Stroke and Thromboembolism in Warfarin-Treated Patients with Atrial Fibrillation: Comparing the CHA_2DS_2-VASc and GARFIELD-AF Risk Scores

Marco Proietti[1,2,3]* MD PhD, José Miguel Rivera-Caravaca[4]* RN PhD,
María Asunción Esteve-Pastor[4] MD PhD,
Francísco Marín[4] MD PhD, Gregory Y.H. Lip[1,5] MD

[1]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom; [2]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy; [3]Geriatric Unit, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy; [4]Department of Cardiology, Hospital Clínico Universitario Virgen de la Arrixaca, Instituto Murciano de Investigación Biosanitaria (IMIB-Arrixaca), CIBER-CV, Murcia, Spain; [4]Department of Internal Medicine and Medical Specialties, Sapienza-University of Rome, Rome, Italy; [5]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark.
[*both authors equally contributed to the manuscript]

The editorial process for this paper was fully handled by Prof Christian Weber, Editor in Chief

Corresponding Author

Marco Proietti MD PhD FESC FEHRA
Geriatric Unit, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico
Via Pace 9, 20122, Milan, Italy
ORCiD: 0000-0003-1452-2478
Twitter Handle: @MProiettiMD
e-mail: marco.proietti@unimi.it

ABSTRACT

Background: Evaluation of thromboembolic risk is essential in anticoagulated atrial fibrillation (AF) patients. The CHA_2DS_2-VASc score is largely validated and recommended by most guidelines. The GARFIELD-AF Stroke score has been proposed as an alternative risk score.

Methods: We analyzed warfarin-treated patients from SPORTIF III and V studies. Any thromboembolic event [TE] was an *adjudicated* study outcome. We compared the two scores capacity in predicting any TE occurrence.

Results 3665 patients (median [IQR] age 72 [66-77] years; 30.5% female) were included in this analysis. After a mean (SD) follow-up of 566.3 (142.5) days, 148 (4.03%) TEs were recorded. Both continuous CHA_2DS_2-VASc and GARFIELD-AF were associated with TE (HR:1.37, 95% CI:1.22-1.53 and HR:2.43, 95% CI:1.72-3.42), with modest predictive ability (c-indexes:0.63, 95% CI:0.59-0.68 and 0.61, 95% CI:0.56-0.66, respectively), with no differences. CHA_2DS_2-VASc quartiles showed an increasing cumulative risk, while in GARFIELD-AF only the highest quartile (Q4) demonstrated an increased TE risk. On multivariate Cox regression analysis, CHA_2DS_2-VASc quartiles were associated with increasing risk of TE whereas for GARFIELD-AF only Q4 showed an association with TE. Discrimination analysis showed that GARFIELD-AF quartiles were associated with a 48.7% reduction in discriminatory ability. Using Decision Curve Analysis (DCA), CHA_2DS_2-VASc was associated with improved clinical usefulness and net clinical benefit, compared with GARFIELD-AF.

Conclusions: In a warfarin-treated trial cohort of AF patients, both CHA_2DS_2-VASc and GARFIELD-AF Stroke scores were associated with adjudicated TE events, with modest predictive capacity. Simpler CHA_2DS_2-VASc score improved discriminatory

capacity compared to more complex GARFIELD-AF score, demonstrating improved clinical usefulness and net clinical benefit.

Keywords: Atrial Fibrillation, Risk Scores, Thromboembolic Events

SUMMARY TABLE

WHAT IS KNOWN ABOUT THIS TOPIC?

- Evaluation of thromboembolic risk is essential in atrial fibrillation (AF) patients.
- The CHA_2DS_2-VASc score is largely validated and recommended by most guidelines
- Among several other risk scores, the GARFIELD-AF Stroke score has been proposed as a possible alternative risk score to CHA_2DS_2-VASc, but no direct comparisons between these two scores have been published.

WHAT DOES THIS PAPER ADD?

