**Vascular disease in patients with atrial fibrillation.**

**A report from Polish participants in the EORP-AF General Long Term Registry**

*Short title: Vascular disease in atrial fibrillation patients*

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**Abstract**

**Objectives:** This study aimed to (1) define the prevalence of vascular disease (VD; ie. coronary (CAD) and/or peripheral artery disease (PAD)) in patients with atrial fibrillation (AF) and describe its associated risk factors; and (2) establish the relationship of VD and associated treatment patterns on adverse events in AF.

**Methods:** Data from 701 Polish AF patients enrolled in the EURObservational Research Programme-Atrial Fibrillation General Long-Term Registry in years 2013-2016 were included in this analysis. During the 1-year follow-up period, the occurrence of major adverse events (MAE; all-cause death, thromboembolic event, myocardial infraction) and its components was evaluated.

**Results:** VD was recorded in 293 patients (44%) and was associated with age, diabetes mellitus, hypercholesterolemia and heart failure (HF). VD patients had numerically higher rates of MAE (8.8%vs.5.7%, p=0.16). Patients with concomitant CAD and PAD had numerically higher MAE rate than those with PAD and CAD alone (21% vs.7.5% and 6.7%, p=0.09). A higher risk of MAE was associated with age>75years, HF, chronic obstructive pulmonary disease, and chronic kidney disease.

Relative to patients with VD on vitamin K antagonists (VKA), those treated with non-VKA-OAC (NOAC) had lower absolute rate of MAE (1.4% vs 10%, p=0.02) but similar risks for thromboembolic and hemorrhagic events. The concomitant use of triple therapy was associated with increased risk of MAE as compared to those on OAC alone or dual therapy (20% vs.4.8%, 3.2%, p=0.02).

**Conclusions:** VD is prevalent in almost two-fifths of AF patients. The incidence of MAE was numerically higher in patients with VD on VKA (vs NOAC) and on triple therapy (vs dual therapy, OAC alone).

**Keywords:** atrial fibrillation; coronary artery disease; peripheral artery disease; anticoagulation; dual therapy; triple therapy

**Introduction**

Coronary artery disease (CAD) and peripheral artery disease (PAD) are common comorbidities, occurring up to 30% of patients with atrial fibrillation (AF) [Inohara, Pastori]. The coexistence of PAD with CAD increases the risk of cardiovascular events and mortality among AF patients [Pastori2016, Nielsen]. As the presence of vascular disease is included in the guideline-recommended thromboembolic risk stratification (CHA2DS2-VASc score) and current European Society of Cardiology (ESC) guidelines recommend that oral anticoagulation (OAC) should be considered in AF patients even with only one non-sex stroke risk factor (Class IIa recommendations), most of the patients with AF and CAD and/or PAD are eligible for anticoagulant therapy [Kirchof].

Despite increasing data from clinical trials, the selection of the optimal anticoagulant strategy for an individual patient with AF and vascular disease remains difficult and requires a balance between the risk of thromboembolic events and the risk of hemorrhagic complications. The EURObservational Research Programme Atrial Fibrillation (EORP-AF) General Long-Term Registry is a prospective multi-national survey conducted by the ESC in 250 centers from 27 European countries to determine clinical features, treatment patterns, and outcomes among patients with AF managed by cardiologists [Boriani].

The objective of the present study was to analyze Polish part of EORP-AF General Long-Term Registry. We aimed to (1) define the prevalence of vascular disease (VD; ie. coronary (CAD) and/or peripheral artery disease (PAD)) in patients with atrial fibrillation (AF) and describe its associated risk factors; and (2) establish the relationship of VD and associated treatment patterns on adverse events in AF.

**Methods**

*Study population*

The cohort analyzed in this study was derived from EORP-AF General Long-Term Registry. The rationale design, and methods of the registry have been previously published [Boriani]. Briefly, EORP-AF General Long-Term Registry is a prospective, observational, international registry of patients with AF. Eligible patients were required to be 18 years of age with electrographically documented AF. Moreover, eligible patients had to be able to adhere to local follow-up every 12 months during 3-year period. An electronic case report form (eCRF) was used to collect information on patient demographics, medical history, medications, vital signs, laboratory data, and imaging and electrocardiographic parameters.

