

Comparative performance of AnTicoagulation and Risk factors In Atrial fibrillation and Global Registry of Acute Coronary Events risk scores in predicting long-term adverse events in patients with acute myocardial infarction

 Gökhan Çetinkal,  Cüneyt Koçaş¹,  Betül Balaban Koçaş,  Şükrü Arslan¹,  Okay Abacı¹,
 Osman Şükrü Karaca¹,  Yalçın Dalgıç¹,  Özgür Selim Ser¹,  Kudret Keskin,  Ahmet Yıldız¹,
 Sait Mesut Doğan¹

Department of Cardiology, Şişli Hamidiye Etfal Training and Research Hospital; İstanbul-Turkey

¹Department of Cardiology, İstanbul University Institute of Cardiology; İstanbul-Turkey

ABSTRACT

Objective: This study is designed to evaluate the recently developed AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) risk score (RS), which determines the predisposition to thromboembolic and hemorrhagic events in atrial fibrillation, as a predictor of prognosis in patients having acute myocardial infarction (AMI), and to compare the predictive ability of ATRIA RS with GRACE RS.

Methods: We analyzed 1627 patients having AMI who underwent coronary angiography and/or percutaneous coronary intervention (PCI) between January 2011 and February 2015. The primary endpoints included all-cause mortality, non-fatal MI, and cerebrovascular events during follow-up.

Results: Multivariate Cox regression analysis showed that the ATRIA RS>3 was an independent predictor of major adverse cardiac events in patients with AMI [hazard ratio, 2.00, 95% confidence interval, 1.54 to 2.60, p<0,001]. The area under the curve (AUC) for ATRIA RS and GRACE RS was 0.66 and 0.67 (p<0.001, and p<0.001), respectively. We performed a pair-wise comparison of receiver operating characteristic curves, and noted the predictive value of ATRIA RS with regard to primary endpoints was similar to that of GRACE RS (By DeLong method, AUC_{ATRIA} vs. AUC_{GRACE} z test=0.64, p=0.52).

Conclusion: ATRIA RS may be useful in predicting prognosis in patients having AMI during long-term follow-up. (*Anatol J Cardiol* 2018; 20: 77-84)

Keywords: ATRIA risk score, acute myocardial infarction, risk stratification

Introduction

Although the incidence of acute coronary syndromes (ACS) is increasing due to the prolongation of life expectancy in populations, better survival rates are also being observed based on advances in cardiac life support and reperfusion therapies (1, 2). Patients suffering from acute myocardial infarction (AMI) are at high risk of in-hospital and long-term adverse cardiovascular events, making risk stratification is very important in predicting adverse outcomes (3). Different scoring systems have been utilized to identify patients at high risk for developing adverse cardiac events. The Global Registry of Acute Coronary Events

(GRACE) risk score (RS) was developed as a well-validated tool for predicting in-hospital and 6-month mortality in patients with ACS (4). Recent studies have demonstrated that CHADS and CHA2DS2-VASc scores, used to estimate the risk of ischemic stroke in patients with atrial fibrillation (AF), were useful tools for predicting long-term prognosis in patients having AMI, in addition to predicting subsequent cardiovascular events compared with GRACE RS (5-8).

New studies have shown that the more recently developed AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) RS, which determines the predisposition to thromboembolic and hemorrhagic events in AF, demonstrates better accuracy

This study was presented as a poster presentation at European Society of Cardiology Congress 2016, 27-31 August 2016, Rome-Italy.

Address for correspondence: Dr. Gökhan Çetinkal, Şişli Hamidiye Etfal Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, Şişli 34360 İstanbul-Türkiye

Phone: +90 212 373 50 00 Fax: +90 212 373 50 04 E-mail: gokhancetinkal@yahoo.com

Accepted Date: 26.04.2018 **Available Online Date:** 17.07.2018

©Copyright 2018 by Turkish Society of Cardiology - Available online at www.anatoljcardiol.com
 DOI:10.14744/AnatolJCardiol.2018.54815



than CHADS and CHA2DS2-VASc scores in predicting ischemic stroke (9-11). However, the value of ATRIA RS in predicting long-term prognosis in patients having AMI remained unknown. This study aims to assess the efficacy of ATRIA RS in predicting long-term prognosis in patients having AMI who have undergone coronary angiography and/or percutaneous coronary intervention (PCI) and to compare its predictive ability with GRACE RS.

Methods

We retrospectively analyzed 1627 patients with a diagnosis of AMI who were hospitalized in our hospital between January 2011-March 2015. The third universal definition of MI was used to define the diagnostic criteria for AMI (12). The exclusion criteria included the following: patients with chronic AF, treatment with thrombolytics, conservative management, unstable angina pectoris, and life expectancy <1 year because of non-cardiac conditions. All patients signed informed consent, and the study protocol was approved by the Local Ethics Committee.

Prior to the procedure, all patients with non-ST segment elevation myocardial infarction (NSTEMI) were administered 300 mg of aspirin and a loading dose of 300 mg clopidogrel, and those with ST segment elevation myocardial infarction (STEMI) received 600 mg of clopidogrel. The femoral route was chosen for all PCI procedures. Patients undergoing PCI received 100 IU/kg heparin during the procedure, with the dose of heparin reduced to 60 IU/kg if a glycoprotein IIb/IIIa inhibitor (GPI) was concurrently being used. GPI use, thrombus aspiration, and stent selection were left to the operator's discretion. Stent thrombosis was defined based on the Bleeding Academic Research Consortium classification. Only patients with definite stent thrombosis during the follow-up (early or late) were included in the study. Contrast-induced acute kidney injury (CI-AKI) was defined as an increase in the serum creatinine level of 0.5 mg/dL or 25% above baseline within 72 hours after contrast administration.

