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Relationship between carotid intima-media thickness and non valvular atrial fibrillation type

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ABSTRACT

Objective: Carotid intima-media thickness (cIMT) is a surrogate marker of subclinical atherosclerosis and it is able to predict both coronary and cerebral vascular events. No data exist on the association between cIMT and non valvular atrial fibrillation (NVAF) type. We conduct this study with the aim to analyze the association between abnormal cIMT and NVAF type. **Methods**: A cross-sectional study of the "Atrial fibrillation Registry for Ankle-brachial index Prevalence Assessment-Collaborative Italian Study (ARAPACIS)" has been performed. Among 2027 patients enrolled in the ARAPACIS, 673 patients, who underwent carotid ultrasound examination to assess cIMT, were included in the study. **Results**: Among the entire population, 478 patients (71%) had cIMT > 0.90 mm. Patients with an abnormal cIMT (>0.90 mm) were significantly older and more likely hypertensive, diabetic and with a previous history of stroke than those with normal cIMT (≤0.90 mm). These patients had more permanent/persistent NVAF and CHA_2DS_2-VASc score ≥ 2 ($p < 0.0001$) compared to those with cIMT <0.90 mm. Excluding all patients affected by previous cardiovascular disease, logistic regression analysis showed that independent predictors of abnormal cIMT were: age class 65–74 yrs. ($p < 0.001$), age class ≥75 yrs. ($p < 0.001$), arterial hypertension ($p < 0.001$), calcium-channel blockers use ($p < 0.001$) and persistent/permanent NVAF ($p = 0.001$). **Conclusion**: Our findings show a high prevalence of abnormal cIMT in NVAF patients, reinforcing the concept that NVAF and systemic atherosclerosis are closely associated. Abnormal cIMT was particularly evident in persistent/permanent NVAF suggesting a more elevated atherosclerotic burden in patients with long-standing NVAF. **Trial registration**: http://clinicaltrials.gov/ct2/show/NCT01161251.

1. Introduction

Non valvular atrial fibrillation (NVAF) is the most frequent and prevalent sustained cardiac supraventricular arrhythmia. Data about prevalence of NVAF in the United States show that it ranged from ≈2.7 million to 6.1 million in 2010, with prevalence expected to rise between ≈5.6 and 12 million in 2050 [1].

NVAF is associated with increased morbidity and mortality,

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mostly for stroke and cardiovascular disease (CVD) [1,2]. Moreover, it is frequently associated with a high number of atherosclerotic risk factors including age, sex, lipid levels, smoking, blood pressure, diabetes and metabolic syndrome [3]. These risk factors might account for the atherosclerotic sequela of NVAF, including myocardial infarction [1]. Hence, signs of subclinical atherosclerosis have been detected in NVAF, such as atherosclerotic plaque in the thoracic aorta [4] or low ankle-brachial index (ABI) [5]. These are both markers of systemic atherosclerosis and may predispose to ischemic stroke and/or myocardial infarction.

Carotid intima-media thickness (cIMT) is another surrogate marker of subclinical atherosclerosis, widely accepted as a measure of arterial thickening, being able to predict both coronary and cerebral vascular events [6–8]. Previous data showed that an increased cIMT is an independent predictor of new-onset NVAF [9,10], suggesting that subclinical atherosclerosis may predispose to NVAF. Based on this, it could be arguable that a different burden of atherosclerotic risk could differentiate paroxysmal versus long-standing NVAF but, so far, no data exist exploring the relationship between specific NVAF types and subclinical atherosclerosis. Therefore, the aim of this study was to investigate the relationship between subclinical atherosclerosis, as assessed by cIMT, and NVAF types in patients included in the ARAPACIS study, an Italian Registry of NVAF population [11].

2. Materials and methods

The study reports on a cross-sectional, pre-specified subgroup analysis of the "Atrial fibrillation Registry for Ankle-brachial index Prevalence Assessment-Collaborative Italian Study (ARAPACIS)" [11]. The ARAPACIS registry is a prospective observational study among internal medicine institutions in Italy. The study has been conceived as longitudinal multicenter for the construction of a network for the recruitment, monitoring and study of NVAF patients. The study has been supported by the Italian Society of Internal Medicine (SIMI), under the ARAPACIS Steering Committee [11] supervision. Thus, for each society regional compartment, the Regional Coordinator [11] supplied a list of centers that would be suitable to participate in this survey. Centers able to ensure an adequate patients quota and to identify, support and maintain an adequate dedicated research staff, entered the study.