- Both CHA_2DS_2-VASc and GARFIELD-AF Stroke scores were associated with adjudicated TE events, with modest predictive capacity
- CHA_2DS_2-VASc was associated with improved clinical usefulness and net clinical benefit, when compared with GARFIELD-AF
- In patients with a good anticoagulation control (TTR ≥70%), the CHA_2DS_2-VASc score maintained (and even improved) its discriminative abilities, while GARFIELD-AF Stroke was non-predictive of most of the outcomes examined.

INTRODUCTION

The risk evaluation for stroke and thromboembolism is part of the baseline assessment of patients with atrial fibrillation (AF)(1). Currently, the majority of the most recent international guidelines about AF diagnosis and management recommend the use of the CHA_2DS_2-VASc score as the preferred clinical tool for stroke risk stratification(2–5). Nevertheless, the CHA_2DS_2-VASc score - like most clinical scores – has only modest predictive value for thromboembolism, and some have advocated improved risk prediction using more complex clinical risk models, or with mixed combinations of clinical variables and biomarkers, often based on complex mathematical-based models(6–8), in order to obtain a more precise, accurate and reliable tool to predict the occurrence of thromboembolic events.

Nonetheless, a recent independent PCORI-systematic review and evidence appraisal investigating several risk scores for the prediction of thromboembolic events, documented how most of the scores have a similar predictive capacity(9), hence the choice of one tool rather than another should be based on the balance between evidence, practicality and precision(10).

Among these new scores, the GARFIELD-AF Stroke score(8), developed from the 'Global Anticoagulation in the Field Atrial Fibrillation' observational registry(11), was found to be superior (at least statistically) to the CHA_2DS_2-VASc score in predicting thromboembolic events, but thus far has had limited validation(12).

The aim of this paper is to provide an independent evaluation of the GARFIELD-AF Stroke score prediction ability, in comparison to the CHA_2DS_2-VASc score, in a

cohort of anticoagulated AF patients derived from a randomized clinical trial with adjudicated clinical outcomes.

METHODS

The authors declare that all supporting data and methods used to derive the results and the related findings are available within the article.

For the present analysis, we used the pooled study populations of the Stroke Prevention using an Oral Thrombin Inhibitor in patients with atrial Fibrillation (SPORTIF) III and V trials. The original protocol and principal results have been previously described(13–15). In brief, the SPORTIF trials were two multicentre Phase III clinical trials comparing the efficacy and safety of the direct thrombin inhibitor, ximelagatran, against warfarin in patients with non-valvular AF. Signed informed consent was required from each participant in accordance with protocol regulations approved by the local review boards governing research involving human subjects, and the Declaration of Helsinki. De-identified datasets with patient-level information were obtained directly from AstraZeneca, and all the analyses were performed independently from the company. In the light of obtaining significant clinical information applicable to the actual management of AF patients, only the warfarin-assigned patients were retrieved for analysis and not those randomized to ximelagatran, which was never approved for treatment. All patients assigned to the warfarin treatment arms and with available data for the clinical variables used to calculate the two bleeding prediction scores were included in the present analysis.

The CHA_2DS_2-VASc score was calculated according to the original model(16). The GARFIELD-AF Stroke score was compiled according to the equation proposed from Fox et al(8) as follows: 1-[0.991344397 exp(0.03048226 * (Age-60) + 0.952524717 * Stroke + 0.432357326 * Bleed + 0.319129628 * Heart Failure + 0.574919171 * Chronic Kidney Disease + 0.654249546 * Other Region + 0.671380382 * Black/Mixed/Other Race - 0.582045773 * Oral Anticoagulant)].

The original SPORTIF trials did not enroll patients outside Europe and North America, hence the 'Other Region' criterion was scored as 0. Chronic kidney disease was defined as a creatinine clearance <60 mL/min as calculated with the Cockroft-Gault formula. In the two SPORTIF trials only 65 (1.8%) patients among those randomized to the warfarin arms (N=3665) were 'Black/Mixed/Other Race'. Hence, given the low prevalence of this criterion and the unavailability of detailed ethnicity data we scored it as 0. All the other criteria were derived from the original case report form. Both the scores were considered as continuous and according to their quartiles, in order to obtain the most relevant clinical information.