Scores

Because ATRIA RS was developed to predict the risk of ischemic stroke in patients with AF, age and prior stroke are considered as major risk factors. When ATRIA RS is calculated in patients with "prior stroke", age is more heavily weighted in the scoring system. The ATRIA RS was calculated for all enrolled patients as "without prior stroke," to balance the effect of age (Table 1).

CHADS RS was calculated as follows: 1 point each for congestive heart failure, hypertension, age >75 years, and diabetes mellitus, and 2 points for history of stroke. CHA2DS2-VASc RS was calculated with additional variables: 1 point each for age >65 years, history of vascular disease, and female gender and 2 points for age >75 years. A history of MI was accepted as vascular disease, and AMI was counted as 1 point for all patients. GRACE RS was calculated based on initial clinical history, and

Table 1. Risk factors used in ATRIA risk score

| Risk factor | Points without prior stroke (points) | Points with prior stroke (points) |
|--------------------------|--------------------------------------|-----------------------------------|
| Age, years | | |
| >85 | 6 | 9 |
| 75–84 | 5 | 7 |
| 65–74 | 3 | 7 |
| <65 | 0 | 0 |
| Female | 1 | 1 |
| Diabetes mellitus | 1 | 1 |
| Congestive heart failure | 1 | 1 |
| Hypertension | 1 | 1 |
| Proteinuria | 1 | 1 |
| eGFR <45 or ESRD | 1 | 1 |

eGFR - estimated glomerular filtration rate; ESRD - end-stage renal disease

electrocardiogram (ECG) and laboratory values estimated upon admission. Patients were divided into tertiles based on the ATRIA RS: ATRIA 0 (n=417), ATRIA 1-2 (n=598), and ATRIA ≥3 (n=612).

Endpoints

The study endpoints, including all-cause death, non-fatal MI, and development of cerebrovascular events (CVE), were combined. Hospitalization due to cardiac reasons, stent thrombosis and stent restenosis during follow-up, and CI-AKI rates were also considered. The mean follow-up time was 15 months (maximum, 36 months).

Statistical analysis

Continuous variables are reported as means ± standard deviation (SD) while categorical variables are presented as percentages. The Kolmogorov–Smirnov test was performed to test the normality of distributions. The one-way analysis of variance (ANOVA) with post-hoc analysis (Tukey and Bonferroni tests) or Kruskal–Wallis test for continuous variables and the chi-square test for categorical variables were used for comparison between the study groups based on the ATRIA RS tertiles. Independent predictors of major adverse cardiac events (MACE) were determined by the Cox regression analyses. MACE-free survival curves were calculated using the Kaplan-Meier method. The survival curves of the groups were compared using the log-rank test. Receiver operating characteristic (ROC) curves compared the performance and predictive accuracy of the ATRIA RS, CHADS RS, CHA2DS2-VASc RS, and GRACE RS for all-cause mortality, MI, and CVE during the long-term follow-up. A goodness-of-fit test for the scoring systems was performed using the Hosmer-Lemeshow method to evaluate differences between the model-predicted and observed event rates. C-statistics for

risk models were compared using the De-Long method. Values of $p < 0.05$ were considered statistically significant. SPSS 21 software (SPSS Inc, Chicago, Illinois, USA) was used to carry out all statistical analyses.

Results

Clinical and demographic features and laboratory parameters

Table 2 and 3 represent the demographic and clinical features, and laboratory parameters of studied patients. Patients in the high ATRIA RS tertile were older with a more frequent his-

tory of diabetes mellitus, hypertension, stroke, MI, and coronary artery bypass grafting (CABG), but they were less frequently current smokers. Ejection fraction, estimated glomerular filtration rate (eGFR), creatine kinase-MB (CK-MB), hemoglobin, leukocytes, low-density lipoprotein (LDL) and total cholesterol levels were tended to decrease progressively from a lower ATRIA RS to higher ATRIA RS tertile. Additionally, the incidence of NSTEMI, length of hospital stay, GRACE RS, systolic blood pressure, heart rate, patients belonging to Killip class >2 , and serum glucose and creatinine level at the time of admission were higher compared to patients with a lower ATRIA RS tertile than higher ATRIA tertiles.

