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# The harm of anticoagulation in patients with low-risk by $CHADS_2$ and reclassified as high-risk by $CHA_2DS_2VASc$: inferences from TRAF cohort

E. OTO[1], S. OKUTUCU[2], D. KATIRCIOGLU ÖZTÜRK[3], N. ATA[4], B. YAVUZ[5], C. GALE[6], A. BURKAN[4], J. CAMM[7], A. OTO[2]

[1]HSE St Luke's General Hospital, Kilkenny, Ireland
[2]Memorial Ankara Hospital, Ankara, Turkey
[3]Medical Information Technology Solutions, Ankara, Turkey
[4]Social Security Institution, Ankara, Turkey
[5]Medical Park Ankara Hospital, Ankara, Turkey
[6]Leeds Institute of Cardiovascular and Metabolic Medicine, Leeds, United Kingdom
[7]St. George's University of London, London, United Kingdom

**Abstract. – OBJECTIVE: There is a gap in the knowledge concerning oral anticoagulation (OAC) in atrial fibrillation (AF) patients with a non-high risk of stroke. CHA2DS2VASc and CHADS2 scores generated imprecise risk estimates for low risk patients. We aimed to assess OAC in patients with low risk by CHADS2 and reclassified as high-risk by CHA2DS2VASc.**

**PATIENTS AND METHODS: In this study, retrospective nationwide population-based study, data were obtained from the Turkish claims and utilization management system. Patients with non-valvular AF (n=451,113) between 2007 and 2012 sub-divided into those with a CHA2DS2VASc≥1 and CHADS2=0 (n=41,273) who were off-warfarin (n=29,448) and on-warfarin (n=11,825). Stroke and systemic embolism, major bleeding, all-cause mortality, net clinical benefit (NCB) and ultimate NCB (UNCB) were assessed.**

**RESULTS: Of the total cohort (mean age 66.1 ± 14.1 years, 56.1% female), CHA2DS2VASc improved the net reclassification index of observed 5-year composite thromboembolic endpoint by 6.9% ($p$<0.05). CHA2DS2VASc reclassified 9.7% low risk patients as high risk. Among reclassified-high-risk category (patients with a CHA2DS2VASc score of ≥1 and CHADS2 score of 0), major bleeding for that prescribed warfarin was 3% and higher than the rate of thromboembolism among those off-warfarin. NCB (-0.035) and UNCB (-0.021) were negative. Death and hospitalization at 1 year were significantly higher for on-warfarin group.**

**CONCLUSIONS: Clinical outcomes, net clinical benefit indices are negative; rates of death and hospitalization were significantly higher for OAC in reclassified category. This emphasizes the importance of greater attention to balancing the risks and benefits of OAC in patients with low risk by CHADS2 and reclassified as high-risk by CHA2DS2VASc.**

*Key Words:*
Anticoagulation, Atrial fibrillation, CHADS2, CHA2DS-2VASc.

## Introduction

Atrial fibrillation (AF), the most common sustained clinical arrhythmia, is associated with a five-fold increased risk of stroke[1-3]. Thromboembolic strokes due to AF are more disabling and fatal, and recurrences are more frequent than other causes of stroke[2,4]. Oral anticoagulants (OAC), such as warfarin, have been shown to be superior to placebo for primary and secondary prevention among patients at moderate-to-high risk of stroke when prescribed according to a calculated stroke risk[4-7]. However, warfarin is associated with a risk of bleeding, which must be considered in the management of patients with AF[8]. Moreover, there is clinical uncertainty regarding the on-warfarin and off-warfarin effects among patients with AF according to the level of stroke risk.

There is a gap in the knowledge base concerning the risks of off-warfarin thromboembolism and on-warfarin major bleeding among patients who have a low risk of stroke. Stroke risk stratification schemes, such as $CHA_2DS_2VASc$ [Cardiac


*Corresponding Author:* Sercan Okutucu, MD; e-mail: Sercanokutucu@yahoo.com

failure, Hypertension, Age≥75 (doubled), Diabetes, Stroke (doubled) – Vascular disease, Age 65–74 and Sex category (female)] and previously $CHADS_2$ [Cardiac failure, Hypertension, Age ≥75, Diabetes, Stroke (doubled)] classify patients to different risk groups[9,10]. Recent guidelines[11,12] have relegated the role of acetylsalicylic acid for the management of AF and, consequently, patients of intermediate risk ($CHADS_2$ or $CHA_2DS_2VASc$ score =1), which constitutes a large proportion of patients with AF; typically, either receive an OAC or no anticoagulant.

The selection of low or intermediate risk patients for OAC or no anticoagulant is not straightforward[2]. The initial $CHADS_2$ risk score was a pragmatic tool. Yet, it failed to identify all patients who were at low risk of stroke and systemic embolism[12]. By contrast, the $CHA_2DS_2VASc$ risk score more readily predicts stroke among lower risk patients with AF who may not justify the use of an OAC and is, therefore, recommended for accurate identification of patients who do not need anticoagulation[12]. Even so, the $CHA_2DS_2VASc$ risk score overestimates the risk of stroke among intermediate risk patients[13,14]. The implications of imprecise stroke risk prediction are huge – overestimation of risk may be associated with medical harm through inappropriate anticoagulation and underestimation associated with thromboembolic events associated with failure to prescribe an OAC.

There are only a few large population-based or whole-country studies concerning off-warfarin thromboembolism and on-warfarin major hemorrhage according to the $CHADS_2$ and current $CHA_2DS_2VASc$ scores for patients with non-valvular AF[15,16]. We have established the first whole-country TuRkish Atrial Fibrillation (TRAF) cohort of individual patient data from a systematic health insurance database which covers nearly all 50,364,653 inhabitants over the age of 18 in the country[3]. Herein, we aimed (i) to compare former $CHADS_2$ and current $CHA_2DS_2VASc$ risk score model performance, and (ii) to report the rates of off-warfarin thromboembolism and on-warfarin major bleeding, mortality and stroke for reclassified-high risk category (patients with a $CHA_2DS_2VASc$ score of ≥1 and $CHADS_2$ score of 0).

