International Journal of Cardiology 231 (2017) 143–149

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

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

Stefania Basili [a], Lorenzo Loffredo [a], Daniele Pastori [a], Marco Proietti [b], Alessio Farcomeni [c], Anna Rita Vestri [c], Pasquale Pignatelli [a], Giovanni Davì [d], William R. Hiatt [e], Gregory Y.H. Lip [b], Gino R. Corazza [f], Francesco Perticone [g], Francesco Violi [a,*], in collaboration with ARAPACIS Study Investigators [h]

[a] Clinica Medica, Atherothrombosis Center, Department of Internal Medicine and Medical Specialties, Sapienza University of Rome, Italy
[b] Institute of Cardiovascular Sciences, University of Birmingham, United Kingdom
[c] Department of Public Health and Infections Disease, Sapienza University of Rome, Italy
[d] Department of Medicine and Aging, University of Chieti "G. d'Annunzio", Italy
[e] Division of Cardiology, University of Colorado School of Medicine and CPC Clinical Research, Aurora, CO, USA
[f] First Department of Internal Medicine, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Italy
[g] Department of Medical and Surgical Sciences, University Magna Græcia of Catanzaro, Italy
[h] See Appendix A

ARTICLE INFO

Article history:
Received 26 October 2016
Received in revised form 21 December 2016
Accepted 2 January 2017
Available online 4 January 2017

Keywords:
Atrial fibrillation
Atherosclerosis
Vascular disease
CHA_2DS_2-VASc score
Stroke
Carotid plaque

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

* Corresponding author at: I Clinica Medica, Viale del Policlinico 155, Roma 00161, Italy.
E-mail address: francesco.violi@uniroma1.it (F. Violi).

http://dx.doi.org/10.1016/j.ijcard.2017.01.001
0167-5273/

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 =

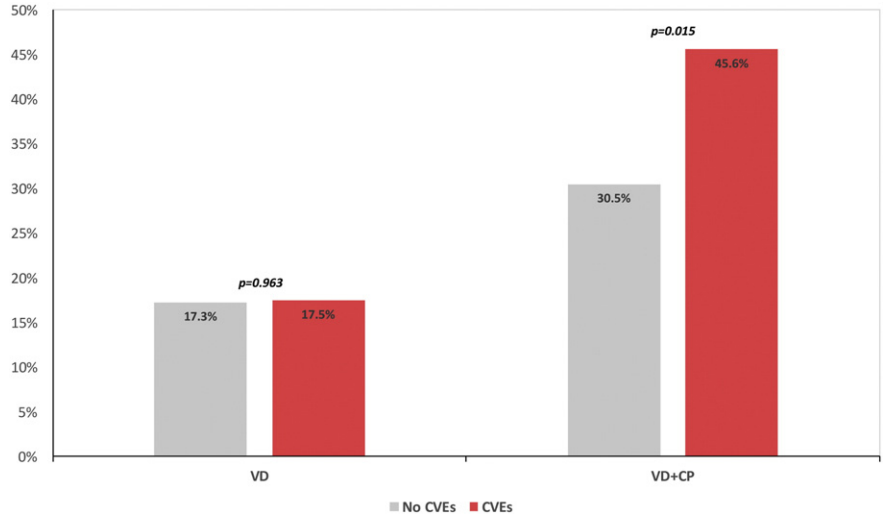

Fig. 1. Proportions of patients with conventional vascular disease (VD) and VD+ ultrasound detection of carotid plaque (CP) according to cerebrovascular events (CVEs) occurrence.

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 stroke/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%].

Table 1
Baseline clinical characteristics according to cerebrovascular events (CVEs) Occurrence.

	No CVEs N = 1971	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/m^2 (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 (%)	1627 (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 (%)	1656 (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 (%)	1190 (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] Inter Quartile range.
[c] Transient ischemic attack.
[d] Vitamin K antagonist.
[e] Angiotensin converting enzyme.
[f] Angiotensin receptor blockers.

3.1. 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, Fig. 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).

3.2. 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).