Table 2. The clinical and demographic features of the study population according to ATRIA score tertiles

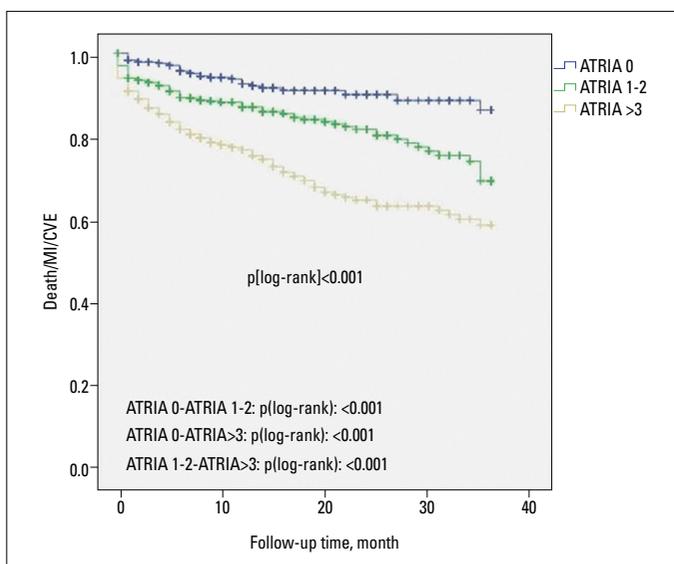
| | ATRIA 0 (n=417) | ATRIA 1-2 (n=598) | ATRIA >3 (n=612) | P value |
|--------------------------------------|--------------------|----------------------|---------------------|---------------------|
| Age, years | 51±8.1 | 53.8±7.2 | 70±8.9 | <0.001 ¹ |
| Male gender | 417 (100%) | 486 (81.3%) | 374 (61.1%) | <0.001 |
| Diabetes mellitus | 0 (0%) | 222 (37.1%) | 319 (52.1%) | <0.001 |
| Hypertension | 0 (0%) | 345 (57.7%) | 437 (71.4%) | <0.001 |
| Hypercholesterolemia | 191 (45.8%) | 306 (51.2%) | 309 (50.5%) | 0.21 |
| Smoking | 289 (76.7%) | 333 (59.5%) | 194 (32.7%) | <0.001 |
| Previous MI | 69 (16.5%) | 127 (21.2%) | 160 (26.1%) | 0.01 |
| Previous PCI | 72 (17.3%) | 143 (23.9%) | 178 (29.1%) | <0.001 |
| Previous CABG | 8 (1.9%) | 45 (7.5%) | 76 (12.4%) | <0.001 |
| Previous stroke | 0 (0%) | 11 (1.8%) | 33 (5.2%) | <0.001 |
| Ejection fraction (%) | 52.9±5.7 | 48.6±9.9 | 48±10.3 | <0.001 ² |
| Length of hospital stay, days | 5.3±3.4 | 6.2±4.1 | 8.2±6.5 | <0.001 ³ |
| Body mass index (kg/m ²) | 28.7±5.8 | 28.6±6.4 | 27.7±4.8 | 0.81 |
| Systolic blood pressure (mm Hg) | 127.5±20.5 | 131.3±24.6 | 135.7±27.1 | <0.001 ⁴ |
| Heart rate (beats per minute) | 74.8±14.6 | 79.1±17.1 | 80.3±18.6 | <0.001 ⁵ |
| GRACE RS | 129.4±27.5 | 135.7±30.7 | 164.1±33.2 | <0.001 ⁶ |
| ATRIA RS | 0 | 1.4±0.5 | 5.2±1.8 | <0.001 ⁷ |
| Anterior MI | 81 (19.4%) | 152 (25.4%) | 98 (16%) | <0.001 |
| Non anterior MI | 161 (38.6%) | 133 (22.2%) | 118 (19.3%) | |
| NSTEMI | 175 (42%) | 313 (52.3%) | 396 (64.7%) | |
| Killip class ≥ 2 | 11 (1.5%) | 38 (6.3%) | 40 (6.5%) | <0.001 |
| In-hospital medication | | | | |
| Statin | 377 (90.4%) | 537 (89.7%) | 550 (89.9%) | 0.83 |
| β blocker | 350 (83.9%) | 496 (82.9%) | 514 (84.1%) | 0.88 |
| ACE-I/ARB | 342 (82%) | 485 (81.1%) | 508 (83.1%) | 0.79 |

ACE-I - angiotensin-converting enzyme inhibitor; ARB - angiotensin receptor blocker; ATRIA - Anticoagulation and Risk Factors in Atrial Fibrillation Risk Score; GRACE RS - Global Registry of Acute Coronary Event, MI - myocardial infarction; PCI - percutaneous coronary intervention; NSTEMI - non-ST-segment Elevation Myocardial Infarction Risk Score
 1- ATRIA 0 vs. ATRIA 1-2 $P < 0.001$; ATRIA 0 vs. ATRIA 3 $P < 0.001$; ATRIA 1-2 vs. ATRIA 3 $P < 0.001$
 2- ATRIA 0 vs. ATRIA 1-2 $P < 0.001$; ATRIA 0 vs. ATRIA 3 $P < 0.001$; ATRIA 1-2 vs. ATRIA 3 $P < 0.001$
 3- ATRIA 0 vs. ATRIA 1-2 $P < 0.001$; ATRIA 0 vs. ATRIA 3 $P < 0.001$; ATRIA 1-2 vs. ATRIA 3 $P < 0.001$
 4- ATRIA 0 vs. ATRIA 1-2 $P < 0.05$; ATRIA 0 vs. ATRIA 3 $P < 0.001$; ATRIA 1-2 vs. ATRIA 3 $P < 0.008$
 5- ATRIA 0 vs. ATRIA 1-2 $P < 0.001$; ATRIA 0 vs. ATRIA 3 $P < 0.001$; ATRIA 1-2 vs. ATRIA 3 $P < 0.49$
 6- ATRIA 0 vs. ATRIA 1-2 $P < 0.004$; ATRIA 0 vs. ATRIA 3 $P < 0.001$; ATRIA 1-2 vs. ATRIA 3 $P < 0.001$
 7- ATRIA 0 vs. ATRIA 1-2 $P < 0.001$; ATRIA 0 vs. ATRIA 3 $P < 0.001$; ATRIA 1-2 vs. ATRIA 3 $P < 0.04$