For the purpose of this study, we only included patients with AF and data on CAD, and PAD, from Poland. Only the baseline and 1-year follow-up visit was analyzed to avoid significant lost to follow up patients that number increased with the years of follow up. The registry was approved by local ethical review boards according to the regulations of each participating country. The study was performed according to the European Union Note for Guidance on Good Clinical Practice CPMP/ECH/135/95 and the Declaration of Helsinki. A signed, informed consent was obtained from each patient after providing detailed information on the registry [Boriani].

*Definitions*

“Vascular disease” was defined as any the presence of the CAD and PAD. The presence of CAD was defined by a positive history of any of the following: stable CAD, myocardial infraction (MI), percutaneous coronary interventions (PCI), coronary artery bypass grafting (CABG). PAD was defined as any the presence of the following: intermittent claudication, previous surgery, percutaneous intervention or thrombosis of abdominal or thoracic aorta, lower extremity vessels, and aortic plaque. This assessment was performed by any physician during the clinical assessment and/or by searching through medical records, if available. The presence or absence of CAD and PAD was recorded in the eCRF of the registry, but with no further details on its clinical manifestations.

Types of AF were defined as follows: (1) first detected AF, (2) paroxysmal AF, (3) persistent AF including long-standing persistent AF, (4) permanent AF. Thromboembolic risk was defined according to the CHA2DS2-VASc score and bleeding risk was assessed based on the HAS-BLED score [ref]. Single antiplatelet therapy (SAPT) was defined as the current use of any one of the following: aspirin, clopidogrel, prasugrel, or ticagrelor. Dual APT (DAPT) was defined as the current use of aspirin plus either clopidogrel, ticlopidine, prasugrel, or ticagrelor. The current study assessed adherence of cardiologists to 2012 ESC recommendations as study was conducted in years 2013-2016 {Camm].

*Primary and secondary endpoints*

During the pre-specified 1-year follow-up period, the occurrence of major adverse events (MAE) was evaluated. Based on the study protocol, MAE recorded were as follows: all-cause death, and any thromboembolic event (TE) (defined as the occurrence of any stroke, transient ischemic attack (TIA), peripheral or pulmonary embolism), MI. As secondary outcomes individual components of MAE, hemorrhagic events (HE) and hospitalization related to cardiovascular, TBE or HE were also evaluated in the analysis.

*Statistical analysis*

Categorical variables were presented as counts and frequencies, and continuous variables were presented as median values with interquartile ranges (IQR). Differences between groups were appropriately assessed using the chi-squared test or Fisher’s exact test for categorical and the Kruskal-Wallis for continuous variables.

A regression analysis was performed to establish the clinical factors significantly associated with the presence of vascular disease and MAE. All clinical variables that had less than 1% of missingness, expect for hypercholesterolemia (2%), smoking (4%), underwent a univariable analysis and those predictors with a level significance of p<0.10 were inserted into a forward multivariable logistic model. List of included variables in univariable model is presented in Table S1 (supplementary material online). All variables with a p<0.10 for the association to MAE at the univariable analysis were inserted in the stepwise multivariable model along with vascular disease. Additional stepwise models were then performed inserting in any model a specific class of drugs with a known role in cardiovascular prevention such as antiplatelets, anticoagulants, statins, angiotensin-converting enzyme (ACE) inhibitors, and calcium-channel blockers (CCB). A two-sided p-value of <0.05 was considered statistically significant. Kaplan–Meier analysis was used to establish the relation of vascular disease to all-cause death and differences in survival were analyzed using the log-rank test. All analyses were performed using StatsModels: Statistic in Python - v0.10.1 documentation.

**Results**

The EORP-AF General Long-Term Registry enrolled 701 patients with AF from 2013 to 2016 at 25 cardiology centers within Poland. Of these, 683 patients had data on CAD and PAD, therefore included into the present analysis (Figure 1): 32% patients were diagnosed with paroxysmal AF, 29% - with persistent AF and 33% - with permanent AF). A high thromboembolic risk (CHA2DS2-VASc score ≥2) was recorded in 79%, while a high risk for bleeding (HAS-BLED score ≥3) was documented in 16%. Of the whole cohort, 17% were treated at least with one antiplatelet drug, while anticoagulant therapy was used in 589 (89%) AF patients. Overall, 395 (60%) patients were treated with a statin.