Study Outcomes

The primary study outcome was the occurrence of any thromboembolic event (TE) intended as the composite of any stroke, systemic embolism (SE) and transient ischemic attack (TIA). Additionally, we considered as study secondary outcomes the occurrence of: i) any stroke/SE; ii) any stroke; iii) ischemic stroke; iv) TIA. All the outcomes were originally adjudicated by a central blinded adjudication committee.

Statistical Analysis

Continuous variables were reported as median [IQR], while categorical variables were expressed as counts and percentages. Differences in survival according to the scores' quartiles for the composite outcome occurrence, assessed by an intention-to-treat approach, were analysed using the Log-Rank test and Kaplan-Meier curves estimates were drafted accordingly. A Cox proportional hazards analysis was used to evaluate the occurrence of the study outcomes according to continuous scores and scores quartiles, adjusted for body mass index, type of AF, chronic kidney disease, use of aspirin, and time in therapeutic range. C-indexes were estimated, with exact estimation of 95% confidence interval (CI), and compared according to De Long, De Long and Clarke-Pearson method(17).

Discrimination and reclassification abilities were evaluated by the integrated discrimination improvement (IDI), relative IDI (rIDI), net reclassification improvement (NRI) and median improvement, as described by Pencina et al(18). Clinical usefulness and net clinical benefit, intended as the ability of correctly identifying patients which would have developed and those which not the events being, as identified at high risk by one score compared to other, were estimated using the decision curve analysis (DCA), according to the method proposed by Vickers et al(19,20).

In addition, we performed a sensitivity analysis about the association and predictive ability for the two risk scores in patients with a good quality of oral anticoagulation therapy (time in therapeutic range [TTR] ≥70%). A two-sided p value <0.05 was considered statistically significant. All analyses were performed using SPSS v. 25.0 (IBM, NY, USA) for MacOS and and survIDINRI package for R v. 3.3.1 for Windows.

RESULTS

All the 3665 AF patients originally included in the warfarin arms of the SPORTIF trials were included in this analysis. Baseline characteristics were reported in Table 1. Overall, 3178 (86.7%) patients had a CHA_2DS_2-VASc ≥2. Distribution of CHA_2DS_2-VASc score can be found in Figure S1. For CHA_2DS_2-VASc score there were 1449 (39.5%) in Q1, 964 (26.3%) in Q2, 710 (19.4%) in Q3 and 542 (14.8%) patients in Q4. For GARFIELD-AF Stroke there were 1164 (31.8%) in Q1, 231 (6.3%) in Q2, 1390 (37.9%) in Q3 and 880 (24.0%) patients in Q4.

After a mean (SD) follow-up of 566.3 (142.5) days, 148 (4.03%) any TE were recorded. Additionally, a total of 93 (2.54%) stroke/SE, 91 (2.48%) stroke, 82 (2.24%) ischemic stroke and 50 (1.36%) TIA were recorded. Kaplan-Meier curves for the primary composite outcome showed that for CHA_2DS_2-VASc score a progressively higher cumulative risk was found according to the increasing score quartiles [Figure 1, Upper Panel]. Conversely, for GARFIELD-AF Stroke, while the first 3 quartiles showed a similar risk, the fourth quartile showed a significantly higher cumulative risk for outcome occurrence [Figure 1, Lower Panel].

In Table 2 we reported the results of the survival analysis. After the multivariate adjustments Cox regression analysis showed that continuous CHA_2DS_2-VASc score was significantly associated with the occurrence of composite primary outcome (any TE) and all the other secondary outcomes. Similarly, the GARFIELD-AF Stroke score was significantly associated with the occurrence of any TE and most of the secondary outcomes, *with the exception of ischemic stroke*.

