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Relationship of peripheral and coronary artery disease to cardiovascular events in patients with atrial fibrillation

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ABSTRACT

Background: To investigate the impact of concomitant asymptomatic peripheral artery disease (PAD) and pre-existing coronary artery disease (CAD) on cardiovascular events (CVEs) in atrial fibrillation (AF) patients.
Methods: Prospective multicenter study including 1138 anticoagulated AF patients. PAD was diagnosed by can ankle-brachial index (ABI) ≤ 0.9, and CAD as a documented myocardial infarction (MI) or cardiac revascularization. The cohort was divided into 4 groups: group 0 (n = 717) with no previous CAD and ABI >0.9; group 1 (n = 168) no previous CAD and ABI ≤ 0.9; group 2 (n = 183) previous CAD and ABI >0.9: and group 3 (n = 70) previous CAD and ABI ≤ 0.9. The primary endpoint was a composite of CVEs.
Results: Mean age was 72.6 years and 41.3% were female. History of CAD was present in 253 (22.2%) patients, and 238 (20.9%) had an ABI ≤ 0.9. Patients with previous CAD were more likely to have a low ABI compared to those without (OR:1.6, 95%CI 1.2–2.3, P = 0.003).
Median follow-up was 35.9 months (IQR 19.2–57.2, 3819 patient-years), and 145 CVEs were recorded (3.8%/year 95%CI 3.2–4.5). Survival analysis showed a progressive increase in the rate of CVEs in the four groups (log-rank test P < 0.001). Multivariable Cox regression analysis showed that as compared to group 0, group 1 (HR:1.8, 95%CI 1.1–2.9, P = 0.01), group 2 (HR:2.2, 95%CI 1.4–3.4, P = 0.001) and group 3 (HR:2.4, 95%CI 1.4–4.4, P = 0.003) were associated with progressive greater risk of CVEs.
Conclusion: Patients with concomitant CAD and asymptomatic PAD are at high risk of CVEs, with a progressive risk with vascular disease burden where PAD was associated with CAD.

1. Introduction

Peripheral artery disease (PAD) and coronary artery disease (CAD) are commonly prevalent in patients with atrial fibrillation (AF) [1]. At least one atherosclerotic risk factor may be found in almost 90% of patients with AF, with the most common ones being arterial hypertension, diabetes mellitus and dyslipidemia, as well as overt coronary artery disease (CAD) [2,3]. AF may frequently occur after a first myocardial infarction (MI) event, and the presence of AF has been shown to be associated with more severe CAD [4]. Conversely, AF patients with pre-existing CAD are at higher risk of ischemic complications, related to both thromboembolism and atherothrombosis [5,6].

Peripheral artery disease (PAD) is a known risk factor for incident AF, especially in elderly patients [7]. Indeed, PAD also increases the thromboembolic risk associated with AF [8,9]. PAD is often asymptomatic and the Ankle-Brachial Index (ABI) is the currently recommended tool to investigate the presence of asymptomatic PAD [10,11]. Indeed, ABI a simple, inexpensive, and non-invasive marker of PAD, and a low ABI (i.e. ≤0.9) is associated with a two-fold greater risk of CAD (acute MI or angina) in the general population [12,13]. The reported prevalence of low ABI in AF patients is about 20% [14], and the presence of asymptomatic PAD in this population was associated with a high risk of vascular events (defined as vascular death, fatal/non-fatal MI, fatal/non-fatal stroke or transient ischemic attack (TIA) [15,16].

Previous studies have reported that coexistence of PAD with CAD increases the risk of cardiovascular events and mortality. For example, one previous study performed in 2424 patients with CAD (defined as having at least one significant stenosis in coronary vessels) showed that the prevalence of newly diagnosed asymptomatic PAD was 14.4% [17], and that low ABI was associated with a 2.4 fold higher incidence of

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the composite endpoint of death, MI, and stroke over 3 years of follow-up [17].

As both CAD and PAD may frequently coexist in AF, it is likely that an accentuated cardiovascular risk is detectable in AF patients with coexistent PAD and CAD. Nevertheless, there are limited published prospective data on the prognosis of AF patients with concomitant PAD *and/or* CAD [9].