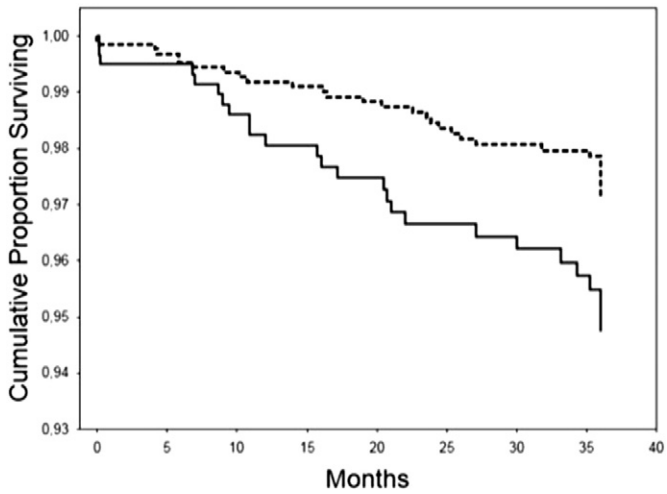

Fig. 2. Event-free survival for stroke/TIA occurrence according to conventional vascular disease (VD) + ultrasound detection of carotid plaque (CP). Thick Solid Line = VD + CP present; Thick Dashed Line = VD+ CP absent; Log-Rank = 5.730, p = 0.017.

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.

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 ($p < 0.001$)

3.3. 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, $p = 0.016$).

4. 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 ARAPACIS 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.

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.

4.1. 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 no 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

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.

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.

5. 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.

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.

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.

