Colchicine in Patients With Coronary Disease Who Underwent Coronary Artery Bypass Surgery: A Meta-Analysis of Randomized Controlled Trials

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Recent randomized evidence has shown that low-dose colchicine lowers the risk of cardiovascular events in patients with chronic coronary artery disease. Colchicine has also been used in coronary artery bypass grafting (CABG), with individual studies suggesting protective effects for postoperative atrial fibrillation (POAF). We performed a meta-analysis of studies assessing the effect of colchicine on outcomes in CABG surgery. We systematically searched 3 libraries (MEDLINE, Web of Science, and the Cochrane Library), selecting all randomized control trials including patients who underwent CABG and were randomized for perioperative administration of colchicine versus standard of care. The primary outcome was incidence of POAF. The inverse variance method (DerSimonian&-Laird) and random-effects model were performed. The leave-one-out analysis was carried out as a sensitivity analysis to address possible outliers. From 205 screened studies, 5 met the inclusion criteria and were selected. The data from 839 patients were included in the final analysis. The included studies were published between 2014 and 2022. The perioperative administration of colchicine was associated with the reduction of POAF rates after CABG compared with standard of care (relative risk 0.54, 95% confidence interval 0.40 to 0.73, p <0.01). The leave-one-out analysis confirmed the robustness of the analysis, with minimal variations of the confidence interval. This meta-analysis of randomized studies suggests that the perioperative administration of colchicine is associated with significant reduction of POAF after CABG. **(Am J Cardiol 2024;231:48−54)**

Keywords: colchicine, coronary artery bypass grafting, postoperative atrial fibrillation

Coronary artery disease (CAD) is one of the foremost causes of mortality worldwide[1] and patients with CAD remain at a high risk for acute cardiovascular events.[2] Inflammation and the development of atherosclerotic plaques has been recognized as the primary mechanism of CAD genesis and progression[3,4] and, therefore, potential beneficial effects of anti-inflammatory therapy in CAD have provoked justified interest. Recent studies have shown that anti-inflammatory therapy in CAD may significantly improve cardiovascular outcomes.[5] Colchicine is an anti-inflammatory drug that has been known for long but was primarily considered a treatment for gout.[6] Recently, it has moved into the spotlight because new randomized evidence demonstrated its potential to lower the risk of adverse cardiovascular events in patients with chronic CAD.[7,8]

Because coronary artery bypass surgery (CABG) is indicated mostly in patients with severe and advanced CAD,[9] and the surgical procedure induces inflammatory processes, it is conceivable that colchicine may elicit beneficial effects in patients with CAD who underwent CABG. Indeed, colchicine effects have been assessed in cardiac surgery, mainly, with a focus on atrial fibrillation (AF)[10] and preventing postpericardiotomy syndrome.[11] In addition, colchicine also attenuates postoperative biomarker release, such as signs for myocardial injury and inflammation in non-CABG surgery.[12] For CABG, there have been several individual studies suggesting protective effects mainly for postoperative AF (POAF).

We, therefore, set out to systematically review previous studies and thoroughly address the effect of perioperative application of colchicine in patients who underwent isolated CABG surgery.

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See page 53 for Declaration of Competing Interest.

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Methods

No ethical approval was required for this analysis because no human or animal subjects were involved. This review was registered with the National Institute for Health Research International Registry of Systematic Reviews (PROSPERO) (CRD42024516681).

We conducted a comprehensive literature search to identify randomized clinical trials comparing the POAF rate in patients who underwent isolated CABG who received perioperative treatment with colchicine versus placebo or standard treatment. Searches were run in December 2023. The following databases were included: Ovid MEDLINE, ScienceDirect, and the Cochrane Library (Wiley). Supplementary Table 1 lists the complete MEDLINE search strategy.