Both CHA_2DS_2-VASc and GARFIELD-AF Stroke scores showed a modest predictive ability for the occurrence of all the study outcomes (Table 2). Accordingly, c-indexes (95% CI) for CHA_2DS_2-VASc score ranged from 0.63 (0.58-0.69) for the composite outcome to 0.65 (0.59-0.70) for ischemic stroke. The c-index (95% CI) for GARFIELD-AF Stroke score ranged from 0.59 (0.53-0.66) for ischemic stroke to 0.61 (0.56-0.66) for the composite outcome. No significant differences between the c-indexes for the two scores were found for any outcome.

When examining the score quartiles (Table 3), we found that for CHA_2DS_2-VASc score increasing quartiles were associated with an increasing risk for all the study outcomes, except for TIA where only the highest quartile (Q4) was significantly associated with risk (Table 3). For the GARFIELD-AF Stroke score, only Q4 was associated to an increased risk for the primary composite outcome. No relationship was found between increasing quartiles and other study outcomes.

Discrimination and Reclassification Analysis

The reclassification analysis of GARFIELD-AF Stroke score vs. CHA_2DS_2-VASc score (Table 4) showed that by using continuous scores, use of the GARFIELD-AF Stroke score was associated with significant reduction in the median improvement for discriminating ischemic stroke.

Based on score quartiles, the GARFIELD-AF Stroke score was associated with a significant reduction in discriminatory capacity for all the study outcomes, with a consistent reduction in the discriminative ability, as evaluated by the rIDI (SD),

ranging from -45.7% (-22.8%) for the any stroke/SE outcome to -123.2% (-47.4%) for ischemic stroke outcome.

Decision Curve Analysis

To evaluate the clinical usefulness and net benefit of using one clinical score rather than the other, we performed a DCA. Use of the CHA_2DS_2-VASc score was associated with improved clinical usefulness and net clinical benefit in predicting the occurrence of ischemic stroke, compared to the GARFIELD-AF Stroke score [Figure 2]. A small clinical benefit was also found in predicting the occurrence of any stroke/SE, any stroke and TIA [Figures S2-S4], although smaller than for ischemic stroke. No difference was observed for the composite outcome of any TE [Figure S5].

Sensitivity Analysis

In the sensitivity analysis (Table 5) in patients with TTR ≥70%, we found that the CHA_2DS_2-VASc score remained significantly associated with all the study outcomes, while the GARFIELD-AF Stroke score remained significantly associated only with the primary outcome and TIA occurrence. When examining the predictive ability of the two scores, CHA_2DS_2-VASc performed even better than in the overall cohort for every study outcome, while the GARFIELD-AF Stroke score did not predict occurrence of any stroke/SE, any stroke and ischemic stroke outcomes, with a numerically weaker predictive ability than CHA_2DS_2-VASc for the remaining outcomes.

DISCUSSION

In this post-hoc subgroup analysis derived from the SPORTIF III and V trials, we showed that while both CHA_2DS_2-VASc and GARFIELD-AF Stroke scores are significantly associated with the occurrence of TEs, although with only modest predictive ability. Second, increasing CHA_2DS_2-VASc score quartiles were significantly associated to an increased risk for the study outcomes. Third, using the GARFIELD-AF Stroke score was associated with a significant reduction in discriminative abilities for all the study outcomes. Fourth, using CHA_2DS_2-VASc score was associated with improved clinical usefulness and net clinical benefit based on Decision Curve Analysis, in predicting the occurrence of ischemic stroke as well as any stroke/SE, any stroke and TIA. Finally, in patients with a good anticoagulation control (TTR ≥70%), the CHA_2DS_2-VASc score maintained (and even improved) its discriminative abilities, while GARFIELD-AF Stroke was non-predictive of most of the outcomes examined.