Appendix A. ARAPACIS Study Investigators

Alessandri C. (Dipartimento di Scienze e Biotecnologie Medico-Chirurgiche, Sapienza-Università di Roma); Serviddio G. (Department of Medical and Surgical Sciences, University of Foggia); Fascetti S. (UOC Medicina Generale, USL 12 Viareggio, Toscana); Palange P. (UOC Medicina Interna I, Dipartimento di Sanità Pubblica e Malattie Infettive, Sapienza-Università di Roma); Greco E., Bruno G. (Medicina 3, Department of Medical Sciences, A.O. Città della Salute e della Scienza, University of Turin); Averna M., Giammanco A. (Dipartimento Biomedico di Medicina Interna e Specialistica, Università di Palermo); Sposito P. (Azienda Ospedaliera Ospedali Riuniti Papardo Piemonte, Messina); De Cristofaro R., De Gennaro L. (Istituto di Medicina Interna e Geriatria, Centro Emostasi e Trombosi, Policlinico A.Gemelli, Roma); Carulli L., Pellegrini E. (UO di Medicina a Indirizzo Nutrizionistico e Metabolico, Dipartimento Integrato di Medicina Endocrinologia Metabolismo e Geriatria. Università degli Studi di Modena e Reggio Emilia); Cominacini L., Mozzini C., Pasini A.F. (Dipartimento di Medicina, Sezione di Medicina Interna D, Università di Verona); Sprovieri M., Spagnuolo V. (UOC Medicina d'Urgenza e PS, Stabilimento Ospedaliero dell'Annunziata, Cosenza); Cerqua G. (UOC Medicina Interna per l'Urgenza, AO S Giovanni Addolorata, Roma); Cerasola G., Mulé G. (Università degli Studi di Palermo); Barbagallo M., Lo Sciuto S., Monteverde A. (UOC di Geriatria e Lungodegenza, Azienda Ospedaliera Universitaria Policlinico, AOUP Palermo); Saitta A., Lo Gullo A. (UOC Medicina Interna, Università di Messina); Malatino L., Cilia C., Terranova V., Pisano M. (Clinica Medica, Ospedale Cannizzaro, Università degli Studi di Catania); Pinto A., Di Raimondo D., Tuttolomondo A., Conigliaro R. (Internal Medicine and Cardio-Angiology Ward, Department of Biomedicine and Internal Medicine, University of Palermo); Signorelli S. (Dipartimento di Medicina Interna e Patologia, Università degli Studi di Catania); De Palma D., Galderisi M., Cudemo G. (Dipartimento di Medicina Clinica e Sperimentale, AUP Federico II di Napoli); Galletti F., Fazio V. (Dipartimento di Medicina Clinica e Chirurgia, Università di Napoli Federico II); De Luca N., Meccariello A. (Centro Ipertensione, AUO Federico II, Napoli); Caputo D., De Donato M. T. (UO Medicina Interna, Azienda Ospedaliera Universitaria San Giovanni di Dio e Ruggi D'Aragona, Salerno); Iannuzi A., Bresciani A. (Divisione di Medicina Interna, Osp. A. Cardarelli, Napoli); Giunta R. (V Divisione Medicina Interna ed Immunoallergologia, Policlinico SUN, Napoli); Utili R., Iorio V. (Medicina Infettivologica e dei Trapianti, Seconda Università di Napoli, AORN dei Colli-Monaldi); Adinolfi L.E., Sellitto C., Iuliano N. (Medicina Interna, Seconda Università di Napoli, Ospedale di Marcianise); Bellis P., Tirelli P. (UOC Medicina Interna e di Urgenza e Pronto Soccorso, P.O. S.M. del Loreto Nuovo, Loreto Mare); Sacerdoti D. (Clinica Medica 5, Dipartimento di Medicina DIMED, Università degli Studi di Padova); Vanni D. (UO Medicina Interna Arezzo, Ospedale San Donato, Azienda USL 8 Arezzo); Iuliano L., Ciacciarelli M., Pacelli A.(Department of Medico-Surgical Sciences and Biotechnology, Vascular Biology & Mass Spectrometry Lab, Sapienza-University of Rome); Palazzuoli A. (UOS Malattie Cardiovascolari Dipartimento di Scienze Mediche Chirurgiche e Neuroscienze, Università di Siena); Cacciafesta M., Gueli N., Lo Iacono C., Brusco S., Verrusio W. (UOC di Medicina Geriatrica e Riabilitazione, Sapienza-Università di Roma, Roma); Nobili L., Tarquinio N., Pellegrini F. (UO Medicina "SS Benvenuto e Rocco", Dipartimento di Medicina Interna, ASUR Marche, Area Vasta n.2, ex ZT 7); Vincentelli G.M. (UOS Breve Osservazione, Ospedale S.G. Calibita "Fatebenefratelli" Isola Tiberina, Roma); Ravallese F., Santini C. (UOC Medicina Interna, Ospedale Vannini, Roma); Letizia C., Petramala L., Zinnamosca L. (UOD Ipertensione Secondaria, Dipartimento di Medicina Interna e Specialità Mediche, Sapienza-Università di Roma); Minisola S., Cilli M., Savoriti C., Colangelo L. (UOC Medicina Interna F e Malattie Metaboliche dell'osso- Sapienza-Università di Roma); Falaschi P., Martocchia A., Pastore F. (UO Geriatria, Azienda Ospedaliera S.Andrea, Facoltà di Medicina e Psicologia, Sapienza-Università di Roma); Bertazzoni G., Attalla El Halabieh E. (UOC Medicina d'Urgenza, Dipartimento di Emergenza ed Accettazione, Sapienza-Università di Roma); Paradiso M., Lizzi E.M., Timmi S. (Ospedale San Giovanni Battista, Ordine di Malta, Roma); Battisti P. (Medicina Interna II, Ospedale San Giovanni-Addolorata, Roma); Cerci S. (UOC Medicina Interna, Ospedali Riuniti Frascati, Marino); Ciavolella M. (UOC Cardiologia-UTIC, Ospedale di Frascati, Roma); Di Veroli C. (Centro dell'Ipertensione Arteriosa e delle Malattie Metaboliche e Renali, Casa di Cura "San Domenico", Roma); Malci F., De Ciocchis A. (UOC di Medicina Interna, Ospedale "A. Angelucci", ASL Roma G, Subiaco); Abate D. (Az. "Ospedali Civili Riuniti" Giovanni Paolo II, Sciacca); Castellino P., Zanoli L., Fidone F. (UOC Medicina Interna, Dipartimento di Medicina Clinica e Sperimentale, Università degli Studi di Catania); Mannarino E., Pasqualini L., Oliverio G. (Medicina Interna, Università degli Studi di Perugia); Pende A., Artom N. (Clinica di Medicina Interna 1, Dipartimento di Medicina Interna, Università di Genova, IRCCS Az. Osp. Univ. San Martino - IST); Ricchio R., Fimognari F.L. (UOC Geriatria, Azienda Ospedaliera di Cosenza, Cosenza); Alletto M., Messina S. (Unità Operativa di Medicina, Ospedale S. Elia, Caltanissetta); Sesti G., Arturi F., Fiorentino T.V., Pedace E. (Università degli Studi "Magna Graecia", UOC Medicina Interna, Policlinico Universitario "Mater Domini"); Scarpino P.E., Carullo G., Maio R., Sciacqua A. (Cattedra di Medicina Interna, UO Malattie Cardiovascolari, Campus Universitario di Germaneto, Università Magna Graecia di Catanzaro); Frugiuele P., Spagnuolo V. (UOC Medicina Interna e Reumatologia "A. Cosco", Stabilimento Ospedaliero Annunziata, Azienda Ospedaliera Cosenza); Battaglia G. (UO Lungodegenza, S.O. Serra San Bruno, ASP Vibo