## Patients and Methods

### Data Source

Data for the TRAF cohort were obtained from the Turkish claims and utilization management system, MEDULA, which processes claims for all health insurance funds in Turkey. Covering close to 100% of the population, MEDULA is comprised of pharmacy, inpatient, outpatient and laboratory claims and across 23 500 pharmacies, 20,000 general practitioners, 850 government hospitals, 60 university hospitals and 500 private hospitals[3]. Medical data entered into the MEDULA database by physicians include patient demographics, prescription details, observed clinical events, outpatient clinics, inpatient hospitalizations and major clinical outcomes. For each hospitalization, the dates of admission and discharge, main diagnoses and major outcomes are recorded. The MEDULA system links to the Turkish national death database, whereby information concerning the date and cause of death are available. The TRAF cohort is formed from extracted anonymized patient-level data. Current study complies with the Declaration of Helsinki. The study was approved by the Research Ethics Committee. All necessary permissions were obtained from the Social Security Institution of Turkey.

### Study Population

We included all individuals with a diagnosis of AF (n=545,008) who were aged over 18 years between 1 January 2008 and 31 December 2012 and who survived the first 30 days following their diagnosis of AF (Figure 1). We excluded those patients who died very early after a diagnosis of AF presumably because their death would be unlikely to be associated with AF. We used International Classification of Diseases (ICD) -10 code I48 (paroxysmal, persistent, or permanent AF) to identify AF. We defined patients as having non-valvular AF according to international guidelines by excluding those who had mitral stenosis

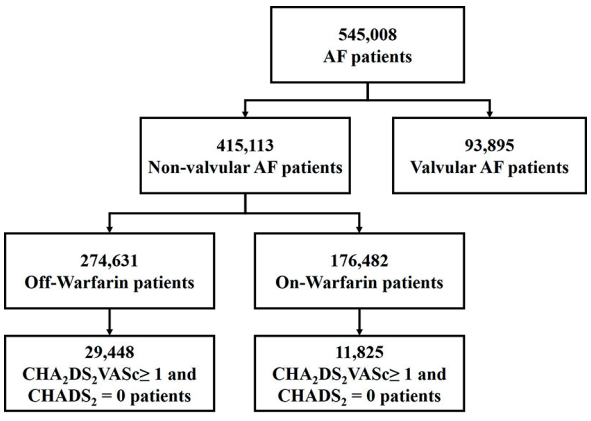


**Figure 1.** Data flow for patients included in the analysis.

**Table I.** Baseline characteristics of the analytical cohort of patients with AF stratified by use of Warfarin.

| | All (n = 451,113) | On warfarin (n = 176,482) | Off warfarin (n = 274,631) | *p*-value |
|---|---|---|---|---|
| Follow-up (months) Median (IQR) | 20 (8-52) | 18 (8-52) | 20 (10-50) | 0.09 |
| Mean (SD) age, years | 66.08 (±14.14) | 65.99 (±12.19) | 66.14 (±15.27) | 0.32 |
| Mean (SD) $CHADS_2$ score | 2.16 (±0.002) | 2.33 (±0.003) | 2.05 (±0.003) | < 0.001 |
| Mean (SD) $CHA_2DS_2VASc$ score | 3.96 (±0.003) | 4.20 (±0.004) | 3.79 (±0.004) | 0.89 |
| Chronic obstructive pulmonary disease (%) | 28.6 (N=129,051) | 28.5 (N=50,262) | 28.7 (N=78,789) | 0.56 |
| Chronic kidney disease (%) | 6.1 (N=27,559) | 5.9 (N=10,467) | 6.2 (N=17,092) | 0.85 |
| Peripheral vascular disease (%) | 6.55 (N=29,573) | 8.4 (N=14,902) | 5.3 (N=14,671) | < 0.001 |
| Heart failure (%) | 41.7 (N=187,922) | 49.3 (N=86,945) | 36.8 (N=100,977) | < 0.001 |
| Coronary artery disease (MI & Ischemic Heart Disease) (%) | 65.1 (N=293,636) | 72.7 (N=128,263) | 60.2 (N=165,373) | < 0.001 |
| Diabetes mellitus (%) | 19.8 (N=89,349) | 21.2 (N=37,331) | 18.9 (N=52,018) | 0.03 |
| Hypertension (%) | 77.6 (N=349,993) | 82.6 (N=145,837) | 74.3 (N=204,156) | < 0.001 |
| Previous stroke /TIA (%) | 5.8 (N= 26,195) | 7.7 (N= 13,537) | 4.6 (N=12,658) | < 0.001 |
| Previous systemic embolism (%) | 1.3 (N=5,723) | 2.1 (N=3,688) | 0.7 (N=2,035) | < 0.001 |
| Thyrotoxicosis (%) | 6.5 (N=29,470) | 6.4 (N=11,331) | 6.6 (N=18,139) | 0.36 |
| Previous major bleeding (%) | 0.4 (N=7,601) | 0.3 (N=4,375) | 0.4 (N=3,226) | 0.12 |

or a history of valve surgery. We defined lone AF as those patients with non-valvular AF who had no comorbidity. For the analytical cohort, we identified 451,113 patients with a diagnosis of non-valvular AF during the 5-year study period. We used the Anatomical Therapeutic Chemical Classification System with Defined Daily Doses (ATC/DDD) Index of drug codes to identify warfarin (B01AA03) prescriptions. During the study period, warfarin was the only OAC available for AF. The ICD-10 codes used for the diagnostic, co-morbidity and clinical endpoint categorizes are listed in **Supplementary Table I**.