The CHA_2DS_2-VASc score was derived from the Euro Heart Survey in AF in 2010(16), and subsequently validated in a large number of independent cohorts, being similar or superior to some complex risk scores(9,21–23). In a recent systematic review developed by the independent US ‘Patient-Centered Outcomes Research Institute’ (PCORI), the CHA_2DS_2-VASc score was amongst those scores with the highest predictive ability(9), with the positive aspects linked to the widespread diffusion and ease of computation(10). Recently, the CHA_2DS_2-VASc score was also found to be predictive of all-cause death in AF patients(24). Given the wide range of evidence available, the CHA_2DS_2-VASc score is now recommended by most international guidelines of AF management(2,3).

The GARFIELD-AF Stroke score, as mentioned above, has been derived and validated from the population of the GARFIELD-AF observational registry, to date one of the largest worldwide observational cohorts available about AF patients(25,26). In the original validation paper, analysis of registry data about more than 39,000 patients from the first four cohorts of the GARFIELD-AF on a 1-year follow-up observation deriving three risk score models about risk of stroke, bleeding and death. Further, the risk models were validated in a registry cohort derived from the 'Outcome Registry for Better Informed Treatment of Atrial Fibrillation' (ORBIT-AF) registry. In the derivation cohort, the GARFIELD-AF Stroke score showed only a modest predictive ability (c-index [95% CI]: 0.69 [0.67-0.71]), statistically superior to the CHA_2DS_2-VASc score (c-index [95% CI]: 0.64 [0.61-0.66]). In the validation cohort, both scores performed similarly, ie. GARFIELD-AF Stroke score: c-index [95% CI]: 0.69 [0.64-0.75] vs CHA_2DS_2-VASc score c-index [95% CI]: 0.69 [0.64-0.74]. More recently, the same authors tested the GARFIELD-AF Stroke score in a Danish nationwide cohort registry of newly diagnosed AF patients(12). In this study the GARFIELD-AF Stroke score showed a statistically better predictive ability than CHA_2DS_2-VASc score (c-index [95% CI]: 0.71 [0.70-0.72] vs. 0.67 [0.66-0.68], respectively)(12). Notwithstanding the large unselected cohort in this paper, the authors censored the follow-up at 1-year follow-up and study population was heterogeneous, including both anticoagulated and non-anticoagulated patients. Also, being a retrospective registry, outcomes were non-adjudicated(12).

In our paper, based on an anticoagulated cohort derived from a randomized controlled trial with a centralized outcomes adjudication process, we have shown that the

CHA_2DS_2-VASc score was more strongly associated with the occurrence of a composite outcome of TEs. Also, the association appeared to have an exposure-effect relationship, with a progressively higher risk according to the higher quartiles of the CHA_2DS_2-VASc score, which better discriminated the risk magnitude across the patients' baseline characteristics and among a high-risk cohort. Based on the respective score quartiles, applying the GARFIELD-AF Stroke score resulted in a reduction in discriminative ability, with up to more than 130% loss of predictive capacity when compared to CHA_2DS_2-VASc score.

Of note, the GARFIELD-AF Stroke score represents a complex risk prediction model, with multiple clinical and other variables which may not be easily and quickly applicable in daily clinical practice, both at the patient's bedside and during outpatient visits. Further, when using DCA, the CHA_2DS_2-VASc score was associated with improved clinical usefulness and net clinical benefit to correctly discriminate those high-risk AF patients who actually developed an ischemic stroke, when compared with GARFIELD-AF.

The sensitivity analysis allows us also to show that in patients with an overall lower risk, such as those with a good anticoagulation control, the CHA_2DS_2-VASc score was still able to provide a significant discrimination of stoke risk, while the GARFIELD-AF Stroke score was non-significantly able to stratify the residual thromboembolic risk.

As reported by Borre and colleagues, most of the published risk scores showed a similar predictive capacity, at least in relation to practical, everyday clinical used(9).

