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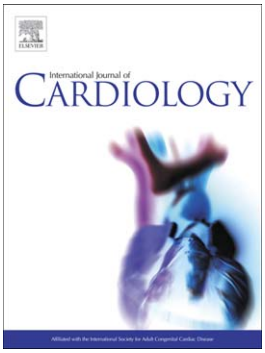

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Carotid plaque detection improves the predictive value of CHA_2DS_2-VASc score in Patients with Non-Valvular Atrial Fibrillation: The ARAPACIS Study.

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Running title: Extracranial Carotid Atherosclerosis in Atrial Fibrillation

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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 2,027 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.

Keywords: Atrial Fibrillation, atherosclerosis, vascular disease, CHA_2DS_2-VASc score, stroke, carotid plaque.

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 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 2,027 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.

METHODS

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 2,027 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, 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 greater than 1.5 mm that protrudes into the lumen that is distinct from the adjacent boundary.

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.

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).

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) (Figure 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) (Figure 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=0.036). Female patients were more represented in the group of CVEs patients, of borderline statistical significance (p=0.052) (Table 1).

Conventional VD alone did not differentiate patients with and without CVEs during follow-up (p=0.963). CP was more prevalent in patients who experienced stoke/TIA during the follow-up (31.6% vs. 16.1%, p=0.002). Inclusion of CP in the VD definition led to a significant increase in VD prevalence [30.9%].

Event-Free Survival Analysis

Conventional VD did not discriminate AF patients who experienced CVEs during the follow-up (Log-Rank: 0.009, p=0.924); conversely, CP presence discriminated patients who experienced stroke/TIA during the follow-up (Log-Rank: 8.61, p=0.003). Adding CP to conventional VD was associated with an enhanced risk of stroke/TIA [Log-Rank: 5.730, p=0.017, Figure 2].

On Cox proportional hazards analysis (Table 2), adjusted for gender, AF type, heart failure, hypertension, statins, previous cardio-vascular event, enrolling center, any antithrombotic therapy and diabetes, VD+CP was independently associated with the occurrence of stroke/TIA during follow-up (p=0.0318).

Reclassification Analysis, Decision Curve Analysis, and C-statistic

Using NRI, adding CP to VD was significantly better than using conventional VD alone in predicting CVEs at 24 months (p=0.0399) and 36 months (p=0.0332). Despite significant reclassification, no significant improvement was found according to IDI analysis (Table 3).

DCA estimates the outcome in a decision-making process based on VD and VD+ CP. It shows that with VD alone a net benefit would not be obtained at all estimable thresholds, while for VD+ CP a rather steep decision curve is obtained, indicating that VD+ CP is useful in the decision-making process. VD+ CP had significantly greater C-statistic (Table 4) than conventional VD alone for CVEs at 24 and 36 months (p<0.001)

Sensitivity Analysis

To verify the role of VD+ CP in preventing the occurrence of CVEs, a sensitivity analysis in patients without previous history of stroke/TIA was performed. The analysis showed that in AF patients without a previous history of stroke/TIA VD+ CP could identify patients at higher risk for CVEs occurrence (Log-Rank: 5.787, p=0.016).

Discussion

In the present study, inclusion of ultrasound detection of carotid plaque in the diagnosis of VD increased the predictive values of CHA_2DS_2-VASc score; this reinforces the concept that systemic atherosclerosis is another mechanism accounting for ischemic stroke in AF [6].

Previous study by ARA PACIS registry demonstrated AF is associated with atherosclerosis of extracranial carotid arteries, as assessed by carotid IMT, but its impact with cerebrovascular disease was not investigated [14]. The present analysis of the ARAPACIS registry supports and extends these finding by demonstrating that carotid plaque is detectable in approximately 17% of AF. Furthermore, during the follow-up, patients with CP were at higher risk of experiencing acute cerebral disease, thereby suggesting that atherosclerosis of carotid artery might also be implicated in cerebral ischemia.

