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# Stroke prediction with an adjusted R-$CHA_2DS_2VASc$ score in a cohort of patients with a Myocardial Infarction

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ABSTRACT

*Introduction:* A new risk stratification scheme incorporating the original $CHADS_2$ score and renal function, entitled R(2)CHADS(2), was validated in the ROCKET-AF and ATRIA study cohorts.
*Aims:* Adjusting and validating a modified R-$CHA_2DS_2VASc$ score as a predictor of ischaemic stroke and all-cause mortality in patients discharged following admission for a Myocardial Infarction (MI).
*Materials and Methods:* Observational retrospective single-centre cohort study including 1711 patients admitted with MI and discharged alive. We tested the prognostic performance of R-$CHA_2DS_2VASc$, based on the original $CHA_2DS_2VASc$ score with few modifications (addition of renal function parameters [glomerular filtration rate and urea], performance of a revascularization procedure and history of atrial fibrillation). R-$CHA_2DS_2VASc$ was evaluated for its discriminative performance and calibration in the prediction of ischaemic stroke (primary endpoint), all-cause mortality and a composite endpoint of ischemic stroke plus all-cause mortality (secondary outcomes) during follow-up.
*Results:* R-$CHA_2DS_2VASc$ score's areas under the curve (AUC) for the occurrence of primary and secondary outcomes were: Ischaemic stroke: AUC 0.717 ± 0.031, $p < 0.001$ (vs. 0.681 ± 0.043 for $CHA_2DS_2VASc$, $p = 0.290$); all-cause mortality during follow-up: AUC 0.811 ± 0.014, $p < 0.001$ (vs. 0.782 ± 0.019 for GRACE, $p = 0.245$); composite endpoint: AUC 0.803 ± 0.014, $p < 0.001$. The integrated discrimination improvement index (IDI) and relative IDI for the primary endpoint were 0.015 and 28.2%, respectively, while the IDI and relative IDI for all-cause mortality were 0.13 and 72.1%, suggesting a large improvement in risk stratification. An R-$CHA_2DS_2VASc$ score below 3 had a negative predictive value of 98.6% for the occurrence of ischaemic stroke.
*Conclusions:* The modified R-$CHA_2DS_2VASc$ score has shown good calibration and high discriminative performance in the prediction of post-discharge ischaemic stroke and all-cause mortality. The inclusion of renal function in thromboembolic risk predicting schemes seems warranted.



## Introduction

According to the World Health Organization, cardiovascular disease is the major cause of death in the world. Ischaemic heart disease and cerebrovascular events account for almost one quarter of all deaths and, despite the tremendous worldwide improvements in health care, physicians still struggle to improve the management of patients with coronary artery and cerebrovascular disease.

Myocardial Infarction (MI) is often a fatal condition. Patients surviving hospitalization are still at high risk for reinfarction, heart failure, sudden cardiac death and stroke. The latter may occur due to a multitude of reasons, including atherosclerotic disease in the carotid territory and intra-cranial arteries and thromboembolic events, of which a significant percentage is cardioembolic.

Identifying those patients at high risk for stroke is as important as the identification of patients at higher risk for reinfarction and sudden cardiac death. The $CHADS_2$ [1] or $CHA_2DS_2$-VASc [2] scores have been developed to estimate overall stroke risk in patients with atrial fibrillation (AF) and identify patients benefiting from antithrombotic therapies. Although a model specifically developed for the prediction of stroke following discharge for a MI has never been developed to this date, the $CHADS_2$ algorithm has been shown to predict all-cause mortality and stroke risk in patients with a MI irrespective of the presence of AF [3]. Furthermore, $CHADS_2$ may also help predict ischemic stroke or transient ischaemic attack in subjects with stable coronary artery disease (CAD) and no baseline AF [4], and in patients without history of AF submitted to angiography for suspicion of CAD

*Abbreviations:* ACCU, Acute Cardiac Care Unit; AF, Atrial Fibrillation; AUC, Area Under the Curve; BUN, Blood Urea Nitrogen; CAD, Coronary Artery Disease; CT, Computed Tomography; GFR, Glomerular Filtration Rate; IDI, Integrated Discrimination Improvement (Index); MDRD, Modified Diet in Renal Disease; MI, Myocardial Infarction; ROC, Receiver Operating Characteristic.

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[5]. The documentation of a strong association between impaired renal function and stroke or systemic embolism [6] led to the validation of a new risk stratification scheme incorporating the original $CHADS_2$ score and renal function, entitled R(2)CHADS(2), in the ROCKET-AF and ATRIA study cohorts [7].

*Aims*

This study aims at adjusting and validating a modified R-$CHA_2DS_2$VASc score as a predictor of ischaemic stroke and all-cause mortality in patients with a MI. Based on the original $CHA_2DS_2$VASc model and following the suggestion of Piccini JP et al of adding renal function to the algorithm [7], the new R-$CHA_2DS_2$VASc score will be adjusted to this clinical context, tested for its overall predictive performance and compared to the original $CHA_2DS_2$VASc and GRACE scores in the prediction of ischaemic stroke and all-cause mortality, respectively.

