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ADA Score for Predicting Cardiovascular Events in Atrial Fibrillation

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Abstract

Objective: To investigate the ADA score for major adverse cardiovascular events (MACE) prediction in patients with atrial fibrillation (AF) on anticoagulation.

Patients and Methods: This is a prospective cohort study including patients with AF receiving anticoagulant therapy from 2013 to 2023 if they consented to participate in the study. Principal endpoint was MACE occurrence – including non-fatal acute myocardial infarction, non-fatal acute ischemic stroke, non-fatal acute peripheral artery event, and cardiovascular death – during 1-year follow-up. Patients were divided into low (ADA score <49), and high risk (ADA score ≥ 49).

Results: Twenty-one out of 1000 patients (2.1%) experienced a MACE. Patients with MACE were older, more frequently affected by coronary artery disease, had lower albumin, higher D-dimer, and higher ADA score values compared to patients without MACE. High-risk patients had more often arterial hypertension, heart failure, and a history of stroke. Patients at higher risk had a significantly greater risk of MACE compared to low-risk patients (risk ratio, 3.39; 95% confidence interval, 1.23-9.32). The c-statistic of ADA score was 0.67 (95% confidence intervals, 0.54 to 0.77) with a sensitivity of 86% (95% confidence intervals, 43% to 99%), and a specificity of 50% (95% confidence intervals, 46% to 94%).

Conclusions: The ADA score has a good performance for MACE prediction in patients with AF. A more aggressive management of cardiovascular risk factors and comorbidities should be warranted for at-risk patients as identified by ADA score ≥ 49.

Keywords: Aging; Atrial fibrillation; Cardiovascular diseases; D-Dimer; Hypoalmuniemia

Non-standard Abbreviations and Acronyms: IDI: Integrated Discrimination Improvement; IQR: Interquartile Range; MACE: Major Adverse Cardiovascular Events; NPV: Negative Predictive Value; NRI: Net Reclassification Improvement; PPV: Positive Predictive Value; ROC: Receiver Operating Characteristic; SD: Standard Deviation

Introduction

Non-valvular atrial fibrillation (AF) is associated – not only with an increased risk of embolic complications – but also with a residual burden of cardiovascular events, despite optimal medical therapy [1,2]. A large number of patients with AF, in fact, have multiple concomitant cardiovascular risk factors (e.g., arterial hypertension, diabetes mellitus, dyslipidemia), which

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contribute to the increased atherosclerotic burden and the increased risk of cardiovascular events [3]. In this regard, data from the ARIC and REGARDS studies showed a nearly two-fold higher risk of myocardial infarction in patients with AF compared to patients without [4,5]. On one hand, identifying these patients is of clinical interest to improve antithrombotic therapy; on the other hand, their management represents a significant clinical challenge due to the need of dual antithrombotic therapy which in turn increase the risk of bleeding [2,6].

Available models for predicting embolic events in AF (e.g., CHA_2DS_2, CHA_2DS_2-VA) were not specifically developed and validated to assess the risk of major adverse cardiovascular events (MACE). Even though some promising data have been recently published, grey areas remain, and a deeper understanding of this topic is warranted [7-9]. The simple ADA score – a prediction model including the three variables of albumin, D-dimer, and age – was recently introduced in clinical practice as it showed good performance in predicting thrombotic events in hospitalized patients with COVID-19 [10]. It has also been validated, with positive results, in other clinical scenarios, including acute myocardial infarction patients undergoing percutaneous coronary intervention and acutely ill hospitalized medical patients [11,12].

For these reasons, we conducted our study with the aim of externally validating the performance of the ADA score for MACE prediction in patients with non-valvular AF receiving anticoagulant therapy.

Methods

Study protocol was approved by local ethical board of Sapienza-University of Rome (Rif. 1306/2007) and conducted in accordance with the principles of Declaration of Helsinki. All patients provided a written informed consent before being included in the study.

