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Carotid plaque detection improves the predictive value of CHA_2DS_2-VASc score in patients with non-valvular atrial fibrillation: The ARAPACIS Study

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ABSTRACT

Background and aims: Vascular disease (VD), as assessed by history of myocardial infarction or peripheral artery disease or aortic plaque, increases stroke risk in atrial fibrillation (AF), and is a component of risk assessment using the CHA_2DS_2-VASc score. We investigated if systemic atherosclerosis as detected by ultrasound carotid plaque (CP) could improve the predictive value of the CHA_2DS_2-VASc score.
Methods: We analysed data from the ARAPACIS study, an observational study including 2027 Italian patients with non-valvular AF, in whom CP was detected using Doppler Ultrasonography.
Results: VD was reported in 351 (17.3%) patients while CP was detected in 16.6% patients. Adding CP to the VD definition leaded to higher VD prevalence (30.9%).
During a median [IQR] follow-up time of 36 months, 56 (2.8%) stroke/TIA events were recorded. Survival analysis showed that conventional VD alone did not increase the risk of stroke (Log-Rank: 0.009, $p = 0.924$), while addition of CP to conventional VD was significantly associated to an increased risk of stroke (LR: 5.730, $p = 0.017$). Cox regression analysis showed that VD + CP was independently associated with stroke (HR: 1.78, 95% CI: 1.05–3.01, $p = 0.0318$). Reclassification analysis showed that VD + CP allowed a significant risk reclassification when compared to VD alone in predicting stroke at 36 months (NRI: 0.192, 95% CI: 0.028–0.323, $p = 0.032$).
Conclusions: In non-valvular AF patients the addition of ultrasound detection of carotid plaque to conventional VD significantly increases the predictive value of CHA_2DS_2-VASc score for stroke.

1. Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice, accounting for approximately one-third of all hospitalizations for a cardiac rhythm abnormality [1]. AF is associated with a fivefold increased risk for stroke, and is estimated to cause 15% of all strokes [2]. Based on evidence from many randomized clinical trials, AF patients are treated with oral anticoagulants such as warfarin or the non-Vitamin K antagonist oral anticoagulants (NOACs) to reduce the risk of thromboembolic stroke [3].

There is increasing evidence that AF is also associated with systemic signs of atherosclerosis, such as aortic plaque or low ankle/brachial index (ABI), which reflects the frequent coexistence of atherosclerotic risk factors such as hypertension, diabetes mellitus, dyslipidemia and metabolic syndrome [4,5]. The coexistence of sub-clinical systemic atherosclerosis suggests that clinical events complicating AF may be also attributable to athero-thrombosis in the carotid distribution [6]. Indeed, "vascular disease" (VD) increases stroke risk in non-valvular AF (NVAF), and is a component of risk assessment using the CHA_2DS_2-VASc score [7]. The usual clinical definition of VD includes a history of MI or claudication with surgical intervention or the presence of aortic

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plaque. We argued that diagnosis of aortic plaque may be cumbersome in clinical practice as it is not a routine analysis and is invasive while carotid atherosclerosis as assessed by Doppler ultrasound is easier to perform, cheaper, not invasive and commonly used to define extra-cranial atherosclerosis in patients with risk factors.

We therefore hypothesized that inclusion of carotid plaque in the CHA_2DS_2-VASc score would better define the prevalence of VD and possibly improve stroke risk prediction by CHA_2DS_2-VASc score in the AF population. We tested this hypothesis in the ARAPACIS study, an observational study including 2027 Italian patients with NVAF, to investigate if documentation of carotid plaque, which was a predefined assessment of atherosclerotic burden, improved the predictive value of the CHA_2DS_2-VASc score.

2. Methods

2.1. Study population

We performed a post-hoc analysis from the "Atrial Fibrillation Registry for Ankle-brachial Index Prevalence Assessment: Collaborative Italian Study" (ARAPACIS) which was a prospective nationwide observational study, conducted by the Italian Society of Internal Medicine (SIMI), investigating the prevalence of asymptomatic PAD as assessed by an ankle-brachial index (ABI) ≤0.90, in NVAF patients. This registry provided information on the prevalence of ABI and its relationship with classic risk factors of atherosclerosis in AF patients [4]. Furthermore, the study showed that, in NVAF, ABI was useful to discriminate patients experiencing MI but not stroke [8]. Details about study protocol and inclusion/exclusion criteria were elsewhere reported [9]. From 1st October 2010 to 31st October 2012 a total of 2027 patients were enrolled and then followed up for three years up to 31st October 2015.

Study protocol was approved for the Coordinator Centre (Sapienza-University of Rome) with the number 1902/17.06.2010. The study was subsequently registered at ClinicalTrials.gov (Unique identifier: NCT01161251). According to the list of enrolling centers reported in the Appendix A, every institution's Ethics Committee approved the study protocol.