Hence, our aim was to investigate the impact of asymptomatic PAD and pre-existing CAD, alone and/or in combination, on cardiovascular events (CVEs) in AF patients on oral anticoagulants.

2. Methods

We performed a prospective multicentre observational cohort study including non-valvular AF patients consecutively recruited from the Atherothrombosis Center of I Clinica Medica of "Sapienza" University of Rome and from the Department of Medical and Surgical Sciences, University Magna Græcia of Catanzaro, Italy from October 1, 2007, through June 30, 2016.

All patients with non-valvular AF aged >18 years and treated with Vitamin K Antagonists were eligible for the study. Exclusion criteria were: presence of mechanical prosthetic heart valves or any severe valvulopathy, chronic infectious diseases (i.e. Human Immunodeficiency Virus infection, Hepatitis C Virus, Hepatitis B Virus) or autoimmune systemic disease, history of active cancer or liver insufficiency (e.g. cirrhosis). Moreover, patients with symptoms of PAD or with a history of peripheral artery revascularization were excluded from this analysis.

At baseline, data regarding comorbidities and concomitant therapies were collected, and anthropometric data were recorded. Cardiovascular risk factors were defined as previously described [18]; AF patients with CAD were defined as those with a documented myocardial infarction (MI) or prior cardiac revascularization. Patients with episodes of angina or chest pain were not included in this group.

2.1. Ankle-brachial index assessment

ABI was measured in all patients using a 8 MHz CW Vascular Doppler (Risingmed Model:RFD-B) using standardized procedures [19]. ABI was calculated as the ratio of systolic blood pressure obtained from the ankle and brachial arteries. Ankle and brachial systolic blood pressures were measured separately for the right and left side, and ABI was assessed separately for the right and left leg using the highest arm and ankle pressures as the denominator and numerator, respectively. ABI was considered as 'abnormal' for values ≤0.9. The proportion of patients with abnormal high ABI ≥1.4 was also calculated.

The cohort was divided into 4 groups: Group 0 (n = 717) with no previous CAD and ABI >0.9; Group 1 (n = 168) no previous CAD and ABI ≤0.9; Group 2 (n = 183) previous CAD and ABI >0.9: and Group 3 (n = 70) previous CAD and ABI ≤0.9.

2.2. Study endpoints

The occurrence of CVEs was the primary endpoint of the study, these including fatal/non-fatal myocardial infarction or ischemic stroke, cardiac revascularization, cardiovascular death, and transient ischemic attack (TIA). Diagnosis of myocardial infarction was made according to the third universal definition [20]. The occurrence of ischemic stroke was determined on clinical manifestations and confirmed by computed tomography or magnetic resonance; TIA was defined according to the Classification of Cerebrovascular Diseases III [21]. If a patient died within 4 weeks of myocardial infarction or ischemic stroke, these events were recorded as fatal myocardial infarction or ischemic stroke, respectively. Death was classified as cardiovascular unless an unequivocal non-cardiovascular cause of death was identified. Cardiovascular death included sudden death, progressive congestive heart failure, and procedure-related death.

2.3. Validation of cardiovascular events

Data on CVEs were prospectively collected during follow-up and only the first event was used for the analysis. Details on CVEs were registered, as well as death certificates, hospital discharge letter or copy of the medical records of hospitalization, and other clinical documentation (i.e. radiology findings and laboratory data) were also obtained from patients, or in case of death, from relatives of patients or from general practitioners. Adjudication of CVEs was performed by a committee composed by two physicians (FV, PP) who did not participate to the recruitment of patients and were unaware of the clinical and laboratory characteristics of enrolled patients. Each member of the committee independently evaluated and adjudicated CVEs in a blinded manner. In case of discordant evaluation or difficult adjudication of an event, the committee decided to award the event in a collegial way.