Valentia); Atzori S., Delitala G. (Clinica Medica, Dipartimento di Medicina Clinica e Sperimentale, AOU Sassari); Angelucci E., Sestili S. (UOC di Clinica Medica, PO Clinicizzato di Chieti); Traisci G., De Feudis L. (UOC Medicina Interna 2, PO di Pescara); Di Michele D., Fava A. (UOC Medicina Interna, Ospedale "G.Mazzini", ASL Teramo); Balsano C., De Ciantis P. (Dipartimento di Medicina Interna e Sanità Pubblica, Università dell'Aquila); Desideri G., Camerota A. (UOC Geriatria e Lungodegenza Geriatrica, Dipartimento Medico ORM, PO Avezzano); Mezzetti M. (UOC Medicina Interna Ospedale del Casentino-Direttore Dr. Emilio Santoro, AUSL8 Arezzo); Gresele P., Vedovati C., Fierro T. (Dipartimento di Medicina Interna, Sezione di Medicina Interna e Cardiovascolare, Università di Perugia); Puccetti L. (Centro Aterosclerosi, Trombosi e Coagulopatie, Università degli Studi di Siena, Azienda Ospedaliero-Universitaria Senese); Bertolotti M., Mussi C. (UO Geriatria, Dipartimento Integrato di Medicina Endocrinologia Metabolismo e Geriatria. Università degli Studi di Modena e Reggio Emilia); Boddi M., Savino A., Contri S., Degl'Innocenti G. (Dipartimento di Medicina Sperimentale e Clinica, Università degli Studi di Firenze); Saller A., Fabris F. (Clinica Medica 1, Medicina Interna CLOPD, Departement of Medicine DIMED, University of Padova); Pesavento R., Filippi L., Vedovetto V. (Dipartimento di Scienze Cardiologiche, Toraciche e Vascolari, Clinica Medica 2, Azienda Ospedaliera-Università di Padova); Puato M. (Clinica Medica IV, Dipartimento di Medicina, Azienda Ospedaliera Universitaria Padova, Padova); Fabris F., Treleani M. (UOA Medicina, Policlinico Universitario, Padova); De Luca E., De Zaiacomo F., Giantin V. (Clinica Geriatrica, Dipartimento di Medicina, Università di Padova); Semplicini A. (Medicina Interna 1, Ospedale SS. Giovanni e Paolo, Venezia); Minuz P., Romano S. (Sezione di Medicina Interna C, Dipartimento di Medicina, Università di Verona, AOUI Verona); Fantin F., Manica A. (Dipartimento di Medicina, Sezione di Geriatria, Università di Verona); Stockner I., Pattis P., Gutmann B. (Divisione di Medicina Interna-Direttore Prof. J. Wiedermann, Ospedale Centrale di Bolzano); Catena C., Colussi G., Sechi L.A. (Clinica Medica, Dipartimento di Scienze Mediche Sperimentali e Cliniche, Università di Udine, Italy); Annoni G., Bruni A.A., Castagna A. (Clinica Geriatrica, Università degli Studi di Milano-Bicocca, Dipartimento di Medicina e Chirurgia, AO San Gerardo, Monza); Spinelli D. (Medicina Interna 1, Dipartimento di Scienze Cliniche e di Comunità, Fondazione IRCCS "Ca Granda" Policlinico, Università di Milano); Miceli E., Padula D. (Clinica Medica I, Reparto 11, IRCCS Policlinico San Matteo di Pavia); Schinco G., Spreafico S. (UOC Geriatria, Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico); Secchi B. (UOC Medicina Interna, Ospedale Bassini, Milano); Vanoli M., Casella G., Pulixi E.A. (SC Medicina Interna, Azienda Ospedaliera della Provincia di Lecco, Ospedale di Merate, Lecco); Sansone L., Serra M.G. (UOC Medicina, Azienda Ospedaliera "Cardinale G. Panico",Tricase (Lecce); Longo S., Antonaci S. (UOC Medicina Interna "Cesare Frugoni", Azienda Ospedaliera Policlinico, Bari); Belfiore A., Frualdo M., Palasciano G., Ricci L. (Clinica Medica "A. Murri"- Bari); Ventrella F. (Struttura Complessa di Medicina Interna, Ospedale "G. Tatarella", Cerignola, ASL Foggia); Bianco C. (UOC Medicina Interna, PO "I. Toraldo", Tropea); Santovito D., Cipollone F. (Centro di Eccellenza Europeo e di Riferimento Regionale per l'Aterosclerosi, l'Ipertensione Arteriosa e le Dislipidemie, Università "G. d'Annunzio", Chieti); Nicolai S., Salvati F. (UO Medicina Interna, Ospedale di Ortona, ASL 02 Abruzzo); Rini G. B., Scozzari F. (UOC Medicina Interna ed Ipertensione, Dipartimento Biomedico di Medicina Interna e Specialistica, Policlinico "P. Giaccone" di Palermo); Muiesan M.L., Salvetti M., Bazza A. (Dipartimento di Scienze Cliniche e Sperimentali, Università di Brescia, 2° Medicina Generale Spedali Civili); Picardi A., Vespasiani-Gentilucci U., De Vincentis A. (Medicina Interna e Epatologia, Dipartimento di Medicina, Università Campus Bio-Medico, Roma); Cosio P., Terzolo M. (Medicina Interna 1, Dipartimento di Scienze Cliniche