Table 3. Biochemical characteristics of the study population according to ATRIA score tertiles

| | ATRIA 0 (n=417) | ATRIA 1-2 (n=598) | ATRIA ≥3 (n=612) | P value |
|------------------------------------------|--------------------|----------------------|---------------------|---------------------|
| Serum glucose level on admission (mg/dL) | 113.4±30.2 | 140.6±64.1 | 149.1±70.2 | <0.001 ¹ |
| Creatinine level on admission (mg/dL) | 0.88±0.16 | 0.94±0.46 | 1.11±0.74 | <0.001 ² |
| eGFR (ml/min/1.73 m ²) | 94.8±19.5 | 88.9±24.9 | 70.7±24.6 | <0.001 ³ |
| Total cholesterol (mg/dL) | 193.1±45.2 | 188.3±47.2 | 181.1±44.3 | <0.001 ⁴ |
| LDL (mg/dL) | 131.4±40.8 | 123.4±38.8 | 118.4±37.6 | <0.001 ⁵ |
| HDL (mg/dL) | 36.2±13.8 | 38.2±12.6 | 41.3±14.3 | <0.001 ⁶ |
| Hemoglobin (gr/dL) | 14.4±1.3 | 13.9±1.7 | 12.8±1.9 | <0.001 ⁷ |
| Leukocyte (/mm ³) | 11439±3416 | 11307±4158 | 9750±3478 | <0.001 ⁸ |
| Platelet (/mm ³) | 249640±67950 | 257010±76047 | 246970±82184 | 0.07 |
| CK-MB (ng/mL) | 18 | 34.2 | 108 | <0.001* |
| Proteinuria | 0 (0%) | 83 (13.9%) | 192 (31.4%) | <0.001 |

CK-MB - creatine kinase-MB; eGFR - estimated glomerular filtration rate; HDL - high-density lipoprotein; LDL - low-density lipoprotein
*Kruskal-Wallis test was performed. Data was given as median (interquartile range).
1- ATRIA 0 vs. ATRIA 1-2 P<0.001; ATRIA 0 vs. ATRIA 3 P<0.001; ATRIA 1-2 vs. ATRIA 3 P 0.04
2- ATRIA 0 vs. ATRIA 1-2 P 0.32; ATRIA 0 vs. ATRIA 3 P<0.001; ATRIA 1-2 vs. ATRIA 3 P<0.001
3- ATRIA 0 vs. ATRIA 1-2 P<0.001; ATRIA 0 vs. ATRIA 3 P<0.001; ATRIA 1-2 vs. ATRIA 3 P<0.001
4- ATRIA 0 vs. ATRIA 1-2 P 0.22; ATRIA 0 vs. ATRIA 3 P<0.001; ATRIA 1-2 vs. ATRIA 3 P 0.02
5- ATRIA 0 vs. ATRIA 1-2 P 0.005; ATRIA 0 vs. ATRIA 3 P<0.001; ATRIA 1-2 vs. ATRIA 3 P 0.06
6- ATRIA 0 vs. ATRIA 1-2 P 0.05; ATRIA 0 vs. ATRIA 3 P<0.001; ATRIA 1-2 vs. ATRIA 3 P<0.001
7- ATRIA 0 vs. ATRIA 1-2 P<0.001; ATRIA 0 vs. ATRIA 3 P<0.001; ATRIA 1-2 vs. ATRIA 3 P<0.001
8- ATRIA 0 vs. ATRIA 1-2 P 0.85; ATRIA 0 vs. ATRIA 3 P<0.001; ATRIA 1-2 vs. ATRIA 3 P<0.001
*ATRIA 0 vs. ATRIA 1-2 P 0.88; ATRIA 0 vs. ATRIA 3 P<0.001; ATRIA 1-2 vs. ATRIA 3 P<0.001

**Figure 1.** Kaplan-Meier curves for primary endpoints at long-term follow-up

Angiographic and procedural characteristics

Angiographic and procedural characteristics of subjects belonging to the 3 study groups are given in Table 4. The mean diameter of stents used, tirofiban use, and need for an aspiration device were significantly lower in the high ATRIA RS tertile. However, the incidence of multivessel disease was higher in this group, although the use of drug-eluting stents was less frequent.

Clinical endpoints

Table 5 shows the primary endpoints and other clinical outcomes during the long-term follow-up, which showed that the all-cause mortality was significantly higher, and MI or hospitalization due to cardiac reasons, CI-AKI, and in-hospital CABG were noticeably more frequent in the high ATRIA RS tertile compared to the other two groups. No statistically significant difference in terms of CVE, stent thrombosis, and restenosis rates was noted between the groups, probably because the number of patients was limited. Figure 1 shows the rates of the primary endpoints, all-cause mortality, and MI among the groups during follow-up. The high ATRIA RS tertile had a significantly higher prevalence of adverse events compared to the other two groups.

