One-Month Dual Antiplatelet Therapy Reduces Major Bleeding Compared With Longer-Term Treatment Without Excess Stent Thrombosis: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

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Dual antiplatelet therapy (DAPT) remains the gold standard in patients who underwent percutaneous coronary intervention (PCI). This meta-analysis aims to evaluate the clinical safety of 1-month DAPT followed by aspirin or a P2Y12 receptor inhibitor after PCI with drug-eluting stents (DES). We searched PubMed, MEDLINE, Embase, Scopus, Google Scholar, Cochrane Central Registry, and *ClinicalTrials.gov* databases and identified 5 randomized controlled trials with 29,831 patients who underwent PCI with DES and compared 1-month versus >1-month DAPT. The primary end point was major bleeding, and the co-primary end point was stent thrombosis. The secondary end point included all-cause mortality, cardiovascular death, myocardial infarction, stroke, and major adverse cardiovascular or cerebrovascular events. Compared with >1-month DAPT, the 1-month DAPT was associated with a lower rate of major bleeding (odds ratio [OR] 0.66, 95% confidence interval [CI] 0.45 to 0.97, p = 0.03, I^2 = 71%), whereas stent thrombosis had a similar rate in both study groups (OR 1.08, 95% CI 0.81 to 1.44, p = 0.60, I^2 = 0.0%). The study groups had similar risks for all-cause mortality (OR 0.89, 95% CI 0.77 to 1.04, p = 0.14, I^2 = 0.0%), cardiovascular death (OR 0.84, 95% CI 0.59 to 1.19, p = 0.32, I^2 = 0.0%), myocardial infarction (OR 1.04, 95% CI 0.89 to 1.21, p = 0.62, I^2 = 0.0%), and stroke (OR 0.82, 95% CI 0.64 to 1.05, p = 0.11, I^2 = 6%). The risk of major adverse cardiovascular or cerebrovascular events was lower (OR 0.86, 95% CI 0.76 to 0.97, p = 0.02, I^2 = 25%) in the 1-month DAPT compared with >1-month DAPT. In conclusion, in patients who underwent PCI with DES, 1-month DAPT followed by aspirin or a P2Y12 receptor inhibitor reduced major bleeding with no risk of increased thrombotic risk compared with longer-term DAPT. **(Am J Cardiol 2024;227:91−97)**

Keywords: acute coronary syndrome, dual antiplatelet therapy, percutaneous coronary intervention, stable coronary artery disease

Introduction

Despite the permanent improvement in the diagnosis and treatment, coronary artery disease (CAD) remains a major cause of morbidity and mortality worldwide, particularly in patients with acute coronary syndrome (ACS).[1,2] In patients with CAD, percutaneous coronary intervention (PCI) is the treatment of choice, both in those with ACS and with stable CAD. The current clinical guidelines recommend 6 to 12 months of dual antiplatelet therapy (DAPT), with aspirin and P2Y12 receptor inhibitors, as a protective measure against arterial thrombosis, after PCI and implantation of drug-eluting stent (DES) in these patients.[3,4] However, it has been shown that DAPT is associated with an increased risk of bleeding, which devalues the benefits of reduced ischemic events[4−6]; hence, attempts to shorten the duration of DAPT to a maximum of 1 month have recently been sought and evaluated.[7−10] These studies showed noninferiority of 1 month of DAPT followed by aspirin or a P2Y12 receptor inhibitor compared with guidelines-based conventional longer-term treatment with DAPT. These 4 randomized clinical trials (RCTs) showed similar results in patients at high bleeding risk[9] and in all comers[7,8,10] who underwent PCI, but their conclusion has not reached clinical guidelines yet. Most recently, data from "Ticagrelor alone versus ticagrelor plus aspirin from month 1 to month 12 after percutaneous coronary intervention in patients with acute coronary syndromes (ULTIMATE-DAPT)" RCT showed that patients with ACS who underwent primary PCI, who

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remained free after 1 month on DAPT treated with ticagrelor alone, had less bleeding without increased thrombotic risk.[11] The objective of the present systematic review was to provide a comprehensive evaluation of short-term (1 month) DAPT in patients who underwent PCI with DES by performing a meta-analysis including the most recent RCT, ULTIMATE-DAPT trial.