Patients followed at the Atherothrombosis Center of the Department of Medical and Cardiovascular Sciences of Sapienza University of Rome were prospectively included from 2013 to 2023 if they have a diagnosis of non-valvular AF and consented to participate in the study. Exclusion criteria included age < 18 years, lack of relevant data or blood sample, refusal to participate in the study. The following data were collected: demographic characteristics (e.g. age, sex category), cardiovascular risk factor (e.g., arterial hypertension, diabetes mellitus), history of cardiovascular disease (e.g., myocardial infarction, ischemic stroke, peripheral arterial disease), thrombotic risk scores (i.e., CHA_2DS_2-VA), concomitant therapies. A blood sample was collected at inclusion for each patient and at 1-year follow-up for 100 randomly selected patients. Details of laboratory measurements are reported in Supplementary Material (Check list).

The ADA score was calculated using the following formula: ADA score = 0.3*age (years) + 0.004*D-dimer (ng/mL) − 0.5*albumin (g/L). A min-max scaling transformation was applied to obtain an ADA score ranging from 0 to 100, as previously reported [10,11]. The optimal ADA score cut-off to discriminate patients with versus without thrombotic events was 49, as proposed by the original derivation study [10].

The outcome of interest comprehends MACE including non-fatal acute myocardial infarction, non-fatal acute ischemic stroke, non-fatal acute peripheral artery event, cardiovascular death during 1-year follow-up.

Sample Collection and Processing

Venous blood samples were collected. For serum analysis, blood was drawn into plain tubes without anticoagulant and allowed to clot at room temperature for approximately 1 hour. For plasma analysis, blood was collected into tubes containing 3.2% sodium citrate as an anticoagulant. All samples were centrifuged at 300 × g for 10 minutes at room temperature. The resulting serum and plasma were aliquoted and stored at −80°C until further analysis.

Measurement of Serum Albumin

Serum albumin concentrations were determined using the Albumin assay kit (DioSystems, REF 23547) following the standard protocol provided by the manufacturer. The measurements were performed on the ACL 9000 analyzer. The method is based on the colorimetric bromocresol green dye-binding technique. Absorbance was measured photometrically, and results were expressed in g/dL. Calibration and internal quality controls were applied before each run to ensure analytical accuracy and precision.

Measurement of plasma D-dimer

Serum D-dimer levels were measured using the HemosIL D-dimer assay (Instrumentation Laboratory, Bedford, MA, USA) according to the manufacturer's instructions. The assay was performed on the ACL 9000 coagulation analyzer (Instrumentation Laboratory). This immunoturbidimetric method is based on latex-enhanced detection of fibrin degradation products. Calibration and quality control procedures were carried out as recommended by the manufacturer. Results were expressed in ng/mL.

Statistical analysis

Baseline characteristics of included patients are reported as descriptive statistics, stratified by groups (i.e., with versus without MACE, and at risk [ADA score ≥49] versus low-risk [ADA score <49]). Categorical variables were reported as counts and percentages. Continuous variables were reported as mean and standard deviation (SD) or median and interquartile range (IQR) values. Categorical variables were compared using chi-squared or Fisher's

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exact tests and continuous variables using Student's t test or the Mann-Whitney U test, as appropriate. Calibration was assessed with Hosmer–Lemeshow test by grouping cases into deciles of risk. Calibration plots were constructed to compare predicted risks to observed risks. Discrimination was assessed c-statistic (i.e., area under receiver operating characteristic [ROC] curve). Comparative discrimination between ADA and CHA_2DS_2-VA scores was assessed with Δ c-statistic (i.e., the difference in c-statistic), integrated discrimination improvement (IDI), and continuous net reclassification improvement (NRI). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of both scores were calculated. RStudio (version 2025.09.1+401, R Core Development Team, Vienna, Austria) was used for the analysis.

Results

Baseline patients' characteristics

Overall, 21 out of 1000 patients (2.1%) experienced a MACE during a 1-year follow-up, and mean ADA score was 49. At 1-year follow-up, mean ADA score did not significantly differ in a subgroup of 100 patients (47, p-value=0.399), whose clinical characteristics did not differ from the entire cohort (not shown). Table 1 reports baseline characteristics of included patients, sorted by MACE occurrence. Patients with MACE were significantly older (82 years vs. 77 years) and more frequently had an history of coronary artery disease (38.9% vs. 15.6%). They also had significantly lower albumin (34 g/L vs. 41 g/L) and higher D-dimer values (789 ng/mL vs. 521 ng/mL) compared to patients without MACE.

Table 1: Characteristics of included patients, sorted by MACE occurrence.