The study selection followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) strategy. After deduplication, records were screened by 2 independent reviewers. In case of discrepancies, the expertise of a third author was consulted. Titles and abstracts were reviewed against the predefined inclusion and exclusion criteria. The inclusion criteria were the direct comparison between patients receiving colchicine versus placebo or standard care without colchicine administration after isolated CABG surgery. If the main cohort of the study did not analyze patients who underwent isolated CABG surgery, a subgroup analysis showing the results of this cohort needed to be available. Only randomized controlled trials (RCTs) were considered for inclusion. Studies with missing outcomes of interest, conference abstracts, proceedings, case reports, noncomparative studies, or publications without a randomized controlled design were excluded. After the initial scan, the full text of the selected studies was analyzed for a second round of eligibility screening. All references of the selected articles were reviewed for relevant studies not captured by the original search.

A total of 2 reviewers (LF and TC) performed data extraction independently. Accuracy was verified by a third author (HK). The extracted variables included study characteristics (publication year, country, sample size, study design, intervention details including the exact dose of applied colchicine, the used POAF definition, duration of follow-up, reported outcomes, and the inclusion and exclusion criteria), patient demographics (age, gender, left ventricular ejection fraction, hypertension, diabetes mellitus, smoking status, previous myocardial infarction (MI), current angina pectoris, chronic obstructive pulmonary disease, weight, height, body mass index, creatinine, on-pump surgery), and absolute numbers of patients with POAF documented until hospital discharge. The quality of the studies included in the quantitative analysis was assessed using the Cochrane risk-of-bias tool for randomized trials (Supplementary Table 2).

The primary outcome of the performed meta-analysis was the incidence of POAF during short-term follow-up.

A meta-analysis was performed to compare the incidence of POAF during short-term follow-up in patients who received a preventive medical approach including colchicine and patients treated with placebo or best standard care without colchicine application. Relative risk (RRs) and 95% confidence intervals (CIs) were calculated. An relative risk ratio greater than 1 indicated that the outcome was more frequently present in the colchicine cohort. The α level was set to 0.05. The inherent clinical heterogeneity between the studies was balanced by way of the implementation of a random-effects models. The results are displayed using forest plots.

Between-study statistical heterogeneity was assessed by estimating I^2. High heterogeneity was defined with a significance level of $p< 0.10$ and I^2 of at least 50% or more. The leave-one-out sensitivity analysis was also performed to find out how each individual study contributed to the robustness of the analysis. All statistical analyses were performed using R (version 4.1.1, R Project for Statistical Computing) within RStudio.

Results

A total of 205 studies were retrieved from the systematic search, of which 5 could be included in the final analysis. Figure 1 shows the PRISMA flowchart representing the process of study selection. The included studies were published between 2014 and 2022 in Iran, Russian Federation, Brazil, and Jordan. All of them were RCTs. A total of 2 of the included publications were single-center trials and 3 were multicenter trials.

Table 1 lists the details of the included studies. The total number of patients investigated in the individual studies led to a total of 1,146 included patients, of whom 885 underwent isolated CABG surgery and, therefore, reported the outcome of interest. The number of patients in the isolated CABG cohorts ranged from 99 to 250. POAF was the only uniformly reported adverse event in all studies and the only 1 that could be included in the meta-analysis.

No studies reported the effects on graft patency, spontaneous MI during follow-up, or long-term mortality and only 1 study reported postoperative pericardial effusions. Therefore, the only adverse event reported suitable for meta-analytical evaluation was POAF.

Supplementary Table 3 lists the demographic data of the included patients for each study. The mean age ranged from 59.0 to 62 years, and the percentage of women ranged from 18.3% to 33.3%. The mean left ventricular ejection fraction, reported in 4 of the 5 studies, showed values between 46.2% and 60%. The mean body mass index, reported by 3 of 5 studies, ranged from 27.5 to 29.3. Between 51.9% and 93.7% of patients had arterial hypertension. Between 19.0% and 59.2% of the patients were afflicted with diabetes mellitus. The percentage of smokers ranged from 19.4% to 49.3%. In this study, 0% to 40.7% of patients had a medical history of MI and 4.2% to 40.7% had angina pectoris, reported by 4 and 2 studies, respectively. The preoperative serum creatinine levels ranged from 0.9 to 1.1 mg/100 ml and were reported by 4 studies. A total of 2 studies reported a chronic obstructive pulmonary disease incidence of 1.9% and 6.2% in their cohort. The percentage of on-pump CABG surgery was reported in 3 studies and ranged from 7.8% to 75.9%.