VD has been included in the CHA_2DS_2-VASc score to improve its ability to predict stroke in AF patients [7]. To further address the role of VD in predicting stroke the ARAPACIS registry investigated two markers of systemic atherosclerosis, namely ABI and CP, to assess their predictive values versus cerebral and coronary heart disease in AF population. While we found that ABI is able to predict coronary heart disease [8], the present study shows that ultrasound detection of carotid plaque was more able to predict ischemic cerebro-

vascular disease. Thus, CP had more frequently detected in AF experiencing CVEs compared to those without CP and independently predicted CVEs after adjusting for confounding variables. Analysis of CP greatly increased the prevalence of VD, which was 17% by conventional definition and 30% by adding CP to conventional VD definition. Then, by including CP in the VD definition, this also improved the predictive value of VD for predicting stroke/TIA compared to conventional VD definition, suggesting that ultrasound detection of carotid plaque may be useful to stratify patients at risk of stroke/TIA in the AF population.

We provide further support to the inclusion of VD as a variable predicting ischemic cerebro-vascular disease in AF population and suggest that CP improves the performance of the CHA_2DS_2-VASc score. This finding supports and extends a previous study reporting that inclusion of carotid plaque in the CHA_2DS_2-VASc score improves its predictive value in an AF population not on treatment with warfarin [15]. Our finding reinforces also the concept that in AF population ischemic stroke is not only of thrombo-embolic but also of athero-thrombotic origin. This suggestion has therapeutic implications as it implies that non-valvular AF could benefit not only from oral anticoagulants but also possibly from anti-atherosclerotic drugs [16]. Thus, further study is needed to see if adding anti-atherosclerotic drugs such statins, which also possess anti-thrombotic properties [16], in addition to oral anticoagulants may be of benefit in further reducing the risk of CVEs in AF population.

Study limitations

The results are limited by: 1) retrospective analysis of an observational cohort, 2) relatively small ischemic cerebrovascular events. Furthermore, analysis of CP was not centralized and, therefore, diagnosis was performed by each single center. However, the analysis should not be biased as each operator followed the AHA definition of CP and data were collected immediately after patient's inclusion. Around 70% of patients in our cohort were taking oral anticoagulant therapy; nevertheless, we had not information on the quality of oral anticoagulation for all participants.

Furthermore, most of our findings are based on NRI, which has limitations. In a simulation study, Pepe et al. [17] showed that with large data sets one might obtain a positive NRI even for a clinically irrelevant biomarker, for instance. We speculate that this situation might not apply in our study, as our sample size is much lower than the one used in Pepe's simulations. Additionally, in the simulations by Pepe et al. [17] a negative difference in C-index was always obtained, while in our study we observed a small but positive increase. It is well known that putatively relevant biomarkers might lead to tiny and non-significant increases in C-indexes; thus, we consider the small increase in C-index simply as a confirmation that the positive NRI is not an artefact.

Conclusions

In non-valvular AF patients the addition of CP to conventional VD increases the predictive value of CHA_2DS_2-VASc score for stroke. Hence, analysis of CP could be included in the routine assessment of CHA_2DS_2-VASc score in AF patients.

Conflicts of interest-The authors declare that they have no conflict of interest.

Dr. Hiatt reports grants from Bayer, Janssen and AstraZeneca, outside the submitted work.

Author contributions:

Basili S.- conception and design of the study, acquisition and interpretation of data.
Loffredo L. - interpretation of data.
Pastori D. - acquisition of data.
Proietti M. – acquisition of data.
Farcomeni A. - analysis of data.
Vestri A.R.- design of the study, analysis of data.
Pignatelli P. - acquisition of data.
Davì G.- critical revision of data
Hiatt W.R. – critical revision of the manuscript.
Lip G.Y.H. – critical revision of the manuscript.
Corazza G.R. – critical revision of the manuscript.
Perticone F.– critical revision of the manuscript.
Violi F. - conception and design of the study; interpretation of data; drafting the article.
ARAPACIS Study Investigators - acquisition of data

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Figure Legends

Figure 1: Proportions of patients with conventional vascular disease (VD) and VD+ ultrasound detection of carotid plaque (CP) according to Cerebrovascular Events (CVEs) occurrence.

