Adverse Clinical Outcomes and Associated Predictors in Rivaroxaban-Treated Atrial Fibrillation Patients With Renal Impairment

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Renal impairment confers worse prognosis in patients with atrial fibrillation (AF) but there is scarce evidence about the influence of direct-acting oral anticoagulants in routine clinical practice. Herein, we compared clinical outcomes between patients with AF with and without renal impairment on rivaroxaban and investigated predictors for clinical outcomes in patients with AF with renal impairment. This was a multicenter study including patients with AF on rivaroxaban for at least 6 months. During 2.5 years follow-up, ischemic strokes (IS)/transient ischemic attacks (TIA)/systemic embolisms (SE)/myocardial infarctions (MI), major bleeding, and major adverse cardiovascular events (MACE) were recorded. Creatinine clearance (CrCl) was estimated using the Cockroft-Gault equation, renal impairment was defined as a CrCl <60 ml/min, and 1,433 patients (34.8% with CrCl <60 ml/min) were included. Patients with CrCl <60 ml/min showed higher event rates for major bleeding (1.87%/year vs 0.62%/year; p = 0.003) and MACE (1.97%/year vs 0.62%/year; p = 0.002) but similar event rates for IS/TIA/SE/MI (0.66%/year vs 0.67%/year; p = 0.955). In patients with renal impairment, CHA_2DS_2-VASc was associated with higher risk of IS/TIA/SE/MI; HAS-BLED and any dependency level were associated with higher risk of major bleeding; and male gender and heart failure were associated with higher risk of MACE. Antiplatelets were independently associated with increased risk of IS/TIA/SE/MI and MACE. In conclusion, in patients with AF on rivaroxaban, the incidence of IS/TIA/SE/MI did not increase in those with renal impairment, suggesting that rivaroxaban may be an effective option in this subgroup. In patients with AF, male gender, heart failure, dependency, antiplatelets, CHA_2DS_2-VASc, and HAS-BLED were associated with increased risk of adverse outcomes. **(Am J Cardiol 2023;203:122−127)**

Atrial fibrillation (AF) increases the risk of stroke,[1,2] and patients with renal impairment present an elevated cardiovascular risk.[3] Indeed, the incidence and prevalence of AF and chronic kidney disease (CKD) are increasing, and both conditions commonly coexist and are closely related to shared risk factors.[4,5] Despite direct-acting oral anticoagulants (DOACs) have demonstrated to be at least as effective and safe as warfarin in CKD,[6] patients with AF and renal impairment are often underrepresented in the pivotal DOACs trials. For this reason, it is not clear if DOACs

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See page 126 for Declaration of Competing Interest.

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reduce the incidence of adverse events in patients with AF with renal impairment compared with patients with AF with preserved renal function, and those factors affecting the risk of adverse events in patients with AF with renal impairment on DOACs have also not been further investigated. Our primary objective was to compare the incidence of clinical outcomes in patients with AF with and without renal impairment under rivaroxaban therapy included in the national, observational, and multicenter *Estudio observacional para la identificación de los factores de riesgo asociados a eventos cardiovasculares Mayores en pacientes con fIbrilación auricular no valvular tratados con un anticoagulante oral directo (rivaroxaban)* (EMIR) study. As secondary objective, we aimed to investigate predictors of adverse clinical outcomes in patients with AF with renal impairment from such cohort.

Methods

The EMIR registry is a postauthorization, observational, and multicenter study including patients ≥18 years old with documented AF and treated with rivaroxaban for at least 6 months at the time of inclusion. Patients participating in another research study, starting rivaroxaban therapy after the inclusion period, with moderate to severe mitral stenosis or prosthetic heart valves, severe cognitive impairment, chronic infectious or systemic autoimmune diseases, active cancer, or significant liver insufficiency, were excluded.

At baseline, demographic data, physical examination, blood sample results, co-morbidities, and previous drugs therapies were recorded in a specific electronic case report form. The risk of thromboembolism was assessed by the $CHADS_2$ and CHA_2DS_2-VASc scores, whereas the bleeding risk was estimated by the HAS-BLED score.