Table 2 lists the detailed results of the individual studies. Figure 2 shows the forest plot for POAF after isolated

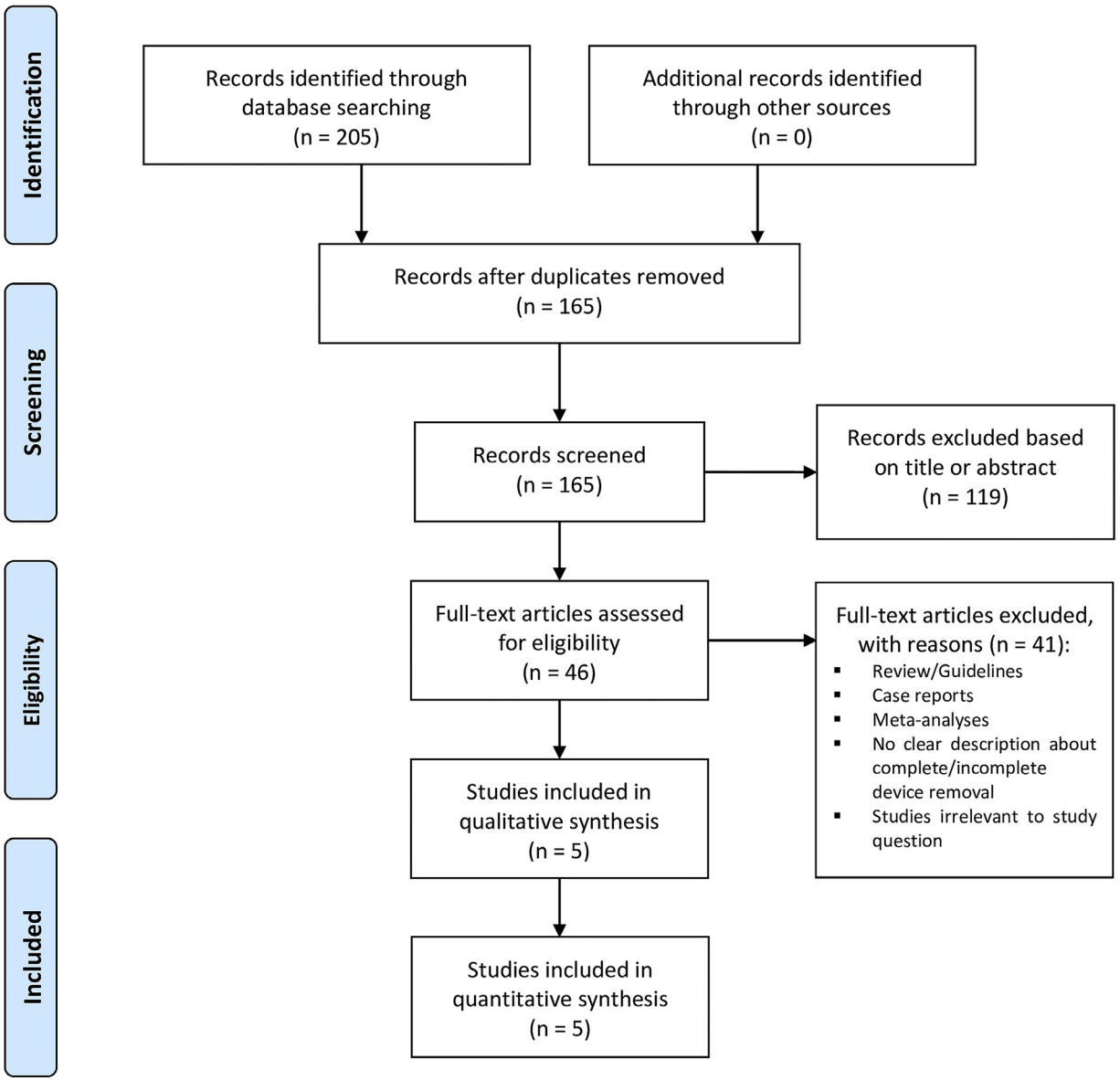

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

CABG surgery. Compared with patients receiving standard treatment or placebo, those treated with additional colchicine medication as part of a preventive approach showed a significantly lower incidence of POAF (RR 0.54, 95% CI 0.40 to 0.73, p <0.01).