The study was conducted in accordance with the EU Guidance on Good Clinical Practice CPMP/ECH/135/95 and the Declaration of Helsinki and its later amendments.

As previously reported [9], all clinical variables of interest and all data about relevant pharmacological therapies were collected at the time of enrolment.

Thromboembolic risk was categorized using CHA_2DS_2-VASc score, calculated by adding 1 point each for the presence of congestive heart failure (HF), hypertension, age from 65 to 74 years, diabetes mellitus, vascular disease (VD) and female sex, and adding 2 points for stroke or transient ischemic attack (TIA) and age 75 years or older [7]. Conventionally, previous MI or symptomatic PAD or aortic plaque defined VD.

The presence of carotid plaque was declared in an electronic case report form. The investigator assessed the presence of an atherosclerotic plaque following the American Society of Echocardiography consensus statement [10] and carotid plaque (CP) was defined as follows: 1) focal wall thickening that is at least 50% or greater than that of the surrounding vessel wall or 2) focal region with carotid intima media thickness >1.5 mm that protrudes into the lumen that is distinct from the adjacent boundary.

2.2. Assessment of cerebrovascular events (CVEs)

An independent committee **(P.F., S. M.L., P.P.E.)** adjudicated adverse events. Occurrence of a CVE was defined for any ischemic stroke or transient ischemic attack (TIA) recorded during the follow-up observation. Ischemic stroke was determined on clinical manifestations and confirmed by radiological findings.

2.3. Statistical analysis

Continuous variables were reported as mean ± SD, or as median and interquartile range (IQR) as appropriate. Comparisons between groups of continuous variables were performed by *t*-test or Mann-Whitney *U* test. Categorical variables, reported as counts and percentages, were compared by Chi-square test or Fisher's exact test, when cell count was less than five. Kaplan-Meier curves were built for CVEs occurrence. A Log-Rank test was performed to analyse differences in survival distributors between subgroups. Univariate and multivariate Cox models were used to assess clinically relevant variables (age, sex, any antithrombotic therapy, diabetes mellitus, statins, hypertension, heart failure, previous cardio- or cerebrovascular events, type of AF and enrolling center) and VD, as well as VD + CP, effects on the incident endpoint of CVEs. A forward stepwise model selection procedure based on the AIC was used to select the best multivariate regression model.

Improvement of VD + carotid plaque over VD alone was assessed by means of continuous Net Reclassification Index (NRI) and median improvement in risk scores (MIRS), which were computed as described by Pencina et al. [11]. The NRI gives roughly the proportion of misclassified cases that are classified correctly with the new information, a NRI of 1 indicates perfect ability to correctly reclassify patients, and a negative NRI indicates that the new score is worse than its competitor. The NRI was evaluated at 12, 24 and 36 months. The Integrated Discrimination Improvement (IDI) is linked to the discrimination slope. A positive IDI indicates that a higher discrimination (difference in average predicted probability for events, compared with non-events) for the VD + carotid plaque over VD alone.

Decision curve analysis (DCA) was computed as described in Vickers et al. [12]. It shows the estimated number of patients that would opt for treatment if their risk of an event was above a threshold probability, for each threshold. DCA can be used to compare prediction models with respect to their net benefit.

Time-dependent C-indexes were estimated by means of the Kaplan-Meier method of Heagerty et al. [13]. Their confidence intervals and p-values were estimated by means of non-parametric bootstrap.

A two-sided p value <0.05 was considered as statistically significant. All analyses were performed using SPSS v. 22 (IBM, NY, USA) and R v. 3.0.2 (R development core team, Vienna, Austria).

3. Results

A detailed description of the overall cohort has been previously reported (9). Briefly, age (mean ± SD) was 73.3 ± 10.0 years with 45.3% (918 patients) females. Of the NVAF types, 842 (41.5%) patients had paroxysmal AF, 284 (14.0%) were persistent AF and 901 (44.5%) had permanent AF. Hypertension was the most prevalent risk factor (82.5%).

According to the conventional VD definition of the CHA_2DS_2-VASc score VD was defined as previous MI or symptomatic PAD or aortic plaque.

VD was reported in 351 (17.3%) patients while CP was detected in 16.6% (n = 336) patients.

Among patients with VD, no significant difference in the occurrence of CVE was observed between patients with or without stroke (17.3 vs. 17.5%, respectively, p = 0.963) (Fig. 1). Conversely, when the contemporary presence of CP was added to VD, a significant difference between patients with vs. without CVE was found (30.5% vs. 45.6%, respectively, p = 0.015) (Fig. 1).

During a median [IQR] follow-up of 36 [22–36] months, 56 CVEs were reported, with an overall incidence of 1.17 per 100 patient-years. Patients with CVEs were older ($p < 0.001$) and with a positive history for previous stroke/TIA ($p < 0.001$). They had higher CHA_2DS_2-VASc score ($p < 0.001$) and more prevalent CHA_2DS_2-VASc score ≥2 (p =

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