Effects of Atrial Fibrillation and Chronic Kidney Disease on Major Adverse Cardiovascular Events

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Atrial fibrillation (AF) is strongly linked to chronic kidney disease (CKD) and both of these conditions contribute to poor cardiovascular outcomes. We evaluated the impact of renal failure on major adverse cardiovascular events (MACE) in AF, and predictive value of the 2MACE score in this post-hoc analysis of the AMADEUS trial. The primary endpoint was MACE (composite of myocardial infarction, cardiac revascularisation and cardiovascular mortality). Secondary endpoints included the composite of stroke, major bleeding and non-cardiovascular mortality, and each of the specific outcomes separately. Of the 4,554 patients, 1,526 (33.5%) were females and the median age was 71 (IQR 64 to 77) years. There were 3,838 (84.3%) non-CKD and 716 (15.7%) CKD patients. The incidence of cardiovascular and non-cardiovascular mortality were 1.41% and 2.44% per 100 patient-years, respectively. There was no significant difference in crude study endpoints between the groups. Multivariable regression analysis found no association between CKD and MACE (HR 1.03 [95% CI, 0.45 to 2.34]). The c-index of the 2MACE score for MACE was 0.65 (95% CI, 0.59 to 0.71, p <0.001). In the presence of CKD, each additional point of the 2MACE score contributed to a greater risk of MACE (HR 3.17 [95% CI, 1.28 to 7.85] vs 1.48 [95% CI, 1.17 to 1.87] in the non-CKD group). In conclusion, the 2MACE score may be a useful tool for clinical risk stratification of high-risk AF patients with CKD and those at high MACE risk could be targeted for more intensive cardiovascular prevention strategies. The presence of CKD was not found to be independently associated with MACE in AF patients. **(Am J Cardiol 2020;132:72−78)**

There is a high incidence of cardiac-related complications in patients with atrial fibrillation (AF). A post-hoc analysis of ROCKET-AF found that 72% of deaths in the study were cardiovascular-related, whereas only 6% were caused by nonhemorrhagic stroke or systemic embolism.[1] The finding suggests that despite a preponderance of cerebrovascular and systemic embolisms in AF, that these do not account for the majority of excess deaths. Pastori et al previously described the 2MACE score which had good discriminative ability for major adverse cardiovascular events (MACE) in patients with AF.[2]

Although AF and chronic kidney disease (CKD) are closely related conditions,[3,4] the influence of CKD on MACE in AF has not been properly investigated. Therefore, the objectives of this study were to evaluate the impact of renal failure on MACE in AF, and the predictive value of the 2MACE score in this setting.

Methods

We included patients from the AMADEUS (Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation) trial. Details of the study design have previously been published.[5] In brief, this was a multicenter, randomized, and open-label noninferiority study with blinded outcomes assessment that compared fixed-dose idraparinux with dose-adjusted vitamin K antagonist in patients with nonvalvular AF. Study participants were enrolled between September 2003 and July 2005. The exclusion criteria included transient AF caused by a reversible condition, any indication for vitamin K antagonist other than AF, active or high-risk of bleeding, creatinine clearance <10 mL/min, severe liver disease, and uncontrolled hypertension.

Serum creatinine, sex, age and ethnicity were available for the calculation of estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[6] Study participants with missing variables to determine eGFR were excluded and the remainder were categorized into 2 groups based on the presence of CKD. For the purposes of this analysis, CKD was defined as eGFR <60 ml/min/1.73 m^2. The primary endpoint was MACE (composite of myocardial infarction [MI], cardiac revascularization, and cardiovascular mortality). Secondary endpoints included OCRE (other clinically relevant events; defined as a composite of stroke, major bleeding and non-cardiovascular mortality) and each of the specific outcomes.

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These endpoints were adjudicated outcomes in this clinical trial cohort.

The 2MACE score was determined by assigning 2 points for metabolic syndrome and age ≥75 years, and 1 point for previous MI or cardiac revascularization, congestive heart failure (ejection fraction <40%), and prior thromboembolism.[2] The CHA_2DS_2-VASc, $CHADS_2$, and HAS-BLED scores were determined as previously described.[7–9]

Continuous variables were assessed for normality with Kolmogorov-Smirnov test. The variables with a normal distribution were described with means and standard deviations, and tested for differences with *t* test. The variables without normal distribution were described with medians and interquartile ranges (IQRs), and tested for differences with Mann-Whitney *U* test. Categorical variables were described with counts and %, and tested for differences with chi-squared test or Fisher's exact test.