### Clinical Endpoints

We defined two composite endpoints, thromboembolism [which included ischemic stroke, unspecified stroke, transient ischemic attack (TIA) and systemic embolism], and International Society on Thrombosis and Haemostasis (ISTH) major bleeding. ISTH major bleeding was defined as (i) fatal bleeding and/or, (ii) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome and/or (iii) bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more; or leading to transfusion of two or more units of whole blood or red cells. (which included intracranial bleeding and any severe bleeding)[17]. We also reported, separately, rates and risks of ischemic stroke, and all-cause mortality at 1 year. We analyzed pre-defined 2 parameters, namely, net clinical benefit (NCB) and ultimate net clinical benefit (UNCB) of warfarin therapy in AF. The following equations illustrates this definition:

**NCB =** (Composite thromboembolism rate off warfarin – composite thromboembolism rate on warfarin) – Weight × (Major bleeding rate on warfarin – bleeding rate off warfarin).

**UNCB =** (Mortality rate off warfarin – mortality rate on warfarin) – Weight × (Major bleeding rate on warfarin – bleeding rate off warfarin).

The weighting factor reflects the relative impact, in terms of death and disability, of intracranial hemorrhage (including intracerebral, subdural, subarachnoid, and other bleedings) while receiving warfarin *vs.* experiencing ultimate endpoint while not receiving warfarin[18,19].

### Ischemic Stroke Risk Scores

For each patient, we calculated their risk of ischemic stroke according to the $CHADS_2$ score and the $CHA_2DS_2VASc$ score[2,20]. The risks of stroke were then categorized according to scores of 0: low, 1: intermediate, and ≥2: high risk. The components of the $CHADS_2$ score were defined using ICD codes for heart failure, hypertension, diabetes mellitus, previous ischemic stroke, unspecified stroke, TIA or systemic embolism and age at data entry. Components of the $CHA_2DS_2VASc$ score were, in addition to these factors used for definition of the $CHADS_2$ score, vascular disease (prior myocardial infarction, peripheral arterial disease) and gender.

### Statistical Analysis

We estimated the risk of time to clinical endpoint using Cox proportional hazards regression, represented as hazard ratios (HR) with 95% confidence intervals (CI). To the components of the $CHADS_2$ and $CHA_2DS_2VASc$ stroke risk scores, we included in the models, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD) and hyperthyroidism/thyrotoxicosis – determined by a statistical significance level of 5% and clinical consensus. Age was included, using categories 19 to 64 years, 65 to 74 years and ≥75 years. Finally, the importance of age and sex was quantified by creating the categories male <65 years (as the reference), female <65 years, female >65 years and male >65 years. Data are demonstrated as mean ± standard deviation (SD) for normally distributed continuous variables, median (interquartile range, IQR) for skew-distributed continuous variables, and frequencies for categorical variables.

The Hosmer-Lemeshow goodness of fit test (HLT) was used to assess the calibration of the models – whether the observed mortality rates matched the expected mortality rates in subgroups of 100 patients. A high HLT $\chi^2$ value and *p*-value <0.05 suggest a significant disagreement between observed and expected rates and therefore a poor model fit[21]. McFadden's pseudo $R^2$ was used to quantify the proportion of the variation in the data explained by the linear expression for the mean part of the model. A pseudo $R^2$ <0.2 suggests a poor model fit, 0.2 to 0.4 a fair model fit and >0.4 a good model fit[22]. The Brier score was used to measure the average squared deviation between the predicted probabilities of composite thromboembolism and the observed thromboembolism rates – the accuracy of the probability assessment. A Brier score of 1 suggests no accuracy, a score of 0 suggests perfect accuracy, and a score of 0.25 suggests half the predicted events are correct and the other half not[23]. The C-statistic was used to evaluate the discriminative performance of the models. A C-statistic close to 1 suggests near-perfect discrimination and close to 0.5 almost no discrimination[23]. The increased discriminative value of $CHA_2DS_2VASc$ over $CHADS_2$ was examined with the net reclassification index (NRI) and the integrated discrimination improvement (IDI)[23]. The NRI was used to quantify the proportion of patients moving up or down the 5-year thromboembolic joint endpoint risk categories of <5% (low), 5% to <10% (intermediate), and ≥10% (high) between the two models. These cut-points were based on formal decision analysis[24]. The IDI considers the change in the estimated prediction probabilities as a continuous rather than pre-specified categorical variable. Both schemes were divided into low, moderate and high predicted risk categories. All analyses were conducted using Stata Version 11.0 (StataCorp, College Station, TX, USA).

## Results

Among the analytical cohort consisting 451,113 patients, (mean age 66.1 ± 14.1 years, 56.1% female) 77.6% had hypertension, 41.7% heart failure, 19.8% diabetes and 5.8% a history of stroke or TIA. The analytical cohort represented 2,083,091 patient-years of follow up, with a median time to censorship of 20 (IQR, 8 to 52) months and no significant difference in median follow-up between on- and off-warfarin groups [18 (8 to 52) *vs.* 20 (10 to 50) months, $p$=0.09]. In total, 274,631 (60.9%) had never been prescribed warfarin. Mode of the scores for $CHA_2DS_2VASc$ (4 *vs.* 5) and $CHADS_2$ (2 *vs.* 3) were lower in the off-warfarin group compared with those on-warfarin. Patients who were prescribed warfarin more frequently had a history of peripheral vascular disease, heart failure, coronary artery disease, diabetes, hypertension, stroke, systemic embolism, and less frequently because of a previous hemorrhage (Table I).

