for clinical determinants of the presence of PAD at baseline

	Odds ratio	95% CI	P-value
Chronic heart failure	2.235	(1.725–2.896)	<0.0001
Hypertension	1.563	(1.138–2.148)	0.0059
Age (per years)	1.033	(1.020–1.045)	<0.0001
Diabetes mellitus	1.691	(1.295–2.208)	0.0001
Previous stroke/TIA	1.632	(1.151–2.314)	0.0060
Female gender	0.608	(0.468–0.791)	0.0002
Any antiplatelet	1.639	(1.277–2.102)	0.0001

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ASA, acetylsalicylic acid; CI, confidence interval; DHP, dihydropyridine; IQR, interquartile range; LVEF, left ventricular ejection fraction; NOACs, non-vitamin K antagonists oral anticoagulants; TIA, transient ischaemic attack.

249 (10.0%) patients had a major adverse event (all-cause death + any TE).

In the292 PAD patients, there were 53 (18.1%) major adverse events, as summarized in the following: (i) 40 (13.7%) all-cause deaths with 19 (6.5%) CV deaths and (ii) any TE in 13 (4.5%). In the 2210 patients without PAD, 196 (8.9%) major adverse events occurred as follows: all-cause death in 123 (5.6%), of which 49 (2.2%) were CV deaths, and 'any TE' in 73 (3.3%).

Figure 2, patients with PAD had higher rates of both CV and all-cause death compared with patients without PAD (6.8 vs. 2.3% and 13.7 vs. 5.6%, respectively). When considering the outcome of any TE, a non-significant numerical difference was found between patients with and without PAD (6.0 vs. 3.7%) (*Figure 2*).

On Kaplan–Meier survival analysis for all-cause death, patients with PAD had a significantly higher risk for all-cause death than patients without PAD ($P < 0.0001$) (*Figure 3*).

On univariate Cox proportional hazards model analysis (Supplementary material online, *Table S2*), clinical variables significantly associated with all-cause death were entered into the multivariable Cox proportional hazards models (*Table 3*).

In *Model 1*, only clinical variables, age (<0.0001), diabetes mellitus ($P = 0.0005$), CHF ($P < 0.0001$), chronic kidney disease ($P < 0.0001$), and the previous occurrence of haemorrhagic events ($P < 0.0009$) were independently associated with the occurrence of all-cause death, but PAD was not independently associated with all-cause death ($P = 0.1096$). In *Model 2*, which included pharmacological therapy with any antiplatelet drug, the same clinical variables were independently associated with all-cause death, but therapy with any antiplatelet drug(s) was not independently associated with all-cause death ($P = 0.2482$).

Other multivariable models were compiled inserting one variable at a time, successively, pharmacological therapy with statins in *Model 3*, ACE inhibitors in *Model 4* and calcium-channel blockers in *Model 5*. These multivariable models showed that all-cause death was independently inversely associated with statins ($P = 0.0019$), ACE inhibitors ($P = 0.0008$), and DHP calcium-channel blockers ($P = 0.0007$). When considering all the drugs together in Model 6, results of previous models were confirmed with statins ($P = 0.0111$), ACE inhibitors ($P = 0.0020$), and DHP calcium-channel blockers ($P = 0.0187$) being all inversely associated with the occurrence of all-cause death. Of note, coronary artery disease was significantly associated with all-cause death on univariate but not multivariate analysis.