Methods

We followed the PRISMA guidelines of the 2020 preferred reporting items for systematic reviews and meta-analysis statements.[12] Because of the study design (meta-analysis), neither institutional review board approval nor patient's informed consent was needed.

Search strategy

we systematically searched PubMed-Medline, EMBASE, Scopus, Google Scholar, Cochrane Central Registry of Controlled Trials, and ClinicalTrial.gov from inception to April 13, 2024, using the following keywords: ("percutaneous coronary intervention" OR "PCI") AND ("drug-eluting stent") AND ("dual antiplatelet therapy" OR "DAPT") AND ("randomized controlled trial" OR "RCT") AND ("1-month" OR "1 month"). In this meta-analysis, we also included abstracts from selected congresses, including Scientific Sessions of the American Heart Association, European Society of Cardiology, American College of Cardiology, and European Society of Atherosclerosis. Only articles published in English were included in the analysis. No filters were applied. GA and PI independently and separately evaluated all articles. The finally selected articles were obtained in full-text and were searched carefully by the same 2 researchers, who extracted necessary data and evaluated the articles' quality. Disagreements were resolved by discussion with a third party (MYH).

Eligibility criteria

studies eligible for inclusion were those fulfilling the following criteria: (1) randomized design comparing the efficacy and safety of 1-month DAPT with that >1-month DAPT treatment in patients who underwent PCI for ACS or stable CAD; (2) minimum follow-up period of 10 months; and (3) full-text studies published in peer-reviewed journals. The exclusion criteria were (1) nonrandomized studies, (2) unpublished studies, and (3) ongoing trials. Observational and unpublished studies were not included in the meta-analysis.

Data extraction

qualified studies were searched, and the following data were collected, including (1) first author's name, (2) date of publication, (3) clinical trial name, (4) place where the study was conducted, (5) number of centers involved, (6) study design, (7) number of patients in each of the 2 study arms who received 1-month or >1-month DAPT treatment, (8) follow-up period, and (9) detailed clinical outcome and nature of events in the 2 groups.

Outcomes and definitions

End points

the primary end point was major bleeding based on Bleeding Academic Research Consortium type 3 or 5 bleeding, and major or clinically relevant nonmajor bleeding was defined as a bleeding event of Bleeding Academic Research Consortium type 2, 3, or 5.[13] The co-primary end point was stent thrombosis, according to the Academic Research Consortium definitions.[14] Secondary end points included all-cause death, cardiovascular (CV) death, major adverse CV or cerebrovascular events (MACCEs), myocardial infarction (MI), and stroke. MACE was defined as the combination of all-cause death, CV death, MI, major bleeding, stent thrombosis, and stroke.

Acute MI was defined according to symptoms, electrocardiographic signs, and biomarkers elevation above the upper normal limit.[14,15] Stroke was defined as an acute symptomatic episode of neurologic dysfunction >24 hours in duration in the absence of therapeutic intervention and neuroimaging evidence of cerebral, spinal, or retinal tissue injury.[16]

Quality assessment

the risk of bias assessment in the included studies was evaluated by the same investigators for each study and was performed systematically using the revised Cochrane RoB2 tool involving 5 domains (randomization process, deviation from intended interventions, missing outcome data, outcome measurement, and selection of reported results).[17] The risk of bias in each study was conventionally classified as "low," "high," or "unclear" (Supplementary Table 1).

Statistical analysis

we performed the pooled analyses of treatment effects and clinical outcomes using the Cochrane Collaborative software, RevMan 5.3.5 (Nordic Cochrane Center, Cochrane Collaboration, 2014, Copenhagen).[18] Baseline characteristics are reported as median and range. Mean and SD values were estimated using the method described by Hozo et al.[19] Analysis was presented in forest plots. A 2-tailed p value <0.05 was considered significant. Meta-analyses were performed using the fixed-effects model, and the random-effect model was used if heterogeneity was encountered. Heterogeneity between studies was assessed using the Cochrane Q test and I^2 index, with $I^2 < 25\%$ indicating low, 25% to 50% moderate and >50% high heterogeneity.[20] Based on a hazard ratio value of 1, above or below, we calculated the relative risk for CV events.[21] Publication bias was assessed using Egger's test and visual inspection of funnel plots. To test the possible effect of trials with large sample sizes on the direction of clinical outcomes, we performed influence analysis.