Multivariate analysis

The Cox multivariate analysis results are demonstrated in Table 6. During the long-term follow-up, a multivariate analysis was performed for the primary endpoints, based on the following variables: ATRIA RS >3, ejection fraction, Killip class >2, previous MI, chronic renal disease, hypertension, diabetes mellitus, hyperlipidemia, age, multivessel disease, and current smoking. Among these variables, ATRIA RS >3, ejection fraction, Killip class >2, previous MI, and chronic renal disease were identified as independent predictors of all-cause death, MI, and CVE. GRACE, CHADS, and CHA2DS2-VASc scores were not included in this model because they involve similar variables. Non-significant results from the Hosmer–Lemeshow test (ATRIA, $p=0.27$;

Table 4. Angiographic and procedural characteristics of the study population according to ATRIA score tertiles

| | ATRIA 0 (n=417) | ATRIA 1-2 (n=598) | ATRIA ≥3 (n=612) | P value |
|------------------------------------|----------------------------|------------------------------|-----------------------------|---------------------|
| Contrast volume (mL) | 241.3±109.9 | 242±116.5 | 232.7±122.6 | 0.32 |
| Number of stents implanted in IRA | 1.06±0.24 | 1.05±0.21 | 1.08±0.28 | 0.25 |
| Average stent diameter in IRA (mm) | 2.94±0.37 | 2.93±0.41 | 2.82±0.38 | <0.001 ¹ |
| Total stent length in IRA (mm) | 21.4±7.6 | 21.6±7.5 | 21.6±8.2 | 0.95 |
| Tirofiban use | 168 (40.3%) | 200 (33.4%) | 130 (21.2%) | <0.001 |
| Thrombus aspiration | 137 (32.9%) | 158 (26.4%) | 106 (17.3%) | <0.001 |
| No. of diseased vessels | | | | |
| 1 vessel | 232 (55.6%) | 266 (44.5%) | 209 (34.2%) | <0.001 |
| 2 vessels | 109 (26.1%) | 185 (30.9%) | 177 (28.9%) | |
| 3 vessels | 52 (12.5%) | 116 (19.4%) | 195 (31.9%) | |
| Infarct related artery | | | | |
| LAD | 153 (36.7%) | 267 (44.6%) | 234 (38.2%) | <0.001 |
| CX | 83 (19.9%) | 98 (16.4%) | 127 (20.8%) | |
| RCA | 150 (36%) | 170 (28.4%) | 159 (26.0%) | |
| LMCA | 1 (0.2%) | 10 (1.7%) | 17 (2.8%) | |
| Stent type | | | | |
| BMS | 192 (46%) | 260 (43.5%) | 218 (35.6%) | <0.001 |
| DES | 114 (27.3%) | 143 (23.9%) | 133 (21.7%) | |
| CABG, in-hospital | 35 (8.4%) | 67 (11.2%) | 85 (13.9%) | 0.02 |

IRA - infarct related artery, LAD - left anterior descending, CX - circumflex, RCA - right coronary artery, LMCA - left main coronary artery, BMS - bare metal stent, DES - drug-eluting stent, CABG - coronary artery by-pass grafting
 1- ATRIA 0 vs. ATRIA 1-2 P 0.78; ATRIA 0 vs. ATRIA 3 P<0.001; ATRIA 1-2 vs. ATRIA 3 P 0.001

Table 5. Primary endpoints and other clinical events during follow-up according to ATRIA score tertiles

| | ATRIA 0 (n=417) | ATRIA 1-2 (n=598) | ATRIA ≥3 (n=612) | P value |
|-----------------------------------------------|----------------------------|------------------------------|-----------------------------|----------------|
| Primary endpoints | | | | |
| Death/MI/CVE | 32 (7.7%) | 92 (15.4%) | 158 (25.8%) | <0.001 |
| All-cause death | 2 (0.5%) | 37 (6.2%) | 85 (13.9%) | <0.001 |
| In-hospital mortality | 0 (0%) | 21 (3.5%) | 38 (6.2%) | <0.001 |
| Myocardial infarction | 30 (7.2%) | 60 (10.1%) | 84 (13.8%) | 0.003 |
| CVE | 0 (0%) | 4 (0.7%) | 3 (0.5%) | 0.26 |
| Hospitalization | 43 (10.3%) | 97 (16.3%) | 124 (20.3%) | <0.001 |
| Contrast-induced acute kidney injury | 45 (10.8%) | 95 (15.9%) | 141 (23%) | <0.001 |
| Definite ST during follow-up, (early or late) | 5 (1.2%) | 6 (1%) | 12 (2%) | 0.33 |
| Stent restenosis during follow-up | 22 (5.3%) | 40 (6.7%) | 35 (5.7%) | 0.61 |

CVE - cerebrovascular event, MI - myocardial infarction; PCI - percutaneous coronary intervention, ST - stent thrombosis

GRACE, p=0.12; CHA2DS2-VASc, p=0.52; CHADS, p=0.27) in this study demonstrated that the calibrations of these four risk scores to predict adverse events were accurate.