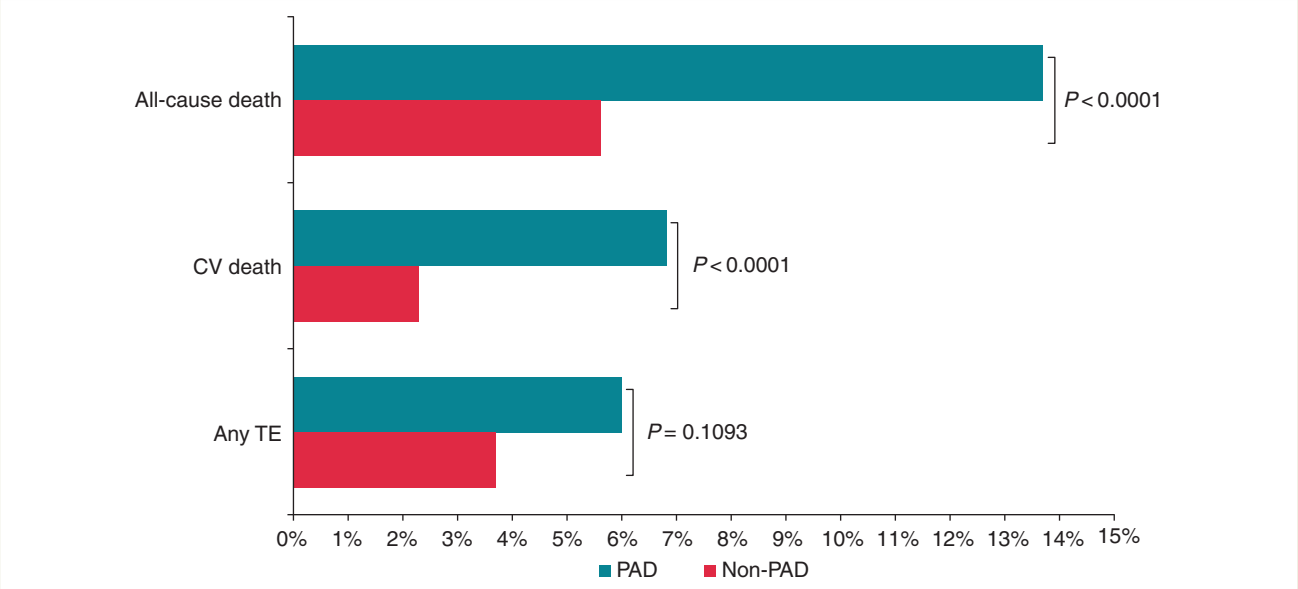

Figure 2 Major adverse event rates according to the presence of PAD. CV, cardiovascular; PAD, peripheral arterial disease; TE, thromboembolic event.

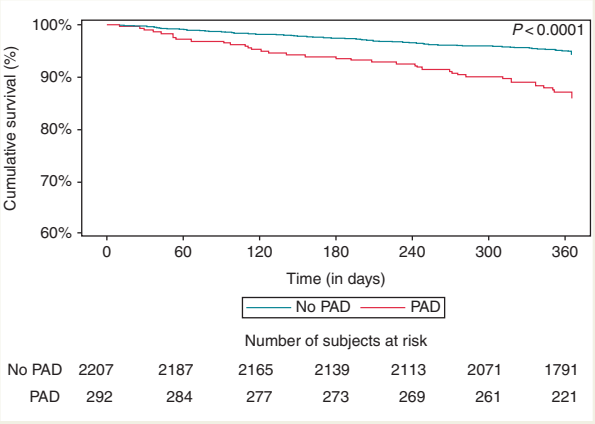

Figure 3 Kaplan–Meier curve for all-cause death according to the presence of PAD. PAD, peripheral arterial disease.

Discussion

In this study, we show first that symptomatic PAD is prevalent in 11% of patients with AF; secondly, various clinical factors frequently associated with AF were also associated with the presence of PAD; thirdly, patients with PAD had higher absolute rates of both CV and all-cause death. Also, the incidence of any TE was numerically higher in PAD patients than in those without. Finally, the survival analysis for all-cause death showed that AF patients with symptomatic PAD were at higher risk than patients without PAD, but this was attenuated by CV drugs (statins, ACE inhibitors, and calcium-channel blockers). However, PAD was not independently associated with all-cause death in AF patients, and neither was coronary artery disease.

Reports on the prevalence of symptomatic PAD in AF patients have been contradictory. In the Danish Diet, Cancer, and Health study, 3.7% of AF patients were affected by PAD.[23] Similarly, in the ROCKET-AF trial, only 5.9% of patients had a diagnosis of PAD at trial entry.[17] The wide difference between those previous reports and our data may reflect the nature of the study itself. In studies based on ICD codes, as with the Danish 'Diet, Cancer, and Health' study, reporting could be affected by wrong coding or selection/sampling bias, while randomized controlled trials are a highly selected cohort that may not reflect the 'real world' epidemiology. Conversely, in an Italian large observational study, patients with AF had a high prevalence (21%) of asymptomatic PAD.[16]

Among the clinical factors identified in our study as associated with PAD, age, hypertension, and diabetes mellitus have been previously identified as risk factors both in general population[2] and in AF patients.[16] Similarly, the majority of studies have highlighted higher prevalence rates in males than in females.[2] The close association with CHF and previous stroke/TIA, along with the higher proportion of AF patients with a previous history of clinically evident atherosclerotic disease among the PAD patients, underlines the relationship between atherosclerotic vascular disease, AF, and CV risk.