Supplementary Table 4 lists the leave-one-out analysis. This cross-validation method demonstrates that all studies confirm the robustness of the analysis. Supplementary Figure 1 shows the funnel plot investigating publication bias.

Discussion

We demonstrate in this manuscript that the perioperative administration of colchicine is associated with significant reduction of postoperative AF after CABG. Current randomized studies of perioperative colchicine after CABG did not uniformly investigate or report any other short- or long-term outcomes and adverse events.

The results of this analysis are highly relevant. CABG remains the most common major cardiac surgical procedure in the United States and worldwide, with almost 400,000 procedures performed each year in the United States alone.[13] This translates into more than a million patients worldwide potentially affected by POAF after CABG, considering the continuously high incidence after cardiac surgery.[14,15] We have reported that POAF is associated not only with increased perioperative mortality and other adverse events (i.e., perioperative stroke, MI, acute renal failure) but also long-term mortality, long-term stroke, and long-standing persistent AF.[14,15] Thus, POAF does not appear to be harmless and preventing it has the potential to improve long-term outcomes.

Colchicine, extracted from the autumn crocus (*Colchicum autumnale*) is one of the oldest medicines still in

Table 1
Summary of included studies (references are reported in the Supplementary Material)

Author	Year	Country	N° of patients (CABG only)	Study Design	Intervention	POAF Definition	Inclusion criteria	Exclusion criteria
Shvartz	2022	Russia	240 (180)	Multicenter	Colchicine 1mg 24h preop + 2-5d postop	>30s	Elective surgery, 40-80 years	Any form of AF, flutter, SV arrythmias, frequent VES, SVES, II/III° AV block, steroid-/antiarrythmic intake, previous heart surgery, renal failure, chronic liver disease, death postop day 1, delayed ICU stay, patients wish to withdraw, mitral valve disease >2°, participation in other trial
Tabbalat	2016	Jordan	360 (250)	Multicenter	Colchicine 2mg 24h preop + 1mg 4h postop + daily until discharge	>5 min	Elective surgery	History of AF, supraventricular arrythmia, no sinus rythm on admission, severe liver diseases, elevated transaminases >1.5x normal limit, serum creatine >2.5mg/dl, known myopathy, elevated preop CK, blood dyscrasias, significant GI diseases, emergency surgery, contraindication for colchicine, current colchicine treatment, pregnancy, lactating women
Tabbalat	2020	Jordan	190 (99)	Multicenter	Colchicine 1mg 24h preop + 0.5mg postop daily until discharge	>5 min	Elective surgery, >18 years	Emergency surgery, history of AF, supraventricular arrythmia, contraindication for colchicine, current colchicine treatment, no sinus rhythm on admission, serum creatine >2.5mg/dl, severe liver diseases, elevated transaminases >1.5x normal limit, myopathy, elevated CK, pregnancy, lactating women
Zarpelon	2015	Brazil	140 (140)	Single-center	Colchicine 1mg 1-0-1 periop + 1mg postop daily until discharge	>5 min or <5min + instability	indication for elective CABG, >18 years	Diagnosed AF, atrial flutter, colchicine contraindication, current use of colchicine, cardiogenic shock, severe arrythmias, neoplasms, noncommunicative patients
Sarzaeem	2014	Iran	216 (216)	Single-center	Colchicine 1mg periop + 1mg postop daily until discharge	>10 min	indication for elective CABG	AF in history/ on admission, >80 years, valvular diseases, arrythmias/AV blocks, chronical lung diseases, severe liver diseases, no isolated CABG, sick sinus syndrome, renal failure, contraindications for colchicine