The process of deriving and validating a clinical risk score is inevitably a reductionist process, which cannot turn the entire complexity of physiopathological process responsible for the stroke determinism into a short list of risk factors, even though weighted according to clinical relevance. The continuous process of searching the "perfect score" appears to be burdened by an ontological bias. Conversely, identifying the most suitable score to be applied in the clinical daily-life needs to take account of the balance between the evidence supporting that particular score, their practicality and precision(10). In the daily clinical management, all these factors should be taken under strong consideration, as simplicity and practicality needs to be balanced against modest differences in prediction(10). Statistical significance is also not the same as clinical prediction. Several other factors to improve clinical risk prediction have been proposed, such as adding biomarkers, but many such biomarkers are non-specific, reflecting a sicker patient or the associated comorbidities(27,28).

Limitations

This study is mainly limited by its post-hoc retrospective nature, even though based on a solid and well-conducted randomized clinical trial. Given that the study cohort was derived from a randomized controlled trial, all thromboembolic factors were recorded and managed, probably resulting in a lower rate of TEs compared to the real-life populations. Furthermore, the exclusion of patients with liver disease from the original cohort, as well as the exclusive use of warfarin as the OAC treatment, together with the fact that all patients were treated, may somewhat limit the generalizability of our results. Moreover, the limited data about non-white ethnicity may introduce a slight bias even although minimized by the very small numbers of

these patients included in the original cohort. Finally, the SPORTIF trials were conducted between 2000 and 2002, and the treatment regimens and clinical practice may have changed over the time. Nonetheless, we analysed a large cohort of AF patients with a high level of data quality and with centrally adjudicated clinical events, in contrast to other studies comparing these scores, which have used non-adjudicated registry data.

CONCLUSIONS

In a warfarin-treated trial cohort of AF patients, both CHA_2DS_2-VASc and GARFIELD-AF Stroke scores were associated with adjudicated TE events, with modest predictive capacity. The simpler CHA_2DS_2-VASc score improved discriminatory capacity (~49%) compared to more complex GARFIELD-AF score, and demonstrated improved clinical usefulness and net clinical benefit using DCA, when compared to the GARFIELD-AF score.

FUNDING

No funding has been received in the preparation of this manuscript. Astra Zeneca provided datasets for the analysis. Astra Zeneca was never involved in any stage of manuscript drafting and preparation.

DISCLOSURES

GYHL has served as consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo. No fees were received personally. GYHL originally authored the paper which designed and validated the CHA_2DS_2-VASc score. Other authors have no disclosures to declare.

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Table 1: Baseline Characteristics

	N = 3665
Age, *years* median [IQR]	72 [66-77]
Female Sex, n (%)	1116 (30.5)
BMI, *kg/m²* median [IQR] *3651*	28.1 [25.0-31.6]
CrCl, *mL/min* median [IQR] *3663*	78.6 [59.1-102.1]
Chronic AF, n (%) *3548*	3269 (89.2)
Hypertension, n (%)	2812 (76.7)
Diabetes Mellitus, n (%)	860 (23.5)
Coronary Artery Disease, n (%)	1619 (44.2)
Stroke/TIA, n (%)	753 (20.5)
Heart Failure, n (%)	1372 (37.4)
Previous Bleeding, n (%)	208 (5.7)
Chronic Kidney Disease, n (%) *3646*	952 (26.1)
Aspirin Use, n (%)	726 (19.8)
TTR, *%* median [IQR] *3624*	68.5 [55.2-79.3]

Legend: AF= Atrial Fibrillation; BMI= Body Mass Index; CrCl= Creatinine Clearance; IQR= Interquartile Range; TIA= Transient Ischemic Attack; TTR= Time in Therapeutic Range.