Results

Search results and trial flow

of 3,402 articles identified in the initial searches, 32 studies were initially considered as potentially relevant.

After a stringent selection process, 5 articles met the inclusion criteria[7–10] (Supplementary Figure 1).

Characteristics of included studies

four studies, with a total of 29,831 patients, met all the inclusion criteria, 14,891 patients had been randomized to receive DAPT for 1 month, and 14,940 received DAPT for >1 month according to conventional recommendations (Supplementary Table 2). The mean follow-up duration was 14.2 months in the 2 groups.

Demographic and clinical data of 1-month DAPT versus >1-month DAPT

the 2 patient groups were not different in age (68.3 ± 10 vs 68.9 ± 9 years, p = 0.72) and proportion of female participants (27.8% vs 26.9%, p = 0.46, respectively). Similarly, cardiac risk factors of the 1-month DAPT group were almost similar to those of the >1-month DAPT group: arterial hypertension (71.6% vs 71.9%, p = 0.86), diabetes (33.9% vs 33.6%, p = 0.52), dyslipidemia (72.7% vs 73.6%, p = 0.56), and current smokers (20.4% vs 19.2%, p = 0.28). Previous coronary intervention procedures and events, including coronary artery bypass graft surgery (CABG), PCI, MI, and bleeding, were also not different between the 2 treatment groups (p >0.05, for all; Supplementary Table 3).

Angiographic data of 1-month DAPT versus >1-month DAPT

angiographic data of the 1-month DAPT group were not different from the >1-month DAPT group: left main (2.9% vs 2.53%, p = 0.13), left anterior descending artery (46.5% vs 41.6%, p = 0.10), left circumflex artery (21.4 vs 22.9%, p = 0.50), right coronary artery (30.4% vs 28.9%, p = 0.33), and CABG (7.1% vs 6.5%, p = 0.22). Patients in the 2 treatment groups, 1-month and >1-month, did not differ in the number of vessels treated per patient, 1, 2, or 3 (p >0.05 for all). Moreover, access site procedures were not significantly different between the 2 treatment groups (p >0.05 for all; Supplementary Table 4).

Primary outcomes

the treatment group of 1-month DAPT had a lower risk for major bleeding (1.72% vs 2.12%, odds ratio [OR] 0.66, 95% confidence interval [CI] 0.45 to 0.97, p = 0.03, I^2 = 71%; Figure 1) but a similar risk for stent thrombosis (0.66% vs 0.60%, OR 1.08, 95% CI 0.81 to 1.44, p = 0.60, I^2 = 0.0%) to the group who received >1-month DAPT (Figure 1).

Secondary outcomes

the 2 treatment groups had similar risk for all-cause mortality (2.36% vs 2.28%, OR 0.89, 95% CI 0.77 to 1.04, p = 0.14, I^2 = 0.0%; Figure 2), CV death (0.97% vs 1.21%, OR 0.84, 95% CI 0.59 to 1.19, p = 0.32, I^2 = 0.0%; Figure 2), MI (2.52% vs 2.48%, OR 1.04, 95% CI 0.89 to 1.21, p = 0.62, I^2 = 0.0%; Figure 2), and stroke (0.89% vs 1.07%, OR 0.82, 95% CI 0.64 to 1.05, p = 0.11, I^2 = 6%; Figure 2). In contrast, the risk of MACE was lower (5.06% vs 5.82%, OR 0.86, 95% CI 0.76 to 0.97, p = 0.02, I^2 = 25%; Figure 2) in patients who received 1-month DAPT compared with those who received >1-month DAPT.