AF = atrial fibrillation; AV = atrioventricular, CABG = coronary artery bypass graft; CK = creatine kinase; GI = gastrointestinal; ICU = intensive care unit; POAF = postoperative atrial fibrillation; SV = supraventricular, VE = ventricular extrasystole.

common use, being used since ancient times.[16] It has different cellular effects that include inhibition of tubulin polymerization, with subsequent disruption of the cellular cytoskeleton, mitosis, and intracellular transport activities.[17] Colchicine preferentially accumulates in neutrophils and, thus, largely affects neutrophil activity.[17] Specifically, colchicine has been shown to inhibit the directed migration of neutrophils to an inflamed focus and decrease adhesion of neutrophils to inflamed endothelium.[17] Colchicine further inhibits the adhesion of leukocytes to inflamed endothelium.[17] However, the application of colchicine is limited by its lethal toxicity at high doses.[18]

Generally, colchicine has been used to treat diverse inflammatory diseases, including gout, familial Mediterranean fever, or pericarditis. Its anti-inflammatory effects affect patients who underwent CABG in several different therapeutical aspects, which we include the following: (1) reduction of POAF, (2) potential effect on postcardiotomy syndrome, and (3) the ability to reduce long-term cardiovascular adverse events, especially MI and ischemia-driven revascularization in chronic CAD.[7]

The effect of colchicine in reducing POAF appears to be more pronounced in patients who underwent CABG than in those who underwent some other noncardiac surgeries.[19] This may possibly be explained by the combination of severe advanced coronary artery disease and the significant inflammatory response induced by the CABG procedure, with a protracted postoperative activation of inflammation being reported after CABG.[20,21] Patients who underwent CABG typically have a high inflammatory burden because of their advanced CAD,[20] and the surgical procedure might further exacerbate this inflammation.[21] Colchicine, with its potent anti-inflammatory properties, might effectively mitigate this response, leading to a substantial reduction in POAF rates and possibly other adverse events. Therefore, this effect is less pronounced in other noncardiac surgeries where the inflammation might not be as severe or multifaceted as in CABG and no effect on POAF has been reported.[19]

Table 2
Incidence of postoperative atrial fibrillation in the included studies

Author	Event (%)	Total	Event (%)	Total	p value
Shvartz	8 (12)	81	25 (25.3)	99	0.026
Tabbalat, 2016	17 (13.1)	130	23(19.2)	120	0.189
Tabbalat, 2020	6 (12.5)	48	9 (17.7)	51	0.660
Zarpelon	7 (9.8)	71	13.0 (18.8)	69	0.271
Sarzaeem	16 (14.8)	85	33 (30.6)	85	0.006

Currently, patients who underwent CABG represent the only subgroup for which guideline recommendations for colchicine might apply. On the basis of RCTs (COLCOT[8] and LoDoCo2[7]) the 2021 European Society of Cardiology (ESC) guidelines on the prevention of cardiovascular disease have recommended that colchicine be considered for secondary prevention of cardiovascular disease, in particular, for those with uncontrolled risk factors and recurrent cardiac events despite optimal medical therapy (class IIb recommendation, level of evidence A).[17,22] In addition, the ESC guidelines indicate that colchicine should be considered for prevention of postcardiotomy syndrome after cardiac surgery (class IIa recommendation, level of evidence A) for 1 month after cardiac surgery.[23] American College of Cardiology/American Heart Association guidelines suggest that colchicine can be considered for postoperative AF prevention (class IIb recommendation, level of evidence B).[24] Thus, the growing evidence of cardiovascular benefit from colchicine seems fully appliable to patients who underwent CABG and it is conceivable that its beneficial effects might combine. This specifically underscores the critical need for targeted anti-inflammatory strategies in the high-risk CABG population.