Variables	Without MACE *N=979*	With MACE *N=21*	p-values
Mean age, years (SD)	77 (10)	82 (6)	0.018
Category of age, n (%) < 65 years 65-74 years > 75 years	 102 (10.4) 272 (27.8) 605 (61.8)	 1 (4.8) 3 (14.3) 17 (81.0)	0.201
Female sex, n (%)	452 (46.3)	9 (42.9)	0.929
Mean BMI, kg/m² (SD)	27 (5)	26 (7)	0.467
Cardiovascular risk factors, n (%)			
Arterial hypertension	823 (85.4)	18 (94.7)	0.412
Diabetes mellitus	221 (23.1)	6 (31.6)	0.552
Current smoker	97 (10.5)	2 (10.5)	1.000
Former smokers	411 (44.3)	8 (42.1)	1.000
Heart failure	143 (15.3)	6 (31.6)	0.105
Stroke/TIA, previous	162 (17.1)	1 (5.6)	0.328
CAD, previous	148 (15.6)	7 (38.9)	0.019
Lab values & scores			
Mean albumin, g/l (SD)	41 (15)	34 (14)	0.038
Mean DDimer, ng/mL (SD)	521 (763)	789 (957)	0.114
Mean ADA score (SD)	49 (10)	55 (10)	0.010
Mean CHA_2DS_2-VA (SD)	3 (1)	4 (1)	0.104
Therapies, n (%)			
DOACs Apixaban Dabigatran Edoxaban Rivaroxaban	 404 (41.4) 220 (22.6) 104 (10.7) 247 (25.3)	 8 (38.1) 3 (14.3) 3 (14.3) 7 (33.3)	0.829
ACE-inhibitors	298 (31.6)	5 (29.4)	1.000
ARB	334 (35.4)	8 (47.1)	0.461
Statins	426 (45.0)	10 (58.8)	0.375
Aspirin	69 (7.3)	4 (23.5)	0.041

ARB: Angiotensin Receptor Blocker; BMI: Body Mass Index; CAD: Coronary Artery Disease; DOACs: Direct Oral Anticoagulants; MACE: Major Adverse Cardiovascular Events; SD: Standard Deviation; TIA: Transient Ischemic Attack

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Mean ADA score was significantly higher (55 vs. 49) and mean CHA_2DS_2-VA score was not significantly higher (4 vs. 3) in patients with compared to patients without MACE.

There were no differences in type of direct oral anticoagulants (DOACs) administration and on ACE-inhibitors, angiotensin receptor blockers, and statins use between the two groups. A higher proportion of patients with MACE received concomitant aspirin therapy (23.5% vs. 7.3%).

In Table 2 we sorted patients by their risk as measured by ADA score. Compared to low-risk patients, a high proportion of those at higher risk had arterial hypertension (88.7% vs. 82.2%), heart failure (18.8% vs. 12.1%), a history of stroke/transient ischemic attack (20.7% vs. 12.7%). A lower proportion of patients at higher risk had diabetes mellitus compared to low-risk patients (20.8% vs. 25.9%). There were slight and not significant differences in DOACs administration between the two groups and the proportions of patients in the two subgroups receiving ACE-inhibitors, angiotensin receptor blockers, and statins were similar. Less than 10% of patients in both groups received concomitant aspirin therapy. More importantly, patients at higher risk had a significantly higher rate of MACE compared to low-risk patients (3.4% vs. 0.6%) for a risk ratio of 3.39 (95% CI, 1.23 to 9.32).

Performance of ADA score for MACE prediction

Table 3 reports the metrics of evaluated prediction models that include c-statistics, sensitivity, specificity, PPV, and NPV. Specifically for ADA score, the c-statistic was 0.67 (95% CI, 0.54 to 0.77), sensitivity 86% (95% CI, 43% to 99%), and specificity 50% (95% CI, 46% to 94%). These values were slightly higher than that of CHA_2DS_2-VA score (Table 3 and Figure 1). Supplementary Figure 1 reports calibration plot for evaluated prediction models while Supplementary Table 1 reports metrics of prediction scores comparison.

Table 2: Characteristics of included patients, sorted by baseline ADA score (at risk versus low-risk of MACE).