For the purpose of this analysis, baseline creatinine was used to assess renal function using the Cockcroft−Gault equation for the estimation of creatinine clearance (CrCl). Renal impairment was defined as a CrCl <60 ml/min. Notably, no exclusion of patients was performed based on a determined cut-off value for CrCl; therefore, patients with a CrCl <30 ml/min (including CrCl <15 ml/min) were suitable for the study.

The study included the collection of information at 4 time points: baseline, follow-up at 1-year, follow-up at 2 years, and the final follow-up at 2.5 years. All study visits coincided with any routine clinical visit of the patient. The assignment of a patient to a particular therapeutic strategy was not decided previously by the study protocol but was left to the discretion of the physician responsible for the patient. Therefore, the present study did not interfere with routine clinical practice. All data were collected by the researchers through clinical interviews or from medical records, according to the usual clinical practice and without any additional procedure in relation to the study.

During the follow-up, all clinical outcomes were recorded. The primary end points for this study were the composite of all ischemic strokes (IS)/transient ischemic attacks (TIA)/systemic embolisms (SE)/myocardial infarctions (MI); major bleeding and major adverse cardiovascular events (MACE; defined as fatal/nonfatal MI, myocardial revascularization, or cardiovascular death). To ensure data collection, if a patient was not able to attend any of the study visits, telephone visits were performed to comply with the follow-up. If the patient died during the follow-up period, a family member attended the telephone visits.

All patients gave their written informed consent for participation. The study obtained the approval of the ethics committee of each of the participating centers and was performed according to the standards laid down in the Declaration of Helsinki and the current Spanish legislation on conducting observational studies (Ministerial Order SAS/3470/2009).

Continuous variables were described as mean (±SD) or as median (and interquartile range), as appropriate. Categorical variables were described using absolute frequencies and percentages.

For the comparison of categorical variables, the chi-square or Fisher's exact test statistic was used, depending on the percentage of cells obtained with an expected frequency of <5. For the comparison of 2 means, the *t* test or Mann-Whitney *U* test will be used, depending on whether the variables followed a normal distribution.

Annual event rates (i.e., incidence rates) with their Poisson 95% confidence interval [CI] were calculated for patients with and without renal impairment as the number of adverse clinical outcomes divided by the exposure period in patients-years, and expressed as number of events per 100 patients-years. The difference between 2 annual event rates and the associated p value was calculated.

To assess which factors were independently associated with adverse outcomes, we performed logistic regression analyses by stepwise selection. A univariate significance level of 0.15 was required to allow a variable into the multivariate model (SLENTRY = 0.15) and a multivariate significance level of 0.05 was required for a variable to stay in the model (SLSTAY = 0.05). Missing data or lost values were not imputed to avoid information bias. Missing data for important variables were controlled by filters when collecting data from the electronic case report form.

A p value <0.05 was considered statistically significant. Data have been analyzed using SPSS v. 18.0 (Armonk, New York).

Results

In total, 1,433 patients with a mean age of 74.2 ± 9.7 years (638, 44.5% female) were included. The mean CHA_2DS_2-VASc score was 3.5 ± 1.5, whereas the mean HAS-BLED was 1.6 ± 1.0.

At inclusion, data about creatinine and weight was available in 1,417 patients. The mean glomerular filtration rate (GFR) in this remained cohort was 74.6 ± 30.5 ml/min and 498 (34.8%) patients had a CrCl <60 ml/min according to the Cockcroft−Gault equation. Specifically, 4 patients (0.3%) had a CrCl <15 ml/min, 39 patients (2.8%) had a CrCl 15 to 29 ml/min, 156 patients (11%) had a CrCl 30 to 44 ml/min, and 299 patients (21.1%) had a CrCl 45 to 59 ml/min. Compared with patients with preserved renal function, patients with CrCl <60 ml/min were older, more frequently female, and had higher prevalence of hypertension, heart failure, previous history of stroke/TIA,