Given the current evidence and the gaps therein, there is an urgent need for RCTs aimed at investigating the different short- and long-term effects of colchicine in patients who underwent CABG, especially on graft patency, MI rates, and long-term persistent AF. Having this in mind, it is striking that large, international, prospective, multicenter RCTs evaluating the effect of colchicine in other nonsurgical areas have been recently conducted and prominently published (i.e., thoracic surgery);[19] however, for CABG, where colchicine might be especially beneficial, such trials are lacking. One potential explanation might be found also in our results. It is worth noting that all RCTs evaluating colchicine in CABG have not been conducted in western countries (Table 1). A possible explanation for these might be the stringent regulations for conducting trials involving

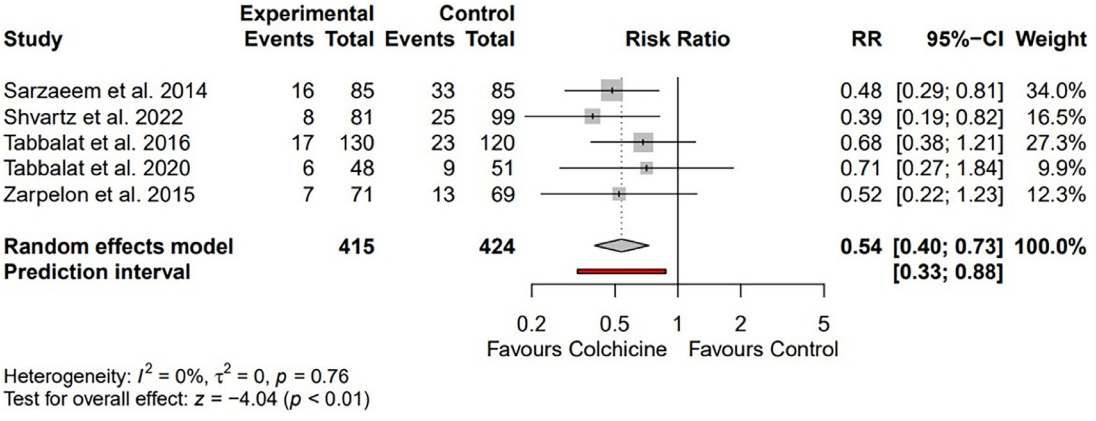

Figure 2. Forest plot for the primary end point (postoperative atrial fibrillation).

new medications or expanding indications in western countries. This might practically be a significant barrier to the execution of RCTs evaluating colchicine in patients who underwent CABG. These regulations designed to ensure patient safety and scientific rigor can also lead to prolonged approval processes and increased costs.

To the best of our knowledge, this is the first meta-analysis to address this important topic, including RCTs. However, this work has some limitations. Some studies were not trials focused only on CABG but presented individual data from these groups. In addition, there is a slight heterogeneity in how colchicine was administered throughout the studies.

In conclusion, we demonstrate in this meta-analysis of randomized studies that the perioperative administration of colchicine is associated with a significant reduction of POAF rates after CABG. However, there remains a critical need for evaluation of long-term data and other cardiovascular adverse events for colchicine use in patients who underwent CABG to complete its risk-benefit assessment.

Declaration of competing interest

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CRediT authorship contribution statement

Hristo Kirov: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing − original draft, Writing − review & editing. **Tulio Caldonazo:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Validation, Visualization, Writing − original draft, Writing − review & editing. **Angelique Runkel:** Conceptualization, Investigation, Methodology, Project administration, Resources, Validation. **Darko Medin:** Formal analysis, Resources, Software. **Johannes Fischer:** Methodology, Project administration, Validation. **Luis Roberto Dallan:** Conceptualization, Investigation, Methodology, Writing − original draft. **Murat Mukharyamov:** Project administration, Resources, Supervision, Validation. **Omar A. Mejia:** Methodology, Supervision, Validation. **Fabio B. Jatene:** Investigation, Methodology, Resources, Validation. **Torsten Doenst:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Supervision, Validation, Visualization, Writing − original draft, Writing − review & editing.

Data Availability

The data underlying this article are available in the article and in its online supplementary material.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2024.09.003.

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