Univariate cox regression analysis was used to compare the hazard ratio (HR) between the groups. Plots of Kaplan-Meier curves were performed and survival distributions compared with log-rank test. Predictive capability of the 2MACE score for primary outcome was investigated using receiver-operating characteristic curves, and the performance was tested against the CHA_2DS_2-VASc, $CHADS_2$, and HAS-BLED scores. Area under the curve (AUC) was used to reflect the c-index, which represents the ability of scores to predict events.

Multivariable regression analyses were performed to identify independent predictors of MACE and evaluate the implementation of these scoring tools as prognostic markers based on renal function. The models were adjusted for important variables that were significantly different between the groups at baseline, excluding those that were already incorporated in each scoring tool. A sensitivity analysis of the primary outcome was performed after propensity score matching that adjusted for possible differences in baseline characteristics between the groups. Patients were matched in a 1:1 ratio based on propensity score generated by logistic regressions with a match tolerance of 0.1 and using the nearest-neighbor technique without replacement. A 2-sided p value of <0.05 was considered statistically significant. Analyses were performed using SPSS software version 24 (IBM Corp, Armonk, New York) and MedCalc version 19.4.0.

Results

The AMADEUS trial recruited 4,576 patients and data was available for calculation of eGFR in 4,554 (99.5%) patients. The final study cohort comprised of 1,526 (33.5%) females with a median age of 71 (IQR 64 to 77) years (Table 1). In the warfarin arm, the median time in therapeutic range was 58 (IQR 45 to 70) %. Median eGFR was 86.2 (IQR 68.7 to 94.0) mL/min/1.73 m^2, of which 3,838

Table 1
Baseline characteristics according to renal function

Variable	Total (n = 4554)	Non-CKD (n = 3838)	CKD (n = 716)	p Value
Age (years), median (IQR)	71 (64 – 77)	73 (66 – 77)	63 (57 – 69)	<0.0001
Women	1526 (33.5%)	1231 (32.1%)	295 (41.2%)	<0.0001
emoglobin levels (g/L), median (IQR)	143 (133 – 153)	143 (132 – 152)	145 (134 – 155)	0.022
eGFR (mL/min/1.73m^2), median (IQR)	86.2 (68.7 – 94.0)	88.6 (79.1 – 95.3)	51.0 (44.1 – 56.0)	<0.0001
AF type				0.456
Paroxysmal	1625 (35.8%)	1357 (35.5%)	268 (37.6%)	
Persistent	434 (9.6%)	372 (9.7%)	62 (8.7%)	
Permanent	2477 (54.6%)	2095 (54.8%)	382 (53.7%)	
Comorbidities				
Coronary artery disease	1403 (30.8%)	1265 (33.0%)	138 (19.3%)	<0.0001
Diabetes mellitus	892 (19.6%)	716 (18.7%)	176 (24.6%)	0.0002
Heart failure	1069 (23.5%)	937 (24.4%)	132 (18.4%)	0.001
Hypertension	3514 (77.2%)	2886 (75.2%)	628 (87.7%)	<0.0001
Prior thromboembolism	1084 (23.8%)	970 (25.3%)	114 (15.9%)	<0.0001
Previous ischemic stroke	573 (12.6%)	505 (13.2%)	68 (9.5%)	0.007
Antiplatelet use				
Aspirin	746 (16.4%)	643 (16.8%)	103 (14.4%)	0.116
Clopidogrel or ticagrelor	66 (1.4%)	60 (1.6%)	6 (0.8%)	0.136
Risk scores				
CHA_2DS_2-VASc score, median (IQR)	3 (2 – 4)	3 (2 – 5)	3 (2 – 4)	<0.0001
CHADS2 score, median (IQR)	2 (1 – 3)	2 (1 – 3)	1 (1 – 2)	<0.0001
HAS-BLED score, median (IQR)	1 (1 – 2)	2 (1 – 2)	1 (1 – 2)	<0.0001
2MACE score (points)				
Median (IQR)	1 (0 – 2)	2 (1 – 3)	0 (0 – 1)	<0.0001
By category				<0.0001
0	1205 (26.5%)	840 (21.9%)	365 (51.0%)	
1	1230 (27.0%)	1022 (26.6%)	208 (29.1%)	
2	1083 (23.8%)	981 (25.6%)	102 (14.2%)	
3	708 (15.5%)	673 (17.5%)	35 (4.9%)	
4	280 (6.1%)	274 (7.1%)	6 (0.8%)	
5	48 (1.1%)	48 (1.3%)	0 (0.0%)	