2.4. Statistical analyses

Categorical variables are reported as counts (percentage). Continuous variables are expressed as mean ± standard deviation. Independence of categorical variables was tested with the $\chi 2$ test. Student *t*-test for paired and unpaired samples was used to compare means. ANOVA with post-hoc Bonferroni corrections were used to compare groups. The cumulative incidence of CVEs was estimated using a Kaplan–Meier product-limit estimator. Survival curves were formally compared using the log-rank test. Multivariable Cox regression analysis was used to calculate the adjusted relative hazard ratios (HR) by each clinical variable. The multivariable model included the following variables: age, female sex, persistent/permanent AF (vs. paroxysmal), arterial hypertension, diabetes. Previous cerebrovascular events, heart failure, smoking, body mass index, antiplatelet drugs, statins, and Group 1 (ABI ≤ 0.9), Group 2 (previous CAD), Group 3 (ABI ≤ 0.9 + previous CAD), all vs. Group 0. All tests were two-tailed and analyses were performed using computer software packages (SPSS-18.0, SPSS Inc. and MedCalc v.14.8.1). Only P values <0.05 were considered as statistically significant.

The local ethical boards approved the protocol study. The study was conducted according to the principles embodied in the Declaration of Helsinki. All patients gave written informed consent before being included in the study.

Table 1
Study cohort characteristics.

	Whole cohort (n = 1138)	Group 0 No previous CAD. ABI > 0.9 (n = 717)	Group 1 No previous CAD. ABI ≤ 0.9 (n = 168)	Group 2 Previous CAD. ABI > 0.9 (n = 183)	Group 3 Previous CAD. ABI ≤ 0.9 (n = 70)	P value
Age (years)	72.6 ± 9.0	71.3 ± 9.1	75.1 ± 9.1	73.7 ± 8.0	76.2 ± 7.7	<0.001*
Women (%)	41.3	43.9	46.4	33.3	22.9	<0.001#
Persistent/permanent AF (%)	56.5	54.1	56.0	59.0	75.7	0.004#
Current smoking (%)	9.8	10.3	11.9	7.7	5.7	0.31#
Body mass index (kg/m^2)	27.6 ± 4.4	27.8 ± 4.6	27.1 ± 4.1	27.5 ± 4.1	27.3 ± 3.6	0.33*
ABI ≤0.9 (%)	20.9	–	–	–	–	–
Arterial hypertension (%)	87.6	85.6	88.1	91.3	97.1	0.01#
Previous CAD (%)	22.2	–	–	–	–	–
Diabetes mellitus (%)	22.4	17.7	26.2	32.2	35.7	<0.001#
Heart failure (%)	16.3	10.9	16.7	28.4	38.6	<0.001#
Previous cerebrovascular events (%)	11.7	8.6	17.9	12.6	25.7	<0.001#
Antiplatelet drugs (%)	18.7	13.7	14.3	39.9	25.7	<0.001#
Statins (%)	46.2	39.1	40.5	70.5	70.0	<0.001#
CHA_2DS_2-VASc score	3.4 ± 1.5	2.9 ± 1.3	3.6 ± 1.4	4.5 ± 1.3	5.0 ± 1.4	<0.001*
Total cholesterol (mg/dl)	177.4 ± 37.0	181.6 ± 35.0	182.1 ± 42.0	164.2 ± 37.0	163.5 ± 33.6	<0.001*
HDL cholesterol (mg/dl)	47.7 ± 13.7	48.9 ± 13.9	48.3 ± 15.3	45.0 ± 11.3	41.8 ± 12.6	<0.001*
LDL cholesterol (mg/dl)	106.2 ± 30.6	109.8 ± 29.8	106.9 ± 31.4	95.8 ± 31.8	99.8 ± 25.4	<0.001*
Triglycerides (mg/dl)	116.8 ± 56.4	114.3 ± 50.5	126.9 ± 74.4	117.9 ± 62.2	116.9 ± 47.9	0.18*
eGFR (sMDRD, ml/min)	74.8 ± 24.0	77.5 ± 23.3	65.1 ± 25.2	75.7 ± 25.2	66.7 ± 18.0	<0.001*

ABI: ankle-brachial index; AF: atrial fibrillation; CAD: coronary artery disease; CHA_2DS_2-VASc: congestive heart failure, hypertension, age (≥75 years), diabetes, stroke/transient ischemic attack, vascular disease, age (65–74 years), sex (Female); eGFR: estimated glomerular filtration rate; HDL: high-density lipoprotein; LDL: low-density lipoprotein; sMDRD: simplified modification of diet in renal disease.

* ANOVA test.

\# χ^2 test.

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