Figure 2: Event-Free Survival for Stroke/TIA Occurrence According to conventional vascular disease (VD) + ultrasound detection of carotid plaque (CP).

Thick Solid Line= VD+CP present; Thick Dashed Line= VD+ CP absent; Log-Rank= 5.730, p=0.017.

[8]Appendix

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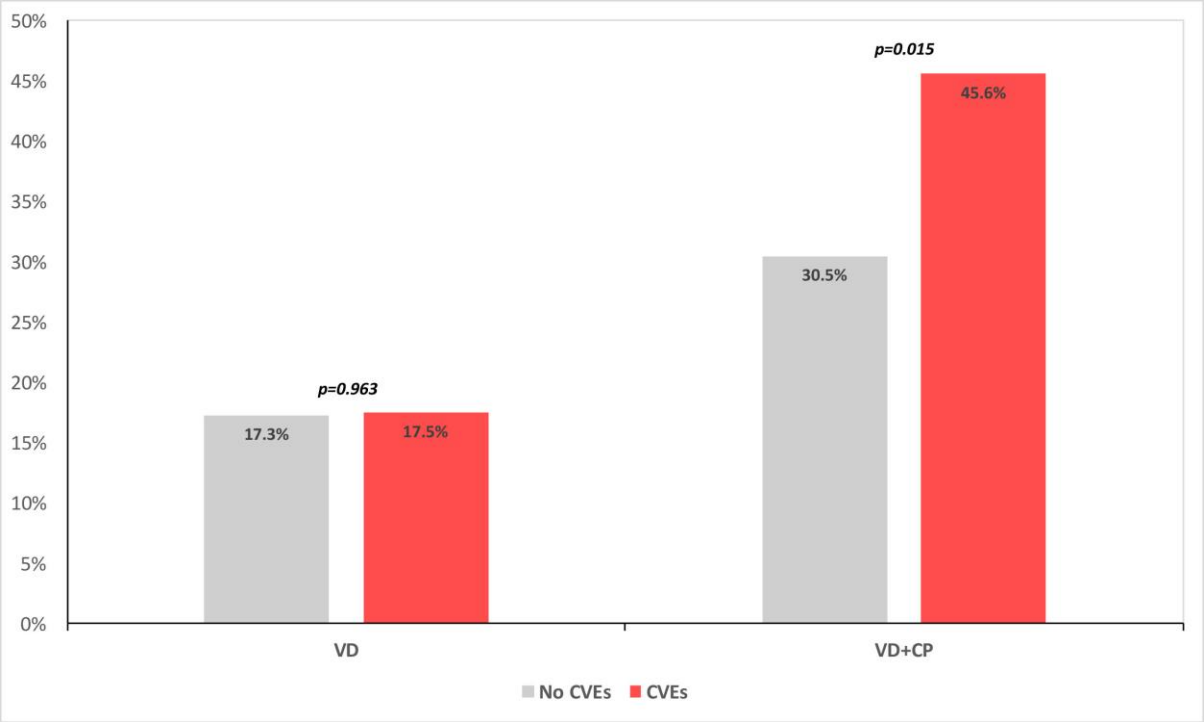
All in Italy.


50%
45%
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5%
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p=0.963
17.3%
17.5%
p=0.015
30.5%
45.6%
VD
VD+CP
No CVEs
CVEs