Table 1
Baseline clinical characteristics

	Overall Cohort (n = 1,433)	Creatinine Clearance ≥60 ml/min (n = 919)*	Creatinine Clearance <60 ml/min (n = 498)*	p Value
Demographic				
Age (years), mean (SD)	74.2 (9.7)	70.4±8.8	81.2±7.0	<0.001
Male sex, n (%)	795 (55.5)	587 (63.9)	204 (41.0)	<0.001
BMI (kg/m^2), mean (SD)	29.1 (4.9)	30.2±5.0	27.2±4.1	<0.001
Comorbidities, n (%)				
Hypertension	1,137 (79.3)	712 (77.5)	411 (82.5)	0.025
Diabetes mellitus	388 (27.1)	269 (29.3)	117 (23.5)	0.020
Heart failure	326 (22.7)	192 (20.9)	133 (26.7)	0.013
History of stroke/TIA	179 (12.4)	712 (77.5)	411 (82.5)	0.025
Coronary artery disease	235 (16.4)	147 (16.0)	85 (17.1)	0.652
Peripheral artery disease	58 (4.0)	712 (77.5)	411 (82.5)	0.025
Hypercholesterolemia	790 (55.1)	512 (55.7)	273 (54.8)	0.747
Current smoking habit	75 (5.2)	60 (6.5)	14 (2.8)	0.003
Current alcohol consumption	130 (9.1)	103 (11.2)	27 (5.4)	<0.001
History of previous major bleeding	46 (3.2)	25 (2.7)	20 (4.0)	0.184
Chronic Obstructive Pulmonary Disease	151 (10.5)	99 (10.8)	50 (10)	0.668
Creatinine clearance (ml/min), mean (SD)	74.6±30.5	90.1±26.4	46.1±10.4	<0.001
Hepatic disease	10 (0.7)	4 (0.4)	6 (1.2)	0.109
Concomitant malignant disease	80 (5.6)	47 (5.1)	32 (6.4)	0.304
Any dependency	140 (9.8)	53 (5.9)	86 (17.7)	<0.001
Partial dependence for daily activities	126 (8.8)	49 (5.4)	76 (15.7)	<0.001
Total dependence for daily activities	14 (1.0)	4 (0.4)	10 (2.1)	0.008
Concomitant antiplatelet use	97 (6.8)	65 (7.1)	31 (6.2)	0.544
Rivaroxaban dosage, n (%)				
20 mg	1,095 (77.3)	841 (91.5)	254 (51.0)	<0.001
15 mg	322 (22.7)	78 (8.5)	244 (49.0)	<0.001
CHA_2DS_2-VASc, mean (SD)	3.5 (1.5)	3.1±1.5	4.2±1.4	<0.001
HAS-BLED, mean (SD)	1.6 (1.0)	1.3±0.9	2.0±1.0	<0.001

* Baseline data for assessing renal function with the Cockcroft−Gault was available in 1,417 patients.

BMI = body mass index; CHA_2DS_2-VASc = congestive heart failure or left ventricular dysfunction (1) hypertension (1) age ≥75 (2) or 65 to 74 (1) diabetes mellitus (1) previous stroke/TIA or systemic embolism (2) vascular disease (peripheral artery disease, myocardial infarction, aortic plaque) (1) sex category (i.e., female gender) (1); HAS-BLED = hypertension (1) abnormal renal and/or liver function (1) previous stroke (1) bleeding history or predisposition (1) labile international normalized ratio (1) elderly (1) drugs or excess alcohol (1); SD = standard deviation; TIA = transient ischemic attack.

dependency, as well as higher CHA_2DS_2-VASc and HAS-BLED scores. In contrast, patients with renal impairment had a higher proportion of smokers and alcohol consumers, and surprisingly, diabetes mellitus was less common in these patients. A summary of baseline characteristics is listed in Table 1.

During a mean follow-up of 2.2 ± 0.6 years, 7 patients (1.41%) with CrCl <60 ml/min suffered an IS/TIA/SE/MI, 16 (3.21%) suffered major bleeding, and 19 (3.82%) suffered MACE. In addition, 59 patients (11.85%) with CrCl <60 ml/min died.

Patients with CrCl <60 ml/min showed higher annual event rates for major bleeding (1.87 per 100 patient-years vs 0.62 per 100 patient-years; p = 0.003), MACE (1.97 per 100 patient-years vs 0.62 per 100 patient-years; p = 0.002), and death (5.52 per 100 patient-years vs 1.30 per 100 patient-years; p <0.001) compared with patients with preserved renal function. However, despite the more common presence of previous stroke/TIA in patients with CrCl <60 ml/min, the annual event rate of IS/TIA/SE/MI was similar between patients with CrCl <60 ml/min and CrCl ≥60 ml/min (0.66 per 100 patient-years vs 0.67 per 100 patient-years; p = 0.955) (Figure 1). A detailed description of annual event rates is listed in Supplementary Table 1.