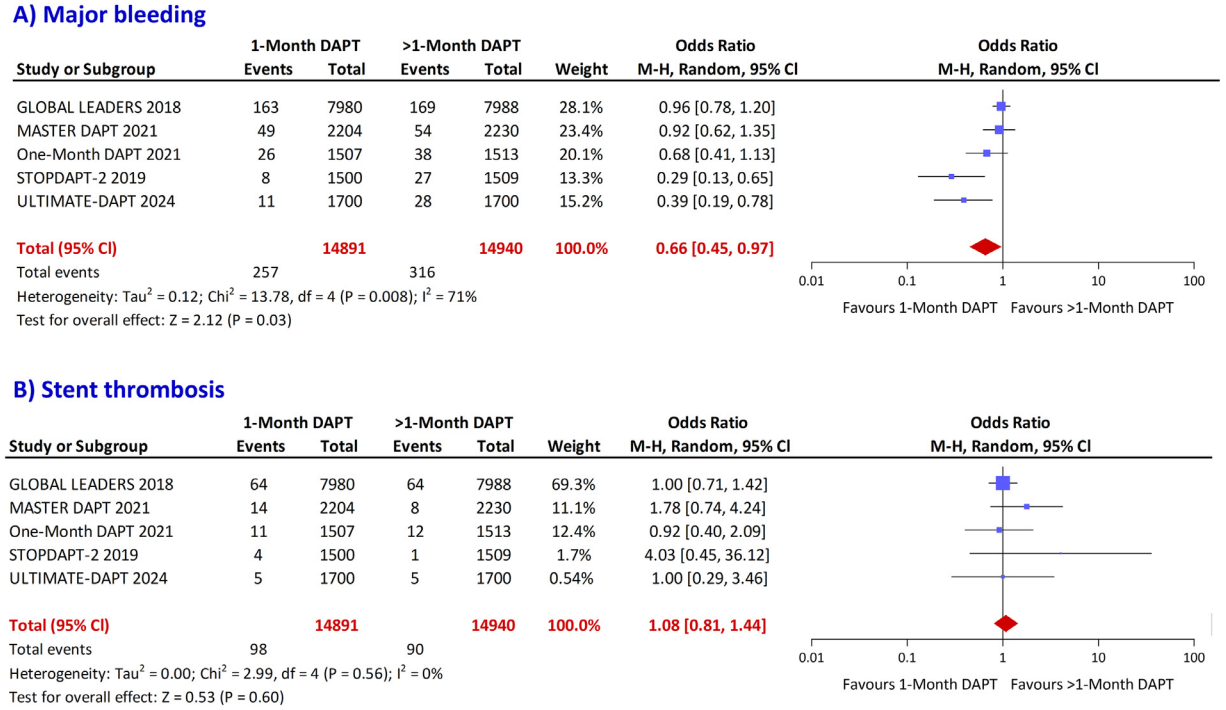

Figure 1. Forest plot comparing primary outcome between 1-month DAPT and >1-month DAPT. (*A*) Major bleeding; (*B*) stent thrombosis. M-H = Mantel-Haenszel.