Fig. 1

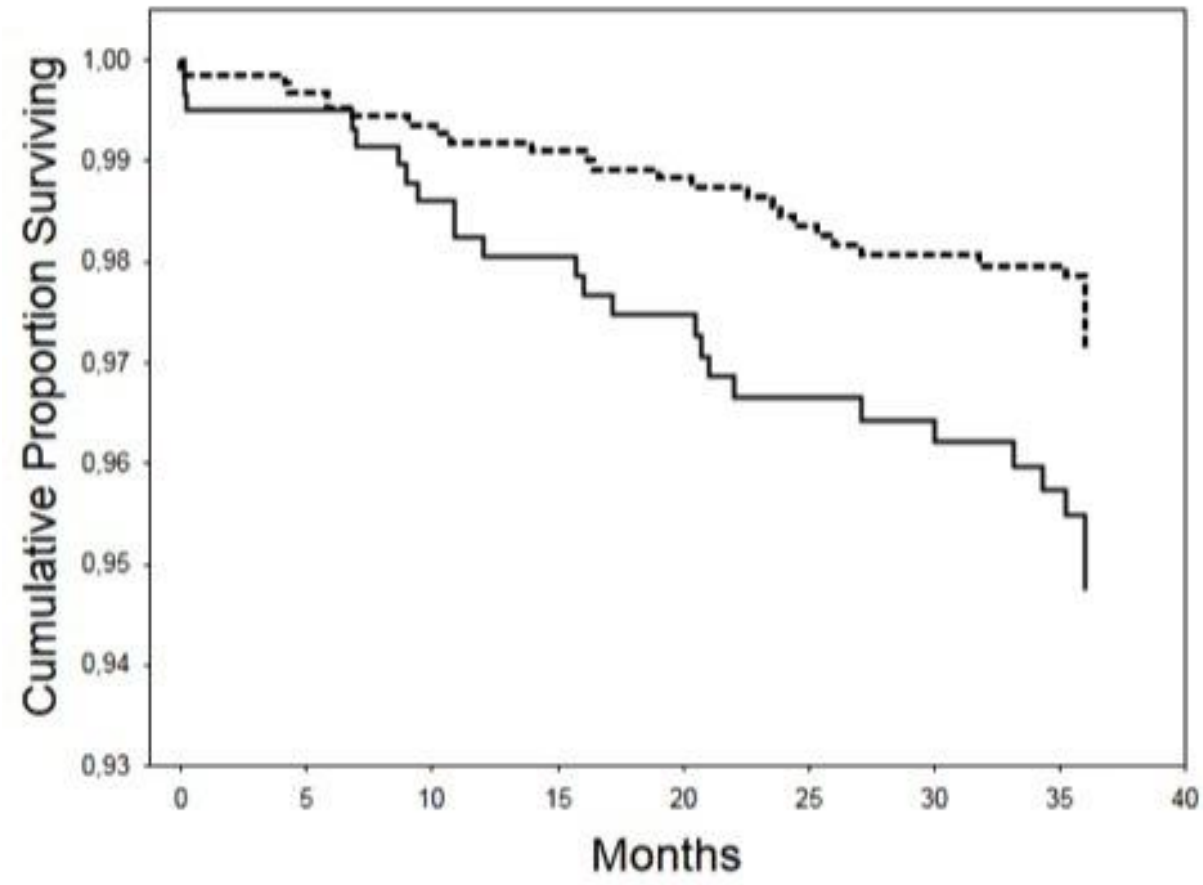
Cumulative Proportion Surviving
1,00
0,99
0,98
0,97
0,96
0,95
0,94
0,93
0
5
10
15
20
25
30
35
40
Months

Fig. 2

Table 1: Baseline Clinical Characteristics According to Cerebrovascular Events (CVEs) Occurrence