Among 136 centers, according to study protocol, 2027 consecutive NVAF patients aged more than 18 years old and referred to outpatient clinics or to internal medicine wards were eligible for the enrollment from 1 October 2010 to 30 October 2012.

2.1. Data collection and validation

In each center, data were collected using an electronic case report form (CRF: http://www.simi.it/attivita/ricerca/arapacis/). Data were transferred to the web-central database (Coordination Center – I Clinica Medica – Sapienza-University of Rome). By using a validation plan, integrated in the data entry software, data were checked for missing or wrong encodings. The SIMI secretary staff performed additional edit checks. A final database was created and validated by the study coordinators. Patients have been identified by a serial number for each center.

2.2. Clinical characteristics

According to a pre-specified subgroup analysis, 673 patients were selected from the original 2027 patients enrolled in the original study cohort. These 673 patients came from 97 enrolling centers with experienced staff in ultrasound diagnostic and equipped with appropriate devices. These staff performed a carotid ultrasound examination to assess subclinical atherosclerosis with cIMT.

Patients were classified according to international guidelines in paroxysmal, persistent or permanent NVAF subtypes [12]. Clinical characteristics, required at baseline, were the following: 1) demographic and anthropometric characteristics (age, sex, weight, height); 2) medical history of CVD risk factors (such as arterial hypertension, dyslipidemia, smoking habit, diabetes mellitus, metabolic syndrome), coronary artery disease or myocardial infarction (MI), stroke or transient ischemic attack (TIA) and symptomatic peripheral arterial disease (PAD) [13–16]; 3) vital signs. CHA_2DS_2-VASc score, as previously described [17], was calculated for each patient. At baseline, a measurement of upper and lower limbs systolic blood pressure for ABI calculation was mandatory. The measurement of ABI was performed as previously described and a value equal or inferior to 0.90 was considered as abnormal [5,18]. Moreover, even if not mandatory, an echocardiogram was performed to evaluate antero-posterior left atrial diameter according to American Society of Echocardiography [19].

2.3. Carotid intima-media thickness measurement

Patients underwent a B-mode ultrasonography of both common carotid arteries by trained certified sonographers performing cIMT measurement in all centers according to American Society of Echocardiography Carotid Intima-Media Thickness Task Force [20].

We defined cIMT values >0.90 mm as abnormal, including cIMT values ≥1.50 mm that was defined as carotid plaque [6].

At the time of cIMT measurement, all patients were clinically and hemodynamically stable, having been enrolled either as outpatients or as inpatients, free from acute events that could precipitate NVAF. Patients were examined supine with the head rotated 45° toward the left side. Imaging was performed in the plane parallel to the neck, with the jugular vein lying immediately above the common carotid artery (or at 45° from the vertical, if the internal jugular vein is not visualized). Images of both common carotid arteries were centered 10–15 mm below (caudal to) the carotid artery bulb. End-diastolic images (smallest diameter of the artery) were captured.

Measurement of cIMT was made on the far wall of the common carotid artery over a 10 mm distance from the common carotid artery bulb. Trained readers traced the 2 key interfaces of the far wall to obtain manual tracings. These tracings were then used to calculate mean cIMT.

2.4. Pharmacological characteristics

Complete information about current therapies was recorded according to drug class assumption. Specifically, we looked for the following drug classes: antithrombotic agents [*i.e.* oral anticoagulants (OAC) and anti-platelets (APs)], beta-adrenergic receptor blockers (beta-blockers), hydroxylmethylglutaryl-coenzyme A reductase inhibitors (statins), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), calcium-channel blockers, anti-arrhythmic agents (amiodarone, propafenone, flecainide), nitrates, digoxin, oral antidiabetics or subcutaneous insulin.

2.5. Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) and differences were evaluated by the Student t or Mann–Whitney U test, depending on the shape of the distribution curve. We reported also median and interquartile range (IQR) [25th–75th percentile]. Categorical variables, expressed as counts