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Optimizing revascularization and conservative therapy in chronic coronary syndrome

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Optimizing revascularization and conservative therapy in chronic coronary syndrome

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Editorial: Optimizing revascularization and conservative therapy in chronic coronary syndrome

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Editorial on the Research Topic
Optimizing revascularization and conservative therapy in chronic coronary syndrome

Introduction

Chronic coronary syndrome (CCS) is the most prevalent form of cardiovascular disease (CVD) and represents the leading cause of disability-adjusted life years and deaths worldwide, according to the latest update from the Global Burden of Disease (GBD) (1). In contrast to acute coronary syndromes (ACS), where early revascularization clearly improves survival and other clinical outcomes, the benefit of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) beyond symptom relief and quality of life improvement in CCS is less certain. Relevant international guidelines emphasize optimal medical therapy (OMT) in all patients and carefully indicate revascularization for prognostically relevant anatomical substrates, impaired left ventricular systolic function, or refractory and limiting angina symptoms despite OMT (2, 3). The clinical reality, however, is a large grey zone where ischemia burden, anatomy, comorbidities, and patient preference must be balanced together to devise an individual and patient-tailored treatment (4, 5). The contemporary personalized approach to CCS should evaluate all aspects of interventions that integrate revascularization, medical therapy, and lifestyle interventions (6, 7).

The *Frontiers in Cardiovascular Medicine* Research Topic entitled "*Optimizing Revascularization and Conservative Therapy in Chronic Coronary Syndrome*" brings together an impressive collection of fifteen articles that collectively advance the field. This editorial synthesizes their main messages around four themes: (1) diagnosis and risk stratification, (2) use and timing of revascularization, (3) technical and procedural optimization, and (4) refinement of conservative therapy.

Refining diagnosis and risk stratification

Several articles explored a fundamental question: which CCS patients truly warrant invasive evaluation and potential revascularization? Zhao et al. introduce ΔGCW, the change in global constructive work derived from strain echocardiography, as an early marker of ischemic risk. Combined with hemoglobin levels, ΔGCW improves discrimination of patients with functionally relevant ischemia, outperforming more conventional echocardiographic indices. This illustrates how advanced echocardiographic indices may refine selection for downstream testing in a non-invasive fashion. Another article by Tremamunno et al. reminds as all that simple clinical tools still matter, showing how exercise ECG may provide a value in CCS. In patients with suspected CCS, a clearly normal or low-risk treadmill test effectively ruled out left main coronary disease on subsequent angiography. In appropriate patients, a reassuring exercise test can thus support continued conservative management and avoid reflexive referral to the catheterization laboratory. Furthermore, Kong et al. examined the use of cardiopulmonary exercise testing (CPET) and demonstrated that lower heart rate at the anaerobic threshold and at the respiratory compensation point correlate with the presence of obstructive coronary artery disease (CAD) even in patients who do not reach maximal effort. These submaximal CPET parameters may therefore serve as surrogate markers of impaired chronotropic response when conventional exercise capacity is limited.

Taken together, these original studies illustrate how an integrated approach to functional assessment—from ECG stress testing through CPET to advanced echocardiographic strain imaging—can better discriminate those CCS patients who truly warrant invasive angiogram and potential revascularization from those who can safely remain on optimized medical therapy and undergo conservative pathway.

Guiding and timing of coronary revascularization

Once we decide to proceed with coronary revascularization, several questions arise, such as how and when to do carry out the procedure.

A network meta-analysis by Liu et al. compared PCI guided by angiography alone, invasive physiology, and intravascular imaging in patients with acute coronary syndromes. Both fractional flow reserve (FFR)-guided and intravascular ultrasound (IVUS)-guided PCI were associated with fewer major adverse cardiovascular events than angiography-guided PCI, with IVUS emerging as the top-ranked strategy. Although focused on ACS, these data suggest that, when we decide to treat, doing so by using physiology and imaging yields better long-term results than relying on the angiography cines alone. Similarly, two manuscripts focused on the timing and completeness of revascularization. He et al. pooled randomized trials comparing immediate vs. staged multivessel PCI in ACS, thus showing that immediate complete revascularization reduced myocardial infarction and repeat revascularization without increasing mortality, supporting a one-sitting strategy in carefully selected, hemodynamically stable patients. Traditionally challenging patients are those with chronic total occlusions (CTO), and decision-making in this patient population is challenging (8). Maestre-Luque et al. provided findings with an observational series in CCS patients with chronic total occlusion (CTO), in whom angiographic complete revascularization, including successful CTO PCI, was associated with fewer mid-term adverse events such as residual ischemia. The symptomatic dimension of CTO PCI is examined by Will et al., who showed that successful CTO recanalization provided consistent outcome improvements by significantly reducing angina frequency and nitrate use, even in the absence of a demonstrable survival advantage. Finally, Bosnjak et al. remind us that revascularization is only part of the story. In patients with stable CAD who underwent revascularization, elevated levels of NT-proBNP and Galectin-3 after the procedure identified a subgroup at higher risk of future events. Persistent biomarker activation despite successful intervention on coronaries likely reflects a diffuse or cardiomyopathic substrate and points to the need for intensified heart-failure–directed therapies. Revascularization in HF remains particularly challenging and recent expert consensus suggests careful and multimodal evaluation of these patients (9). It also opens a research avenue: can biomarker-guided post-PCI strategies further improve outcomes in CCS?

Technical nuances and procedural safety of coronary revascularization

A third cluster of manuscripts addresses practical challenges once the guide catheter is in the coronary ostium.

Wu et al. explore the impact of a myocardial bridge overlying an LAD CTO. Using IVUS-guided PCI, authors demonstrate that the presence of a bridge portends higher rates of restenosis, target lesion revascularization, and major adverse events at follow-up. An intramyocardial segment subjected to repetitive systolic compression appears to be an inherently hostile environment for stents. This argues for meticulous planning, careful stent sizing and expansion, and, where feasible, strategies that avoid extensive stenting within the bridged segment. Side-branch occlusion in LAD/diagonal bifurcation PCI is the focus of a validation study of the V-RESOLVE score. Wu et al. confirm that side-branch loss, although relatively infrequent, is strongly associated with worse clinical outcomes. High V-RESOLVE scores, driven by adverse bifurcation anatomy and limited side-branch protection, identified cases at high risk. Importantly, the underuse of intracoronary imaging was also linked to these adverse events. We now know that intravascular imaging during PCI improves safety and efficacy of the procedure, thus significantly reducing risks of death, MI, repeat revascularization, and stent thrombosis (10). Furthermore, a

study by Xi et al. exemplifies the use of a risk score to trigger more protective strategies, including systematic wiring of the side branch, provisional or planned two-stent techniques, and liberal use of intravascular imaging. At the access-site level, Wang et al. provide data on immediate removal of brachial artery sheaths after PCI. By reversing approximately half of the procedural heparin dose with protamine, operators were able to remove sheaths at the end of the procedure without increasing major bleeding, while maintaining a low incidence of pseudoaneurysm formation. For centers that still use brachial access, this protocol can simplify post-procedural care and shorten immobilization, provided that local surveillance is maintained.

Optimizing conservative therapy around revascularization

Revascularization decisions in CCS are inseparable from the background of OMT. One trial in this collection, by Wang et al., examines the combination of ticagrelor and extended-release metoprolol in elderly patients after PCI for ACS. Compared with standard care, the combination therapy improved left ventricular function, exercise capacity, and quality-of-life scores and was associated with more favorable profiles of inflammatory and myocardial injury biomarkers. These findings reinforce existing guideline recommendations on dual antiplatelet therapy and beta-blockade while emphasizing that elderly patients, who are often undertreated, can derive substantial functional benefit from combined cardioprotective therapies. More broadly, the special issue underscores that "conservative therapy" is anything but a mere passive concept. Across the articles, meticulous risk factor control, anti-ischemic medication, and HF-directed therapies remain the bedrock upon which any revascularization strategy rests. The question is rarely "stent or pills?" but rather "which patient, at which time, gains incremental benefit from an invasive strategy on top of already optimized medical care?"

A look ahead: research gaps and future clinical implications

Diagnostic pathways for CCS will likely become more integrated and will involve multimodal imaging and biomarker stratification in the future. As we see in this Special Collection, exercise ECG, CPET-derived heart-rate indices, and advanced echocardiographic measures such as ΔGCW each contribute complementary information. The key research need is to define practical algorithms that combine these tools in a cost-effective, patient-centered way and that can be implemented beyond tertiary centers. When revascularization is elected as a treatment option, the evidence increasingly favors doing it completely and doing it well: complete multivessel PCI in stable ACS patients, pursuit of complete revascularization in suitable CTOs, and liberal use of intravascular imaging and physiology help us make the right decisions and optimize stent deployment. Randomized data specific to CCS, particularly in patients with extensive comorbidities or complex anatomy, remain limited and should be a priority for future clinical trials.

In conclusion, the 15 articles in this Research Topic move us beyond the simplistic dichotomy of "revascularization vs. conservative therapy". Instead, they support a more nuanced vision: CCS as a disease continuum in which high-quality diagnostic modalities, personalized decisions about timing and completeness of revascularization, technical excellence in the cath lab, and rigorous optimization of medical therapy are interlocking components. For clinicians, this means fewer automatic reflexes and more thoughtful, evidence-based conversations with patients.

Author contributions

JB: Writing – original draft, Conceptualization, Supervision, Writing – review & editing. DM: Writing – review & editing, Formal analysis, Validation. AG: Writing – review & editing, Formal analysis, Validation. DM: Data curation, Validation, Formal analysis, Writing – review & editing.

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Global Burden of Cardiovascular Diseases and Risks 2023 Collaborators. Global, regional, and national burden of cardiovascular diseases and risk factors in 204 countries and territories, 1990–2023. *J Am Coll Cardiol*. (2025) 86(22):2167–243. doi: 10.1016/j.jacc.2025.08.015

2. Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, et al. 2024 ESC guidelines for the management of chronic coronary syndromes. *Eur Heart J*. (2024) 45(36):3415–537. doi: 10.1093/eurheartj/ehae177 Erratum in: Eur Heart J. 2025 46(16):1565. doi: 10.1093/eurheartj/ehaf079.

3. Rao SV, O'Donoghue ML, Ruel M, Rab T, Tamis-Holland JE, Alexander JH, et al. 2025 ACC/AHA/ACEP/NAEMSP/SCAI guideline for the management of patients with acute coronary syndromes: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *J Am Coll Cardiol*. (2025) 85(22):2135–237. Erratum in: J Am Coll Cardiol. 2025 85 (18):1800. doi: 10.1016/j.jacc.2025.03.500. doi: 10.1016/j.jacc.2024.11.009

4. Montone RA, Ford TJ, Galli M, Rinaldi R, Bland A, Morrow A, et al. Stratified medicine for acute and chronic coronary syndromes: a patient-tailored approach. *Prog Cardiovasc Dis*. (2024) 85:2–13. doi: 10.1016/j.pcad.2024.06.003

5. Borovac JA. Unlocking the gates of ISCHEMIA: moving toward personalized angina management for chronic coronary syndrome. *J Am Coll Cardiol*. (2024) 83(15):1367–9. doi: 10.1016/j.jacc.2024.03.001

6. Montone RA, Rinaldi R, Niccoli G, Andò G, Gragnano F, Piccolo R, et al. Optimizing management of stable angina: a patient-centered approach integrating revascularization, medical therapy, and lifestyle interventions. *J Am Coll Cardiol*. (2024) 84(8):744–60. doi: 10.1016/j.jacc.2024.06.015

7. Ferrari R, Camici PG, Crea F, Danchin N, Fox K, Maggioni AP, et al. Expert consensus document: a "diamond" approach to personalized treatment of angina. *Nat Rev Cardiol*. (2018) 15(2):120–32. doi: 10.1038/nrcardio.2017.131

8. Galassi AR, Vadalà G, Werner GS, Cosyns B, Sianos G, Hill J, et al. Evaluation and management of patients with coronary chronic total occlusions considered for revascularisation. A clinical consensus statement of the European association of percutaneous cardiovascular interventions (EAPCI) of the ESC, the European association of cardiovascular imaging (EACVI) of the ESC, and the ESC working group on cardiovascular surgery. *EuroIntervention*. (2024) 20(3):e174–84. doi: 10.4244/EIJ-D-23-00749

9. Mielniczuk LM, Ahmad T, Borovac JA, Brown K, Cooper LB, Fida N, et al. Management of ischemic heart disease in patients with heart failure: JACC: heart failure position statement. *JACC Heart Fail*. (2025) 13(12):102731. doi: 10.1016/j.jchf.2025.102731

10. Stone GW, Christiansen EH, Ali ZA, Andreasen LN, Maehara A, Ahmad Y, et al. Intravascular imaging-guided coronary drug-eluting stent implantation: an updated network meta-analysis. *Lancet*. (2024) 403(10429):824–37. doi: 10.1016/S0140-6736(23)02454-6

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Complete vs. incomplete percutaneous revascularization in patients with chronic total coronary artery occlusion

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Introduction: There is current controversy surrounding the benefits of percutaneous coronary intervention (PCI) of chronic total coronary occlusions (CTO). We aimed to evaluate the impact of complete percutaneous revascularization on major adverse cardiovascular events (MACE) in patients with CTO.