Vascular disease was recorded in 293 patients (44%). Baseline clinical characteristics in patients with and without vascular disease are summarized in Table 1, while detailed characteristics in subgroup of patients with vascular disease (CAD, PAD and CAD+PAD) are summarized in supplementary Table S2. Patients with vascular disease were older, more prevalent permanent AF, hypertension, diabetes mellitus, hypercholesterolemia, heart failure (HF), chronic kidney disease (CKD). On echocardiography, patients with vascular disease were characterized by lower ejection fraction, heart cavities enlargement and left ventricular hypertrophy as compared to those without vascular disease. Laboratory tests showed lower estimated glomerular filtration rate and cholesterol values among the vascular disease group.

As expected, patients with vascular disease had higher CHA2DS2-VASc and HAS-BLED scores than patients without vascular disease. At followup, TE were recorded in 13% (vs 11% in those without vascular disease, p=0.40) and HE in 9.9% (vs 6.0%, p=0.06).

*Pharmacological therapies*

Patients with vascular disease were more commonly treated with antiplatelet drugs, usually acetylsalicylic acid, than those without (p<0.0001). Similarly, clopidogrel (p<0.0001), ACE inhibitors (p<0.0001), aldosterone receptor antagonists (p<0.0001), diuretics (p<0.0001) and statins (p<0.0001) were more used in vascular disease patients (Table 2).

In patients treated with OAC (n = 589), the temporal trend of treatment patterns was assessed by the year of patient enrollment (Figure 2). In both groups, the prescription rate of NOAC increased in parallel with decreasing rates of VKA over time. This trend was consistent regardless of vascular disease status and concomitant use of antiplatelet therapy.

Time from most recent MI or PCI until enrolment is summarized in [Table](https://www-1sciencedirect-1com-1000002r60735.han3.wum.edu.pl/science/article/pii/S000287031930095X" \l "t0015) S3 (supplementary material online). A total of 32 patients were receiving DAPT in addition to OAC (“triple therapy”), and of these, 6 (19%) were taking DAPT for >1 month despite high bleeding risk (HAS-BLED score > 3), 3 (9.4%) with low bleeding risk (HAS-BLED score <3) were taking DAPT for >12 or did not have a history of MI and/or PCI. As a result, the use of DAPT was considered as inappropriate in 9 (28%) of patients receiving DAPT and OAC. A total of 40 patients were receiving dual therapy (SAPT with OAC), and of these patients, 38 (95%) was considered as inappropriate as they were receiving dual therapy within >12 months (HAS-BLED score > 3) or within <1month />12month (HAS-BLED score < 3) or did not have a history of MI and/or PCI. Among patients on OAC alone (n=183), 62 (34%) were treated inappropriate as they received OAC alone within <12 months from MI/PCI.

On multivariable logistic analysis (Table 3), age>75 years (p<0.0001), diabetes mellitus (p<0.0001), hypercholesterolemia (p<0.0001) and HF (p<0.0001) were significantly associated with the presence of vascular disease. Of note, presence of AF type, hypertension, CKD, HE was associated with vascular disease on univariable but not multivariable analysis.

*Major adverse events and survival analysis*

Follow-up data was available for a total of 497 (75%) patients (Figure 1). Of the whole cohort available at the pre-specified 1-year follow-up, 35 (7.0%) patients had a MAE (including 28 patients (5.6%) who died). In the 215 patients with vascular disease, there were 19 (8.8%) MAE, as summarized in the following: all-cause deaths in 15 (7.0%), any TE in 1 (0.5%), MI in 4 (1.9%). In the 282 patients without vascular disease, 16 (5.7%) MAE occurred as follows: all-cause death in 13 (4.6%), any TBE in 1 (0.4%), MI in 3 (1.1%).

Despite a higher rate of MAE and its components, HE in patients with vascular disease as compared to those without, the differences did not reach statistical significance. On Kaplan–Meier survival analysis for all-cause death, patients with vascular disease had a non-significantly higher risk for all-cause death than patients without vascular disease (p=0.26) (Figure 4).