### Risk Factors for Ischemic Stroke

On multivariable analysis, for patients who were off-warfarin the risk of thromboembolic endpoints increased with age (65 to 74 years: HR 3.16, 95% CI 2.98 to 3.35; ≥75 years: 4.28, 4.05 to 4.52, for the thromboembolic composite endpoint) (Table II). Significant independent associations were evident for prior ischemic stroke (HR 2.45, 2.33 to 2.58), systemic embolism (HR 1.88, 1.64 to 2.15), hypertension (HR 1.42,1.35 to 1.49), diabetes (HR 1.19, 1.14 to 1,24), females (HR 1.11, 1.07 to 1.15), heart failure (HR 1.36, 1.31 to 1.40) and hyperthyroidism/thyrotoxicosis (HR 1.12, 1.05 to 1.19). However, peripheral vascular disease, coronary artery disease, CKD and COPD were not significant risk factors for thromboembolism. Females aged <65 years had a lower risk of thromboembolism than males <65 years (HR 0.83, 95% CI 0.75 to 0.92), though there was a significant increase in thromboembolic risk by age for females (females >65 years: 3.67, 3.40 to 3.95).

**Table II.** Associations between baseline factors and stroke and systemic embolism in patients without anticoagulant treatment (N = 274,631).

| | Ischemic Stroke or Embolism | | | | | | | | Ischemic Stroke | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Univariable | | | | Multivariable | | | | Univariable | | | | Multivariable | | | |
| | Sig. | HR | 95,0% CI for HR | | Sig. | HR | 95,0% CI for HR | | Sig. | HR | 95,0% CI for HR | | Sig. | HR | 95,0% CI for HR | |
| | | | Lower | Upper | | | Lower | Upper | | | Lower | Upper | | | Lower | Upper |
| **COPD** | 0.00 | 1.46 | 1.41 | 1.51 | 0.98 | 1.00 | 0.96 | 1.04 | 0.00 | 1.46 | 1.41 | 1.52 | 0.84 | 1.00 | 0.96 | 1.04 |
| **Embolism** | 0.00 | 2.44 | 2.13 | 2.79 | 0.00 | **1.88** | 1.64 | 2.15 | 0.00 | 1.90 | 1.63 | 2.22 | 0.00 | **1.45** | 1.24 | 1.70 |
| **Chronic Renal Failure** | 0.00 | 1.47 | 1.38 | 1.56 | 0.61 | 1.02 | 0.96 | 1.08 | 0.00 | 1.40 | 1.32 | 1.50 | 0.41 | 0.97 | 0.91 | 1.04 |
| **Peripheral Arterial Disease** | 0.00 | 1.66 | 1.56 | 1.77 | 0.00 | 1.11 | 0.97 | 1.23 | 0.00 | 1.48 | 1.38 | 1.59 | 0.00 | 1.06 | 0.95 | 1.21 |
| **CHF** | 0.00 | 2.08 | 2.01 | 2.15 | 0.00 | **1.36** | 1.31 | 1.40 | 0.00 | 2.11 | 2.03 | 2.18 | 0.00 | **1.36** | 1.31 | 1.41 |
| **Ischemic Heart Disease** | 0.00 | 1.25 | 1.21 | 1.29 | 0.15 | 1.03 | 0.99 | 1.07 | 0.00 | 1.22 | 1.18 | 1.27 | 0.77 | 1.01 | 0.97 | 1.04 |
| **Myocardial Infarction** | 0.00 | 1.24 | 1.17 | 1.32 | 0.11 | 1.05 | 0.99 | 1.12 | 0.00 | 1.25 | 1.17 | 1.33 | 0.07 | 1.06 | 1.00 | 1.13 |
| **Diabetes** | 0.00 | 1.40 | 1.34 | 1.45 | 0.00 | **1.19** | 1.14 | 1.24 | 0.00 | 1.38 | 1.32 | 1.44 | 0.00 | 1.17 | 1.12 | 1.22 |
| **Hypertension** | 0.00 | 2.10 | 2.00 | 2.20 | 0.00 | **1.42** | 1.35 | 1.49 | 0.00 | 2.15 | 2.04 | 2.25 | 0.00 | **1.44** | 1.37 | 1.52 |
| **Ischemic Stroke** | 0.00 | 3.40 | 3.23 | 3.58 | 0.00 | **2.45** | 2.33 | 2.58 | 0.00 | 3.50 | 3.32 | 3.68 | 0.00 | **2.51** | 2.38 | 2.65 |
| **Thyroid Disease** | 0.00 | 1.16 | 1.09 | 1.24 | 0.00 | **1.12** | 1.05 | 1.19 | 0.00 | 1.17 | 1.09 | 1.25 | 0.00 | **1.12** | 1.04 | 1.19 |
| **Age <= 64*** | 0.00 | ~ | ~ | ~ | 0.00 | ~ | ~ | ~ | 0.00 | ~ | ~ | ~ | 0.00 | ~ | ~ | ~ |
| **Age >= 65 & Age <= 74** | 0.00 | 3.86 | 3.65 | 4.09 | 0.00 | **3.16** | 2.98 | 3.35 | 0.00 | 4.12 | 3.88 | 4.38 | 0.00 | **3.36** | 3.16 | 3.58 |
| **Age >= 75** | 0.00 | 5.55 | 5.26 | 5.85 | 0.00 | **4.28** | 4.05 | 4.52 | 0.00 | 5.99 | 5.66 | 6.33 | 0.00 | **4.58** | 4.32 | 4.86 |
| **Gender = F^** | 0.00 | 1.19 | 1.15 | 1.23 | 0.00 | **1.11** | 1.07 | 1.15 | 0.00 | 1.22 | 1.18 | 1.26 | 0.00 | **1.13** | 1.09 | 1.17 |
| **Gender = F & Age >= 65** | 0.00 | 5.62 | 5.23 | 6.04 | 0.00 | **4.36** | 4.06 | 4.70 | 0.00 | 5.92 | 5.49 | 6.38 | 0.00 | **4.56** | 4.23 | 4.93 |

$p<0.05$. *age range 19 to 64 years. ^females <65 years.