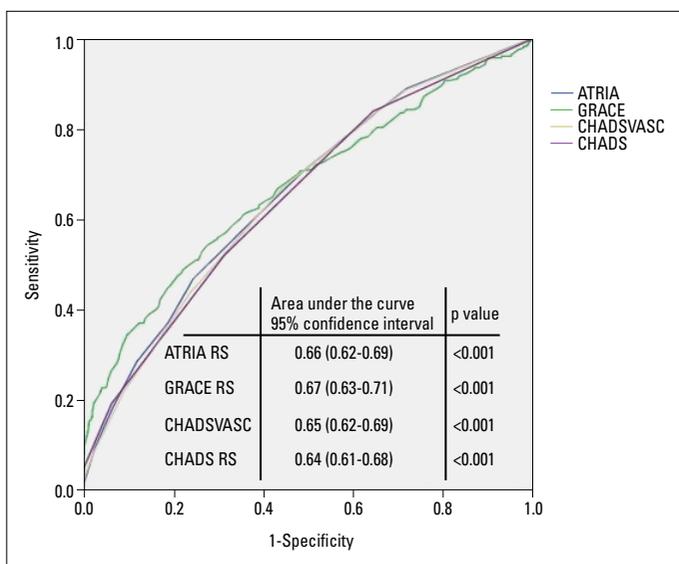
ROC analysis

ROC analysis comparing the predictive accuracy of ATRIA RS, GRACE RS, CHA2DS2-VASc RS, and CHADS RS for all-cause

Table 6. Multivariate and univariate predictors of primary endpoints

| | Univariate | | Multivariate | |
|-----------------------|-----------------------|---------|-----------------------|---------|
| | Hazard ratio (95% CI) | P value | Hazard ratio (95% CI) | P value |
| ATRIA ≥ 3 | 2.38 (1.88-3.01) | <0.001 | 2.00 (1.54-2.60) | <0.001 |
| Ejection fraction | 0.94 (0.93-0.95) | <0.001 | 0.96 (0.94-0.97) | <0.001 |
| Killip class>2 | 2.30 (2.02-2.61) | <0.001 | 1.75 (1.50-2.04) | <0.001 |
| Previous MI | 1.64 (1.26-2.12) | <0.001 | 1.32 (1.01-1.74) | 0.049 |
| Chronic renal disease | 3.05 (2.18-4.26) | <0.001 | 1.83 (1.27-2.64) | 0.001 |
| Hypertension | 1.33 (1.06-1.68) | 0.016 | | |
| Diabetes mellitus | 1.49 (1.18-1.89) | 0.001 | | |
| Hyperlipidemia | 1.22 (0.96-1.54) | 0.11 | | |
| Age | 1.03 (1.02-1.04) | <0.001 | | |
| Multivessel disease | 2.91 (1.35-6.30) | <0.001 | | |
| Anterior MI | 1.52 (1.15-2.00) | 0.003 | | |
| Current smoking | 1.33 (1.04-1.69) | 0.023 | | |

HR - hazard ratio; CI - confidence interval; MI - myocardial infarction

**Figure 2.** ROC analysis comparing the performance and predictive accuracy of ATRIA RS, GRACE RS, CHA2DS2-VASc RS, and CHADS RS for primary endpoints

mortality, MI, and CVE during the long-term follow-up is shown in Figure 2. Based on a 95% CI, the areas under the curve (AUC) for ATRIA RS, GRACE RS, CHA2DS2-VASc, and CHADS RS was 0.66, 0.67, 0.65, and 0.64 respectively ($p < 0.001$, for all RS). We performed a pair-wise comparison of ROC curves, and noted that the predictive value of ATRIA RS with regard to the primary endpoint was similar to that of GRACE RS, CHA2DS2-VASc RS, and CHADS RS (by DeLong method, AUC_{ATRIA} vs. AUC_{GRACE} z test=0.64, $p=0.52$; AUC_{ATRIA} vs. $AUC_{\text{CHA2DS2-VASc}}$ z test=0.80, $p=0.42$; AUC_{ATRIA} vs. AUC_{CHADS} z test=0.76, $p=0.44$).

Discussion

Our study showed that ATRIA RS was a predictor of prognosis in patients with AMI who underwent coronary angiography and/or PCI. Our study also demonstrated that ATRIA RS was similar to GRACE RS to determine long-term prognosis. Additionally, ATRIA RS ≥ 3 was found to be an independent predictor of MACE in this group. One of the most important features of our study is, this is the first one that demonstrates the value of ATRIA RS in predicting long-term adverse events in a group of patients having AMI.

Initially, the ATRIA RS was used for stroke risk stratification in patients with chronic AF. Authors stated that ATRIA RS showed a better performance than CHADS and CHA2DS2-VASc scores in predicting ischemic stroke, especially in the low-risk group (9). Recent studies have showed similar results in different patient cohorts (10, 11). A new meta-analysis demonstrated that ATRIA RS was superior to CHA2DS2-VASc score in predicting stroke risk, although the CHA2DS2-VASc score was better than the ATRIA RS in identifying low-risk patients (13). Although AF risk score involve similar components, age was the predominant factor in the application of ATRIA RS. Researchers have designed this score keeping in mind the increased risk of ischemic stroke in elderly patients. Probably this situation increases definitive diagnostic performance of ATRIA RS.