Table 2: Survival and Predictive Analysis for Thromboembolic Outcomes for CHA_2DS_2-VASc and GARFIELD-AF Stroke Scores

	CHA_2DS_2-VASc		GARFIELD-AF	
	HR (95% CI)*	**c-index (95% CI)**	**HR (95% CI)***	**c-index (95% CI)**
Any Stroke/SE/TIA	1.37 (1.22-1.53)	0.63 (0.59-0.68)	2.43 (1.72-3.42)	0.61 (0.56-0.66)
Any Stroke/SE	1.35 (1.17-1.55)	0.63 (0.58-0.69)	2.36 (1.55-3.61)	0.61 (0.55-0.67)
Any Stroke	1.36 (1.18-1.57)	0.64 (0.58-0.69)	2.22 (1.44-3.42)	0.60 (0.54-0.66)
Ischemic Stroke	1.39 (1.20-1.61)	0.65 (0.59-0.70)	1.00 (0.95-1.04)	0.59 (0.53-0.66)
TIA	1.40 (1.15-1.69)	0.64 (0.56-0.71)	2.35 (1.32-4.18)	0.60 (0.52-0.69)

Legend: *adjusted for body mass index, type of atrial fibrillation, chronic kidney disease, use of aspirin, time in therapeutic range;

CI= Confidence Interval; HR= Hazard Ratio; SE= Systemic Embolism; TIA= Transient Ischemic Attack.

Table 3: Survival Analysis for Thromboembolic Outcomes for CHA_2DS_2-VASc and GARFIELD-AF Stroke Scores Quartiles

	CHA_2DS_2-VASc Score Quartiles*			
	Q1 (ref.)	**Q2**	**Q3**	**Q4**
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Any Stroke/SE/TIA	-	1.83 (1.13-2.98)	2.25 (1.37-3.71)	3.66 (2.28-5.90)
Any Stroke/SE	-	1.84 (1.00-3.38)	2.54 (1.39-4.67)	3.67 (2.02-6.67)
Any Stroke	-	1.96 (1.05-3.61)	2.69 (1.45-4.98))	3.72 (2.02-6.86)
Ischemic Stroke	-	2.13 (1.10-4.13)	3.08 (1.60-5.94)	3.90 (2.01-7.57)
TIA	-	1.78 (0.80-3.98)	2.17 (0.94-5.01)	3.64 (1.65-8.02)
	GARFIELD-AF Score Quartiles*			
	Q1 (ref.)	**Q2**	**Q3**	**Q4**
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Any Stroke/SE/TIA	-	0.97 (0.40-2.31)	1.18 (0.75-1.86)	2.44 (1.58-3.77)
Any Stroke/SE	-	1.40 (0.52-3.77)	1.12 (0.61-2.07)	1.86 (0.96-3.60)
Any Stroke	-	1.40 (0.52-3.76)	1.14 (0.62-2.11)	1.81 (0.93-3.51)
Ischemic Stroke	-	0.53 (0.12-2.31)	1.07 (0.57-2.00)	1.47 (0.74-2.94)
TIA	-	0.44 (0.06-3.39)	1.03 (0.48-2.22)	1.86 (0.82-4.20)

Legend: *adjusted for body mass index, type of atrial fibrillation, chronic kidney disease, use of aspirin, time in therapeutic range; CI= Confidence Interval; HR= Hazard Ratio; SE= Systemic Embolism; TIA= Transient Ischemic Attack.

Table 4: Reclassification Analysis of GARFIELD-AF Stroke vs. CHA_2DS_2-VASc Risk Scores

	Scores as Continuous Variable					
	IDI (95% CI)	**p**	**NRI (95% CI)**	**p**	**Med. Improv. (95% CI)**	**p**
Any Stroke/SE/TIA	-0.001 (-0.007 / 0.006)	0.786	-0.061 (-0.195 / 0.097)	0.517	-0.001 (-0.011 / 0.007)	0.159
Any Stroke/SE	-0.001 (-0.005 / 0.008)	0.856	-0.049 (-0.183 / 0.135)	0.886	-0.001 (-0.007 / 0.006)	0.507
Any Stroke	-0.001 (-0.007 / 0.007)	0.736	-0.062 (-0.217 / 0.127)	0.617	-0.001 (-0.009 / 0.005)	0.388
Ischemic Stroke	-0.002 (-0.006 / 0.002)	0.328	-0.118 (-0.267 / 0.028)	0.119	**-0.002 (-0.009 / -0.001)**	**0.020**
TIA	-0.001 (-0.008 / 0.002)	0.428	-0.099 (-0.309 / 0.087)	0.318	-0.001 (-0.011 / 0.007)	0.159