Variables	At risk patients *ADA score < 49* *N=474*	Low-risk patients *ADA score ≥ 49* *N=526*	p-values
Mean age, years (SD)	71 (10)	82 (6)	<0.001
Category of age, n (%) < 65 years 65-74 years > 75 years	 99 (20.9) 202 (42.6) 173 (36.5)	 4 (0.8) 73 (13.9) 449 (85.4)	<0.001
Female sex, n (%)	209 (44.1)	252 (48.1)	0.229
Mean BMI, kg/m² (SD)	28 (5)	26 (5)	<0.001
Cardiovascular risk factors, n (%)			
Arterial hypertension	387 (82.2)	454 (88.7)	0.005
Diabetes mellitus	121 (25.9)	106 (20.8)	0.074
Current smoker	60 (13.2)	39 (7.9)	0.010
Former smokers	199 (43.8)	220 (44.7)	0.836
Heart failure	55 (12.1)	94 (18.8)	0.005
Stroke/TIA, previous	59 (12.7)	104 (20.7)	0.001
CAD, previous	67 (14.5)	88 (17.5)	0.239
Lab values & scores			
Mean albumin, g/l (SD)	53 (11)	31 (9)	<0.001
Mean DDimer, ng/ml (SD)	418 (691)	626 (820)	<0.001
Mean ADA score (SD)	41 (7)	57 (6)	<0.001
Mean CHA_2DS_2-VA (SD)	3 (1)	4 (1)	<0.001
Therapies, n (%)			
DOACs Apixaban Dabigatran Edoxaban Rivaroxaban	 193 (40.8) 127 (26.8) 37 (7.8) 116 (24.5)	 219 (41.9) 96 (18.4) 70 (13.4) 138 (26.4)	0.004
ACE-inhibitors	149 (32.2)	154 (30.9)	0.726
ARB	160 (34.6)	182 (36.6)	0.549
Statins	214 (46.1)	222 (44.5)	0.657
Antiplatelets	34 (7.4)	38 (7.7)	0.576

ARB: Angiotensin Receptor Blocker; BMI: Body Mass Index; CAD: Coronary Artery Disease; DOACs: Direct Oral Anticoagulants; MACE: Major Adverse Cardiovascular Events; SD: Standard Deviation; TIA: Transient Ischemic Attack

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Table 3: Comparison of ADA score, CHA_2DS_2-VA score, and CHA_2DS_2-VA plus ADA scores in MACE prediction.

	MACE		
	ADA score	***CHA_2DS_2-VA score***	***CHA_2DS_2-VA plus ADA scores***
Goodness of fit, p-values	0.814	0.912	0.955
c-statistic, (95% CI)	0.67 (0.54 to 0.77)	0.60 (0.37 to 0.79)	0.69 (0.57 to 0.79)
Sensitivity, (95% CI)	0.86 (0.43 to 0.99)	0.86 (0.24 to 1.00)	0.76 (0.43 to 0.95)
Specificity, (95% CI)	0.50 (0.46 to 0.94)	0.31 (0.09 to 0.94)	0.64 (0.44 to 0.87)
NPV, (95% CI)	0.99 (0.98 to 1.00)	0.99 (0.98 to 1.00)	0.99 (0.99 to 0.99)
PPV, (95% CI)	0.04 (0.03 to 0.11)	0.03 (0.03 to 0.07)	0.04 (0.03 to 0.09)
MACE includes fatal and non-fatal ischemic stroke/transient ischemic attack, acute myocardial infarction, acute peripheral artery event, cardiovascular death			

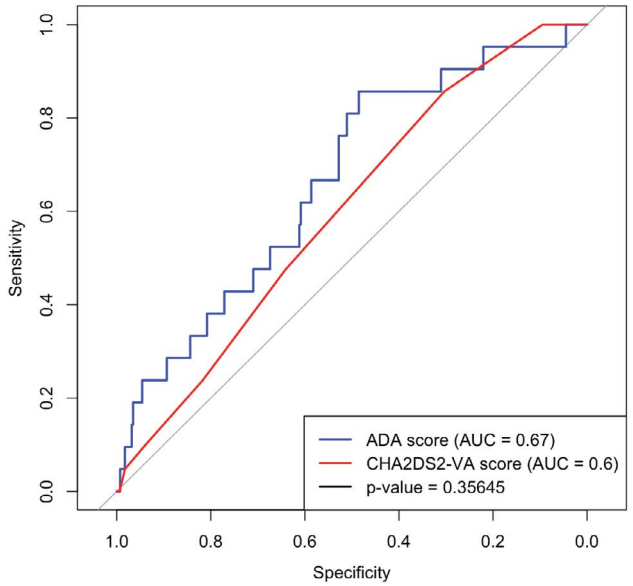

Figure 1: Comparisons between CHA_2DS_2-VA score versus ADA score in MACE prediction.