AF = atrial fibrillation; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; IQR = interquartile range.

Table 2
Major adverse events according to renal function

	CKD vs non-CKD	
	HR (95% CI)	p Value
MACE	0.53 (0.24 − 1.14)	0.104
Myocardial infarction	0.62 (0.19 − 2.04)	0.430
Cardiac revascularisation	0.82 (0.32 − 2.09)	0.671
Cardiovascular mortality	0.41 (0.15 − 1.13)	0.084
OCRE	0.66 (0.43 − 1.01)	0.054
Any stroke	0.52 (0.19 − 1.45)	0.212
Major bleeding	0.70 (0.39 − 1.25)	0.224
Non-cardiovascular mortality	0.61 (0.32 − 1.17)	0.137

CI = confidence interval; CKD = chronic kidney disease; HR = hazard ratio; MACE = major adverse cardiovascular events; OCRE = other clinically relevant events.

(84.3%) patients had an eGFR ≥60 mL/min/1.73 m^2 (non-CKD group) and 716 (15.7%) patients had an eGFR <60 mL/min/1.73 m^2 (CKD group). Patients recruited with CKD were younger, more likely to be females and had a higher prevalence of hypertension and diabetes mellitus but lower prevalence of coronary artery disease (CAD), heart failure, prior thromboembolism and anemia.

After a median (IQR) follow-up of 346 (185 to 457) days, there were 79 (1.7%) MACE and 220 (4.8%) OCRE which occurred at a rate of 1.94% and 5.43% per 100 patient-years (PYs), respectively. The incidence of cardiovascular mortality was 1.41% per 100 PYs and non-cardiovascular mortality was 2.44% per 100 PYs. Overall, there was no statistical difference in crude incidence of MACE, OCRE or specific major adverse events between the groups (Table 2). The HR for the CKD versus non-CKD group for MACE was 0.53 (95% confidence interval [CI] 0.24 to 1.14, p = 0.104), and OCRE was 0.66 (95% CI 0.43 to 1.01, p = 0.054). Kaplan-Meier survival analyses found no statistical difference in terms of MACE (log-rank p = 0.098) and OCRE (log-rank p = 0.053) between both groups (Figure 1).

On multivariable regression analysis, independent predictors for MACE were age (HR 1.06 per year increase [95% CI 1.03 to 1.10]), CAD (HR 2.03 [95% CI 1.28 to 3.19]) and heart failure (HR 1.65 [95% CI 1.03 to 2.66]) (Figure 2), after adjustment for sex, presence of CKD, diabetes mellitus, hypertension and prior thromboembolism. The presence of CKD was not found to be independently associated with MACE (HR 1.03 [95% CI 0.45 to 2.34]).

Using receiver-operating characteristic curve analysis, the AUC of the 2MACE score for prediction of MACE was 0.65 (95% CI 0.59 to 0.71, p <0.001) (Figure 3). The AUC of the CHA_2DS_2-VASc, $CHADS_2$ and HAS-BLED scores were lower at 0.64 (95% CI 0.57 to 0.70), 0.61 (95% CI 0.55 to 0.67) and 0.63 (95% CI 0.57 to 0.69), respectively. However, these differences were not statistically significant when compared with the 2MACE score (p >0.05). Each additional point of the 2MACE score was associated with an adjusted HR for MACE of 1.57 (95% CI 1.26 to 1.96, p <0.001). In the presence of CKD, each additional point of the 2MACE score was associated with a greater risk of MACE (HR 3.17 [95% CI 1.28 to 7.85] vs 1.48 [95% CI 1.17 to 1.87] in the non-CKD group), after adjustment for other comorbidities (Table 3). In general, similar increments were obtained when the CHA_2DS_2-VASc, $CHADS_2$ and HAS-BLED scores were utilized. In terms of MACE, there was a significant interaction between CKD and 2MACE (p = 0.036) that was not demonstrated with the other risk scores (p >0.05).