Methods: A retrospective observational study was conducted of consecutive patients referred for invasive coronary angiography at a single center between January 2018 and December 2019 and at least a CTO. The patients were divided into two groups according to the result of the procedure: complete revascularization of CTO (CR-CTO) versus incomplete revascularization (ICR-CTO) (patients with at least one non-recanalized CTO). Short- and mid-term clinical outcomes were evaluated. The primary endpoint was a composite of MACE that included all-cause death, non-fatal myocardial infarction, non-fatal stroke, or unplanned revascularization.

Results: In total, 359 patients with CTO were included. The median age was 68 years [interquartile range (IQR) 60–77 years], 66 (18%) were women and 169 (47.3%) had diabetes mellitus. In all, 167 (46.5%) patients received complete revascularization. After a median follow-up of 42 months (IQR 46–50 months), the primary endpoint occurred in 39 (23.4%) patients in the CR-CTO group and in 75 (39.1%) in the ICR-CTO group (HR 0.50, 95% CI 0.34–0.74; $p < 0.001$). This association remained significant in an inverse probability weighted model considering prognostic factors (adjusted HR 0.61, 95% CI 0.41–0.92; $p = 0.018$) and was driven by lower rates of all-cause death (adjusted OR 0.50, 95% CI 0.23–0.84; $p = 0.01$).

Conclusions: Complete revascularization of CTO was associated with a lower risk of MACE in the midterm follow up.

KEYWORDS

chronic total occlusion, percutaneous coronary intervention, coronary artery disease, major adverse cardiovascular events, myocardial infarction

1 Introduction

Chronic total occlusions (CTO) are a relatively common finding in patients with coronary artery disease (CAD). The prevalence of these lesions can reach up to 15%–25% of patients with stable angina pectoris (1), and up to 10%–15% of those presenting with ST-segment elevation myocardial infarction (STEMI) (2, 3). The presence of a CTO confers a worse prognosis for patients in terms of quality of life (4) and global mortality (5).

Percutaneous coronary intervention of chronic total occlusions (CTO-PCI) is a technically demanding procedure that requires trained and experienced professionals. Nevertheless, the success rate of CTO recanalization has improved in recent years because of the development of new techniques, advances in devices, and increasing experience. Recent prospective registries report procedural success rates in the range of 75%–90% (6–9).

There is controversial evidence on the benefits of CTO-PCI. Large observational studies and randomized control trials (RCT) have shown a positive effect of CTO-PCI on health status (10), left ventricular ejection fraction (LVEF) (11, 12), burden of ventricular arrhythmia (13), and overall survival (14). However, there are neutral or negative clinical trials that did not show evidence of LVEF recovery (15, 16) or a treatment effect on MACE (17).

The combination of the procedural complexity and the lack of robust evidence supporting a beneficial prognostic effect of CTO-PCI poses a major barrier for the widespread implementation of CTO recanalization. In fact, only 4%–10% of PCIs aim for CTO revascularization (8, 18).

This study sought to evaluate the association between complete or incomplete revascularization of CTOs and mid-term clinical outcomes in a high-volume center.

2 Materials and methods

2.1 Study design and population

An observational, longitudinal, retrospective study was conducted of all consecutive patients discharged with a diagnosis of CTO at a single center between January 2018 and December 2019. The inclusion criteria were as follows: (i) diagnosis of chronic total occlusion involving at least one of the three main genuine coronary vessels [left anterior descending coronary artery (LAD), left circumflex coronary artery (LCA), right coronary artery (RCA)]; and (ii) age equal to or greater than 18 years at diagnosis. The exclusion criteria were as follows: (i) surgical treatment of chronic total occlusion; (ii) in-hospital death during the same hospitalization when CTO was diagnosed; and (iii) patients' habitual residence located out of the region. Patients were divided into two groups according to the result of the percutaneous procedure: complete revascularization of CTO (CR-CTO) (patients with all CTO lesions located on the three main coronary vessels being revascularized) versus incomplete revascularization of CTO (ICR-CTO) (patients with at least one non-recanalized CTO located on one of the three main coronary arteries). This study was conducted according to the Declaration of Helsinki and was approved by the local clinical research ethics committee. The data were anonymized, and confidentiality was preserved, in accordance with the Regulation 2016/679—Protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation).

2.2 Procedures and medications

CTO-PCI indication was made by a multidisciplinary team comprising clinical cardiologists, interventional cardiologists, and cardiac surgeons considering the risks and benefits of the intervention, technical aspects of the lesions, and patient preferences. The decisions were in accordance with the clinical guidelines (19, 20) and established standards of practice (21). The extent of CAD and the SYNTAX score (Synergy between PCI with TAXUS and Cardiac Surgery) were assessed at the angiographic laboratory by interventional cardiologists. Medical treatment was optimized by the clinicians after routine clinical practice (20). Clinical and procedural data, treatment at discharge, and outcomes during the follow-up were reviewed through electronic health records.

2.3 Definitions

Chronic total occlusion was defined as angiographically proven anterograde flow obstruction of a coronary artery, known, or suspected to have lasted >3 months [with Thrombolysis In Myocardial Infarction (TIMI) flow = 0] (22), based on the patient's history. When no definite evidence of occlusion duration existed, the diagnosis of CTO was made based on angiographic morphology by at least two experienced interventional cardiologists. Successful revascularization was defined as angiographic final residual stenosis <20% by visual estimation and TIMI flow grade 3 after CTO recanalization.

Myocardial infarction (MI) was defined following the universal definition endorsed by the European Society of Cardiology (23). Worsening heart failure (WHF) was defined as the need for increasing diuretic dose or hospitalization for intravenous therapy. Clinically relevant bleeding was defined as a bleeding event type 2, 3, or 5 according to the Bleeding Academic Research Consortium (BARC) (24).

2.4 Endpoints

The primary endpoint was a composite of MACE, based on *Academic Research Consortium-2* criteria (25), which included: all-cause death, non-fatal myocardial infarction, non-fatal stroke, or unplanned revascularization.

Secondary endpoints were the individual components of the primary endpoint, worsening heart failure, visit to the emergency department or unplanned hospitalization due to chest pain, and clinically relevant bleeding.

2.5 Statistical analysis

Data are expressed as absolute and percent frequency in the case of qualitative variables. Quantitative variables are expressed as mean ± standard deviation or median (interquartile range), depending on variable distribution. The normality of distribution was assessed using the Shapiro–Wilk test and Q–Q plots. Between-group comparisons were performed using the Student's *t*-test or its non-parametric equivalent, the Mann–Whitney *U*-test, for continuous variables, and the chi-square test or Fisher's exact test for categorical variables. To evaluate the risk of MACE, time-to-event analyses were conducted using Kaplan–Meier and Cox proportional hazards methods. Logistic regression models were fitted to calculate the odds ratio for the secondary endpoints. All the models were adjusted by inverse probability of treatment weighting (IPTW) (26). Propensity scores were calculated using a logistic regression model that included those covariates with a prognostic impact according to previous literature: age, sex, glomerular filtration, diabetes mellitus, LVEF, localization of CTO, and extent of CAD. A standardized mean difference (SMD) of <10% was considered to indicate good balance. Confidence intervals for the IPTW coefficients were obtained using robust sandwich-type variance estimators (27). All tests were two-tailed and were considered significant when $p < 0.05$. Statistical analyses were performed using R software (version 4.0.3; R Foundation for Statistical Computing, Austria).

TABLE 1 Baseline clinical characteristics.

	CR-CTO $N = 167$	ICR-CTO $N = 192$	*p*
Age (years)	66 (59–74)	70 (61–92)	<0.001
Female sex	31 (18.6)	35 (18.2)	0.935
Obesity	85 (52)	100 (61)	0.120
Diabetes	94 (49.7)	75 (44.9)	0.363
Hypertension	121 (72.5)	147 (77.8)	0.245
Hyperlipidemia	92 (55.1)	113 (59.8)	0.371
Current or former smoker	49 (29.5)	41 (21.8)	0.096
EGFR (ml/min/1.73 m^2)	96 (71–121)	89 (65–117)	0.036
Chronic kidney disease	26 (16.2)	45 (26.8)	0.021
Atrial fibrillation	18 (11)	30 (16)	0.168
LVEF (%)	57.1 (46–68)	53.8 (40–64)	0.082
LVEF <40%	19 (17.9)	33 (23.6)	0.283
History of stroke	12 (7.3)	14 (7.5)	0.940
History of PVD	22 (13.3)	28 (15.1)	0.629
History of CAD	78 (46.7)	68 (36)	0.040
Multivessel CAD	75 (44.9)	128 (66.7)	<0.001
Prior PCI	67 (40.1)	43 (22.4)	0.007
Prior CABG	2 (1.2)	10 (5.2)	0.016
Clinical presentation			
Chest pain	135 (81.8)	145 (78.4)	0.422
Dyspnea	39 (23.6)	55 (30.2)	0.168
Heart failure	29 (17.7)	45 (25)	0.099
Evidence of ischemia	74 (44.8)	45 (24.7)	<0.001

CABG, coronary artery bypass grafting; CAD, coronary artery disease; EGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; PAD, peripheral vascular disease; PCI, percutaneous coronary intervention. Data are expressed as absolute and percent frequency for qualitative variables Quantitative variables are expressed as mean ± standard deviation.

3 Results

3.1 Baseline clinical and angiographic characteristics

A total of 359 patients were included. The median age was 68 years (IQR 60–77), 66 (18%) patients were women, and 169 (47.3%) had diabetes mellitus. The mean LVEF was 55% ± 13%. Most patients were symptomatic at diagnosis (80% chest pain, 20.6% heart failure). Complete revascularization of CTO was performed in 167 (46.5%) patients (CR-CTO group), whereas 192 (53.5%) patients had at least a non-revascularized CTO (ICR-CTO group). CR-CTO patients were younger [66 (IQR 59–74) vs. 70 (IQR 61–79) years; $p < 0.001$] and had greater glomerular filtration rate [95.9 (IQR 70.9–121.5) vs. 88.8 (IQR 56.4–117.1) mL/min/1.73 m^2; p 0.036]. They were more likely to have a history of coronary artery disease [78 (46.7%) vs. 68 (36.0%); $p = 0.040$] and prior PCI [67 (52.8%) vs. 43 (35.8%); $p = 0.007$], but they had lower rates of prior coronary artery bypass grafting (CABG) [2 (1.7%) vs. 10 (8.4%); $p = 0.016$]. This group also had more evidence of myocardial ischemia using non-invasive tests [74.0 (44.8%) vs. 45 (24.7%); $p < 0.001$]. The main clinical characteristics are summarized in Table 1.

There were 407 angiographically diagnosed CTO in 359 patients, 211 (51.8%) located in the RCA, 103 (25.3%) in the LCA, and 93 (22.9%) in the LAD. The mean SYNTAX score was 21.4 (95% CI 17.5–25.8), without differences between groups. Technical success was achieved in 203 (89%) out of a total of 228 attempted lesions. In those patients with incomplete revascularization, 234 CTO were diagnosed and 179 (76.5%) were left to pharmacological treatment. This group carried a greater rate of multivessel coronary artery disease (including CTO and non-CTO lesions) [128 (66.7%) vs. 75 (44.9%); $p < 0.001$]. The main angiographic and procedure characteristics are provided in Table 2.

TABLE 2 Angiographic characteristics.

