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

Short title: MACE with AF and CKD

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# Abstract

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 64-77) 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,0.45-2.34]). The c-index of the 2MACE score for MACE was 0.65 (95% CI,0.59-0.71, *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,1.28-7.85] vs 1.48 [95% CI,1.17-1.87] 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.

**Keywords** Atrial fibrillation; chronic kidney disease; major adverse cardiovascular events; 2MACE

# Introduction

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 non-haemorrhagic 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 multicentre, randomised, open-label non-inferiority study with blinded outcomes assessment that compared fixed-dose idraparinux with dose-adjusted vitamin K antagonist (VKA) in patients with non-valvular 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 VKA 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 categorised 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 m2. The primary endpoint was MACE (composite of myocardial infarction (MI), cardiac revascularisation 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. 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 CHA2DS2-VASc, CHADS2 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 (ROC) curves, and the performance was tested against the CHA2DS2-VASc, CHADS2 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-neighbour 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, NY) 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 - 77) years (Table 1). In the warfarin arm, the median time in therapeutic range was 58 (IQR 45 - 70) %. Median eGFR was 86.2 (IQR 68.7 - 94.0) mL/min/1.73 m2, of which 3,838 (84.3%) patients had an eGFR ≥60 mL/min/1.73 m2 (non-CKD group) and 716 (15.7%) patients had an eGFR <60 mL/min/1.73 m2 (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 anaemia.

After a median (IQR) follow-up of 346 (185 - 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 vs non-CKD group for MACE was 0.53 (95% confidence interval [CI] 0.24 - 1.14, *p* = 0.104), and OCRE was 0.66 (95% CI 0.43 - 1.01, *p* = 0.054). Kaplan-Meier survival analysis 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 - 1.10]), CAD (HR 2.03 [95% CI 1.28 - 3.19]) and heart failure (HR 1.65 [95% CI 1.03 - 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 - 2.34]).

Using ROC curve analysis, the AUC of the 2MACE score for prediction of MACE was 0.65 (95% CI 0.59 - 0.71, *p* < 0.001) [Figure 3]. The AUC of the CHA2DS2-VASc, CHADS2 and HAS-BLED scores were lower at 0.64 (95% CI 0.57 - 0.70), 0.61 (95% CI 0.55 - 0.67) and 0.63 (95% CI 0.57 - 0.69), respectively. However, these differences were not statistically significant when compared to 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 - 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 - 7.85] vs 1.48 [95% CI 1.17 - 1.87] in the non-CKD group), after adjustment for other comorbidities. In general, similar increments were obtained when the CHA2DS2-VASc, CHADS2 and HAS-BLED scores were utilised. 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 vs non-CKD groups (HR 1.04 [95% CI 0.26 - 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 CHA2DS2-VASc, CHADS2 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 to 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 embolisation was found to be AF and this was associated with a 9-fold increased risk of cardiovascular mortality compared to 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 CHA2DS2-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 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 CHA2DS2-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 - 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 oxidised 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 two 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 CHA2DS2-VASc, CHADS2 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.

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# Figure Legends

**Figure 1**. Kaplan-Meier analysis for composite outcomes of MACE (composite of myocardial infarction, cardiac revascularisation and cardiovascular mortality; 1A), and OCRE (composite of stroke, major bleeding and non-cardiovascular mortality; 1B). (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, CHA2DS2-VASc, CHADS2 and HAS-BLED scores