### Risk Score Performance

The CHADS2 and $CHA_2DS_2VASc$ risk scores discriminated thromboembolic endpoints equally well (C-statistics both 0.73), and both had good accuracy (Brier scores both 0.04). However, model fits were equally poor (HLT both $p<0.001$, pseudo R2 both <10%). For $CHA_2DS_2VASc$ compared with $CHADS_2$, the net reclassification index was 6.9% ($p<0.05$) and integrated discrimination improvement was 3.7% ($p<0.05$) for the off-warfarin group.

When we used the thromboembolic risk cut points derived from formal decision analysis, according to the $CHADS_2$ score there were 40,661 (14.8%), 70,916 (25.8%) and 163,054 (59.4%) patients classified as low, intermediate and high risk, respectively. According to the $CHA_2DS_2VASc$ score, there were 11,213 (4.1%), 27,563 (10.0%) and 235,855 (85.9%) patients classified as low, intermediate and high risk, respectively. The $CHADS_2$ risk scheme reclassified 4,410 (32.6%) high risk patients as low risk, and 16,320 (6.2%) low risk patients as high risk **(Supplementary Table II)**. Equally, the $CHA_2DS_2VASc$ risk scheme reclassified 4,321 (32.0%) high risk patients as low risk, and 25,234 (9.7%) low risk patients as high risk. Among patients off-warfarin, the rates of thromboembolic and ischemic stroke increased with increasing $CHADS_2$ and $CHA_2DS_2VASc$ scores (Table III). Notably, for patients who did not receive warfarin, the rates of thromboembolism were low for those who were classified as low risk according to $CHADS_2$ and low to intermediate risk by $CHA_2DS_2VASc$ (0.34, 0.55 and 0.68, respectively).

### Clinical Endpoints

There were 29,448 off-warfarin patients and 11,825 on-warfarin patients who had a $CHADS_2$ score of 0 and a $CHA_2DS_2VASc$ score ≥1. For this group, the mean value of $CHA_2DS_2VASc$ score was 1.32 (± 0.003) for those off-warfarin and 1.49 (± 0.006) for those on-warfarin. In this reclassified-high risk category compared with the off-warfarin subgroup, patients in the on-warfarin subgroup were older (55.5 ± 12.6 *vs.* 48.9±15.4 years, $p<0.005$), and more frequently had CKD (3.1% *vs.* 1.2%), COPD 16.7 % *vs.* 7.4%), male gender (38.7% *vs.* 31.8%).-

Among reclassified-high risk category, in the off-warfarin subgroup, 290 patients (0.98%) had a thromboembolic endpoint and 179 (0.61%) had a major hemorrhage, whereas in the on-warfarin subgroup, 354 patients (3.0%) had a major hemorrhage and 112 patients (0.94%) had a thromboembolic endpoint. At 1 year, mortality and hospitalization rates were 4.1% (1222) and 2.0% (575 patients) for the off-warfarin subgroup and 2.7% (318 patients) and 13.5% (1591 patients) for the on-warfarin subgroup ($p<0.005$ for both parameters).

In reclassified high-risk category, NCB (-0.035) and UNCB (-0.021) were negative and there was harm with oral anticoagulation in this category. In remaining patients with OAC indication ($CHADS_2 > 1$ and $CHA_2DS_2VASc$ score >1 for man and $CHA_2DS_2VASc$ score >2 for woman), treatment was beneficial and NCB (0.004) and UNCB (0.039) were higher than reclassified high-risk category ($p<0.001$ for both parameters).

## Discussion

The main findings of the present study are as follows: (i) in reclassified-high risk category (patients with a $CHA_2DS_2VASc$ score of ≥1 and $CHADS_2$ score of 0), the rate of major hemorrhage for those prescribed warfarin was significant and much higher than the rate of thromboembolism among those who did not receive warfarin, (ii) NCB (-0.035) and UNCB (-0.021) were negative and there was harm with oral anticoagulation in this category, (iii) rates of death and hospitalization at 1 year were significantly higher for on-warfarin group.

Stroke risk stratification schemes, such as $CHA_2DS_2VASc$ and previously $CHADS_2$ classify patients to different risk groups[9,10,25-27]. Among these 2 scores, $CHA_2DS_2VASc$ significantly reclassified about 7% of patients, there was evidence for movement of large numbers of patients up and down risk cut-offs for both risk scores. Each risk score defined approximately one-third of high risk as low risk. We found the risk scores, endorsed by international guidelines, had similar discriminatory performance and equally poor goodness of fit when assessed according to a variety of indices. The uncertainty around the estimation of outcomes among the reclassified-high risk category (with a $CHA_2DS_2VASc$ ≥1 and $CHADS_2 = 0$) resulted with one-fifth of patients with non-valvular AF being prescribed warfarin of whom 3.0% had a major hemorrhage and 0.9% of the remaining off-warfarin group having a thromboembolic event at a median follow-up of about one and a half years. Even though the $CHA_2DS_2VASc$ score is superior at identifying patients at a lower risk

of thromboembolism[10], $CHA_2DS_2VASc$ score can overestimate the risk of the low risk patients assessed by $CHADS_2$. Importantly, the decision to not prescribe an OAC resulted in a lower than expected stroke rate (0.9% composite thromboembolic event rate at median 20 months in TRAF *vs.* 1.3%-year stroke rate for $CHA_2DS_2VASc \geq 1$)[28].