Sensitivity analysis using a propensity score matched cohort of 714 patients with similar baseline characteristics (p >0.05) across the groups found no statistically significant difference in terms of MACE between the CKD versus non-CKD groups (HR 1.04 [95% CI 0.26 to 4.14, p = 0.961]).

Discussion

The main findings in this study were that although CKD per se was not found to be an independent predictor of MACE in AF patients, it appeared to have synergistic effect with other comorbidities included in the 2MACE score. As a result, each component in this tool contributed to a greater risk of MACE in the presence of CKD. Furthermore, the 2MACE score may be a useful tool for clinical risk stratification of high-risk subgroups in AF with better predictive capabilities than the CHA_2DS_2-VASc, $CHADS_2$ and HAS-BLED scores.

There exists a bidirectional relationship between AF and CAD such that AF may herald or occur as a result of manifest CAD.[10,11] It was estimated that the prevalence of AF in patients with the established atherosclerotic disease was 5-fold higher compared with the general population.[12] Furthermore, AF itself was independently associated with an increased risk of MI and cardiovascular mortality.[13] A systematic review of observational studies found that the incidence of MI in AF patients ranged from 0.4% to 2.5% per year.[14] However, the authors also reported that the rate of MI was up to 11.5% per year among AF patients with known stable CAD. A possible cause of MI in patients with AF may be related to embolic events to the coronary arteries. Indeed, the most frequent cause of MI secondary to coronary embolization was found to be AF and this was associated with a 9-fold increased risk of cardiovascular mortality compared with MI due to other causes.[15]

A study of consecutive patients with acute coronary syndrome from the Analysis of Delay in Acute Myocardial Infarction (ARIAM) registry demonstrated that new-onset AF was an independent predictor for MACE and mortality.[16] Similar findings were described by Worme et al who performed a retrospective analysis of the Global Registry of Acute Coronary Events (GRACE) registry.[17] Among patients with atherosclerotic disease, AF was associated with a 2-fold increase in MACE during a 4-year follow-up period.[18] Interestingly, authors of the study reported that there was a linear correlation between MACE and CHA_2DS_2-VASc score.

Overall, there is limited and conflicting evidence on the effects of CKD on MACE in patients with AF. Polovina et al demonstrated that there was a significantly greater prevalence of CKD among AF patients who suffered a MACE (26.8% vs 17.6% without MACE).[19] In a large cohort study involving 77,752 AF patients with or at risk of atherosclerotic disease, the cumulative incidence of MACE at 4 years was 9.9%, occurring at a rate of 2.95 events/100