	CR-CTO $N = 167$	ICR-CTO $N = 192$	*p*
Total number of CTO	173	234	
SYNTAX score	20.2 (15.3–24.7)	22.5 (17.5–26.8)	0.143
LAD CTO	52 (30)	41 (17.5)	0.035
Medical treatment	0 (0)	27 (66)	
PCI success	52 (100)	10 (24)	
PCI failure	0 (0)	4 (10)	
LCA CTO	30 (17.3)	73 (31.2)	<0.001
Medical treatment	0 (0)	56 (76.7)	
PCI success	30 (100)	8 (11)	
PCI failure	0 (0)	9 (12.3)	
RCA CTO	91 (52.7)	120 (51.3)	0.124
Medical treatment	0 (0)	96 (80)	
PCI success	91 (100)	12 (10)	
PCI failure	0 (0)	12 (10)	

CTO, chronic total occlusion; CR-CTO, complete revascularized CTO; ICR, incomplete revascularized CTO; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; PCI, percutaneous coronary intervention. Percentages are calculated over the total number of CTO.

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3.2 Clinical outcomes

After a median follow-up of 42 months (IQR 46–50 months), the primary endpoint occurred in 39 (23.4%) patients in the CR-CTO group and in 75 (39.1%) patients belonging to the ICR-CTO group (HR 0.50, 95% CI 0.34–0.74, $p < 0.001$) (Figure 1). To adjust for prognostic relevant confounders, we fitted an IPTW adjusted Cox model. The covariables included in the model showed an excellent balance with SMD <10% (Figure 2). In the IPTW adjusted Cox's model, the association remained significant [adjusted HR (HRadj) 0.61, 95% CI 0.41–0.92, $p = 0.018$]. Complete revascularization was also associated with a lower rate of all-cause death [adjusted OR (ORadj) 0.5, 95% CI 0.3–0.84, $p = 0.01$]. In the unadjusted analysis, the CR-CTO group showed a lower rate of non-fatal MI (OR 0.40, 95% CI 0.17–0.92, $p = 0.038$) and WHF (OR 0.47, 95% CI 0.27–0.81, $p = 0.007$). However, in the adjusted IPTW analysis, there was a numerical but not significant difference in the risk of non-fatal MI (ORadj 0.53, 95% CI 0.21–1.2, $p = 0.146$) and WHF (ORadj 0.62, 95% CI 0.36–1.06, $p = 0.088$) events. There were no differences between the groups in the rate of non-fatal stroke (ORadj 0.7, 95% CI 0.25–2.37, $p = 0.693$), unplanned revascularization (ORadj 1.4, 95% CI 0.6–3.2, $p = 0.425$), visit to the emergency department or unplanned hospitalization due to chest pain (ORadj 0.93, 95% CI 0.59–1.47, $p = 0.764$), and clinically relevant bleeding (ORadj 0.78, 95% CI 0.45–1.34, $p = 0.375$).

The results of the analyses of primary and secondary endpoints in the unweighted and weighted population are provided in Table 3.

4 Discussion

In this study, we found that complete CTO percutaneous revascularization compared to incomplete revascularization (a) was associated with lower overall risk of MACE and that (b) this lower risk was driven by overall mortality.

Most baseline characteristics of patients were analogous to the studies involving CTO: multiple cardiovascular risk factors, preserved LVEF, complex CAD, and previous history of

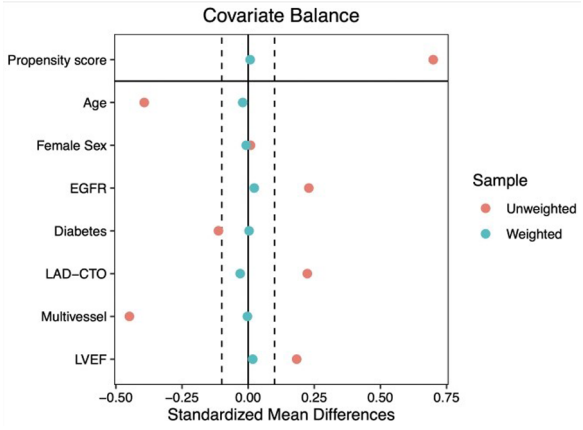

FIGURE 2
Covariate balance in the unweighted and weighted population. EGFR, estimated glomerular filtration rate; LAD-CTO, left anterior descending chronic total occlusion; LVEF, left ventricular ejection fraction.

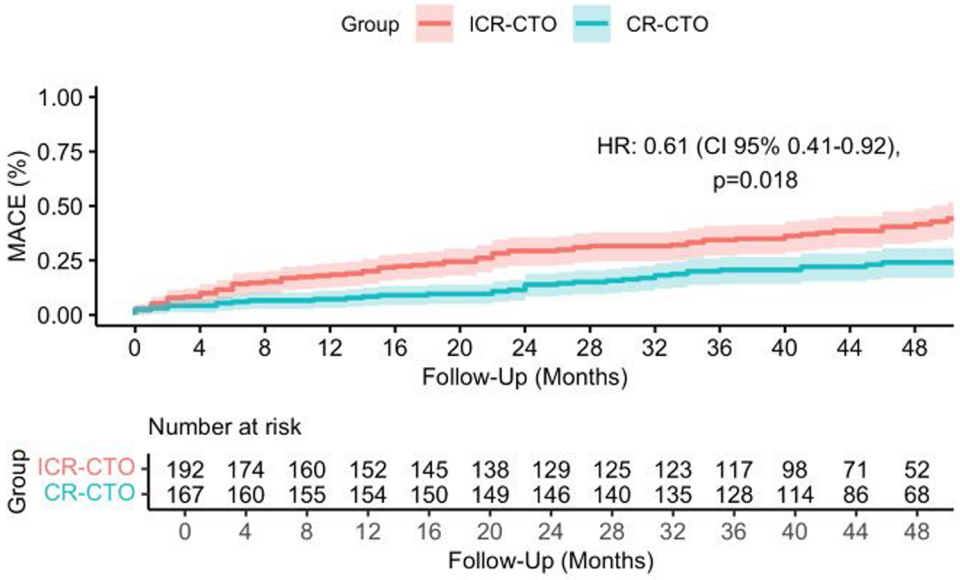

FIGURE 1
Kaplan–Meier curve for major adverse cardiovascular events. CR-CTO, complete revascularized chronic total occlusion; ICR-CTO, incomplete revascularized chronic total occlusion.

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TABLE 3 Primary and secondary endpoints: results of the analyses in the unweighted and weighted population.

	CR-CTO $N = 167$	ICR-CTO $N = 192$	Unadjusted model		IPTW adjusted model	
	n (%)	*n* (%)	HR (CI 95%)	*p*	HR (CI 95%)	*p*
Primary endpoint						
MACE	39 (23.4)	75 (39.1)	0.50 (0.34–0.74)	<0.001	0.61 (0.41–0.92)	0.018
Secondary endpoints						
All-cause death	24 (14.4)	62 (32.3)	0.35 (0.20–0.59)	<0.001	0.5 (0.3–0.84)	0.010
Non-fatal MI	8 (5)	21 (11)	0.40 (0.17–0.92)	0.038	0.53 (0.21–1.2)	0.146
Non-fatal stroke	6 (3.6)	8 (4.2)	0.85 (0.28–2.51)	0.780	0.7 (0.25–2.37)	0.693
Unplanned revascularization	13 (7.8)	12 (6.2)	1.26 (0.55–2.89)	0.570	1.4 (0.6–3.2)	0.425
Worsening heart failure	24 (14.4)	50 (26)	0.47 (0.27–0.81)	0.007	0.62 (0.36–1.06)	0.088
Chest pain (emergency/hospital)	46 (27)	54 (28)	0.97 (0.61- 1.54)	0.903	0.93 (0.59–1.47)	0.764
Clinically relevant bleeding	25 (15)	38 (19)	0.71 (0.41–1.24)	0.232	0.78 (0.45–1.34)	0.375

CI, confidence interval; CR-CTO, complete revascularized chronic total occlusion; ICR-CTO, incomplete revascularized chronic total occlusion; IPTW, inverse probability of treatment weighting; HR, hazard ratio; MI, myocardial infarction; OR, odds ratio. The covariates included in the IPTW adjusted model were age, sex, glomerular filtration, diabetes mellitus, heart failure, localization of CTO, extent of CAD.

revascularization by PCI or CABG. However, the median age was slightly higher than the reported by other observational works (7, 8, 28). ICR-CTO was mostly a consequence of the operator's decision to not attempt CTO-PCI. It might be explained by the presence of some factors in this group that increased the procedural risk: older age, lower rates of glomerular filtration, more severe coronary artery disease, and greater burden of previous CABG. In particular, renal function is an important factor during decision-making (29). The association between complete revascularization and a lower risk of MACE was present after adjusting for relevant prognostic factors that were included in the IPWT adjusted Cox model. Patients in the CR-CTO group had lower overall mortality, suggesting a beneficial effect of complete revascularization of CTO. We did not find differences in non-fatal MI or WHF between groups in the adjusted analysis. The similar rates of non-fatal MI could be explained by the fact that the risk of subsequent MI might be driven by the progression of mild atherosclerotic plaques and the presence of new unstable non-CTO lesions, rather than by previous non-revascularized CTO. Concerning WHF, some factors might explain our findings: there were no differences in previous history of heart failure or LVEF between groups and most patients had preserved ejection fraction, which could limit the benefit of CTO-PCI in terms of LVEF recovery. Interestingly, we did not find differences in the rates of major bleeding events, which might be considered a potential falsification endpoint supporting the robustness of the adjustment (30). The rate of successful procedures (90%) is in line with the results reported in high-volume and experienced centers (8, 9, 31).

There have been controversial and conflicting findings about CTO-PCI in observational studies and RCTs. Regarding symptoms and quality of life, the revascularization of CTO has proved to be beneficial compared to optimal medical treatment in the EURO-CTO trial (10). The IMPACTOR-CTO trial showed a reduction in inducible ischemia burden (32), measured by magnetic resonance image (MRI), with CTO-PCI. Concerning LVEF and cardiac remodeling, some observational studies have reported an improvement after CTO recanalization (11, 12), the EXPLORE trial suggested a beneficial effect only for patients with CTO-PCI targeting LAD (15), and the REVASC trial did not find a benefit in terms of LVEF recovery (16). In relation to hard endpoints, the two largest RCTs so far have shown no impact of CTO recanalization on MACE (10, 17), with some limitations to point out. First, the EURO-CTO was not designed to test hard endpoints and the follow-up period was short. Second, the DECISION-CTO had high rates of crossover between treatment groups, they evaluated a combined strategy of PCI both for CTO and non-CTO lesions, and the sample size was smaller than planned, which reduced the power to test MACE. On the contrary, several non-randomized studies have suggested a positive effect of CTO-PCI on hard endpoints. Multicenter prospective study IRCTO showed a reduction of MACE and cardiovascular death in CTO-PCI patients during a short-term follow-up (33), and other observational studies obtained similar results (34, 35). The ERCTO prospective registry revealed lower rates of MACE, including cardiac death, myocardial infarction, and non-planned revascularization, in completely retrograde revascularized patients (36). Azzalini et al. suggested that even a mild degree of incomplete revascularization in patients with CTO (residual SYNTAX score between 1 and 8) is associated with a higher incidence of MACE on long-term follow-up (37). In addition, several meta-analyses of observational studies have reported a beneficial effect of CTO-PCI. Some of them showed a reduction of MACE for complete revascularization of CTO versus optimal medical treatment alone (28–39). Others have compared successful versus unsuccessful revascularization of CTO and obtained a significant benefit of complete recanalization on long-term MACE and reduced needs for subsequent CABG (14, 40, 41).

Our results are in line with previous large observational studies and multicenter registries and point toward a potential benefit of complete CTO revascularization in terms of MACE. Potential explanations for our findings include a reduction in ischemic burden and the risk for arrhythmias, the better outcomes in case of an acute coronary syndrome (the area at risk of necrosis is higher for incomplete revascularized CTO patients when an

atherosclerotic plaque is unstable in a non-CTO vessel) or the improvement in left ventricular function and cardiac remodeling.