Multivariate logistic regression analyses performed in the 498 patients with CrCl <60 ml/min demonstrated that the CHA_2DS_2-VASc score and the concomitant use of antiplatelets were independently associated with a higher risk of IS/TIA/SE/MI, with odds ratios (ORs) of 1.84 (95% CI 1.11 to 3.07, p = 0.018) and 12.28 (95% CI 2.50 to 60.18, p = 0.002), respectively. For major bleeding events, any dependence degree for activities of daily living (OR 3.42; 95% CI 1.17 to 9.98, p = 0.025) and the HAS-BLED score (OR 2.25; 95% CI 1.41 to 3.59, p = 0.001) were significantly associated with higher risk of major bleeding. Finally, male gender (OR 3.15; 95% CI 1.07 to 9.35, p = 0.038), the presence of heart failure (OR 4.42; 95% CI 1.64 to 11.93, p = 0.003), and the use of antiplatelet agents (OR 7.32; 95% CI 2.48 to 21.59, p <0.001) were also found to be independently associated with an increased risk of MACE (Table 2).

Discussion

It is well known that CKD is common in patients with AF. In the present study, we showed that patients with renal impairment suffered more frequently from worse clinical outcomes, and antiplatelet use, dependency, heart failure, male

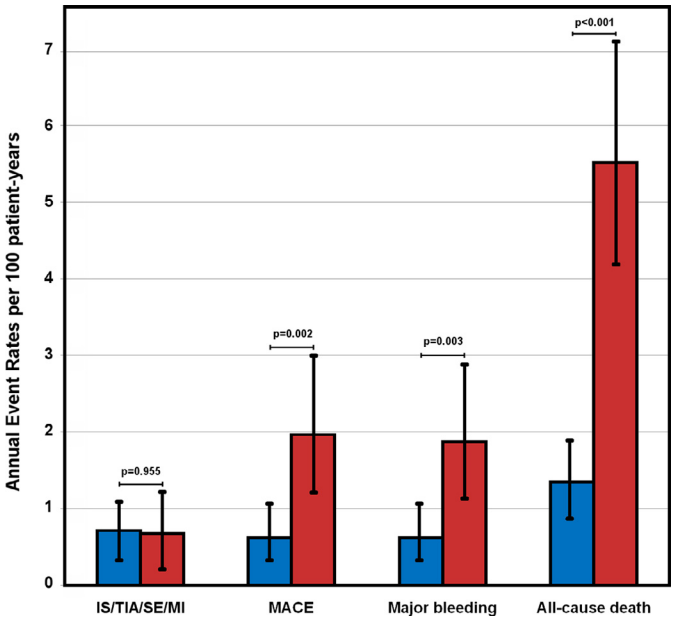

Figure 1. Comparison of event rates at 2.5 years of follow-up in patients with and without renal impairment.
Blue bar = creatinine clearance ≥60 mL/min.
Red bar = creatinine clearance <60 mL/min.

gender, and higher CHA_2DS_2-VASc and HAS-BLED scores were the main risk factors in this subpopulation of patients.

Previous studies have demonstrated that patients with AF with CKD are more prone to die and have thrombotic and bleeding events.[7] In the Fibrilación Auricular: influencia del Nivel y Tipo de Anticoagulación Sobre la Incidencia de Ictus y Accidentes hemorrágicos (FANTASIIA) Registry, the presence of severe CKD was an independent risk factor for cardiovascular mortality, MACE, and major bleeding, and worsening of renal function was associated with mortality and major bleeding.[8] In a large cohort study, CKD status in patients with AF was independently associated with higher risks of major bleeding and mortality, but not with thromboembolism,[9] which agrees with our observations. However, there is no doubt that patients with CKD are at increased risk, and therefore an appropriate oral anticoagulation therapy is particularly needed in these patients.