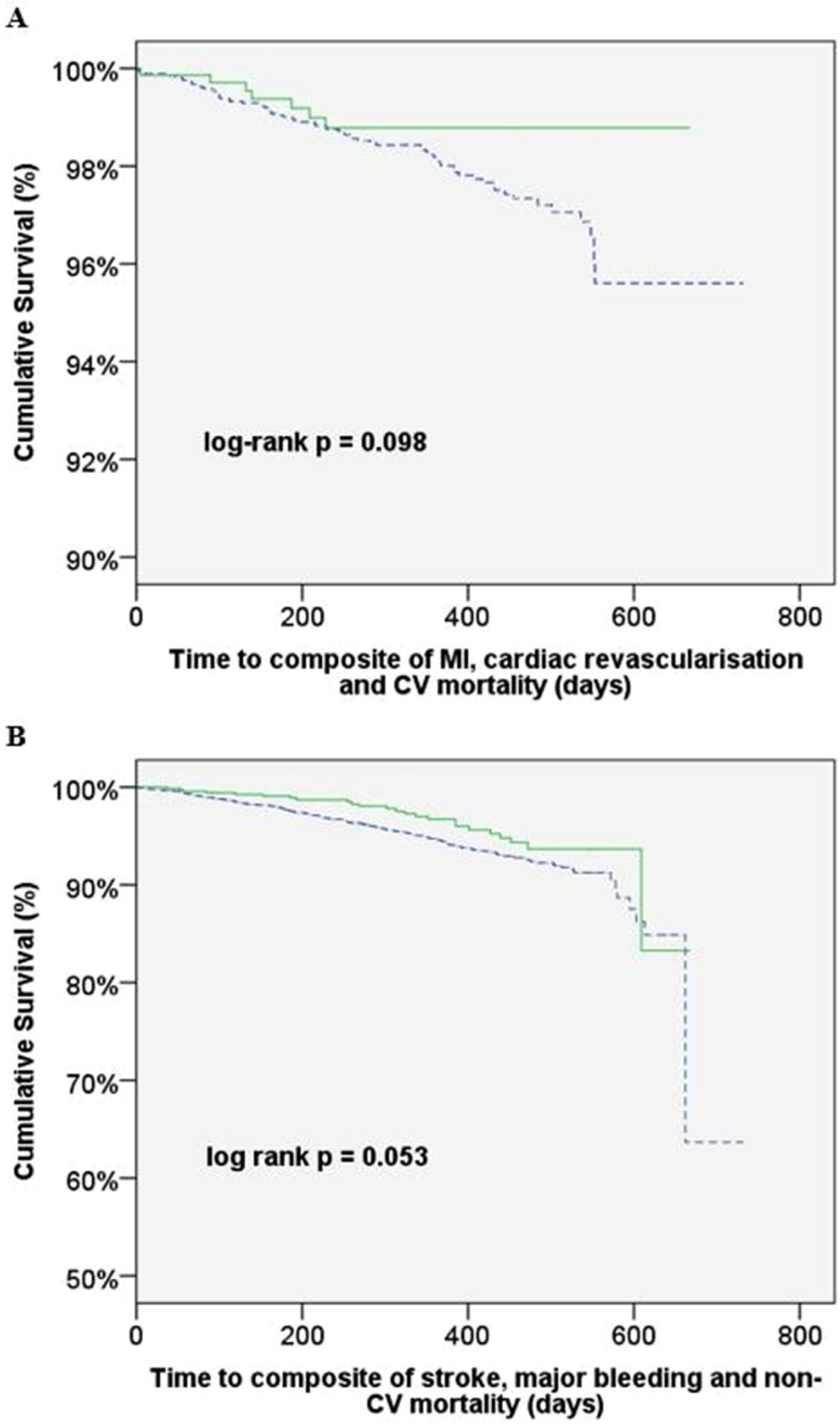

Figure 1. Kaplan-Meier analysis for composite outcomes of MACE (composite of myocardial infarction, cardiac revascularisation and cardiovascular mortality; (*A*), and OCRE (composite of stroke, major bleeding and non-cardiovascular mortality; (*B*). (dashed line: non-CKD; solid line: CKD).

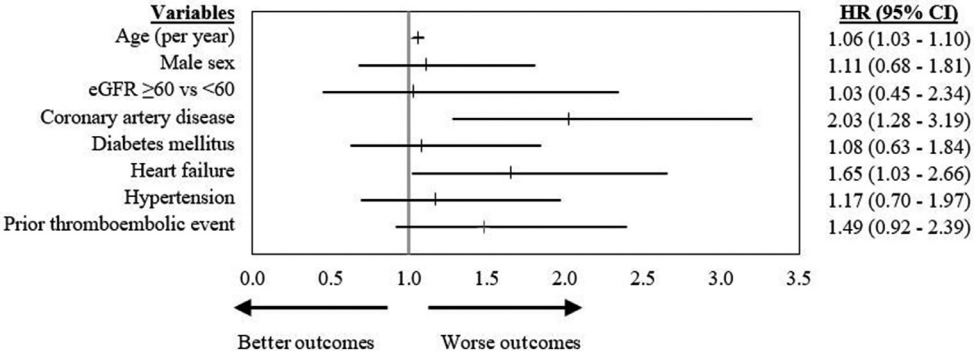

Figure 2. Multivariable cox regression analysis for independent predictors of MACE (composite of myocardial infarction, cardiac revascularisation and cardiovascular mortality).