Considering the continuous technical advancements and improvements in CTO-PCI success rates, the revascularization of CTOs seems an appealing option that potentially leads to an added prognostic benefit, especially in symptomatic patients. It should be acknowledged that non-randomized studies are necessary to continue building a body of evidence in CTO-PCI, where well-designed and powered RCTs are lacking. Two ongoing randomized control trials (NOBLE-CTO and ISCHEMIA-CTO) could shed light on the prognostic value of CTO-PCI.

Our research has some limitations. The observational nature of our study provides only associative evidence, and we cannot rule out the presence of residual confounding factors due to the lack of randomization. There is also potential for survival or selection bias (unfavorable patients' characteristics and a more complex anatomy might have influenced the decision for a conservative treatment). To minimize those issues, we conducted a propensity score-based analysis accounting for prognostic factors. Furthermore, the single-center design of the study might limit the generalization of our results to other centers depending on the operator's experience. Finally, since the SARS-Cov-2 pandemic occurred during the study period, our results might have been influenced by changes in the healthcare system's accessibility. The lower accessibility to hospitals during the pandemic might have resulted in an underestimation of cardiovascular events.

In conclusion, patients with CTO who received complete revascularization had a lower midterm risk of MACE, mainly driven by a reduction in the rates of all-cause death. These results suggest a potential benefit of PCI-CTO and supply real-world data for routine practice that could help to guide clinical decision-making. More randomized control trials are needed to generate robust evidence on this topic.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Comité de Ética de la Investigación Provincial de Córdoba. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

LM-L: Conceptualization, Formal Analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. RG-M: Conceptualization, Formal Analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. JS: Writing – original draft, Writing – review & editing. FH: Writing – original draft, Writing – review & editing. LB-M: Writing – original draft, Writing – review & editing. JJ: Writing – original draft, Writing – review & editing. IG: Writing – original draft, Writing – review & editing. JP: Writing – original draft, Writing – review & editing. MA: Writing – original draft, Writing – review & editing. MR: Writing – original draft, Writing – review & editing. SO: Supervision, Validation, Writing – original draft, Writing – review & editing. MP: Supervision, Validation, Writing – original draft, Writing – review & editing.

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References

1. Fefer P, Knudtson ML, Cheema AN, Galbraith PD, Osherov AB, Yalonetsky S, et al. Current perspectives on coronary chronic total occlusions. *J Am Coll Cardiol*. (2012) 59(11):991–7. doi: 10.1016/j.jacc.2011.12.007

2. Claessen BEPM, van der Schaaf RJ, Verouden NJ, Stegenga NK, Engstrom AE, Sjauw KD, et al. Evaluation of the effect of a concurrent chronic total occlusion on long-term mortality and left ventricular function in patients after primary

percutaneous coronary intervention. *JACC Cardiovasc Interv*. (2009) 2(11):1128–34. doi: 10.1016/j.jcin.2009.08.024

3. Claessen BE, Dangas GD, Weisz G, Witzenbichler B, Guagliumi G, Mockel M, et al. Prognostic impact of a chronic total occlusion in a non-infarct-related artery in patients with ST-segment elevation myocardial infarction: 3-year results from the HORIZONS-AMI trial. *Eur Heart J*. (2012) 33(6):768–75. doi: 10.1093/eurheartj/ehr471

4. Kucukseymen S, Iannaccone M, Grantham JA, Sapontis J, Juricic S, Ciardetti N, et al. Association of successful percutaneous revascularization of chronic total occlusions with quality of life. *JAMA Netw Open*. (2023) 6(7):e2324522. doi: 10.1001/jamanetworkopen.2023.24522

5. Råmunddal T, Hoebers LP, Henriques JPS, Dworeck C, Angerås O, Odenstedt J, et al. Prognostic impact of chronic total occlusions. *JACC Cardiovasc Interv*. (2016) 9 (15):1535–44. doi: 10.1016/j.jcin.2016.04.031

6. Christopoulos G, Karmpaliotis D, Alaswad K, Yeh RW, Jaffer FA, Wyman RM, et al. Application and outcomes of a hybrid approach to chronic total occlusion percutaneous coronary intervention in a contemporary multicenter US registry. *Int J Cardiol*. (2015) 198:222–8. doi: 10.1016/j.ijcard.2015.06.093

7. Salisbury AC, Sapontis J, Grantham JA, Qintar M, Gosch KL, Lombardi W, et al. Outcomes of chronic total occlusion percutaneous coronary intervention in patients with diabetes. *JACC Cardiovasc Interv*. (2017) 10(21):2174–81. doi: 10.1016/j.jcin.2017.08.043

8. Amat-Santos IJ, Martin-Yuste V, Fernández-Díaz JA, Martin-Moreiras J, Caballero-Borrego J, Salinas P, et al. Procedural, functional and prognostic outcomes following recanalization of coronary chronic total occlusions. Results of the Iberian registry. *Rev Esp Cardiol (Engl Ed)*. (2019) 72(5):373–82. doi: 10.1016/j.rec.2018.05.020

9. Konstantinidis NV, Werner GS, Deftereos S, Di Mario C, Galassi AR, Buettner JH, et al. Temporal trends in chronic total occlusion interventions in Europe. *Circ Cardiovasc Interv*. (2018) 11(10). doi: 10.1161/CIRCINTERVENTIONS.117.006229

10. Werner GS, Martin-Yuste V, Hildick-Smith D, Boudou N, Sianos G, Gelev V, et al. A randomized multicentre trial to compare revascularization with optimal medical therapy for the treatment of chronic total coronary occlusions. *Eur Heart J*. (2018) 39(26):2484–93. doi: 10.1093/eurheartj/ehy220

11. Chung C, Nakamura S, Tanaka K, Tanigawa J, Kitano K, Akiyama T, et al. Effect of recanalization of chronic total occlusions on global and regional left ventricular function in patients with or without previous myocardial infarction. *Catheter Cardiovasc Interv*. (2003) 60(3):368–74. doi: 10.1002/ccd.10641

12. Kirschbaum SW, Baks T, van den Ent M, Sianos G, Krestin GP, Serruys PW, et al. Evaluation of left ventricular function three years after percutaneous recanalization of chronic total coronary occlusions. *Am J Cardiol*. 2008;101 (2):179–85. doi: 10.1016/j.amjcard.2007.07.060

13. Nombela-Franco L, Iannaccone M, Anguera I, Amat-Santos IJ, Sanchez-Garcia M, Bautista D, et al. Impact of chronic total coronary occlusion on recurrence of ventricular arrhythmias in ischemic secondary prevention implantable cardioverter-defibrillator recipients (VACTO secondary study). *JACC Cardiovasc Interv*. (2017) 10(9):879–88. doi: 10.1016/j.jcin.2017.02.008

14. Khan MF, Wendel CS, Thai HM, Movahed MR. Effects of percutaneous revascularization of chronic total occlusions on clinical outcomes: a meta-analysis comparing successful versus failed percutaneous intervention for chronic total occlusion. *Catheter Cardiovasc Interv*. (2013) 82(1):95–107. doi: 10.1002/ccd.24863

15. Henriques JPS, Hoebers LP, Råmunddal T, Laanmets P, Eriksen E, Bax M, et al. Percutaneous intervention for concurrent chronic total occlusions in patients with STEMI. *J Am Coll Cardiol*. (2016) 68(15):1622–32. doi: 10.1016/j.jacc.2016.07.744

16. Mashayekhi K, Nührenberg TG, Toma A, Gick M, Ferenc M, Hochholzer W, et al. A randomized trial to assess regional left ventricular function after stent implantation in chronic total occlusion. *JACC Cardiovasc Interv*. (2018) 11 (19):1982–91. doi: 10.1016/j.jcin.2018.05.041

17. Lee SW, Lee PH, Ahn JM, Park DW, Yun SC, Han S, et al. Randomized trial evaluating percutaneous coronary intervention for the treatment of chronic total occlusion. *Circulation*. (2019) 139(14):1674–83. doi: 10.1161/CIRCULATIONAHA.118.031313

18. Werner G, Hochadel M, Zeymer U, Kerber S, Schumacher B, Grube E, et al. Contemporary success and complication rates of percutaneous coronary intervention for chronic total coronary occlusions: results from the ALKK quality control registry of 2006. *EuroIntervention*. (2010) 6(3):361–6. doi: 10.4244/EIJV6I3A60

19. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. (2019) 40(2):87–165. doi: 10.1093/eurheartj/ehy394

20. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. (2020) 41(3):407–77. doi: 10.1093/eurheartj/ehz425

21. Galassi AR, Werner GS, Boukhris M, Azzalini L, Mashayekhi K, Carlino M, et al. Percutaneous recanalisation of chronic total occlusions: 2019 consensus document from the EuroCTO club. *EuroIntervention*. (2019) 15(2):198–208. doi: 10.4244/EIJ-D-18-00826

22. Stone GW, Kandzari DE, Mehran R, Colombo A, Schwartz RS, Bailey S, et al. Percutaneous recanalization of chronically occluded coronary arteries. *Circulation*. (2005) 112(15):2364–72. doi: 10.1161/CIRCULATIONAHA.104.481283

23. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). *Eur Heart J*. (2019) 40(3):237–69. doi: 10.1093/eurheartj/ehy462

24. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials. *Circulation*. (2011) 123(23):2736–47. doi: 10.1161/CIRCULATIONAHA.110.009449

25. Garcia-Garcia HM, McFadden EP, Farb A, Mehran R, Stone GW, Spertus J, et al. Standardized end point definitions for coronary intervention trials: the academic research consortium-2 consensus document. *Circulation*. (2018) 137(24):2635–50. doi: 10.1161/CIRCULATIONAHA.117.029289

26. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med*. (2015) 34(28):3661–79. doi: 10.1002/sim.6607

27. Austin PC. Variance estimation when using inverse probability of treatment weighting (IPTW) with survival analysis. *Stat Med*. (2016) 35(30):5642–55. doi: 10.1002/sim.7084

28. Khanra D, Mishra V, Jain B, Soni S, Bahurupi Y, Duggal B, et al. Percutaneous coronary intervention provided better long term results than optimal medical therapy alone in patients with chronic total occlusion: a meta-analysis. *Indian Heart J*. (2020) 72(4):225–31. doi: 10.1016/j.ihj.2020.07.013

29. Kim CH, Yang JH, Park TK, Song YB, Hahn JY, Choi JH, et al. Revascularization vs. Medical therapy for coronary chronic total occlusions in patients with chronic kidney disease. *Circ J*. (2018) 82(8):2136–42. doi: 10.1253/circj.CJ-17-1272

30. Groenwold RHH. Falsification end points for observational studies. *JAMA*. (2013) 309(17):1769. doi: 10.1001/jama.2013.3089

31. Ojeda S, Pan M, Gutiérrez A, Romero M, Chavarría J, de Lezo JS, et al. Bifurcation lesions involved in the recanalization process of coronary chronic total occlusions: incidence, treatment and clinical implications. *Int J Cardiol*. (2017) 230:432–8. doi: 10.1016/j.ijcard.2016.12.088

32. Obedinskiy AA, Kretov EI, Boukhris M, Kurbatov VP, Osiev AG, Ibn Elhadj Z, et al. The IMPACTOR-CTO trial. *JACC Cardiovasc Interv*. (2018) 11(13):1309–11. doi: 10.1016/j.jcin.2018.04.017

33. Tomasello SD, Boukhris M, Giubilato S, Marzà F, Garbo R, Contegiacomo G, et al. Management strategies in patients affected by chronic total occlusions: results from the Italian registry of chronic total occlusions. *Eur Heart J*. (2015) 36 (45):3189–98. doi: 10.1093/eurheartj/ehv450

34. George S, Cockburn J, Clayton TC, Ludman P, Cotton J, Spratt J, et al. Long-term follow-up of elective chronic total coronary occlusion angioplasty. *J Am Coll Cardiol*. (2014) 64(3):235–43. doi: 10.1016/j.jacc.2014.04.040

35. Yang JH, Kim BS, Jang WJ, Ahn J, Park TK, Bin SY, et al. Optimal medical therapy vs. percutaneous coronary intervention for patients with coronary chronic total occlusion—a propensity-matched analysis. *Circ J*. (2016) 80(1):211–7. doi: 10.1253/circj.CJ-15-0673

36. Galassi AR, Sianos G, Werner GS, Escaned J, Tomasello SD, Boukhris M, et al. Retrograde recanalization of chronic total occlusions in Europe. *J Am Coll Cardiol*. (2015) 65(22):2388–400. doi: 10.1016/j.jacc.2015.03.566