*Antithrombotic therapies in patients with vascular disease*

In AF patients with concomitant vascular disease who were treated with OAC (n = 186), clinical outcomes (MAE and its components, HE and all-cause hospitalization) were compared according to the status (presence or absence) of antiplatelet therapy (Table 5). The risk of both MAE and all-cause death was significantly higher among patients treated with VKA as compared to those on NOAC (10% vs 1.4%, p=0.02; 7.8% vs 0%, p=0.02). Moreover, the rate of MAE and all-cause death was higher among patients on triple therapy (DAPT+OAC) as compared to those who were on dual therapy (SAPT+OAC) or OAC alone (20% vs 3.2%, 4.8%, p=0.02; 16% vs 3.2%, 3.1%, p=0.01).

*Determinants of major adverse events*

On univariable analysis, clinical variables significantly associated with MAE were entered into the multivariable Cox proportional hazards models along with vascular disease (Table 6). In Model 1, HF (p=0.008) and CKD (p=0.048) were independently associated with the occurrence of MAE, but vascular disease was not independently associated with MAE (p=0.98). In Model 2, which included pharmacological therapy with any antiplatelet drug, the same clinical variables and any antiplatelet drug were independently associated with MAE.

Other multivariable models were compiled inserting one variable at a time, successively, pharmacological therapy with any OAC in Model 3, statins in Model 4, ACE inhibitors in Model 5 and CCB in Model 6. These multivariable models showed that MAE was independently inversely associated only with OAC (p=0.02) and any antiplatelets use increased risk of MAE (p=0.02). When considering all the drugs together in Model 7, results of previous models were confirmed with antiplatelets drugs (p=0.03) being associated with the occurrence of MAE.

In additional multivariable analysis, independent predictors for MAE occurrence were HF (p=0.01), CKD (p=0.04) in whole study group, age>75 years (p=0.04), diabetes mellitus (p=0.02), HF (p=0.04) among vascular disease group and only COPD in non-vascular disease group (p=0.02) (supplementary material online, Table S4).

**Discussion**

The analysis of Polish participants of the EORP-AF General Long-Term registry provides an important view on patients with AF and concomitant vascular disease. The major findings of the present study are as follows. First, vascular disease is prevalent in almost two-fifths of patients with AF and is related to various atherosclerotic risk factors. Second, the overall use of OAC was high, 89%, and comparable between patients with and without vascular disease. In addition, the use of NOAC increased over time in parallel with decreased VKA use regardless of vascular disease status. Third, the incidence of MAE and its components was numerically higher in patients with vascular disease than in those without. Moreover, patients with concomitant CAD and PAD had numerically higher mortalitythan those with PAD and CAD alone. Fourth, relative to patients with vascular disease on NOAC, those treated with VKA had higher absolute rate of MAE but similar risks for TE and HE. Finally, in AF patients with vascular disease, the concomitant use of antiplatelet therapy was associated with increased risk of MAE, its components and HE.

Reports on the prevalence of vascular disease and its components have been contradictory. Reported PAD prevalence in the AF population, varies from 4.1% to as high as 16.8% [Violi], whereas CAD prevalence varies from 17.0% to 46.5% [Michniewicz]. Compared to our results, in whole EORP-AF General Long-Term registry, the prevalence of CAD and PAD was 29.3% and 8.1%, respectively [Boriani]. With reference to vascular disease, Olesen et al found a prevalence of 17.5% in the Danish AF population [Olesen], while Pastori et al reported a prevalence of 27.7% in Italian AF patients [Pastori]. The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II (ORBIT-AF II) reported that almost one-third of patients with new-onset AF had vascular disease [Inohara].

In our study, 10.4%, 37% and 44% of AF patients were recognized with PAD, CAD and vascular disease, respectively. The wide difference between those previous reports and our data according vascular disease prevalence may reflect the nature of the study itself. In studies based on ICD codes [Olesen], reporting could be affected by selection bias or wrong coding, while randomized controlled trials are a highly selected cohort that may overestimate of vascular disease prevalence.

Among the clinical factors identified in our study as associated with vascular disease, age, hypercholesterolemia, HF, and diabetes mellitus have been previously identified as risk factors both in general population [Shammas] and in AF patients [Olesen, Anandasundaram, Shahid, Inohara]. Of note, HF and diabetes mellitus were independent predictors of MAE among patients with vascular disease. This close association with HF and previous history of clinically evident atherosclerotic disease (diabetes mellitus) for both occurrence of vascular disease and MAE among AF patients, reemphasizes that all these factors may be intimately related, perhaps also from a pathophysiological perspective [Börschel].