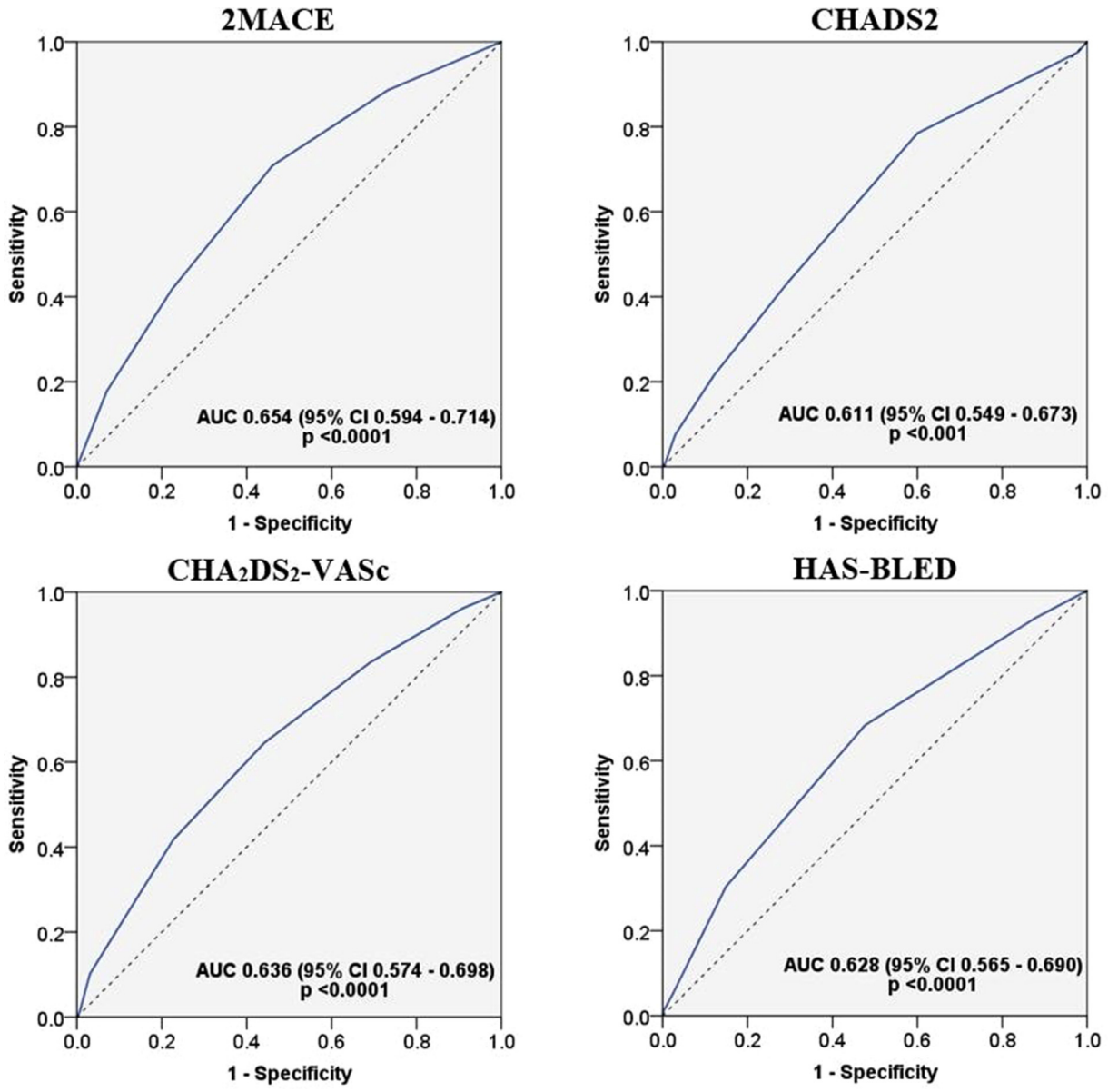

Figure 3. Receiver-operating characteristic curves comparison for MACE (composite of myocardial infarction, cardiac revascularisation and cardiovascular mortality) with the 2MACE, CHA_2DS_2-VASc, $CHADS_2$ and HAS-BLED scores.