37. Azzalini L, Candilio L, Ojeda S, Dens J, La Manna A, Benincasa S, et al. Impact of incomplete revascularization on long-term outcomes following chronic total occlusion percutaneous coronary intervention. *Am J Cardiol*. (2018) 121 (10):1138–48. doi: 10.1016/j.amjcard.2018.01.033

38. Li KHC, Wong KHG, Gong M, Liu T, Li G, Xia Y, et al. Percutaneous coronary intervention versus medical therapy for chronic total occlusion of coronary arteries: a systematic review and meta-analysis. *Curr Atheroscler Rep*. (2019) 21(10):42. doi: 10.1007/s11883-019-0804-8

39. Ma Y, Li D, Li J, Li Y, Bai F, Qin F, et al. Percutaneous coronary intervention versus optimal medical therapy for patients with chronic total occlusion: a meta-analysis and systematic review. *J Thorac Dis*. (2018) 10(5):2960–7. doi: 10.21037/jtd.2018.04.140

40. Gao L, Wang Y, Liu Y, Cao F, Chen Y. Long-term clinical outcomes of successful revascularization with drug-eluting stents for chronic total occlusions: a systematic review and meta-analysis. *Catheter Cardiovasc Interv*. (2017) 89(S1):574–81. doi: 10.1002/ccd.26934

41. Christakopoulos GE, Christopoulos G, Carlino M, Jeroudi OM, Roesle M, Rangan B V, et al. Meta-analysis of clinical outcomes of patients who underwent percutaneous coronary interventions for chronic total occlusions. *Am J Cardiol*. (2015) 115(10):1367–75. doi: 10.1016/j.amjcard.2015.02.038

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Heart failure biomarkers in revascularized patients with stable coronary heart disease as clinical outcome predictors

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Introduction: The aim of this study was to investigate serum levels of galectin-3 (Gal-3) and N-terminal pro-brain Natriuretic Peptide (NT-proBNP) in patients with stable obstructive coronary artery disease, as well as their potential to predict clinical outcomes.

Methods: This was a single-center cross-sectional cohort study. 168 patients were divided into three groups: percutaneous coronary intervention (PCI) group (N 64), coronary artery bypass graft surgery (CABG) group (N 57), and group with no coronary stenosis (N 47). Gal-3 and NT-proBNP levels were measured and the Syntax score (Ss) was calculated.

Results: The mean value of Gal-3 was 19.98 ng/ml and 9.51 ng/ml ($p < 0.001$) in the study group and control group, respectively. Highest value of Gal-3 was found in the group of subjects with three-vessel disease ($p < 0.001$). The mean value of NT-proBNP in the study group was 401.3 pg/ml, and in the control group 100.3 pg/ml ($p = 0.159$). The highest value of NT-proBNP was found in the group of subjects with three-vessel disease ($p = 0.021$). There was a statistically significant association between Gal-3, NT-proBNP and occurrence of adverse cardiovascular event ($p = 0.0018$; $p = 0.0019$).

Conclusion: Gal-3 and NT-proBNP could be used as an additional tool for diagnosis and severity assessment of stable obstructive coronary artery disease. Furthermore, it could help identify high-risk patients who could experience major adverse cardiovascular events.

KEYWORDS

galectin-3, NT-proBNP, coronary artery disease, biomarker, chronic coronary syndrome, cardiac outcome

1 Introduction

Cardiovascular diseases, despite progress in early diagnosis and treatment, remain the leading cause of death and disability worldwide. Opposite of acute coronary syndromes (ACS), characterized by unstable phases of the atherothrombotic process in epicardial arteries, chronic coronary syndrome (CCS) is caused by rigid stenosis of the blood

vessel and disturbances in the form of angina due to a mismatch of blood demand and supply of the myocardium during exertion (1).

In the stratification of patients with cardiovascular diseases, in addition to non-invasive and invasive imaging techniques for evidence of coronary disease, appropriate biomarkers are also used to recognize high-risk patients and respond therapeutically in time. Biomarkers allow us to diagnose the disease in a simple way, and monitor its outcome, complications as well as therapeutic effects (2).

Numerous studies have examined the predictive significance of N-terminal probrain natriuretic peptide (NT-proBNP) in patients with heart failure but also in acute coronary syndromes. In patients with CCS, NT-proBNP could also give predictive information on all cause mortality independent of invasive measures of the severity of coronary artery disease and left ventricular function (LVEF) (3). In recent years, several more biomarkers have emerged that have proven to be predictors of outcomes in heart failure. One of them is galectin-3 (Gal-3), a protein that is part of the galectin family, secreted by macrophages; involved in numerous pathophysiological mechanisms such as inflammation and the development of fibrotic tissue (4). Gal-3 plays an important role in heart failure development, but also has a major role in the atherosclerotic process. From the beginning to the development of atheromatous plaque, which ultimately results in ACS, inflammation and oxidative stress are important factors in all phases of atherosclerosis. Gal-3 is a mediator that is produced from macrophages and endothelium and is actively involved in controlling a variety of inflammatory cell behavior traits (5). Adverse matrix remodeling has been observed due to its involvement in proliferation, phagocytosis, neutrophil extravasation, macrophage chemotaxis, and type-1 collagen deposition in the extracellular matrix (5–7). Serum levels of galectin-3 are rarely variable; once elevated, they often remain elevated and are unaffected by standard heart failure treatment (8). The Gal-3 level was considerably higher in ST-segment elevation myocardial infarction (STEMI) patients than in the healthy control group. Also, patients with multivessel coronary artery disease in contrast to healthy individuals had greater levels of Gal-3, which suggests that Gal-3 has an important role in atherosclerotic plaque formation (5). A high level of Gal-3 was also observed in patients with unstable coronary disease and chronic coronary syndrome, which implies that active atherosclerosis as an inflammatory process is continuously present (6, 9). Galectin-3 is involved in the remodeling of the left ventricle, but it also plays a significant role in the remodeling of the atria, both electrical and structural, leading to the occurrence of one of the most common heart rhythm disorders, atrial fibrillation (AF). Presence of pronounced tissue fibrosis and inflammation in the AF is an indirect indicator of the galectin-3 involvement in the entire pathophysiological process. Patients subjected to ablation with a higher basal concentration of serum Gal-3 had more frequent recurrent attacks of paroxysmal AF and a higher rate of redo procedures, indicating that Gal-3 could serve as a predictor of the procedure success (10, 11).

Ventricular remodeling as part of heart failure syndrome has early onset, and serum levels of cardiac biomarkers are elevated in the very initial part of the process, before the development of disease symptoms. Given that most studies monitor the rate of hospitalization and the occurrence of fatal outcomes, early detection of the preclinical stage and early therapeutic actions are of key importance in optimizing therapy and preventing unwanted clinical outcomes (12).

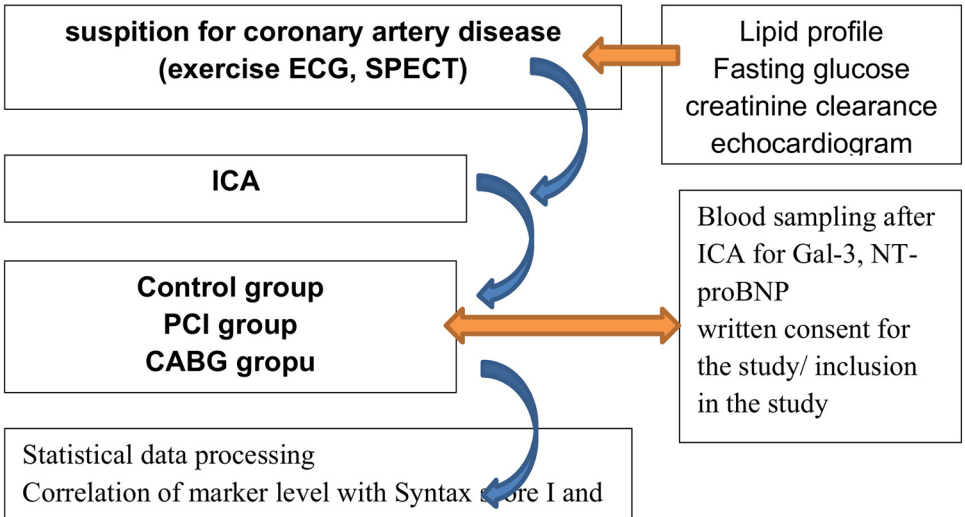
The aim of this study was to determine the predictive value of galectin-3 and NT-proBNP on the clinical outcome and occurrence of major adverse cardiovascular events (MACE) in revascularized patients with chronic coronary syndrome over a period of 5 years.

2 Materials and methods

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of University Hospital Center Osijek (No 25-1:5020-7/2013). Informed consent was obtained from all subjects involved in the study. This was a single-center cross-sectional cohort study including 168 subjects with stable obstructive coronary artery disease defined as the presence of angina symptoms on exertion, indication for invasive cardiology procedure, coronary angiography and evidence of ischemic heart disease, i.e., chronic coronary syndrome (formerly known as stable angina pectoris). All patients were prescribed drug therapy in accordance with current guideline (13). Before the actual coronary angiography, the patients underwent the following procedures: blood samples were obtained to determine hemogram, fasting blood glucose, creatinine, and lipid profile; ergometry (treadmill or cycle ergometer; SPECT); and cardiac ultrasonography. Given that Gal-3 and NT-proBNP can be elevated in many pathological conditions, exclusion criteria were as follows: acute coronary syndrome, heart failure (acute or chronic), chronic kidney disease, liver disease (acute or chronic hepatitis, liver cirrhosis), diabetes mellitus type 2, high-grade hypertension, acute infection, autoimmune disease and cancer. The flow chart of patient selection is presented in Figure 1.

Patients were then divided into three groups: percutaneous coronary intervention (PCI) group (N64), coronary artery bypass graft surgery (CAG) group (N57) and group with no coronary stenosis (N 47). The control group consisted of subjects with completely normal epicardial arteries. All patients with stenosis <70% as well as those who had verified marginal irregularities of blood vessels (non-obstructive coronary disease) were excluded. Depending on the method of revascularization of patients with proven coronary disease, the subjects were divided into two groups: percutaneous coronary intervention (PCI) or aortocoronary bypass (CABG) group. The decision on the method of revascularization was made by the heart team (non-interventional, interventional cardiologist, cardiac surgeon). Immediately after the coronary angiography, and before distribution of subjects into groups, blood samples were taken for the analysis of cardiac biomarkers, NT-proBNP and Gal-3.

Patients were followed prospectively for a period of 5 years and the rate of adverse cardiovascular events (MACE) was recorded. Major adverse cardiac events included: all-cause mortality, cardiovascular death, myocardial infarction type I, target vessel revascularization, ischemic cerebrovascular insult, and atrial fibrillation. To objectify the severity of coronary disease, Syntax score I and II were determined using the online Syntax Score Calculator (http://syntaxscore.org/calculator/start.htm) (14).



Inclusion criteria	Exclusion criteria
Chronic coronary syndrome	Acute coronary syndrome
Positive treadmill test or SPECT	Heart failure (acute or chronic)
Epicardial artery stenosis >70%	Chronic kidney disease
EFLK >50%	Liver disease
	Diabetes mellitus type II
	High grade hypertension
	Acute infection
	Autoimmune disease
	Cancer

FIGURE 1
Flow charts screening and inclusion of subject. ICA, invasive coronary angiografy; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ECG, electrocardiogram; SPECT, single photon computed tomography.

2.1 NT-proBNP

NT-proBNP was determined by Elecsys proBNP II Roche Diagnostic test. The test principle is a two-step sandwich for an 18 min application using Cobas 601. The sample material is Li heparin, K2-EDTA and K3-EDTA plasma. LOQ*—LoQ—20% CV at ≤50 pg/ml C is 50 pg/ml. The normal range of NT-proBNP is <125 pg/ml: Package Insert Elecsys NT-proBNP 09315284190 and 09315284214 v3 (15, 16).

2.2 Galectin-3

The concentration of Gal-3 in serum was measured using an enzyme immunoassay (EIA) 004110 galectin-3 (LabCorp, Burlington, North Carolina) and expressed in ng/ml. The calculated overall intra-assay coefficient of variation was 7.5%, and the inter-assay coefficient of variation was 5.4%. A serum Gal-3 concentration below 17.8 ng/ml was considered normal and set as a cutoff value (17). Blood samples for NT-proBNP

and Gal-3 determination were taken at the same time, immediately after coronagraphy.