There are many studies favoring the use of the $CHA_2DS_2VASc$ to identify patients at low risk of stroke[29-34]. Recent data and current guidelines suggest OAC to prevent thromboembolism in male AF patients with a CHA2DS2-VASc score of 1 and in female AF patients with a CHA2DS2-VASc score[1,35]. We found that not all of the factors used in the $CHA_2DS_2VASc$ score carried equal risk. The strongest predictors were age, followed by previous stroke, previous systemic emboli, hypertension, heart failure, diabetes, hyperthyroidism/thyrotoxicosis, and female; whereas peripheral vascular disease (as well as chronic kidney disease, and COPD) were not significant independent predictors. The lack of association between stroke and coronary artery or peripheral artery disease is consistent with the conclusions from the ATRIA study[36] and ROCKET AF subgroup analysis[37]. However, our finding of no association between stroke and renal failure was inconsistent with some[36,38], but not all studies[20].

Uncertainty around the optimal method to estimate stroke risk in low-to-intermediate risk patients with non-valvular AF is not new. Many studies have debated the strengths and weaknesses of the $CHADS_2$ and $CHA_2DS_2VASc$ scores. For example, data from the ATRIA study[36] suggest that the categorized $CHADS_2$ score is a better predictor of composite thromboembolism than categorized $CHA_2DS_2VASc$, whereas other studies support the use of the $CHA_2DS_2VASc$ score[29,34,39]. This, in the context of the findings from our study, suggests that the recommendation for an OAC among reclassified-high risk category ($CHA_2DS_2VASc \geq 1$ and $CHADS_2 = 0$) patients with non-valvular AF, is based upon a careful discussion about the pros and cons of an OAC with the patient until an optimal score is devised. International guidelines recommend the use of the $CHADS_2$ score to rule in warfarin for patients with a score of 2, and the $CHA_2DS_2VASc$ score as a more detailed risk

**Table III.** Stroke or thromboembolism at risk in relation to $CHADS_2$ and $CHA_2DS_2$-VASc scores in 274,631 patients without warfarin throughout follow-up.

| $CHADS_2$ classification | | | Ischemic stroke | | | Ischemic Stroke/TIA/Systemic Embolism | | |
|---|---|---|---|---|---|---|---|---|
| Score | Risk categories | % | n | Total population | % | n | Total population | % |
| **0** | Low | 14.81 | 277 | 40661 | 0.68 | 336 | 40661 | 0.83 |
| **1** | Intermediate | 25.82 | 1342 | 70916 | 1.89 | 1500 | 70916 | 2.12 |
| **2** | | | 2486 | 66787 | 3.72 | 2710 | 66787 | 4.06 |
| **3** | | | 2821 | 51211 | 5.51 | 2996 | 51211 | 5.85 |
| **4** | High | 59.37 | 2739 | 25198 | 10.87 | 2831 | 25198 | 11.24 |
| **5** | | | 2441 | 16093 | 15.17 | 2507 | 16093 | 15.58 |
| **6** | | | 587 | 3765 | 15.59 | 609 | 3765 | 16.18 |
| **$CHA_2DS_2VASc$ classification** | | | **Ischemic stroke** | | | **Ischemic Stroke/TIA/Systemic Embolism** | | |
| Score | Risk categories | % | n | Total population | % | n | Total population | % |
| **0** | Low | 4.08 | 38 | 11213 | 0.34 | 46 | 11213 | 0.41 |
| **1** | Intermediate | 10.04 | 151 | 27563 | 0.55 | 188 | 27563 | 0.68 |
| **2** | | | 539 | 38413 | 1.40 | 620 | 38413 | 1.61 |
| **3** | | | 1220 | 47202 | 2.58 | 1353 | 47202 | 2.87 |
| **4** | | | 2049 | 49215 | 4.16 | 2204 | 49215 | 4.48 |
| **5** | High | 85.88 | 2471 | 44171 | 5.59 | 2625 | 44171 | 5.94 |
| **6** | | | 2503 | 30306 | 8.26 | 2609 | 30306 | 8.61 |
| **7** | | | 2114 | 16503 | 12.81 | 2185 | 16503 | 13.24 |
| **8** | | | 1302 | 8108 | 16.06 | 1343 | 8108 | 16.56 |
| **9** | | | 306 | 1937 | 15.80 | 316 | 1937 | 16.31 |
| **Total** | | | **12693** | **274631** | **4.62** | **13489** | **274631** | **4.91** |

factor approach for those with a $CHADS_2$ score of 1 or 2[2]. Results from our study emphasize the need for comprehensive risk factor review which includes that of a patient's bleeding risk.

### Strengths and Limitations of the Study

The TRAF registry is the largest whole country database of patients with AF that has complete ascertainment for stroke, embolic and hemorrhagic outcomes. Up to the time of identification of the sampling frame, the only OAC in use in Turkey was warfarin – thereby allowing an informative analysis of the impact of its use by stroke risk score in consecutive patients with non-valvular AF. Our data was linked to healthcare utilization, prescribing and outcomes data which enabled the accurate estimation of on- and off-warfarin risk of thromboembolic and hemorrhagic events in a large and generalizable subset of patients. However, our study has limitations. Owing to its design there will be systematic bias such as that from the erroneous recall of a patient's history, prescription recording inaccuracies, misclassification of endpoints and under-reporting of events which did not reach the attention of medical services. Specifically, we were not able to validate the justification for ineligibility to receive care as this information was not sensitive enough – so for some patients it may have been appropriate to withhold specific interventions. We were only able to identify death from all-causes and the assumption was that deaths not related to AF or its thromboprophylaxis management were equally balanced between groups. Baseline risk was assessed, and outcomes were noted during the 5-year study period. However, risk does not remain static. There was no data regarding time in therapeutic range which estimates the percentage of time a patient's INR is within the desired treatment range and is widely used as an indicator of anticoagulation control. Information about antiplatelet medication using status was absent. Finally, we did not consider novel oral anticoagulants, which have lower risks of hemorrhage, and therefore may have reduced the on-OAC rates of harm to favor of the use of the $CHA_2DS_2VASc$ score.