Moreover, the higher occurrence of both CV death and any TE in AF patients with PAD reinforces the emerging concept that atherosclerotic vascular disease and AF may be more intimately related, perhaps also from a pathophysiological perspective.[14,24,25] This has been supported by data from sub-analyses of studies showing higher rates of CV events and death in patients with concomitant AF and vascular disease (previous MI or PAD);[9] as well as studies showing that AF patients carry a higher risk of clinically relevant atherosclerotic disease.[13] Indeed, recent studies have shown that AF patients are at higher risk of MI,[13] in hospitalized patients,[11]

Table 3 **Cox proportional hazards multivariable models for all-cause death**

	Hazard ratio	95% CI	*P*-value
Model 1			
Peripheral arterial disease	1.375	(0.931–2.030)	0.1096
Age (per years)	1.060	(1.041–1.080)	<0.0001
Diabetes mellitus	1.840	(1.308–2.589)	0.0005
Chronic heart failure	2.344	(1.583–3.471)	<0.0001
Chronic kidney disease	2.592	(1.820–3.691)	<0.0001
Haemorrhagic events	2.085	(1.350–3.220)	0.0009
Model 2			
Peripheral arterial disease	1.406	(0.949–2.081)	0.0892
Age (per years)	1.066	(1.046–1.086)	<0.0001
Diabetes mellitus	1.886	(1.339–2.657)	0.0003
Chronic heart failure	2.347	(1.582–3.481)	<0.0001
Chronic kidney disease	2.608	(1.829–3.721)	<0.0001
Haemorrhagic events	2.067	(1.337–3.194)	0.0011
Any antiplatelet	0.818	(0.582–1.150)	0.2482
Model 3			
Peripheral arterial disease	1.401	(0.947–2.072)	0.0916
Age (per years)	1.063	(1.044–1.083)	<0.0001
Diabetes mellitus	1.916	(1.359–2.702)	0.0002
Chronic heart failure	2.373	(1.598–3.525)	<0.0001
Chronic kidney disease	2.558	(1.788–3.658)	<0.0001
Haemorrhagic events	1.867	(1.198–2.909)	0.0058
Statins	0.584	(0.416–0.820)	0.0019
Model 4			
Peripheral arterial disease	1.345	(0.907–1.994)	0.1408
Age (per years)	1.065	(1.045–1.085)	<0.0001
Diabetes mellitus	1.808	(1.281–2.551)	0.0008
Chronic heart failure	2.544	(1.706–3.794)	<0.0001
Chronic kidney disease	2.439	(1.705–3.490)	<0.0001
Haemorrhagic events	1.927	(1.243–2.987)	0.0034
ACE inhibitors	0.544	(0.381–0.776)	0.0008
Model 5			
Peripheral arterial disease	1.330	(0.897–1.970)	0.1557
Age (per years)	1.065	(1.045–1.085)	<0.0001
Diabetes mellitus	1.925	(1.365–2.713)	0.0002
Chronic heart failure	2.243	(1.514–3.324)	<0.0001
Chronic kidney disease	2.670	(1.869–3.816)	<0.0001
Haemorrhagic events	2.008	(1.297–3.109)	0.0018
Calcium-channel blockers	0.394	(0.200–0.776)	0.0071
Model 6			
Peripheral arterial disease	1.324	(0.888–1.974)	0.1685
Age (per years)	1.064	(1.044–1.084)	<0.0001
Diabetes mellitus	1.903	(1.345–2.693)	0.0003
Chronic heart failure	2.562	(1.712–3.833)	<0.0001
Chronic kidney disease	2.478	(1.722–3.566)	<0.0001
Haemorrhagic events	1.703	(1.089–2.664)	0.0196
Any antiplatelet	0.966	(0.679–1.374)	0.8489
Statins	0.635	(0.447–0.902)	0.0111
ACE inhibitors	0.570	(0.399–0.814)	0.0020
Calcium-channel blockers	0.442	(0.224–0.873)	0.0187

ACE, angiotensin-converting enzyme; CI, confidence interval. Hosmer and Lemeshow goodness-of-fit test for each model: $P = 0.5255$.

outpatients,[26] or even in AF patients with low thromboembolic risk.[27] Sudden death is also increased in AF patients.[1]

When reviewing the relationship between AF, PAD, and all-cause death, the available evidence seems conflicting. Various studies involving PAD patients have documented a higher risk of all-cause death in those patients with concomitant AF, but this risk was not independent of other risk factors.[6,28] In the ROCKET-AF study, the absolute risk of all-cause death was higher in AF patients with PAD, but there was a non-significant independent association of PAD and all-cause death.[17] The Diet, Cancer, and Health study also found a significant association between PAD and all-cause death in AF patients.[23] In our study, the absolute rate of all-cause death was significantly higher in PAD patients, but we did not find an independent relationship from other clinical variables on multivariable analysis.