2.3 Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 27 and MedCalc Statistical Software version 22.014. An independent samples *t*-test was used to examine the significance of differences in mean NT-proBNP and Gal-3 values between patient groups, assuming equal and unequal variances when appropriate. A correlation analysis using Spearman correlation coefficients was conducted to determine the association between Gal-3, Syntax I, Syntax II PCI, and Syntax II CABG. Spearman correlation coefficients were also calculated to assess the relationship between NT-proBNP, Syntax I, Syntax II PCI, and Syntax II CABG. Cox regression was used to assess predictors of the rate of major adverse cardiovascular events (MACE). Statistical significance was set at $p < 0.05$.

3 Results

There were 168 subjects included in the study: 47 subjects were in the control group (healthy population). Depending on the decision of the heart team, subjects with coronary disease (vessel stenosis ≥70%) were divided into two groups: the group subjected to percutaneous coronary intervention with stent implantation (PCI group, $N = 64$) and aortocoronary bypass graft (CABG group, $N = 57$). The mean age of the subjects in the study group was 63.48 ± 9.23 years, while in the control group, it was 63.17 ± 8.34 years. There was no significant difference between the values of serum cholesterol fractions, age or sex distribution, body mass index (BMI), LVEF, and renal function between the 3 groups. Baseline characteristics of subjects are summarized in Table 1.

The mean value of Gal-3 in the study (PCI + CABG) group was 19.98 ng/ml, while in the control group, it was 9.51 ng/ml ($t = 9.075$, $p < 0.001$). There was no significant difference in the levels of Gal-3 between the PCI and CABG groups, 18.84 and 21.27 ng/ml, respectively ($t = -1.402$, $p = 0.164$). However, there was a statistically significant difference between the control and PCI group ($t = -6.607$, $p < 0.001$), and the control and CABG group ($t = -7.418$, $p < 0.001$). Statistical significance was also observed in the group of patients with one-vessel disease ($t = -6.871$, $p < 0.001$), two-vessel disease ($t = -3.864$, $p < 0.001$), and three-vessel disease ($t = -7.100$, $p < 0.001$), when compared to the control group, Table 2.

The mean value of NT-proBNP in the study group (PCI + CABG) was 401.30 pg/ml, while in the control group, it was 100.30 pg/ml ($t = -1,415$, $p < 0.159$). Levels of NT-proBNP were similar between the PCI and CABG groups, 164.66 and 667.00 pg/ml, respectively ($t = -1,811$, $p = 0.075$). At the same time, a significant difference was observed between the control and PCI group ($t = -2.399$, $p = 0.018$), and the control and CABG group ($t = -2.042$, $p = 0.046$). There was no significant difference seen in the sub-analysis of the serum NT-proBNP level results between patients with single- and two-vessel disease. Statistical significance was observed in the group of patients with three-vessel disease ($t = -2,422$, $p = 0.021$), Table 2.

The results of the Spearman correlation analysis presented in Table 3 showed that there was a positive relationship between Syntax I and Gal-3 ($\rho = 0.323$, $p < 0.001$) as well as between Syntax II PCI and Gal-3 ($\rho = 0.266$, $p = 0.034$). A positive relationship was also found between Syntax I and NT-proBNP ($\rho = 0.343$, $p < 0.001$). In addition, according to the Spearman correlation analysis, since the assumptions for Pearson's correlation coefficient

TABLE 1 Baseline characteristics of subjects.

Variable	Control group	PCI group	CABG group
N	47	64	57
Age (year)	63.17 ± 8.34	62.13 ± 9.81	65.00 ± 8.34
Gender	M 55.32%, F 44.68%	M 56.25%, F 43.75%	M 52.63%, F 47.37%
LVEF	60.32 ± 8.63	57.62 ± 10.27	59.48 ± 10.27
TAPSE	22.46 ± 2.05	22.23 ± 2.01	22.25 ± 2.16
BMI	27.35 ± 1.65	27.83 ± 1.83	28.47 ± 1.93
CrCl	75.71 ± 9.55	73.83 ± 15.27	74.64 ± 9.23
TC mmol/L	5.47 ± 1.25	5.34 ± 0.97	
TG mmol/L	1.83 ± 0.89	1.68 ± 0.56	
LDL-c mmol/L	3.5 ± 0.93	3.42 ± 0.81	
Aspirin	97%	98%	96%
Aspirin[a]		98%[a]	100%[a]
Clopidogrel[a]		100%[a]	100%[a]
Statin	88%	92%	89%
CCB	55%	33%	35%
ACEI	55%	70%	67%
BB	77%	81%	83%
Other	20%	33%	37%

ACEi, angiotensin convertase enzyme inhibitor; BB, beta-blockers; BMI, body mass index; CCB, calcium channel blocker; CrCrl, creatinine clearance; F, female; Gal-3, galectin-3; LVEF, left ventricular ejection fraction; M, male; TC, total cholesterol; TG, triglycerides. Other—drugs that do not have IA level of evidence in the treatment of stable coronary heart disease, mainly symptomatic therapy (long-acting nitrates, trimetazidine).
[a]After revascularization.

TABLE 2 The difference in Gal-3 and NT-proBNP levels according to different groups of patients.

Variable	Galectin-3 (ng/ml)	NT-proBNP (pg/ml)
Control	9.51 ± 5.19	100.30 ± 135.81
PCI + CABG group	19.98 ± 9.58, $t = 9.075^{b}$, $p < 0.001$*	401.30 ± 1,453.50, $t = -1.415^{a}$, $p = 0.159$
PCI group	18.84 ± 8.59, $t = -6.607^{a}$, $p < 0.001$*	164.66 ± 142.88, $t = -2.399^{a}$, $p = 0.018$*
CABG group	21.27 ± 10.52, $t = -7.418^{b}$, $p < 0.001$*	667.00 ± 2,090.08, $t = -2.042^{b}$, $p = 0.046$*
One-VD	18.31 ± 6.91, $t = -6.871^{a}$, $p < 0.001$*	336.65 ± 1,158.37, $t = -1.389^{a}$, $p = 0.168$
Two-VD	17.04 ± 8.42, $t = -3.864^{b}$, $p < 0.001$*	919.77 ± 2,938.07, $t = -1.308^{b}$, $p = 0.205$
Three-VD	26.46 ± 12.61, $t = -7,100^{b}$, $p < 0.001$*	326.94 ± 509.125, $t = -2.422^{b}$, $p = 0.021$*

[a]*t*-test, equal variances assumed.
[b]*t*-test, equal variances not assumed.
*Statistically significant at $p < 0.05$; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery; VD, vessel disease.

TABLE 3 Spearman correlation analysis between Gal-3, NT-proBNP, and syntax score groups.

Variable	Galectin-3 (ng/ml)	NT-proBNP (pg/ml)
Syntax I ($N = 120$) (12.26 ± 7.43)	$\rho = 0.323$, $p < 0.001$*	$\rho = 0.343$, $p < 0.001$*
Syntax II PCI ($N = 64$) (25.98 ± 6.48)	$\rho = 0.266$, $p = 0.034$*	$\rho = 0.135$, $p = 0.287$
Syntax II CABG ($N = 57$) (27.93 ± 9.42)	$\rho = 0.013$, $p = 0.921$	$\rho = 0.108$, $p = 0.426$

*Statistically significant at $p < 0.05$.

were not met, there was a statistically significant correlation between Gal-3 and NT-proBNP ($\rho = 0.441$, $p < 0.001$) in all CAD patients regardless of the type of revascularization.

3.1 Cox regression analysis

Unadjusted Cox regression analysis was performed to identify predictors of major adverse cardiovascular events (MACE). The influence of age, gender, Gal-33, and NT-proBNP on MACE was investigated. Out of 168 patients, 41 (24.4%) experienced MACE. Figure 2 shows MACE-free rate during follow-up in the study group.

The most common event in the group of patients who experienced MACE, was death of any cause (all-cause mortality), namely in the group of patients who underwent CABG revascularization. Given the relatively small number of other MACE events, no additional statistical analysis was possible, Table 4.

The forward method was used to select the variables in the model. According to the chi-square test, the final model was significantly improved over the initial model ($\chi^2 = 14.388$, $p = 0.001$). Therefore, there were risk factors related to MACE. The results of the Cox regression analysis are presented in Table 5. The Wald test was used to assess whether the regression coefficients are significantly different from 0. The results of the Wald test indicated that there was a statistically significant association between GAL3 and MACE, and NT-proBNP and

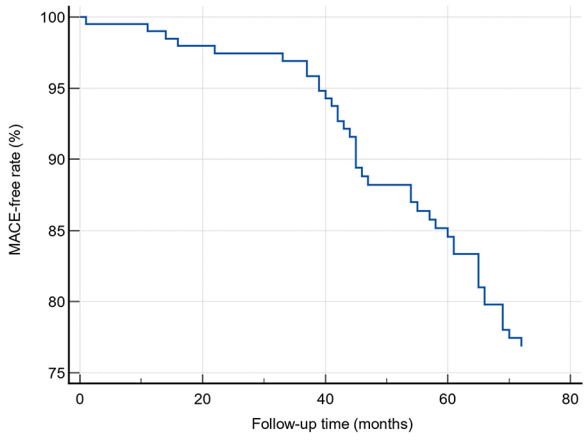


FIGURE 2
MACE-free rate during follow-up.

TABLE 4 The number of major adverse cardiac events.

Group	All cause death	CV death	MI	TLR	HF	CVI	AF
PCI	3	2	3	1	2	1	1
CABG	14	5	2	1	4	1	2
Control	1	0	0	0	0	2	1

PCI, percutaneous; CABG, coronary artery bypass graft surgery; CV, cardiovascular; MI, myocardial infarction; TLR, target lesion revascularization; HF, heart failure; cerebrovascular insult; AF, atrial fibrillation.

MACE. The variables age, gender, troponin, and CRP were not included in the model since they did not contribute to the prediction of MACE. Positive regression coefficients indicated that the risk of MACE increased with increasingGAL3 and NT-proBNP levels. The risk associated with these variables is given by the exponents of the regression coefficients. For each 1 ng/ml increase in GAL3 the hazard rate for MACE increased by 4.1%. A 1 pg/ml increase in NT-proBNP was associated with an 0.02% increased risk of MACE. Table 5 shows the 95% confidence interval for Exp(b).

4 Discussion

Early detection of the presence of cardiovascular disease, symptom relief, regulation of risk factors, and revascularization of blood vessels have a key role in improving the length and quality of patients with cardiovascular disease, as well as preventing major unwanted cardiovascular events, primarily the occurrence of myocardial infarction and heart failure. To achieve this goal, non-invasive, as well as invasive tests are used which often lead to additional medical costs. Biomarkers in cardiology are used to diagnose mainly acute conditions. Thus, troponin is used in the diagnosis of acute myocardial infarction, NT-proBNP as evidence of heart failure, while hsCRP serves as an indicator of an acute inflammatory process, of any etiology (18, 19).

Stable coronary artery disease, presently known as chronic coronary syndrome, usually does not require the use of classic cardiac biomarkers for diagnosis. Our aim was to demonstrate how stable coronary disease is not as stable as it seems; the pathophysiological process of the disease and the progression of atherosclerosis is still present, and patients with the chronic coronary syndrome can have different clinical outcomes depending on the activity of the disease, i.e., depending on the serum level of cardiac biomarkers.

Previous studies have established an association between NT-proBNP elevation and recurrent cardiovascular events in people with stable coronary disease (20). The greatest significance of NT-proBNP is in monitoring patients with heart failure, but as shown in our study, NT-proBNP can stratify high-risk patients in the group with stable coronary disease. Mishra and colleagues' investigation yielded similar results, indicating that NT-proBNP alone is a powerful predictor of major CV events. When combined with clinical risk variables, NT-proBNP performs better in risk categorization for adverse CV events than BNP (21). In our group of patients (PCI + CABG), NT-proBNP did

TABLE 5 Results of the Cox regression analysis.