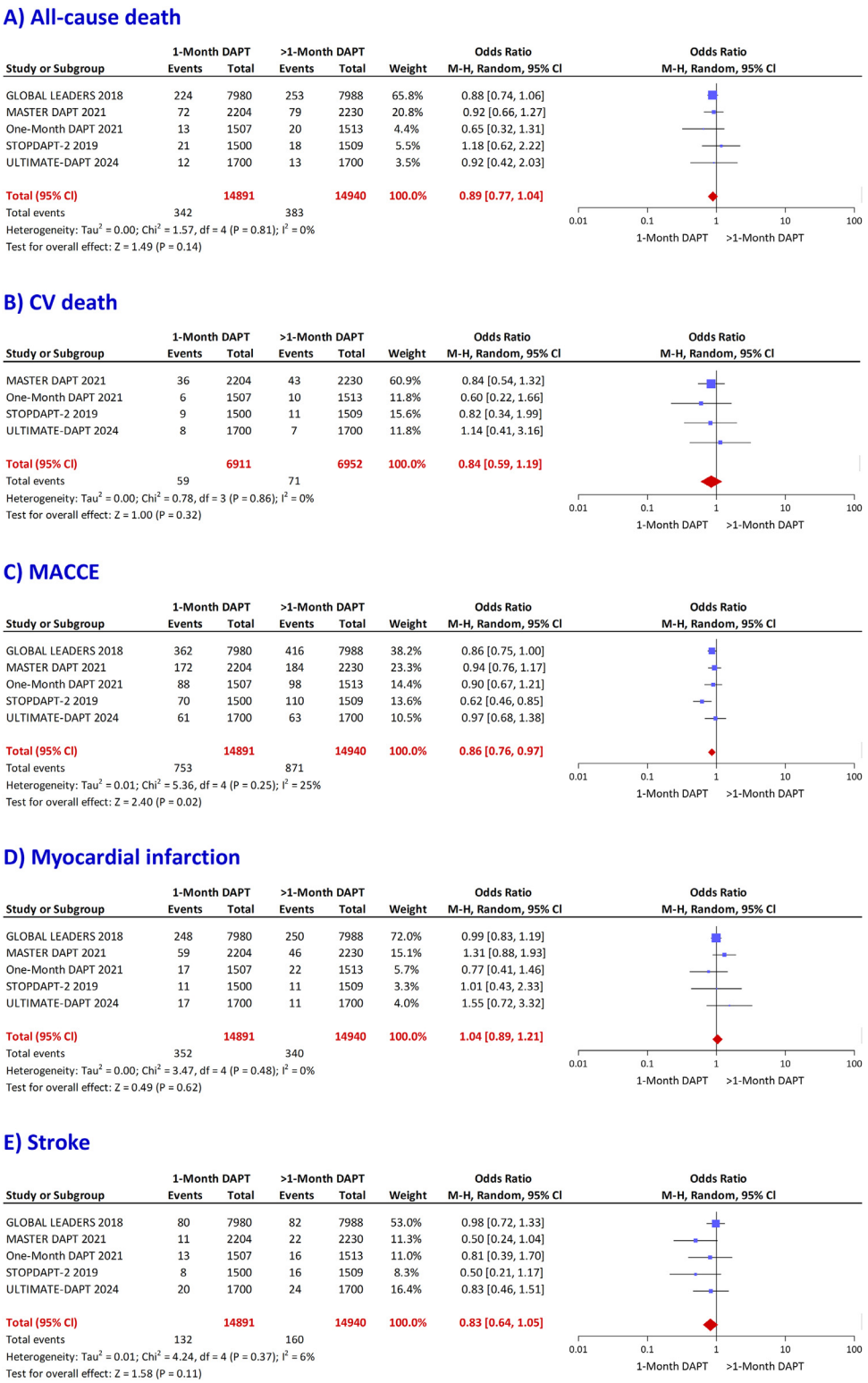

Figure 2. Forest plot comparing secondary outcome between 1-month DAPT and >1-month DAPT. (*A*) All-cause; (*B*) CV death; (*C*) MACE; (*D*) MI; (*E*) stroke. M-H = Mantel-Haenszel.

Discussion

The main findings of this meta-analysis can be summarized as follows: (1) in patients who underwent PCI with DES, 1-month DAPT followed by aspirin or a P2Y12 receptor inhibitor reduced clinically major bleeding compared with longer-term DAPT; (2) 1-month DAPT followed by aspirin or a P2Y12 receptor inhibitor was not inferior in protecting patients from stent-related thrombosis compared with longer-term DAPT; and (3) MACCE in the form of

combined all-cause mortality, CV death, major bleeding, stent thrombosis, and stroke was significantly less in 1-month DAPT compared with >1-month DAPT.