Table 3
Multivariable regression for major adverse cardiovascular events based on 2MACE, CHA_2DS_2-VASc, CHADS2 and HAS-BLED scores

	2MACE*		CHA_2DS_2-VASc†		CHADS2‡		HAS-BLED§	
MACE	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	*p* value	HR (95% CI)	p Value
Non-CKD group	1.48 (1.17 − 1.87)	0.001	1.41 (1.17 − 1.71)	<0.001	1.42 (1.12 − 1.80)	0.004	1.28 (0.94 − 1.76)	0.122
CKD group	3.17 (1.28 − 7.85)	0.013	2.03 (1.07 − 3.86)	0.031	2.57 (1.05 − 6.32)	0.039	2.10 (0.81 − 5.44)	0.126

CI = confidence interval; CKD = chronic kidney disease; HR = hazard ratio; MACE = major adverse cardiovascular events; MI = myocardial infarction.
* Adjusted for anemia, diabetes mellitus, hypertension and sex.
† Adjusted for anemia.
‡ Adjusted for anemia, coronary artery disease and sex.
§ Adjusted for anemia, coronary artery disease, diabetes mellitus, heart failure and sex.

PYs.[20] The authors found that CKD stage ≥3 was independently associated with MACE. However, it was observed that the study had low rates (64.4%) of oral anticoagulation use among patients with a valid indication. In contrast, a prospective cohort study by Blann et al found that eGFR was not independently associated with MACE, after adjustment for other risk factors.[21] The authors reported that the CHA_2DS_2-VASc score and number of clinic visits were the only independent predictors of MACE. However, it was acknowledged that renal function was likely to remain important due to its effects on anticoagulation therapy.[21] In our study, there was no association between CKD and MACE in AF, after accounting for other risk factors. This was further confirmed in our sensitivity analysis using a propensity score matched cohort of patients with similar baseline characteristics. In addition, though there was a significant number of MACE, the predominant complications were stroke, major bleeding and non-cardiovascular mortality.

The 2MACE score was previously developed for risk stratification of MACE in AF. Results from internal and external derivation cohorts showed a c-index of 0.79 and 0.66, respectively.[2] Pastori et al demonstrated that each additional point of the 2MACE score was associated with an adjusted HR of 1.61 (95% CI 1.40 to 1.85), which is similar to that found in the present analysis. Moreover, a new finding from this study is that the 2MACE score may be useful in a high-risk subgroup of AF patients, such as those with CKD.

There are several potential mechanisms linking AF, CKD and CAD. All these conditions have been associated with chronic low-grade inflammation and oxidative stress that may involve increased levels of oxidized lipoproteins known to cause endothelial injury.[22−25] Furthermore, each has been shown to be related to hypercoagulability [25−27] and endothelial dysfunction.[28−30]

In terms of limitations, the findings from this study were based on a post-hoc analysis of the AMADEUS trial and should therefore be interpreted with caution. Given that diabetes mellitus and hypertension are 2 important causes of CKD, we may have detected a significant difference in the results with a longer follow-up duration. Exclusion of patients with creatinine clearance of <10 mL/min indicates that the results should not be extrapolated to patients with end-stage renal disease. Furthermore, our trial participants may not be representative of the real-world population who tend to be older with more comorbidities. The CHA_2DS_2-VASc, $CHADS_2$ and HAS-BLED scores were not specifically developed to evaluate MACE, though the former has been found to be useful for this purpose.[18,21] This analysis highlights that the HAS-BLED score which was designed as a bleeding risk assessment tool should not be used to assess MACE.

The 2MACE score may be a useful tool for clinical risk stratification of high-risk AF patients with CKD. Those at high MACE risk could be targeted for more intensive cardiovascular prevention strategies. The presence of CKD was not found to be independently associated with MACE in AF patients.

Author contributions

Wern Yew Ding: Data curation; Formal analysis; Methodology; Visualization; Roles/Writing - original draft. *Gregory Y. H. Lip:* Conceptualization; Project Administration; Supervision; Validation; Writing - review & editing. *Daniele Pastori:* Validation; Writing - review & editing. *Alena Shantsila:* Data curation; Project Administration; Supervision; Validation; Writing - review & editing

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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