Covariate	Regression coefficient (*b*)	Standard error	Wald statistics	*p*	Exp (*b*)	95% confidence interval for Exp (*b*)
Gal-3	0.040197	0.012960	9.6188	0.0019	1.0410	(1.0149, 1.0678)
NT-proBNP	0.000179	0.000057	9.7688	0.0018	1.0002	(1.0001, 1.0003)

not reach a significant difference compared to the healthy population; only when the PCI and CABG groups were divided and compared to controls, did we get a weaker but significant difference. There was no difference in the level of NT-proBNP between the PCI and CABG groups. This could be explained due to inclusion criteria that were based on clinical data and normal heart ultrasound findings (EFLV > 50% and diastolic dysfunction of 1st degree), while NT-proBNP was performed later in the study.

As was previously demonstrated by our group, Gal-3 could serve as a useful biomarker in determining and assessing the severity of coronary heart disease in patients with suspected CAD (22). It was significantly elevated in the study group (PCI + CABG) compared to the control group, while there was no difference between the PCI and CABG groups. There was a clear difference in the level of Gal-3 in the group of subjects with PCI compared to the control group, as well as in the CABG group compared to the control. Similar results were obtained by Jannsen H et al., but the significance of Gal-3 was decreased after adjusting for other biomarkers of hemodynamic stress, myocardial lesion, inflammation, and renal dysfunction (23). In our study, these patients were excluded to prevent bias.

Based on current research, it can be concluded that Gal-3 is a strong predictor of cardiovascular mortality in several different groups of patients: in the identification of high-risk individuals among the healthy population, in patients with peripheral arterial disease as well as in patients with acute coronary syndrome (24–27). It could be hypothesized that Gal-3, based on pathophysiological factors, indicates an active process of atherosclerotic plaque formation, as well as myocardial damage. Stratification of patients with CAD, with a particularly high risk of MACE, according to the multimarker panel principle has recently become extremely important (28). Compared to hsCRP and TnI, NT-proBNP is a better predictor of MACE, specifically a composite of cardiovascular death and secondary myocardial infarction and cardiovascular death alone in subjects with proven coronary disease (29).

So far, Gal-3 has been tested in multipanels that included patients with stable CAD, but after recovering from acute coronary syndrome, and patients with chronic coronary syndrome not necessarily including patients with obstructive CAD (29, 30). In both studies, patients with elevated NT-proBNP and Gal-3 had a higher rate of MACE as well as in our group of revascularized patients with chronic coronary syndrome and obstructive CAD without previous cardiovascular incidents.

The main results of our investigation indicate that Gal-3 and NT-proBNP were elevated in patients with proven obstructive coronary disease. The highest level of NT-proBNP and Gal-3 was registered in the group of patients with three-vessel disease, and in the group of patients who experienced MACE, confirming the thesis that both biomarkers play an important role in the pathophysiological process of plaque destabilization, Gal-3 as a reflection of the active inflammation in the process of atherosclerosis, and NT-proBNP as a result of hemodynamic changes due to ventricular dysfunction and stress.

Within the group that experienced MACE, the highest all-cause mortality rate was recorded within the group that underwent CABG. The group of patients undergoing cardiosurgical revascularization is more vulnerable than the group undergoing PCI. Although the Synatx II CABG score was not significantly higher compared to the Syntax II PCI score, patients who underwent CABG had involvement of the left main, as well as three-vessel and multivessel disease. The postoperative outcome also depends on the anatomy of the blood vessels, adequate graft ability, the use of left intermamaria and right intermamaria artery and/or saphenous vein graft, and the virtuosity of the surgeons themselves, not only the Syntax score.

Considering the relatively small sample, the proportion of single components of MACE events was not sufficient for statistical analysis and conclusions.

Increasing the number of specific biomarkers in the screening of patients with obstructive CAD would certainly improve the sensitivity and specificity of the entire panel, allowing timely stratification of patients who would benefit most from the optimization of therapy and earlier revascularization before the very appearance of MACEs.

Based on the results of this study it can be concluded that even in the group with stable coronary disease, there is still a group of patients who will have a worse clinical outcome despite revascularization and optimal medical therapy, it is evident that the pathophysiological process of atherosclerosis and destabilization persists in such patients, and to prevent MACE events, it is necessary to reduce the activity of macrophages, and the secretion of Gal-3. Furthermore, Gal-3 could be a target for developing new pharmacotherapeutic options in the treatment of ischemic heart disease.

5 Conclusions

Gal-3 and NT-proBNP, two biomarkers that have shown a high predictive value of MACE in patients with heart failure, can also serve as an excellent tool in the selection of high-risk patients with ischemic heart disease. Elevated values of these two biomarkers found in patients with acute coronary syndrome indicate their potential role in the destabilization of atherosclerotic plaque. In the group of patients with chronic coronary syndrome, the elevated concentration of NT-proBNP and Gal-3 can serve as a marker of disease activity and detect patients who will experience unwanted MACE regardless of the type of revascularization (PCI or CABG) and optimal drug therapy.

5.1 Limitations

It is a single-center cohort study with a relatively small number of patients. Further prospective studies with a larger number of patients should be performed to explore the relationship between cardiac biomarkers and CAD, as well as the impact of biomarkers on the occurrence of each MACE component (death, cardiovascular death, myocardial infarction type I, ischemic stroke, occurrence of atrial fibrillation, cardiac failure, target vessel revascularization).

The serum level of biomarkers was not serially determined since the intention was to correlate the initial values of the biomarkers with the extent of coronary disease as well as the subsequent occurrence of adverse events in the 5-year follow-up period. However, this would be the next step in future research to obtain data on biomarker dynamics and its impact on long-term outcomes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of University Hospital Center Osijek (No 25-1:5020-7/2013). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

IB: Conceptualization, Data curation, Investigation, Methodology, Resources, Validation, Visualization, Writing – original draft, Formal Analysis, Software, Writing – review & editing. DB: Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. KS-R: Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. HR: Funding acquisition, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. IM: Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. DD: Data curation, Formal Analysis, Methodology, Project administration, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. IB-Ć: Conceptualization, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Knuuti J. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes the task force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). *Russ. J. Cardiol.* (2020) 25:119–80. doi: 10.15829/1560-4071-2020-2-3757

2. Braunwald E. Biomarkers in heart failure. *N Engl J Med.* (2008) 358(20):2148–59. doi: 10.1056/NEJMra0800239

3. Kragelund C, Grønning B, Køber L, Hildebrandt P, Steffensen R. N-terminal pro-B-type natriuretic peptide and long-term mortality in stable coronary heart disease. *N Engl J Med.* (2005) 352(7):666–75. doi: 10.1056/NEJMoa042330

4. Ho JE, Liu C, Lyass A, Courchesne P, Pencina MJ, Vasan RS, et al. Galectin-3, a marker of cardiac fibrosis, predicts incident heart failure in the community. *J Am Coll Cardiol.* (2012) 60(14):1249–56. doi: 10.1016/j.jacc.2012.04.053

5. Tsai TH, Sung PH, Chang L, Sun CK, Yeh KH, Chung SY, et al. Value and level of galectin-3 in acute myocardial infarction patients undergoing primary percutaneous coronary intervention. *J Atheroscler Thromb.* (2012) 19:1073–82. doi: 10.5551/jat.12856

6. Falcone C, Lucibell S, Mazzucchelli I, Bozzini S, D'Angelo A, Schirinzi S, et al. Galectin-3 plasma levels and coronary artery disease: a new possible biomarker of acute coronary syndrome. *Int J Immunopathol Pharmacol.* (2011) 24:905–13. doi: 10.1177/039463201102400409

7. Aksan G, Gedikli Ö, Keskin K, Nar G, Inci S, Yildiz SS, et al. Is galectin3 a biomarker, a player-or both-in the presence of coronary atherosclerosis? *J Investig Med.* (2016) 64:764–70. doi: 10.1136/jim-2015-000041

8. Lok DJ, Van Der Meer P, de la Porte PW, Lipsic E, Van Wijngaarden J, Hillege HL, et al. Prognostic value of galectin-3, a novel marker of fibrosis, in patients with chronic heart failure: data from the DEAL-HF study. *Clin Res Cardiol.* (2010) 99(5):323–8. doi: 10.1007/s00392-010-0125-y

9. Hara A, Niwa M, Kanayama T, Noguchi K, Niwa A, Matsuo M, et al. Galectin-3: a potential prognostic and diagnostic marker for heart disease and detection of early stage pathology. *Biomolecules.* (2020) 10(9):1277. doi: 10.3390/biom10091277

10. Clementy N, Piver E, Bisson A, Andre C, Bernard A, Pierre B, et al. Galectin-3 in atrial fibrillation: mechanisms and therapeutic implications. *Int J Mol Sci.* (2018) 19:976. doi: 10.3390/ijms19040976

11. Zhang G, Wu Y. Circulating galectin-3 and atrial fibrillation recurrence after catheter ablation: a meta-analysis. *Cardiovasc Ther.* (2019) 2019:4148129. doi: 10.1155/2019/4148129

12. D'Amato A, Prosperi S, Severino P, Myftari V, Labbro Francia A, Cestiè C, et al. Current approaches to worsening heart failure: pathophysiological and molecular insights. *Int J Mol Sci*. (2024) 25(3):1574. doi: 10.3390/ijms25031574

13. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. ESC scientific document group. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. (2020) 41(3):407–77. Erratum in: Eur Heart J. 2020 November 21;41(44):4242. doi: 10.1093/eurheartj/ehz425

14. Ong AT, Serruys PW, Mohr FW, Morice MC, Kappetein AP, Holmes DR Jr, et al. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study: design, rationale, and run-in phase. *Am Heart J*. (2006) 151(6):1194–204. doi: 10.1016/j.ahj.2005.07.017

15. McKie PM, Burnett JC Jr. NT-proBNP: the gold standard biomarker in heart failure. *J Am Coll Cardiol*. (2016) 68(22):2437–9. doi: 10.1016/j.jacc.2016.10.001

16. Package Insert Elecsys NT-proBNP 09315284190 and 09315284214 v3. Available online at: https://labogids.sintmaria.be/sites/default/files/files/probnp_ii_2017-08_v12.pdf (Accessed May 08, 2019).

17. *Galectin-3*. Waltham, Mass: BG Medicine Inc (2010). Document LAB-IVD-001R04.

18. Kaptoge S, Di Angelantonio E, Pennells L, Wood AM, White IR, Gao P, et al. C-reactive protein, fibrinogen, and cardiovascular disease prediction. *N Engl J Med*. (2012) 367(14):1310–20. doi: 10.1056/NEJMoa1107477

19. Netto J, Teren A, Burkhardt R, Willenberg A, Beutner F, Henger S, et al. Biomarkers for non-invasive stratification of coronary artery disease and prognostic impact on long-term survival in patients with stable coronary heart disease. *Nutrients*. (2022) 14(16):3433. doi: 10.3390/nu14163433

20. Schnabel R, Rupprecht HJ, Lackner KJ, Lubos E, Bickel C, Meyer J, et al. Atherogene investigators. Analysis of N-terminal-pro-brain natriuretic peptide and C-reactive protein for risk stratification in stable and unstable coronary artery disease: results from the AtheroGene study. *Eur Heart J*. (2005) 26(3):241–9. doi: 10.1093/eurheartj/ehi036

21. Mishra RK, Beatty AL, Jaganath R, Regan M, Wu AH, Whooley MA. B-type natriuretic peptides for the prediction of cardiovascular events in patients with stable coronary heart disease: the heart and soul study. *J Am Heart Assoc*. (2014) 3(4):e000907. doi: 10.1161/JAHA.114.000907

22. Bošnjak I, Bedeković D, Selthofer-Relatić K, Roguljić H, Mihaljević I, Bilić-Ćurčić I. Role of galectin-3 in diagnosis and severity assessment of epicardial artery lesions in patients with suspected coronary artery disease. *BMC Cardiovasc Disord*. (2023) 23(1):268. doi: 10.1186/s12872-023-03310-y

23. Jansen H, Koenig W, Jaensch A, Mons U, Breitling LP, Scharnagl H, et al. Prognostic utility of galectin-3 for recurrent cardiovascular events during long-term follow-up in patients with stable coronary heart disease: results of the KAROLA study. *Clin Chem*. (2016) 62(10):1372–9. doi: 10.1373/clinchem.2016.257550