## Materials and Methods

*Study design*

Observational retrospective single-centre cohort study including all patients admitted to our hospital's Acute Cardiac Care Unit (ACCU) diagnosed with MI between December 1, 2006 and September 30, 2011. Using collected baseline data at the time of MI diagnosis and outcome data, we tested the prognostic performance of a post-discharge ischaemic stroke prediction model entitled R-$CHA_2DS_2$VASc, which was based on the renowned $CHA_2DS_2$VASc score with few modifications to improve its applicability and performance in a cohort of patients with a Myocardial Infarction. R-$CHA_2DS_2$VASc was evaluated for its overall discriminative performance and calibration in the prediction of ischaemic stroke and all-cause mortality during follow-up and compared to the original $CHA_2DS_2$VASc and GRACE scores.

This research has been approved by our Institutional review board.

*Patients and Eligibility Criteria*

1852 patients (age 68.3 ± 13.5, from 29 to 99 years old) were consecutively admitted to our ACCU diagnosed with MI according to its Universal Definition [8]. Patients were classified as having acute MI with ST-segment elevation (STEMI) or MI without ST-segment elevation (NSTEMI). Intrahospital mortality was observed in 141 patients and the remaining 1711 constitute the study's cohort. Table 1 describes the baseline sample characteristics.

*Data Collection*

Through extensive review done by 3 co-investigators blind to the purpose of the study (IA, FC, LP), the following data were collected: demographic features, cardiovascular risk factors, previous medical history (including history of AF [irrespective of its timing, duration and etiology], stroke, peripheral arterial disease or coronary heart disease), analytical study at admission (including complete blood count, biochemical and clotting tests) and angiographic data. Glomerular filtration rate (GFR – using the Modified Diet in Renal Disease [MDRD] formula), the GRACE score for 6-month post-discharge mortality and the $CHA_2DS_2$-VASc scores were calculated for all patients.

*Study End Points and Patient Follow-up*

The primary endpoint of this study was the occurrence of a primary International Classification of Diseases diagnosis of ischaemic stroke during follow-up, confirmed through cerebral computed tomography (CT) when deemed necessary by the attending Neurologist. The secondary outcomes were all-cause mortality during follow-up and a composite endpoint of ischaemic stroke and all-cause mortality.

Patients were followed for a mean of 17.4 ± 8.7 months following their discharge. Follow-up data was obtained through review of clinical records from outpatient clinic and hospital ward and emergency department admissions, including the reports of performed cerebral CT, when appropriate, and through phone calls by the end of a 2-year period after discharge for patients not followed at our institution (a minority of cases, as most patients were followed at our hospital). Outcomes were assessed by 3 co-investigators blind to the purpose of the study (IA, FC, PD).

**Table 1**
Description of study sample.

| | OVERALL SAMPLE (n = 1711) |
|---|---|
| **Age** | 67.7 ± 13.5 |
| **Male gender** | 66.6% |
| **STEMI** | 42.1% |
| **Diabetes Mellitus** | 32.9% |
| **History of stroke** | 8.6% |
| **Previously known arterial hypertension** | 75.6% |
| **History of atrial fibrillation** * | 15.3% |
| **Previously known CAD** | 27.7% |
| **Previously known PAD** | 12.2% |
| **Maximum Killip-Kimball class** | 1.38 ± 0.75 |
| **Heart failure during hospitalization** ** | 24.5% |
| **Moderate to severe LV systolic dysfunction** | 19.8% |
| **GFR (mL/min/1.73 $m^2$)** | 71.2 ± 30.0 |
| **GFR (mL/min) ≥60/30-60/<30** | 65.3%/26.2%/8.5% |
| **BUN (mg/dL)** | 8.82 ± 5.8 |
| **BUN ≥25 mg/dL** | 2.5% |
| **Performance of revascularization** | 66.5% |
| **Mean $CHADS_2$** | 1.84 ± 1.25 |
| **Mean $CHA_2DS_2$-VASc** | 3.50 ± 1.7 |
| **Mean GRACE score for 6-month mortality** | 121.843.8 |
| **Discharged on dual anti-platelet therapy** | 90.1% |
| **Discharged on oral anticoagulation** | 5.3% |
| **Mortality during follow-up** | 14.8% (n = 253) |
| **Stroke during follow-up** | 4.3% (n = 74) |

NOTE: STEMI – ST elevation Myocardial Infarction; CAD – Coronary artery disease; PAD – Peripheral artery disease; GFR – Glomerular filtration rate; BUN – Blood urea nitrogen. * Up to hospitalization; ** Defined as a maximum Killip-Kimball class >1.

*Statistical Analysis*

Statistical analysis was done using SPSS, v.17.0. When needed, baseline characteristics were described with mean ± standard deviation for continuous data and counts and proportions for categorical data. The Kolmogorov-Smirnov test was used to test the normal distribution of continuous variables. The Chi-square test, Student's t-test and non-parametric equivalent tests were used when appropriate. Regression estimation techniques were applied to replace missing values whenever the number of missing values was negligible (less than 5% of the cohort; this arbitrary cutoff was agreed by the authors), otherwise cases with missing values would have been omitted. P values <0.05 (two-sided) were considered statistically significant.

A model for prediction of post-discharge stroke was developed from the original $CHA_2DS_2$-VASc score, comprising all its primordial variables plus two renal function parameters (GFR by MDRD formula and blood urea nitrogen) and performance of a revascularization procedure. History of AF or the occurrence of this arrhythmia during hospitalization would add 2 points to the score. Table 2 gives a detailed assessment of stroke and follow-up all-cause mortality univariate prediction ability of parameters included in the R-$CHA_2DS_2$VASc score, while Table 3 illustrates R-$CHA_2DS_2$VASc score calculation.