	Scores as Quartiles						
	IDI (SD)	**rIDI (SD)**	**p**	**NRI Overall (SD)**	**NRI Non-Event (SD)**	**NRI Event (SD)**	**p**
		%		*%*	*%*	*%*	
Any Stroke/SE/TIA	**-0.003 (-0.001)**	**-48.7 (-18.4)**	**0.008**	-8.7 (-6.5)	-29.3 (-1.3)	20.6 (6.4)	0.183
Any Stroke/SE	**-0.002 (-0.001)**	**-45.7 (-22.8)**	**0.045**	-5.4 (-8.0)	-29.1 (-1.3)	23.7 (7.9)	0.500
Any Stroke	**-0.002 (-0.001)**	**-74.3 (-30.9)**	**0.016**	-6.0 (-8.1)	-29.1 (-1.3)	23.1 (8.0)	0.460
Ischemic Stroke	**-0.003 (-0.001)**	**-123.2 (-47.4)**	**0.009**	-10.9 (-8.5)	-29.2 (-1.3)	18.3 (8.4)	0.199
TIA	-0.001 (-0.001)	-67.2 (-37.5)	0.073	-15.1 (-10.5)	-29.1 (-1.3)	20.6 (6.4)	0.149

Legend: Grey cells and bold text depict statistically significant results; CI = Confidence Interval; IDI = Integrated Discrimination Improvement; NRI = Net Reclassification Improvement; rIDI= Relative Integrated Discrimination Improvement; SD= Standard Deviation; SE= Systemic Embolism; TIA= Transient Ischemic Attack.

Table 5: Sensitivity Analysis for Thromboembolic Outcomes for CHA_2DS_2-VASc and GARFIELD-AF Stroke Scores in Patients with High Quality Anticoagulation Control

	CHA_2DS_2-VASc		GARFIELD-AF	
	HR (95% CI)*	**c-index (95% CI)**	**HR (95% CI)***	**c-index (95% CI)**
Any Stroke/SE/TIA	1.50 (1.24-1.81)	0.69 (0.62-0.75)	2.59 (1.40-4.78)	0.62 (0.54-0.69)
Any Stroke/SE	1.41 (1.09-1.83)	0.67 (0.58-0.75)	1.88 (0.78-4.56)	0.58 (0.48-0.69)
Any Stroke	1.41 (1.09-1.83)	0.67 (0.58-0.75)	1.88 (0.78-4.56)	0.58 (0.48-0.69)
Ischemic Stroke	1.36 (1.03-1.78)	0.66 (0.56-0.75)	1.19 (0.42-3.38)	0.55 (0.44-0.66)
TIA	1.62 (1.23-2.13)	0.70 (0.62-0.78)	3.49 (1.50-8.13)	0.65 (0.54-0.76)

Legend: *adjusted for body mass index, type of atrial fibrillation, chronic kidney disease, use of aspirin; CI= Confidence Interval; HR= Hazard Ratio; SE= Systemic Embolism; TIA= Transient Ischemic Attack.

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FIGURES LEGENDS

Figure 1: Kaplan-Meier Curves for Any Stroke/SE/TIA according to CHA_2DS_2-VASc and GARFIELD-AF Stroke Scores Quartiles

Legend: SE= Systemic Embolism; TIA= Transient Ischemic Attack.

Figure 2: Decision Curve Analysis according to CHA_2DS_2-VASc and GARFIELD-AF Stroke Scores for Ischemic Stroke Occurrence

Legend: Blue Line= GARFIELD-AF Stroke; Red Line= CHA_2DS_2-VASc.