e Biologiche, AOU San Luigi Gonzaga, Università di Torino); Madaffari B., Parasporo B. (UO Medicina Interna "Morelli", Azienda Ospedaliera Bianchi Melacrino Morelli, Reggio Calabria); Fenoglio L., Bracco C., Melchio R. (SC Medicina Interna, AO S. Croce e Carle, Cuneo); Gentili T., Salvi A. (Medicina Generale - Settore Subintensivo, Azienda Ospedaliero-Universitaria "Ospedali Riuniti", Ancona); Nitti C. (Medicina Generale - Settore Ordinario, Azienda Ospedaliero-Universitaria "Ospedali Riuniti", Ancona); Gabrielli A., Martino G.P. (Clinica Medica, Azienda Ospedaliero-Universitaria "Ospedali Riuniti", Ancona); Capucci A., Brambatti M., Sparagna A. (Clinica di Cardiologia, Ospedale Torrette, Ancona); Tirotta D. (UO Medicina Generale IV, Ospedale Cervesi, Cattolica); Andreozzi P., Ettorre E., Viscogliosi G., Servello A., Musumeci M. (Area Geriatria, DAI Medicina Interna, Sapienza-Università di Roma); Rossi Fanelli F., Delfino M., Giorgi A. (UOC Medicina Interna H, Sapienza-Università di Roma); Glorioso N., Melis G., Marras G., Matta M. (Ambulatorio Ipertensione Arteriosa e Patologie Correlate, AOU Sassari); Sacco A. (UOC Medicina Interna, PO Madonna delle Grazie, Matera); Stellitano E., Scordo A. (UO Medicina, PO "Tiberio Evoli", Melito Porto Salvo); Russo F., Caruso A.A. (UOC Medicina Generale di Rogliano, AO di Cosenza); Porreca E., Tana M. (UO Medicina Interna e Geriatria, Università G. D'Annunzio, Chieti-Pescara); Ferri C., Cheli P. (Divisione di Medicina Interna e Nefrologia - Ospedale San Salvatore, Dipartimento MeSVA, Università dell'Aquila); Portincasa P. (Clinica Medica "Murri", Dipartimento di Scienze Mediche e Oncologia Umana, Università degli Studi di Bari); Muscianisi G. (ASP Reggio Calabria, Saline Joniche); Giordani S., Stanghellini V. (Dipartimento di Scienze Mediche e Chirurgiche, Università degli Studi di Bologna); Sabbà C. (UOC Geriatria e Centro di assistenza e ricerca sovraziendale per le malattie rare, Bari); Mancuso G., Bartone M., Calipari D. (UOC Medicina Interna, Presidio Ospedaliero "Giovanni Paolo II", ASP di Catanzaro); Arcidiacono G., Bellanuova I. (UOC Cardiologia e UTIC, PO "Centro"- ARNAS Garibaldi, Catania); Ferraro M., Marigliano G. (ASP Cosenza); Cozzolino D., Lampitella A., Acri V. (Dipartimento di Internistica Clinica e Sperimentale, Seconda Università di Napoli); Galasso D., Mazzei F., Galasso S. (RSA Madonna di Porto Gimigliano, Catanzaro); Buratti A. (Azienda Ospedaliera della Provincia di Pavia, UO Medicina Interna, Ospedale Civile, Casorate Primo, Pavia); Porta M., Brizzi M.F. (SC Medicina Interna 1U, Azienda Ospedaliera "Città della Salute e della Scienza", Torino); Fattorini A., Sampietro F., D'Angelo A. (Servizio di Coagulazione ed Unità Ricerca Trombosi, IRCCS Ospedale San Raffaele, Milano); Manfredini R., Pala M., Fabbian F., (UOC Clinica Medica, Azienda Ospedaliera-Universitaria S. Anna, Ferrara); Moroni C., Valente L., Lopreiato F. (Laboratorio di Ecocardiografia-Cardiologia Preventiva, DAI Cuore e Grossi Vasi, Sapienza-Università di Roma); Parente F. (UOC Medicina Interna, PO "Vito Fazzi", Lecce); Granata M. (Immunologia Clinica A, Sapienza-Università di Roma, Roma); Moia M., Braham S. (Fondazione IRCCS Ca'Granda, Ospedale Maggiore Policlinico, Milano); Rossi M., Pesce M. (Dipartimento di Medicina Clinica e Sperimentale, Università di Pisa); Gentile A., Catozzo V. (UO Medicina, LDP Loreto, Dipartimento di Medicina Interna, ASUR Marche, Area Vasta n.2, ex ZT 7); Baciarello G., Cosimati A. (UOC Cardiologia Preventiva e Riabilitativa, Sapienza-Università di Roma); Ageno W., Rancan E., Guasti L. (Dipartimento di Medicina Clinica e Sperimentale, Università dell'Insubria, Varese); Ciccaglioni A., Negri S., Polselli M. (Centro Elettro-Stimolazione Cardiaca, Sapienza-Università di Roma); Prisco D., Marcucci R. (SOD Patologia Medica, AOU Careggi, Firenze); Ferro D., Cangemi R., Perri L., Polimeni L., Catasca E., Vicario T., Russo R., Saliola M., Del Ben M., Angelico F., Calvieri C., Bucci T., Baratta F. (I Clinica Medica, Sapienza-Università di Roma); Migliacci R., Porciello G. (S. C. Medicina Interna, Ospedale della Valdichiana, Cortona, USL 8 Arezzo); Corrao S. (Dipartimento BioMedico di Medicina Interna e Specialistica, Università degli Studi di Palermo).