Various studies involving AF patients have documented a higher risk of all-cause death in those AF patients with concomitant vascular disease. Based on the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) study, the composite of cardiovascular death, MI or stroke are twice as likely in patients with more than one vascular disease (MI, stroke or PAD) than in those with isolated vascular disease (14.7% vs 7.7%, p<0.001) [Bhatt]. In recent study by Pastori et al, the rate of cardiovascular events (MI, cardiac revascularization, cardiovascular death, TIA) progressively increased from 2.4%/year in patients without PAD and CAD, to 5.6%/year and 6.1%/year in those with PAD and CAD alone respectively, to 8.1%/year in patients with concomitant PAD and CAD. Indeed, as compared to a group of patients without CAD and PAD, those with concomitant CAD and PAD were characterized by a 2.4 fold higher risk of cardiovascular events. This higher risk of major adverse cardiovascular and neurological events was also evident from the ORBIT-AF II study, among patients with as compared to those without vascular disease. Similar to our study, there were no statistically significant differences in TE between patients with vascular disease and those without (1.75% vs 1.07%, p=0.787) [Inohara]. A subanalysis of ROCKET-AF trial also reported similar rates of TE within anticoagulated patients with polyvascular disease (any combination of two of more: CAD, PAD, carotid artery disease) as compared to dose with single-bed vascular disease and without vascular disease [Chen].

Hence, vascular disease may produce a very small independent effect (<15% increase in risk) in the NOAC era [Singer]. In our study, for example, vascular disease was not associated with increased risk of HE, consistent with previous studies [Inohara, Chen]. The limited proportion of patients who had both CAD and PAD in our study population may have resulted in non-significant difference in major bleeding between those with and without vascular disease.

When reviewing the relationship between AF, PAD, and all-cause death, the available evidence seems conflicting. Despite documented a higher risk (varying from 1.3 to 2.5 fold) of the primary end‐point of stroke, thromboembolism or death in patients with coexist PAD and AF [Anandasundaram], in various studies this risk is often not independent of other risk factors [Proietti, Winkel, Goto, Jones], and some studies have suggested no interaction between the presence of PAD and worse clinical outcomes among AF patients [Watson, Lin].

Our study also shows that pharmacological therapy with OAC was inversely associated with MAE and use of antiplatelet therapies increased risk of MAE. It has largely been assumed that combination of antiplatelet and OAC therapy increases a patient's risk of bleeding (from 2% in DAPT alone to 14% with addition of OAC) [Romero]. Therefore, the selection of the optimal anticoagulant strategy for an individual patient with AF and vascular disease remains difficult and requires a balance between the risk of TE and HE. Similar to previous reports, the use of NOAC increased over time in parallel with the decrease in VKA therapy in our study cohort [Zhu, Inohara]. The combination of antiplatelet drug and VKA in patients with AF and CAD was associated with an increased bleeding risk compared with VKA monotherapy, without the added benefit of reducing the risk of thromboembolism or cardiovascular risk [Lamberts]. These results were confirmed in the ORBIT-AF II study [Inohara], which additionally found a lower bleeding rate among patients treated with NOAC compared to patients treated with VKA. The use of NOAC in combination with DAPT was associated with a significant reduction in the risk of bleeding with similar anticoagulant efficacy compared to VKA in combination with DAPT [Sindet-Pedersen][Gibson] [Cannon].

*Limitations*

EORP-AF General Long-Term registry was a European cardiologist-based registry, so this could have led to an overestimate of vascular disease prevalence. Conversely, this could have resulted in enrolment of patients with more severe conditions that could have reduced the influence of vascular disease on event rates. Moreover, the relatively short follow-up period, and missing follow-up data in 25% of patients could have limited the influence of vascular disease in determining MAE.

**Conclusions**

Vascular disease is prevalent in almost two-fifths of AF patients. The incidence of MAE was numerically higher in patients with VD on VKA (vs NOAC) and on triple therapy (vs dual therapy, OAC alone).

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**Conflict of interests:**

**Monika Gawałko**

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