PCI with DES has become the conventional treatment of obstructive CAD irrespective of its presentation, stable or ACS, but with a significant risk of in-stent thrombosis.[22] Over the years, evidence became strong supporting the use of DAPT for protecting patients from such intervention related risk, as supported by guidelines.[3,4] However, DAPT themselves have been reported to carry a significant bleeding risk with clinical sequences in many of those patients.[23] To rectify such a clinical dilemma, clinicians and researchers attempted to investigate the safety of short DAPT treatment of only 1-month after coronary PCI and stenting. Indeed, only a few RCTs have been allowed to compare the new 1-month DAPT strategy with the standard longer use of DAPT as recommended by current guidelines. In this study, we meta-analyzed the currently available 5 RCTs, which compared the 2 treatment arms in a sizable number of patients requiring PCI and stenting for significant symptomatic CAD. Our analysis of these RCTs has shown that patients who underwent PCI with DES, 1-month DAPT followed by aspirin or a P2Y12 receptor inhibitor had significantly less major bleeding compared with longer-term DAPT, with no increased thrombotic risk irrespective of age, gender, cardiac risk factors, and previous coronary intervention procedures and events (CABG, PCI, MI, and bleeding). One-month DAPT was also associated with less MACCE compared with >1-month treatment, probably as a result of the cumulative effect of bleeding and similar death and stroke in patients with 1-month treatment. The similar overall and CV mortality we found in this analysis suggests a potential safe place for 1-month DAPT treatment in routine interventional CAD management, irrespective of the nature of the disease, stable or unstable.

In-stent thrombosis is related to the foreign nature of the stent, although it is less in the new generations of the DES compared with the old-fashioned bare metal ones.[24] It has never been ascertained how long DAPT takes to stabilize blood platelets-stent interaction, after which DAPT has no additional benefit. Our findings support a period of 1 month for the stents to achieve such balance. Therefore, a longer period of treatment would not only have no thrombosis prevention effect but potentially harmful side effects in the form of bleeding, as our results have shown.

This study provides strong evidence supporting the safety of using a 1-month DAPT compared with the conventionally recommended 6 to 12 months of treatment after PCI with DES for significant obstructive CAD. The thrombosis rate was not different between the 2 approaches, as were the other conventional CV risk factors. Most important of all was the significantly less bleeding complication with 1-month DAPT compared with longer period conventional strategy, thus supporting the additive significant benefit of patients commencing PCI on 1-month DAPT instead of the currently recommended 6-month treatment.

One of the important limitations of the study is the issue of the statistical power of meta-analysis, with few studies included. The number of available RCTs we could include in our analysis was small, but the consistency of the findings in all of them added to the power of the study. We were not involved with the data collection, but there was no justification for questioning the accuracy of the 4 well-designed RCTs we included. This is supported by the lack of heterogeneity between them. Although some of the data we analyzed were previously published, our detailed analysis adds extra scientific power supporting the use of 1-month DAPT treatment after PCI and DES, irrespective of the type of angina.

One-month treatment with DAPT after PCI with DES is not inferior to the guidelines recommended 6 to 12 months of treatment. Furthermore, the 1-month approach was associated with reduced bleeding and less MACCE; hence, it should be supported as a future strategy for optimum antithrombotic protective measures after PCI.

Author Contributions

GB, PI, and GA contributed to the conceptualization, study design, methodology, and project administration. IB, RK, and AB performed statistical analysis and interpretation of the data. GB, SE, and MYH wrote and critically revised the draft of the manuscript. All authors have read and agreed to the published version of the manuscript.

Declaration of competing interest

The authors have no competing interests to declare.

CRediT authorship contribution statement

Gani Bajraktari: Writing − review & editing, Writing − original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Ibadete Bytyçi:** Validation, Methodology, Formal analysis, Data curation. **Genc Abdyli:** Software, Resources, Methodology, Investigation, Formal analysis, Data curation. **Pranvera Ibrahimi:** Writing − original draft, Supervision, Methodology, Investigation, Data curation, Conceptualization. **Artan Bajraktari:** Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation. **Rona Karahoda:** Visualization, Software, Resources, Methodology, Investigation, Data curation, Conceptualization. **Shpend Elezi:** Writing − review & editing, Visualization, Validation, Supervision. **Michael Y. Henein:** Writing − review & editing, Writing − original draft, Visualization, Validation, Supervision.

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.2024.07.010.

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