Table 2
Factors independently associated with adverse events in patients with renal impairment

	Multivariate analysis OR (95% CI); *p value*
Ischemic stroke/transient ischemic attack/systemic embolism/myocardial infarction	
CHA_2DS_2-VASc	1.84 (1.11−3.07); p = 0.018
Use of antiplatelets	12.28 (2.50−60.18); p = 0.002
Major bleeding	
HAS-BLED	2.25 (1.41−3.59); p = 0.001
Any dependence degree	3.42 (1.17−9.98); p = 0.025
MACE	
Male sex	3.15 (1.07−9.35); p = 0.038
Heart failure	4.42 (1.64−11.93); p = 0.003
Use of antiplatelets	7.32 (2.48−21.59); p <0.001

CHA_2DS_2-VASc = congestive heart failure or left ventricular dysfunction (1) hypertension (1) age ≥75 (2) or 65 to 74 (1) diabetes mellitus (1) previous stroke/TIA or systemic embolism (2) vascular disease (peripheral artery disease, myocardial infarction, aortic plaque) (1) sex category (i.e., female gender) (1); CI = confidence interval; HAS-BLED = hypertension (1) abnormal renal and/or liver function (1) previous stroke (1) bleeding history or predisposition (1) labile international normalized ratio (1) elderly (1) drugs or excess alcohol (1);

MACE = major adverse cardiovascular events; OR = odds ratio.

Current evidence suggests that rivaroxaban and apixaban are safe and at least as effective as warfarin in patients with AF and stage 4 to 5 CKD or on dialysis.[10] In Medicare beneficiaries with stages 3 to 5 CKD and new-onset AF, DOACs were at least as effective and safe as warfarin.[11] Another study, including more than 54,000 patients, showed that DOACs were associated with lower risk for MACE and mortality compared with vitamin K antagonists, and the strength of the association was most apparent in those with reduced GFR.[12] In the same line, a recent study demonstrated that DOAC use compared with warfarin in patients with AF with impaired renal function was associated with lower risk of mortality and bleeding across all levels of CKD.[13] Specifically, rivaroxaban appears to be a reasonable alternative to warfarin for patients with AF and moderate to severe CKD (stages from IIIb to V), as there were no significant differences in the risk of IS/SE or major bleeding between rivaroxaban and warfarin-treated patients.[14,15] Another study showed that rivaroxaban was associated with a lower incidence of IS and intracranial hemorrhage compared with phenprocoumon in patients with AF and renal impairment. In our cohort, patients with impaired renal function had a higher prevalence of previous stroke/TIA but the incidence of IS/TIA/SE/MI was similar between patients with CrCl <60 ml/min and CrCl ≥60 ml/min. This is a relevant finding highlighting that rivaroxaban is a viable option for patients with AF with renal impairment, although patients on rivaroxaban should have their kidney function regularly assessed to ensure consistency with the drug label.[16]

Regarding risk factors for adverse events in patients with AF with impaired renal function, the CHA_2DS_2-VASc and HAS-BLED scores were independently associated with IS/TIA/SE/MI and major bleeding, respectively. Both scores have been extensively validated in AF, and our study demonstrated that they are also useful in this particular high-risk subgroup. Indeed, the CHA_2DS_2-VASc score has recently been found to predict cardiovascular and all-cause mortality in patients with CKD,[17,18] and the HAS-BLED score showed a moderate predictive ability in patients with CKD with AF.[19] In addition, dependence and loss of autonomy are often associated with frailty, which has demonstrated to be common in patients with AF and associated with a higher risk of bleeding.[20] Thus, geriatric assessment including frailty, cognitive impairment, and falls should be considered in all patients with AF to improve decision-making.[21]

In contrast, previous studies demonstrated that male gender and heart failure increase the risk of MACE in patients with AF,[22−25] and both have been confirmed now in these patients with AF with renal disease. Moreover, the association found between the use of antiplatelets and the risk of MACE could be explained by the fact that patients on antiplatelets usually have concomitant vascular disease, which is related to higher risk profile, particularly of cardiovascular outcomes.[3] However, despite the prescription of antiplatelets is common in patients with AF, it is not related to lower rates of thrombotic events or mortality but a higher risk of bleeding.[26,27]

This study has some limitations. As this was an observational study, no control group was available, and comparisons could only be made with other studies. This study was performed in Spain, and patients were mainly followed by cardiology specialists, hence the results of this study could be extended only to those patients with a similar clinical profile and healthcare setting. In addition, we recognize that the proportion of patients with the appropriate dose of rivaroxaban based on the CrCl is suboptimal, and this may have an impact on clinical outcomes. However, as a "real world" study with no specific intervention beyond enrollment, no interference with the dosing strategy was implemented.