Among the factors influencing the association between PAD and all-cause death, our study shows that pharmacological therapy with statins, ACE inhibitors, and calcium-channel blockers was inversely associated with all-cause mortality. Conversely, the role of antiplatelet therapies was inconclusive, being inversely associated with all-cause death but not being statistically significant. Indeed, the combined use of such pharmacological therapies in preventive CV strategies seems effective in the general population and is currently recommended by European guidelines for both general population[29] and PAD patients.[30] Nonetheless, definitive data on CV risk reduction for AF patients with concomitant symptomatic PAD are lacking.

The role of statin therapy in lowering the incidence of CV events and death in PAD patients among the general population, even if never specifically tested in a properly designed study in this setting, has largely been confirmed.[31] For all-cause death, data from the Reduction of Atherothrombosis for Continued Health (REACH) registry showed that statin therapy in patients with PAD conferred an almost 20% relative risk reduction.[32] Conversely, a large Cochrane systematic review on pharmacological therapy for PAD documented inconclusive results of statins and all-cause death, with a non-statistical significant inverse relationship with statins.[33] Angiotensin-converting enzyme inhibitors in general PAD patients may reduce CV events,[34] but definitive data for ACE inhibitors in modulating major adverse events in AF patients with PAD are lacking.[35]

The calcium-channel blockers have previously been shown to be effective in reducing CV events in general population.[36] Indeed, calcium-channel blockers may have an anti-atherosclerotic action.[37] In particular, DHP calcium-channel blockers may slow the progression of coronary artery disease[37,38] and downmodulate subclinical atherosclerosis, both in animal models[39] and in large randomized clinical trials,[40] independent of blood pressure reduction. Even if specific data in PAD patients are not available, cross-sectional data from the 'Atrial Fibrillation Registry for Ankle-brachial Index Prevalence Assessment: Collaborative Italian Study' found an inverse association between calcium-channel blockers and subclinical atherosclerosis[25] in AF patients. Our data also suggest a potential relevant role of calcium-channel blockers in PAD patients with AF.

It has largely been assumed that antiplatelet therapy is effective in reducing CV events in this clinical setting,[31] and thus in international guidelines, aspirin is recommended as being effective in reducing adverse events,[30] given the data from the Antithrombotic Trialists' Collaboration meta-analysis.[41] However, recent meta-analyses showed that the benefits of aspirin appear inconclusive,[42] while therapy with thienopyridines was perhaps more effective in reducing major adverse events.[43] Our study data seem to support this evidence, with a non-significant association between antiplatelet therapy (mainly aspirin) and all-cause death. Given their associated comorbidities and concomitant risk factors, PAD patients need to be managed in a holistic manner.[31] The beneficial effects of pharmacological therapies seen in our study emphasize this concept even in AF patients with concomitant PAD.

Limitations

EURObservational Research Programme Atrial Fibrillation was a European cardiologist-based registry, so this could have led to an overestimate of PAD prevalence. Conversely, this could have resulted in enrolment of patients with more severe conditions that could have reduced the influence of PAD on event rates. As reported, asymptomatic PAD is a relevant issue in the assessment of this condition. The lack of an objective assessment of PAD and the absence of a more detailed description of the related clinical status are major limitations to our study. Moreover, the relatively small number of PAD patients, the short follow-up period, and missing follow-up data in ~16% of patients could have limited the influence of PAD in determining all-cause death or thromboembolism. Finally, EORP-AF was an observational study and was not adequately powered to detect survival differences according to the presence of PAD; thus, our data require confirmation from properly designed larger studies, focused on patients with a well-defined PAD diagnosis.

Conclusions

In conclusion, PAD is prevalent in AF patients and related to various atherosclerotic risk factors. Even if PAD is associated with higher risk of all-cause death on univariate analysis, this risk was significantly lowered and was no longer evident after adjusting for the use of CV prevention drugs (statins, ACE inhibitors, and calcium-channel blockers).

Supplementary material

Supplementary material is available at *Europace* online.

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