Coordinamento Scientifico Studio ARAPACIS: Pignataro F.S., Napoleone L., Talerico G., Amoroso D., Romiti G.F., Ruscio E., Toriello F., Todisco T.

Data and Safety Monitoring Board: Di Tanna G., Sacchetti M.L., Puddu P.E.

Simi Young Internists (GIS) Group: Anzaldi M., Bazzini C., Bianchi P.I., Boari B., Bracco C., Buonauro A., Buttà C., Buzzetti E., Calabria S., Capeci

W., Caradio F., Carleo P., Carrabba M.D., Castorani L., Cecchetto L., Cicco S., Cimini C., Colombo B.M., De Giorgi A., De Vuono S., Del Corso L., Denegri A., Di Giosia P., Durante Mangoni E., Falsetti L., Forgione A., Giorgini P., Grassi D., Grembiale A., Hijazi D., Iamele L., Lorusso G., Marchese A., Marra A.M., Masala M., Miceli G., Montebianco Abenavoli L., Murgia G., Naccarato P., Padula D., Pattoneri P., Perego F., Pesce P., Piano S., Pinna M., Pinto D., Pretti V., Pucci G., Raparelli V., Salinaro F., Salzano A., Santilli F., Scarpini F., Scicali R., Sirico D., Suppressa P., Talia M., Tassone E.J., Torres D., Vazzana N., Vecchio C.R., Vidili G., Vitale F., Zaccone V.