## Conclusions

Imprecision of stroke risk assessment among patients with a reclassified-high risk category resulted in the prescription of warfarin to one-fifth of patients of whom 3% had a major hemorrhage and only 0.9% of those off-warfarin having a thromboembolic event at 20 months. There was harm with oral anticoagulation in this category, net clinical benefit indices are negative; rates of death and hospitalization at 1 year were significantly higher for on-warfarin group. Whilst newer OAC may help alleviate this problem, our results emphasize the importance of greater attention to balancing the risks and benefits of OAC therapy in low-to-intermediate risk patients with non-valvular AF.

**Competing Interests**

AJC has research grants and personal fees from Bayer Pharma AG (Wuppertal, Germany), Boehringer Ingelheim (Ingelheim am Rhein, Rheinland-Pfalz, Germany), Daiichi Sankyo (Tokyo, Japan), Bristol-Myers Squibb and Pfizer Alliance (New York, United States). AO has Medtronic proctorship fee and speaker honoraria from Daiichi Sankyo Daiichi Sankyo (Tokyo, Japan), Bayer Pharma AG (Wuppertal, Germany), Bristol-Myers Squibb and Pfizer Alliance (New York, USA). Other authors have no competing interests and nothing to declare.

## References

1) Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P and Group ESCSD. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016; 37: 2893-2962.
2) Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010; 31: 2369-2429.
3) Yavuz B, Ata N, Oto E, Katircioglu-Ozturk D, Aytemir K, Evranos B, Koselerli R, Ertugay E, Burkan A, Ertugay E, Gale CP, Camm AJ, Oto A. Demographics, treatment and outcomes of atrial fibrillation in a developing country: the population-based TuRkish Atrial Fibrillation (TRAF) cohort. Europace 2017; 19: 734-740.
4) Connolly SJ. Preventing stroke in patients with atrial fibrillation: current treatments and new concepts. Am Heart J 2003; 145: 418-423.
5) Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. Arch Int Med 1994; 154: 1449-1457.
6) Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients

with atrial fibrillation: a meta-analysis. Ann Int Med 1999; 131: 492-501.
7) Xian Y, Wu J, O'Brien EC, Fonarow GC, Olson DM, Schwamm LH, Bhatt DL, Smith EE, Suter RE, Hannah D, Lindholm B, Maisch L, Greiner MA, Lytle BL, Pencina MJ, Peterson ED and Hernandez AF. Real world effectiveness of warfarin among ischemic stroke patients with atrial fibrillation: observational analysis from Patient-Centered Research into Outcomes Stroke Patients Prefer and Effectiveness Research (PROSPER) study. BMJ 2015; 351: h3786.
8) Apostolakis S, Lane DA, Buller H and Lip GY. Comparison of the CHADS2, CHA2DS2-VASc and HAS-BLED scores for the prediction of clinically relevant bleeding in anticoagulated patients with atrial fibrillation: the AMADEUS trial. Thromb Haemost 2013; 110: 1074-1079.
9) Gage BF, van Walraven C, Pearce L, Hart RG, Koudstaal PJ, Boode BS and Petersen P. Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. Circulation 2004; 110: 2287-2292.
10) Lip GY, Nieuwlaat R, Pisters R, Lane DA and Crijns HJ. 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 2010; 137: 263-272.
11) January CT, Wann LS, Alpert JS, Calkins H, Cleveland JC, Jr., Cigarroa JE, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM and Yancy CW. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014; 64: e1-e76.
12) Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P and Guidelines ESCCfP. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J 2012; 33: 2719-2747.
13) Christophersen IE, Yin X, Larson MG, Lubitz SA, Magnani JW, McManus DD, Ellinor PT and Benjamin EJ. A comparison of the CHARGE-AF and the CHA2DS2-VASc risk scores for prediction of atrial fibrillation in the Framingham Heart Study. Am Heart J 2016; 178: 45-54.
14) Fox KAA, Lucas JE, Pieper KS, Bassand JP, Camm AJ, Fitzmaurice DA, Goldhaber SZ, Goto S, Haas S, Hacke W, Kayani G, Oto A, Mantovani LG, Misselwitz F, Piccini JP, Turpie AGG, Verheugt FWA, Kakkar AK and Investigators G-A. Improved risk stratification of patients with atrial fibrillation: an integrated GARFIELD-AF tool for the prediction of mortality, stroke and bleed in patients with and without anticoagulation. BMJ Open 2017; 7: e017157.
15) Melgaard L, Gorst-Rasmussen A, Lane DA, Rasmussen LH, Larsen TB and Lip GY. Assessment of the CHA2DS2-VASc score in predicting ischemic stroke, thromboembolism, and death in patients with heart failure with and without atrial fibrillation. JAMA 2015; 314: 1030-1038.
16) Chao TF, Lip GY, Liu CJ, Tuan TC, Chen SJ, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Chen TJ, Chiang CE and Chen SA. Validation of a modified CHA2DS2-VASc score for stroke risk stratification in Asian patients with atrial fibrillation: a nationwide cohort study. Stroke 2016; 47: 2462-2469.
17) Kaatz S, Ahmad D, Spyropoulos AC, Schulman S and Subcommittee on Control of A. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost 2015; 13: 2119-2126.
18) Glasziou PP and Irwig LM. An evidence based approach to individualising treatment. BMJ 1995; 311: 1356-1359.
19) Singer DE, Chang Y, Fang MC, Borowsky LH, Pomernacki NK, Udaltsova N and Go AS. The net clinical benefit of warfarin anticoagulation in atrial fibrillation. Ann Int Med 2009; 151: 297-305.
20) Friberg L, Rosenqvist M and Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish atrial fibrillation cohort study. Eur Heart J 2012; 33: 1500-1510.
21) Hosmer DW, Hosmer T, Le Cessie S, Lemeshow S. A comparison of goodness-of-fit tests for the logistic regression model. Stat Med 1997; 16: 965-980.
22) McFadden, DL. Conditional logit analysis of qualitative choice behaviour. In: Zarembka, P. ed. Frontiers of econometrics Newyork; 1974: 105-142.
23) Steyerberg EW, Vickers AJ, Cook NR, Gerds T, Gonen M, Obuchowski N, Pencina MJ, Kattan MW. Assessing the performance of prediction models: a framework for traditional and novel measures. Epidemiology 2010; 21: 128-138.
24) Eckman MH, Singer DE, Rosand J, Greenberg SM. Moving the tipping point: the decision to anticoagulate patients with atrial fibrillation. Circ Cardiovasc Qual Outcomes 2011; 4: 14-21.
25) Li TT, Gong X, Gao HQ, Wang ZH, Wang J, Zhang Y, Liu W, Tian HB. Derivation of a simple clinical model to categorize the probability of acute myocardial infarction in patients with atrial fibrillation. Eur Rev Med Pharmacol Sci 2019; 23: 5422-5431.
26) Zhang F, Yang XC, Jia XW, Tang XH, Wang Z, Wang ZQ. Von Willebrand factor and ADAMTS13 plasma in older patients with high CHA2DS2-VASc Score with and without atrial fibrillation. Eur Rev Med Pharmacol Sci 2017; 21: 4907-4912.
27) Sayin B, Okutucu S, Yilmaz MB, Ozdemir K, Aydinlar A, Sahin DY, Altun A, Acikel S, Okuyan E, Sucu M, Ongen Z, Ersanli MK, Yilmaz O, Demir M, Pekdemir H, Topsakal R, Sahiner ML, Aras D, Oto A. Antithrombotic treatment patterns and stroke prevention in patients with atrial fibrillation in TURKEY: inferences from GARFIELD-AF registry. Anatol J Cardiol 2019; 21: 272-280.
28) Lip GY, Frison L, Halperin JL, Lane DA. Identifying patients at high risk for stroke despite anticoagulation: a comparison of contemporary stroke risk