Finally, there were significant differences between patients with and without renal impairment. Despite our aim not to demonstrate that renal impairment was an independent risk factor for clinical outcomes, we understand that these differences between subgroups of patients hinder a potential proper analysis of the independent role of renal function on the risk of worse clinical outcomes. Moreover, we acknowledge that only 43 patients (3%) included had a CrCl <30 ml/min. These are usually the most fragile patients, and they often cause concerns in clinical practice when deciding on oral anticoagulation. For these reasons, our results should be interpreted with caution and only in an exploratory way or as hypothesis-generating.

In conclusion, in the present study, rivaroxaban showed promising results in patients with AF with moderate renal impairment. The rate of major bleeding and MACE was higher in patients with AF with impaired renal function but the rate of IS/TIA/SE/MI was not particularly increased despite the high risk of this group, which suggests that rivaroxaban may be an effective therapeutic option even in patients with renal impairment. In patients with AF and renal impairment, male gender, heart failure, dependency, antiplatelet use, and higher CHA_2DS_2-VASc and HAS-BLED, were associated with a higher risk of adverse clinical outcomes.

Declaration of Competing Interest

JM Rivera-Caravaca is a consultant for Idorsia Pharmaceuticals LTD. M. Anguita Sanchez has received financial compensation from Bayer for participating in the EMIR registry. M. Sanmartín Fernández has received speaker and advisory fees from the following companies in the past 3 years: Bayer, Boehringer-Ingelheim, BMS, and Pfizer. C. Rafols is an employee of the Medical Department, Bayer Hispania S.L, which is the sponsor of the EMIR study. G. Barón-Esquivias has received lecture fees from Bayer, Boehringer-Ingelheim, Daiichi Sankyo, Pfizer-BMS, Sanofi, Novartis, and Rovi; and financial compensation from Bayer for participating in the EMIR study and an institutional grant from Novartis. J. Cosín-Sales has received financial compensation from Bayer for participating in the EMIR registry. R. Freixa-Pamias has received consultancy/lecturing fees from Bayer, BMS/Pfizer, Boehringer-Ingelheim, and Daiichi Sankyo; and financial compensation from Bayer for participating in the EMIR study. I. Lekuona Goya has received financial compensation from Bayer for participating in the EMIR study. JM Vázquez Rodríguez has received lecture fees from Bayer, Boehringer-Ingelheim, Pfizer, Bristol Myers Squibb, and Daiichi Sankyo; and financial compensation from Bayer for participating in the EMIR study. AI Pérez-Cabeza has received consultancy/lecturing fees from Bayer, Boehringer-Ingelheim, Pfizer, Bristol Myers Squibb, and Daiichi Sankyo. I. Ureña Montilla has received financial compensation from Bayer for participating in The EMIR study; speaker and advisory fees from the following companies: Bayer, Novartis, Daiichi Sankyo, Vifor, Boehringer-Ingelheim, and Amgen. A. Alvarez-Vieitez Blanco has received financial compensation from Bayer for participating in the EMIR study. F. Arribas Ynsaurriaga has received consultancy/lecture fees and research funding from Daiichi Sankyo, Pulse Dynamics, Medtronic, Boston Scientific, Bayer, Bristol Myers Squibb, Arrhythmia Network Technology SL/BAROSTIM, Abbott, Novartis, Janssen-Cilag, Biosensors, and Edwards Lifesciences; and received financial compensation from Bayer for participating in the EMIR registry. F Marín has received consultancy/lecturing fees from Bayer, Boehringer-Ingelheim, Pfizer, Bristol Myers Squibb, and Daiichi Sankyo.

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None.

Author contributions

JMRC and FM wrote the manuscript. All authors contribute to the inclusion of patients, to the record of data in the electronic case report form, reviewed and edited the manuscript, made a critical revisions, and approved the final version.

Ethical approval

The study obtained the approval of the ethics committee of each of the participating centers. All patients gave their written informed consent for participation.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2023.06.105.

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