All in Italy.

References

[1] P. Kirchhof, G. Breithardt, J. Bax, et al., A roadmap to improve the quality of atrial fibrillation management: proceedings from the fifth Atrial Fibrillation Network/European Heart Rhythm Association consensus conference, Europace 18 (2016) 37–50.

[2] G.Y. Lip, D.A. Lane, Stroke prevention in atrial fibrillation: a systematic review, JAMA 313 (2015) 1950–1962.

[3] C.T. Ruff, R.P. Giugliano, E. Braunwald, et al., Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials, Lancet 383 (2014) 955–962.

[4] F. Violi, G. Daví, W. Hiatt, et al., Prevalence of peripheral artery disease by abnormal ankle-brachial index in atrial fibrillation: implications for risk and therapy, J. Am. Coll. Cardiol. 62 (2013) 2255–2256.

[5] D. Pastori, P. Pignatelli, F. Angelico, et al., Incidence of myocardial infarction and vascular death in elderly patients with atrial fibrillation taking anticoagulants: relation to atherosclerotic risk factors, Chest 147 (2015) 1644–1650.

[6] F. Violi, L. Loffredo, Thromboembolism or atherothromboembolism in atrial fibrillation? Circ. Arrhythm. Electrophysiol. 5 (2012) 1053–1055.

[7] G.Y. Lip, R. Nieuwlaat, R. Pisters, et al., Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation, Chest 137 (2010) 263–272.

[8] F. Violi, G. Davì, M. Proietti, et al., Ankle-brachial index and cardiovascular events in atrial fibrillation: ARAPACIS prospective study, Thromb. Haemost. 115 (2016) 856–863.

[9] V. Raparelli, M. Proietti, C. Buttà, et al., Medication prescription and adherence disparities in non valvular atrial fibrillation patients: an Italian portrait from the ARAPACIS study, Intern. Emerg. Med. 9 (2014) 861–870.

[10] J.H. Stein, C.E. Korcarz, R.T. Hurst, et al., Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine, J. Am. Soc. Echocardiogr. 21 (2008) 93–111.

[11] M.J. Pencina, R.B. D'Agostino Sr., E.W. Steyerberg, Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers, Stat. Med. 30 (2011) 11–21.

[12] A.J. Vickers, A.M. Cronin, E.B. Elkin, et al., Extensions to decision curve analysis, a novel method for evaluating diagnostic tests, prediction models and molecular markers, BMC Med. Inform. Decis. Mak. 8 (2008) 53.

[13] P.J. Heagerty, T. Lumley, M.S. Pepe, Time-dependent ROC curves for censored survival data and a diagnostic marker, Biometrics 56 (2000) 337–344.

[14] M. Proietti, C. Calvieri, L. Malatino, et al., Relationship between carotid intima-media thickness and non valvular atrial fibrillation type, Atherosclerosis 238 (2015) 350–355.

[15] W. Bekwelem, P.N. Jensen, F.L. Norby, E.Z. Soliman, S.K. Agarwal, G.Y. Lip, W. Pan, A.R. Folsom, W.T. Longstreth Jr., A. Alonso, S.R. Heckbert, L.Y. Chen, Carotid atherosclerosis and stroke in atrial fibrillation: the Atherosclerosis Risk in Communities Study, Stroke 47 (2016) 1643–1646.

[16] F. Violi, C. Calvieri, D. Ferro, et al., Statins as antithrombotic drugs, Circulation 127 (2013) 251–257.

[17] M.S. Pepe, J. Fan, Z. Feng, T. Gerds, J. Hilden, The Net Reclassification Index (NRI): a misleading measure of prediction improvement even with independent test data sets, Stat. Biosci. 7 (2015) 282–295.