stratification schemes in an anticoagulated atrial fibrillation cohort. Stroke 2010; 41: 2731-2738.
29) Olesen JB, Torp-Pedersen C, Hansen ML, Lip GY. The value of the CHA2DS2-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a CHADS2 score 0-1: a nationwide cohort study. Thromb Haemost 2012; 107: 1172-1179.
30) Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, Selmer C, Ahlehoff O, Olsen AM, Gislason GH, Torp-Pedersen C. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ 2011; 342: d124.
31) Chao TF, Lin YJ, Tsao HM, Tsai CF, Lin WS, Chang SL, Lo LW, Hu YF, Tuan TC, Suenari K, Li CH, Hartono B, Chang HY, Ambrose K, Wu TJ, Chen SA. CHADS(2) and CHA(2)DS(2)-VASc scores in the prediction of clinical outcomes in patients with atrial fibrillation after catheter ablation. J Am Coll Cardiol 2011; 58: 2380-2385.
32) Potpara TS, Polovina MM, Licina MM, Marinkovic JM, Prostran MS, Lip GY. Reliable identification of "truly low" thromboembolic risk in patients initially diagnosed with "lone" atrial fibrillation: the Belgrade atrial fibrillation study. Circ Arrhythm Electrophysiol 2012; 5: 319-326.
33) Chao TF, Liu CJ, Chen SJ, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Wu TJ, Chen TJ, Tsao HM, Chen SA. Atrial fibrillation and the risk of ischemic stroke: does it still matter in patients with a CHA2DS2-VASc score of 0 or 1? Stroke 2012; 43: 2551-2555.
34) Chao TF, Liu CJ, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Chen TJ, Lip GY, Chen SA. Using the CHA2DS2-VASc score for refining stroke risk stratification in 'low-risk' Asian patients with atrial fibrillation. J Am Coll Cardiol 2014; 64: 1658-1665.
35) Chao TF, Liu CJ, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Chen TJ, Lip GY, Chen SA. Should atrial fibrillation patients with 1 additional risk factor of the CHA2DS2-VASc score (beyond sex) receive oral anticoagulation? J Am College Cardiol 2015; 65: 635-642.
36) Singer DE, Chang Y, Borowsky LH, Fang MC, Pomernacki NK, Udaltsova N, Reynolds K, Go AS. A new risk scheme to predict ischemic stroke and other thromboembolism in atrial fibrillation: the ATRIA study stroke risk score. J Am Heart Association 2013; 2: e000250.
37) Jones WS, Hellkamp AS, Halperin J, Piccini JP, Breithardt G, Singer DE, Fox KA, Hankey GJ, Mahaffey KW, Califf RM, Patel MR. Efficacy and safety of rivaroxaban compared with warfarin in patients with peripheral artery disease and non-valvular atrial fibrillation: insights from ROCKET AF. Eur Heart J 2013; 34 (Abstract Supplement): 809-810.
38) Schmitt J, Duray G, Gersh BJ, Hohnloser SH. Atrial fibrillation in acute myocardial infarction: a systematic review of the incidence, clinical features and prognostic implications. Eur Heart J 2009; 30: 1038-45.
39) Chao TF, Liu CJ, Tuan TC, Chen SJ, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Chen TJ, Chiang CE, Chen SA. Comparisons of CHADS and CHADS-VASc scores for stroke risk stratification in atrial fibrillation: Which scoring system should be used for Asians? Heart Rhythm 2016; 13: 46-53.