Advanced age is the predominant risk factor for cardiovascular and cerebrovascular diseases, as well as an independent predictor of poor outcomes after AMI (1, 14-16). As age is a dominant factor in calculating the ATRIA RS, this may explain similar predictive performance of ATRIA RS compared to GRACE RS in our study. And that further explains its appropriateness for risk stratification in patients with AMI. Elderly patients have a poorer

prognosis after AMI due to not receiving evidence-based medical therapy, increased risk of bleeding, lower rates of undergoing CAG and/or PCI, delay in hospital admission, higher prevalence of comorbidities such as renal and hepatic insufficiency, heart failure, hypertension, DM, and their vulnerable health status (16, 17). However, in recent studies, the mortality rates have declined because of better use of guideline-mediated therapies (18). Also less utilization of drug-eluting stents (DES) in patients with high ATRIA RS may have contributed to increased mortality and adverse events. Because current studies showed that using of DES in patients with ACS had better mortality, repeat revascularization, and definite stent thrombosis rates (19).

Recent studies have shown that risk score such as HASBLED, CHADS, and CHA2DS2-VASc were predictors of MACE and all-cause mortality in patients with AMI (5-8, 20, 21). Although all these scores were developed for predicting thromboembolic and hemorrhagic events in patients with AF, based on different studies and current guidelines, their constituent components, such as old age, diabetes mellitus, renal dysfunction, heart failure, and prior vascular disease are common predictors of a poor prognosis in patients having AMI (1-3, 14-16).

Capodanno et al. (21) conducted a study to investigate the value of HASBLED and CHA2DS2-VASc scores in patients who underwent DES implantation. The study included 1330 patients who underwent DES implantation without AF. Among those included, 845 were diagnosed with ACS (unstable angina, STEMI, or NSTEMI). Similar to our study, they found that the risk of MACE increased as the scores increased. They also compared these risk score with thrombolysis in myocardial infarction (TIMI) and GRACE RS in patients with ACS, demonstrating that all these scoring systems had similar discriminative capacity in predicting adverse events. However, the discriminative capacity of the age, creatinine, and ejection fraction (ACEF) scores was superior to HASBLED and CHA2DS2-VASc scores in predicting MACE in all groups. Although our study was similar to this one, there were some major differences: We enrolled patients regardless of treatment modality-either PCI/CABG or medical therapy. PCI was the treatment of choice in patients with STEMI, whereas the treatment choice varied between PCI/CABG or medical therapy in the NSTEMI group based on their coronary anatomy and comorbidities.

Kim et al. (7) evaluated the effectiveness of the CHA2DS2-VASc score as a long-term prognostic factor in patients having AMI. More than 15000 patients hospitalized for STEMI (n=8970) or NSTEMI (n=6711) were enrolled in the study regardless of the treatment method or presence of AF. The study indicated that as the score increased, MACE too was significantly higher at the long-term follow-up. Comparison between the CHA2DS2-VASc score and other popular risk scores such as GRACE or TIMI RS was not performed in this study.

Risk stratification is recommended as per current international ACS guidelines. Particularly in patients presenting with NSTEMI, the recommendation is to identify patients requiring

immediate reperfusion and at high risk for adverse in-hospital events (3). However, patients presenting with STEMI also have a sufficiently high risk in undergoing emergency coronary intervention (1). Despite improvements in hospital care, PCI techniques, and pharmacotherapies using novel anti platelet agents, the perceived risk of in-hospital and long-term adverse cardiac events is still high in patients with ACS. Therefore, our goal of risk stratification in patients having ACS is not to determine appropriate timing of PCI, but more importantly to identify the risk of adverse cardiac events after the procedure, as that would influence discharge planning and follow-up schedules. In this perspective, using ATRIA RS instead of GRACE RS may be an easy and user-friendly way to identify high-risk patients, because there is no need to use calculators or computer programs to calculate ATRIA RS.

Study limitations

This study has some limitations: Ours was a relatively small-sized retrospective study conducted in a single center. Although designed as a retrospective study, we followed patients prospectively. The current guidelines recommend using new-generation DES and novel anti platelet agents to reduce mortality in patients with AMI, although new-generation DES were less commonly used in our study. Clopidogrel was the drug of choice compared to new-generation antiplatelet agents such as ticagrelor and prasugrel. A prospective study with a larger number of patients, longer follow-up times, greater use of new-generation DES, and antiplatelet drugs may affect results of the study.

Conclusion

Our study shows that in patients with AMI undergoing CAG and/or PCI, the ATRIA RS, GRACE RS, CHA2DS2-VASc RS and CHADS RS have comparative discriminative ability in predicting long-term adverse events. When we compared ATRIA RS with these previously well-validated scores, it was found to be useful in predicting the prognosis of AMI for long-term follow-up. The ATRIA RS, which includes a significant portion of the long-term prognostic risk factors in the coronary artery disease population, may also be used more commonly in this patient group.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept – G.Ç., C.K., B.B.K., Ş.A.; Design – G.Ç., C.K.; Supervision – C.K., K.K., A.Y., S.M.D.; Fundings – A.Y., S.M.D. Materials – None; Data collection &/or processing – B.B.K., O.Ş.K., Y.D., S.M.D.; Analysis &/or interpretation – O.Ş.K., Y.D., S.M.D.; Literature search – O.Ş.K., Y.D., S.M.D.; Writing – G.Ç., B.B.K., Ş.A.; Critical review – K.K., A.Y., S.M.D.