Discussion

The results of our study show that ADA score is a good model for MACE prediction in patients with non-valvular AF receiving anticoagulant therapy. Patients at risk (ADA score ≥ 49) had a roughly four-fold increased risk of MACE compared to low-risk patients.

From a thrombotic standpoint, all three variables included in the ADA score are relevant and are strongly associated with MACE. Specifically, it is well known that older individuals have higher odds of developing cardiovascular events compared to the younger ones [13,14]. One possible explanation for this phenomenon may be the prolonged exposure to cardiovascular risk factors in the older population [15,16]. It has been reported that even a relatively low burden of these risk factors is associated with a significant increases in the long-term risk of cardiovascular disease [15]. Furthermore, an independent effect of aging on cardiovascular risk has been observed for both myocardial infarction and stroke, possibly due to intrinsic biological aging process [16,17]. D-Dimer – a fibrin degradation product – also predicts the long-term risk of arterial events and cardiovascular mortality, independently by other relevant risk factors [18,19]. A sub-analysis of the LIPID study, which include approximately 8,000 patients with stable coronary heart disease, showed a progressive increase in the risk of myocardial infarction, ischemic stroke, and cardiovascular mortality across increasing D-dimer quartiles [18]. Similar findings were reported in several studies involving patients with AF, in whom D-dimer levels were significantly associated with cardiovascular events and cardiovascular mortality [19-21]. Finally, recent data confirmed that hypoalbuminemia is a relevant risk factor for cardiovascular events development [22,23]. A systematic review and meta-analysis including nearly two million patients reported a two-fold increase in the risk of both acute myocardial infarction and acute ischemic stroke in patients with hypoalbuminemia compared to patients without [22]. Notably, the prevalence of hypoalbuminemia ranged from 19% in hospitalized surgical patients to 33% of medical outpatients, and up to 44% of hospitalized medical patients [22,24-26]. Hypoalbuminemia has been associated not only with the development of AF but also with both thrombotic and bleeding complications in patients with AF receiving anticoagulant therapy [22,24-26].

Our study extends this previous knowledge showing that combining these three variables in the ADA score may constitute a cheap toll to identify those patients with AF at high risk of MACE development despite optimal medical therapy. Our results also suggest the need for a more aggressive management of cardiovascular risk factors and comorbidities in at risk patients as identified by ADA score (i.e., ≥ 49). Even if it should be hypothesized that these latter patients may have a higher inflammatory status possibly justifying the higher D-Dimer and lower albumin values, further studies will be needed.

Our study has some limitations that warrant discussion. First, we included a single center population possibly being

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not completely representative of patients with AF. Second, we cannot exclude that MACE occurrence during follow-up have a different pathophysiological nature (e.g., embolic versus atherosclerotic) possibly limiting the interpretation of results. Third, we cannot evaluate if ADA score modification during follow-up may be associated with a change in cardiovascular risk. The similar ADA score at 1-year follow-up of the evaluated subgroup of patients, however, strengthen the results of main analysis.

In conclusion, ADA score shows good performance in MACE prediction in patients with AF. A more aggressive management of cardiovascular risk factors and comorbidities should be warranted to at risk patients as identified by ADA score (i.e., ≥ 49) that showed a roughly four-fold increased risk of MACE compared to low-risk patients.

Author Contributions: Study conception and design: Pignatelli P., Violi F.; Data acquisition: Cammisotto V., Bartimoccia S., Castellani V., Pannunzio A., Menichelli D.; Statistical analysis: Valeriani E., Violi F.; Interpretation of the data: All authors; Drafting of the manuscript: Pignatelli P., Valeriani E., Violi F.; Critical revision of the manuscript for important intellectual content: All authors; Final approval of the manuscript: All authors.

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