	No CVEs N=1,971	CVEs N=56	P value
Age, *years* (median [IQR [b]])	74.4 [67.7-80.2]	80.1 [72.5-84.6]	***<0.001***
Female Gender, n (%)	885 (44.9)	33 (57.9)	***0.052***
BMI[a], *kg/m²* (median [IQR])	27.2 [24.5-30.5]	26.8 [23.9-30.5]	0.473
Atrial Fibrillation Type			0.741
Paroxysmal, n (%)	821 (41.7)	21 (36.8)	
Persistent, n (%)	276 (14.0)	8 (14.0)	
Permanent, n (%)	873 (44.3)	28 (49.2)	
Hypertension, n (%)	1,627 (82.6)	46 (80.7)	0.711
Hypercholesterolemia, n (%)	754 (38.3)	27 (47.4)	0.164
Smoking Habit, n (%)	295 (15.0)	9 (15.8)	0.865
Diabetes, n (%)	454 (23.0)	12 (21.1)	0.724
Heart Failure, n (%)	398 (20.2)	14 (24.6)	0.420
Previous Stroke/TIA [c], n (%)	220 (11.2)	15 (26.3)	***<0.001***
CHA_2DS_2-VASc (median [IQR])	3 [2-4]	4 [3-5]	***<0.001***
CHA_2DS_2-VASc Classes			***0.036***
Class 0, n (%)	78 (4.0)	1 (1.8)	
Class 1, n (%)	236 (12.0)	1 (1.8)	
Class ≥2, n (%)	1,656 (84.1)	55 (96.5)	
Antithrombotic Therapy			0.226
None, n (%)	307 (15.6)	9 (15.8)	
Antiplatelets, n (%)	381 (19.3)	8 (14.0)	
VKA [d]*, n (%)*	1,190 (60.4)	40 (70.2)	
Antiplatelets+VKA, n (%)	92 (4.7)	0 (0.0)	
Statins, n (%)	718 (36.4)	18 (31.6)	0.451
ACE[e] **Inhibitors**, n (%)	698 (35.4)	17 (29.8)	0.382
ARBs [f], n (%)	671 (34.1)	20 (35.1)	0.872
Beta-Blockers, n (%)	799 (40.6)	23 (40.4)	0.975
Calcium Channel Blockers, n (%)	534 (27.1)	17 (29.8)	0.649

[a] Body Mass Index; [b]InterQuartile Range; [c]Transient Ischemic Attack; [d]Vitamin K Antagonist; [e]Angiotensin Converting Enzyme; [f]Angiotensin Receptor Blockers;

Table 2: Cox Regression Analysis[a] for Cerebrovascular Events [Stroke/ Transient Ischemic Attack (TIA)].

	HR[b]	95% CI[c]	P
Previous Stroke/TIA	2.41	1-31-4.44	0.0047
Age (per year)	1.07	1.03-1.10	0.0001
Conventional VD[d]	0.97	0.48-1.94	0.9288
Previous Stroke/TIA	2.42	1.32-4.46	0.0044
Age (per year)	1.07	1.03-1.10	0.0003
VD+CP[e]	1.78	1.05-3.01	0.0318

[a] level of entry into the model was set at a p-value = 0.10; [b]adjusted hazard ratio; [c]confidence interval; [d]conventional vascular disease (Myocardial infarction, aortic plaque, symptomatic peripheral artery disease); [e] ultrasound detection of carotid plaque.

Table 3: Reclassification Analysis for Cerebrovascular Events (CVEs) occurrence

	NRI[a]	**95% CI**[b]	***p***	**IDI**[c]	**95% CI**[b]	***p***
VD[d]+CP[e] *vs. VD*[d] *at 12 months*	0.186	-0.058-0.396	0.1462	0.001	-0.000-0.005	0.2259
VD[d]+CP[e] *vs. VD*[d] *at 24 months*	**0.193**	**0.010-0.353**	**0.0399**	0.003	-0.001-0.010	0.1262
VD[d]+CP[e] *vs. VD*[d] *at 36 months*	**0.192**	**0.028-0.323**	**0.0332**	0.005	-0.000-0.014	0.0997

[a]Net Reclassification Improvement; [b]Confidence Interval; [c]Integrated Discrimination Improvement; [d]Conventional Vascular Diseases (Myocardial infarction, aortic plaque, symptomatic peripheral artery disease); [e] ultrasound detection of carotid plaque.

Table 4: C-index for Cerebrovascular Events (CVEs) occurrence.

	C-index	95% CI[a]	*p*
VD[b]+CP[c] *at 12 months*	0.568	0.498-0.637	0.054
VD[b] *at 12 months*	0.557	0.499-0.621	0.068
VD[b]+CP[c] *at 24 months*	**0.609**	**0.561-0.663**	**<0.001**
VD[b] *at 24 months*	**0.553**	**0.512-0.596**	**0.016**
VD[b]+CP[c] *at 36 months*	**0.626**	**0.586-0.666**	**<0.001**
VD[b] *at 36 months*	**0.591**	**0.555-0.627**	**<0.001**

[a]Confidence Interval; [b]Conventional Vascular Diseases (Myocardial infarction, aortic plaque, symptomatic peripheral artery disease); [c] ultrasound detection of carotid plaque.