References

- Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al.; ESC Scientific Document Group. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016; 37: 267-315. [CrossRef]
- Nichols M, Townsend N, Scarborough P, Rayner M. Cardiovascular disease in Europe 2014: epidemiological update. *Eur Heart J* 2014; 35: 2950-9. [CrossRef]
- Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012; 33: 2569-619.
- Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ* 2006; 333: 1091.
- Poçi D, Hartford M, Karlsson T, Herlitz J, Edvardsson N, Caidahl K. Role of the CHADS₂ score in acute coronary syndromes: risk of subsequent death or stroke in patients with and without atrial fibrillation. *Chest* 2012; 141: 1431-40. [CrossRef]
- Huang SS, Chen YH, Chan WL, Huang PH, Chen JW, Lin SJ. Usefulness of the CHADS₂ score for prognostic stratification of patients with acute myocardial infarction. *Am J Cardiol* 2014; 114: 1309-14.
- Kim KH, Kim W, Hwang SH, Kang WY, Cho SC, Kim W, et al. The CHA₂DS₂-VASc score can be used to stratify the prognosis of acute myocardial infarction patients irrespective of presence of atrial fibrillation. *J Cardiol* 2015; 65: 121-7. [CrossRef]
- Chua SK, Lo HM, Chiu CZ, Shyu KG. Use of CHADS₂ and CHA₂DS₂-VASc scores to predict subsequent myocardial infarction, stroke, and death in patients with acute coronary syndrome: data from Taiwan acute coronary syndrome full spectrum registry. *Plos One* 2014; 9: e111167. [CrossRef]
- Singer DE, Chang Y, Borowsky LH, Fang MC, Pomernacki NK, Udaltsova N, et al. A new risk scheme to predict ischemic stroke and other thromboembolism in atrial fibrillation: the ATRIA study stroke risk score. *J Am Heart Assoc* 2013; 2: e000250. [CrossRef]
- van den Ham HA, Klungel OH, Singer DE, Leufkens HG, van Staa TP. Comparative Performance of ATRIA, CHADS₂, and CHA₂DS₂-VASc Risk Scores Predicting Stroke in Patients With Atrial Fibrillation: Results From a National Primary Care Database. *J Am Coll Cardiol* 2015; 66: 1851-9. [CrossRef]
- Aspberg S, Chang Y, Atterman A, Bottai M, Go AS, Singer DE. Comparison of the ATRIA, CHADS₂, and CHA₂DS₂-VASc stroke risk scores in predicting ischaemic stroke in a large Swedish cohort of patients with atrial fibrillation. *Eur Heart J* 2016; 37: 3203-10. [CrossRef]
- Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al.; Writing Group on the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction, ESC Committee for Practice Guidelines (CPG). Third universal definition of myocardial infarction. *Eur Heart J* 2012; 33: 2551-67. [CrossRef]
- Zhu W, Fu L, Ding Y, Huang L, Xu Z, Hu J, et al. Meta-analysis of ATRIA versus CHA₂DS₂-VASc for predicting stroke and thromboembolism in patients with atrial fibrillation. *Int J Cardiol* 2017; 227: 436-42. [CrossRef]
- Rosengren A, Wallentin L, Simoons M, Gitt AK, Behar S, Battler A, et al. Age, clinical presentation, and outcome of acute coronary syndromes in the Euroheart acute coronary syndrome survey. *Eur Heart J* 2006; 27: 789-95. [CrossRef]
- Fox KA, Eagle KA, Gore JM, Steg PG, Anderson FA; GRACE and GRACE2 Investigators. The Global Registry of Acute Coronary Events, 1999 to 2009--GRACE. *Heart* 2010; 96: 1095-101. [CrossRef]
- Dai X, Busby-Whitehead J, Alexander KP. Acute coronary syndrome in the older adults. *J Geriatr Cardiol* 2016; 13: 101-8.
- Avezum A, Makdisse M, Spencer F, Gore JM, Fox KA, Montalescot G, et al. Impact of age on management and outcome of acute coronary syndrome: observations from the Global Registry of Acute Coronary Events (GRACE). *Am Heart J* 2005; 149: 67-73. [CrossRef]
- Puymirat E, Aissaoui N, Cayla G, Lafont A, Riant E, Mennuni M, et al. Changes in One-Year Mortality in Elderly Patients Admitted with Acute Myocardial Infarction in Relation with Early Management. *Am J Med* 2017; 130: 555-63. [CrossRef]
- Sabaté M, Räber L, Heg D, Brugaletta S, Kelbaek H, Cequier A, et al. Comparison of newer-generation drug-eluting with bare-metal stents in patients with acute ST-segment elevation myocardial infarction: a pooled analysis of the EXAMINATION (clinical Evaluation of the Xience-V stent in Acute Myocardial InfArction) and COMFORTABLE-AMI (Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction) trials. *JACC Cardiovasc Interv* 2014; 7: 55-63.
- Hsieh MJ, Lee CH, Chen CC, Chang SH, Wang CY, Hsieh IC. Predictive performance of HAS-BLED risk score for long-term survival in patients with non-ST elevated myocardial infarction without atrial fibrillation. *J Cardiol* 2017; 69: 136-43. [CrossRef]
- Capodanno D, Rossini R, Musumeci G, Lettieri C, Senni M, Valsecchi O, et al. Predictive accuracy of CHA₂DS₂-VASc and HAS-BLED scores in patients without atrial fibrillation undergoing percutaneous coronary intervention and discharged on dual antiplatelet therapy. *Int J Cardiol*. 2015; 199: 319-25. [CrossRef]