24. de Boer RA, van Veldhuisen DJ, Gansevoort RT, Muller Kobold AC, van Gilst WH, Hillege HL, et al. The fibrosis marker galectin-3 and outcome in the general population. *J Intern Med*. (2012) 272(1):55–64. doi: 10.1111/j.1365-2796.2011.02476.x

25. Madrigal-Matute J, Lindholt JS, Fernandez-Garcia CE, Benito-Martin A, Burillo E, Zalba G, et al. Galectin-3, a biomarker linking oxidative stress and inflammation. With the clinical outcomes of patients with atherothrombosis. *J Am Heart Assoc*. (2014) 3:e000785. doi: 10.1161/JAHA.114.000785

26. George M, Shanmugam E, Srivatsan V, Vasanth K, Ramraj B, Rajaram M, et al. Value of pentraxin-3 and galectin-3 in acute coronary syndrome: a short-term prospective cohort study. *Ther Adv Cardiovasc Dis*. (2015) 9(5):275–84. doi: 10.1177/1753944715578405

27. Li M, Guo K, Huang X, Feng L, Yuan Y, Li J, et al. Association between serum galectin-3 levels and coronary stenosis severity in patients with coronary artery disease. *Front Cardiovasc Med*. (2022) 9:818162. doi: 10.3389/fcvm.2022.818162

28. Nikorowitsch J, Ojeda F, Lackner KJ, Schnabel RB, Blankenberg S, Zeller T, et al. Head-to-head comparison of the incremental predictive value of the three established risk markers, hs-troponin I, C-reactive protein, and NT-proBNP, in coronary artery disease. *Biomolecules*. (2020) 10:394. doi: 10.3390/biom10030394

29. Higueras J, Martín-Ventura JL, Blanco-Colio L, Cristóbal C, Tarín N, Huelmos A, et al. Impacto de los niveles plasmáticos de pro-péptido natriurético tipo B aminoterminal, proteína quimiotáctica de monocitos-1 y galectina3 en la capacidad predictiva de eventos de la escala clínica LIPID en la enfermedad coronaria estable [impact of plasma pro-B-type natriuretic peptide amino-terminal and galectin-3 levels on the predictive capacity of the LIPID clinical risk scale in stable coronary disease]. *Clin Investig Arterioscler*. (2015) 27(2):57–63. (Spanish). doi: 10.1016/j.arteri.2014.06.003

30. Tuñón J, Blanco-Colio L, Cristóbal C, Tarín N, Higueras J, Huelmos A, et al. Usefulness of a combination of monocyte chemoattractant protein-1, galectin-3, and N-terminal probrain natriuretic peptide to predict cardiovascular events in patients with coronary artery disease. *Am J Cardiol*. (2014) 113(3):434–40. doi: 10.1016/j.amjcard.2013.10.012

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The impact of successful chronic total occlusion percutaneous coronary intervention on clinical outcomes: a tertiary single-center analysis

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Background: The benefit of chronic total occlusion (CTO)-percutaneous coronary intervention (PCI) is controversial because of a lack of high-quality evidence. We aim to evaluate the impact of CTO-PCI on symptoms, quality of life and mortality.

Methods: We conducted a retrospective single center study of patients with CTO-PCI in a tertiary center in Austria. The study outcomes were Canadian Cardiovascular Society (CCS) angina score, quality of life measured by Seattle Angina Questionnaire (SAQ), and death at median follow up for patients with successful vs. failed CTO-PCI.

Results: A total of 300 patients underwent CTO-PCI for coronary artery disease, of which 252 (84%) were technically successful with median follow up of 3.4 years. There were no significant differences in in-hospital or all-cause mortality, major adverse cardiovascular event, or stent-related complications between the groups of failed and successful CTO-PCI. Among patients with successful CTO-PCI there was a significant improvement in CCS score, which was not found for the group with failed CTO-PCI. Successful reopening was associated with significant benefits of the SAQ domains of angina with stressful activity [3.7 ± 0.9 vs. 3.1 ± 0.5, $p = 0.004$, use of nitrates (4.7 ± 0.5 vs. 3.0 ± 1.0) $p = 0.005$] and satisfaction from angina relief (4.4 ± 1.1 vs. 3.6 ± 1.4 $p < 0.001$).

Conclusion: While there was no significant difference in mortality, successful CTO-PCI was associated with greater reduction in angina and the use of nitrates compared to unsuccessful CTO-PCI.

KEYWORDS

coronary artery disease (CAD), chronic total occlusion (CTO), percutaneous coronary intervention (PCI), quality of life, symptoms, mortality

Introduction

Coronary angiography and percutaneous coronary intervention (PCI) are important cornerstones for the diagnosis and treatment of coronary artery disease (CAD) (1–3). The prevalence of coronary chronic total occlusions (CTO) in patients suffering from chronic coronary syndrome (CCS) is reported with 15%–25% (4, 5). Nevertheless, treatment of coronary CTOs remains uncommon in daily clinical practice (6, 7). Many cardiologists may hesitate to refer patients for revascularization due to the limited high-level evidence on its prognostic impact. Additionally, some operators may feel reluctant to attempt revascularization of CTO lesions because of procedural complexity, lack of specific skills, increased risks of complications, and the necessity for special equipment. However, recent strategical and technological advancements, improvement of equipment, better education, and training, as well as growing awareness of the high technical success (5, 8, 9) and low complication rates (8, 10) of CTO-PCI in the medical community, have lately resulted in the adoption of this treatment option in a larger population of patients (5, 11).

Despite the extensive research in the field of CTO-PCI over the last decades, whether chronic occlusions should be treated with optimal medical therapy (OMT) or PCI remains controversial. It is widely agreed that CTO-PCI has the potential to improve exercise limiting ischemic symptoms of angina or angina equivalents such as dyspnea in carefully selected patients (12–14). However, randomized controlled trials (RCT) have failed to demonstrate an effect of CTO-PCI on hard endpoints such as mortality (15). Widely, a major problem in this field of research is that CTO lesions are not well represented in large PCI trials. Generally, CTOs are excluded from RCTs. Specific RCTs on CTO-PCI often included less symptomatic patients since physicians may feel reluctant to randomize highly symptomatic patients to a conservative treatment arm. It is obvious that a difference in hard clinical endpoints in less symptomatic population at lower risk is difficult to demonstrate. Popular examples are the ORBITA (16) and ISCHEMIA (17) trials who failed to show a benefit for PCI over OMT in stable CAD. However, a recent, big observational study led by Park et al. (18) including 1,547 patients was able to show a long-term survival benefit of CTO-PCI. The primary endpoint, cardiac death at 10 years, was significantly reduced in the CTO-PCI cohort compared with the conservative treatment group. The findings of this study are consistent with previously reported observational data experiencing similar outcomes (19–21). However, to this day, no single large RCT on CTO-PCI vs. OMT has demonstrated a survival benefit of CTO recanalization.

The current state of CTO-PCI practice in Austria is largely unexplored. The aim of this project was to investigate if successful CTO-PCI leads to improvement in patient symptoms and prognosis in daily clinical practice.

Methods

We retrospectively evaluated all consecutive CTO-PCI cases performed at a single tertiary care academic medical center in Austria from January 2016 until December 2021 that had a complete clinical follow-up. We compared the clinical, technical, and procedural characteristics, as well as patient-reported change in Canadian Cardiovascular Society (CCS) angina grade and Seattle Angina Questionnaire (SAQ). Furthermore, we examined all-cause mortality and major adverse cardiovascular events (MACE) between patients with technically successful vs. failed CTO-PCI procedures.

Coronary CTOs were defined as coronary lesions with Thrombolysis in Myocardial Infarction (TIMI) grade 0 flow of at least 3-month duration. Estimation of the duration of occlusion was clinical, based on the first onset of angina, prior history of MI in the target vessel territory, or comparison with a prior angiogram. Antegrade wire escalation (AWE) was defined as antegrade PCI during which the guidewire crossed the lesion from "true to true" lumen. A procedure was defined as retrograde if an attempt was made to cross the lesion through a collateral vessel or bypass graft supplying the target vessel distal to the lesion. Antegrade dissection/re-entry (ADR) was defined as antegrade PCI during which a guidewire was intentionally introduced into the subintimal space proximal to the lesion, or re-entry into the distal true lumen was attempted following intentional or inadvertent subintimal guidewire or device crossing.

Success was defined as successful CTO revascularization with achievement of <30% residual diameter stenosis within the treated segment and restoration of TIMI grade 3 antegrade flow. In-hospital MACE included any of the following adverse events prior to hospital discharge: all-cause mortality, recurrent symptoms requiring urgent repeat target vessel revascularization (TVR) with PCI or emergent coronary artery bypass graft (CABG) surgery and stroke.

Follow-up started from the date of the CTO procedure and ended on the first occurrence of either of: date of death, emigration, or end of the study (December 31, 2021). All patients who underwent CTO-PCI in the observation period were contacted and interviewed via phone to examine symptom improvement, if written informed consent was obtained.

Systolic function was evaluated by left ventricular ejection fraction (LVEF,%) measured by the Simpson's 2D biplane method from transthoracic echocardiography.

Statistical analysis

Statistical analysis was performed on Stata 13.0 (College Station, USA). Categorical variables were expressed as percentages and were compared using Pearson's Chi-square test or 2-tailed Fisher's exact test. Continuous variables were presented as mean ± standard deviation or median with interquartile range (IQR) and were compared using the *t*-test or Wilcoxon rank-sum test, as appropriate. For the comparison of

the CCS class at baseline to follow up for successful and failed CTO-PCI, we used a paired *t*-test and changes in CCS class were presented in a figure. A Kaplan-Meier survival curve was constructed which was stratified by successful or failed CTO-PCI. Stepwise logistic regression with a *p*-value cutoff of 0.1 was used to identify factors associated with death and successful CTO-PCI. A two-sided *P*-value of 0.05 was considered statistically significant.

The Institutional Ethics Review Board of Karl Landsteiner University approved this study (Ethics Committee approval EK Nr: 1017/2021. The reporting of this study is in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) recommendations (22). All procedures were undertaken in accord with Helsinki Declaration and postulates of good clinical practice.

Results

In this retrospective analysis, we examined the clinical characteristics and procedural outcomes of 300 patients who underwent coronary angiography and percutaneous coronary intervention (PCI) of chronic coronary syndrome. We report that 48 CTO-PCI procedures were not successful (16%) while CTO-PCI was successful in 252 of patients (84%) according to predefined procedural success criteria.

The demographics and comorbidities of patients with CTO-PCI are shown in Table 1. The mean age of the entire cohort was 66.2 ± 9.9 years, with no statistically significant difference regarding age observed between the failed and successful CTO-PCI (67.0 ± 9.1 vs. 64.4 ± 10.3 years respectively, $p = 0.11$). Gender distribution showed a slight predominance of males. In terms of comorbidities, there were significantly fewer patients with regular alcohol consumption (44.6% vs. 60.4%, $p = 0.045$) and peripheral artery disease (9.9% vs. 29.2%, $p < 0.001$) in the group with successful CTO-PCI.

The angina class and coronary lesion characteristics are shown in Table 2. There was no significant difference in CCS score for patients with successful and failed CTO-PCI. The proportion of patients with three-vessel coronary disease was significantly higher in patients with failed CTO-PCI compared to those with successful CTO-PCI (58.3% vs. 46.8%, $p = 0.018$, respectively). Among patients with successful CTO-PCI the mean number of stents was significantly greater (3.7 vs. 0.8, $p < 0.001$). No statistically significant differences were observed between two groups concerning in the utilization of rotablation.

The medications that were administered during the procedure are reported in Table 3. Periprocedural administration of most medications did not significantly differ between the two groups. There were modest differences in use of bivalirudin ($p = 0.022$), heparin ($p = 0.001$), nitroglycerine ($p < 0.001$), protamine sulfate ($p < 0.001$) and norepinephrine ($p = 0.008$). We observed significant differences in the use of dual antiplatelet therapy (DAPT) and duration of DAPT comparing the groups with successful and failed CTO-PCI.

Echocardiographic and biochemical/laboratory characteristics of enrolled patients are shown in Supplementary Tables 1, 2, respectively. There were no significant differences in echocardiographic parameters between patients with successful and failed CTO-PCI. There were no differences in blood parameters for patients with successful vs. failed CTO-PCI aside from significantly greater pre-procedural hemoglobin count (13.9 vs. 13.3 g/dl, $p = 0.031$) and LDL cholesterol levels (93 vs. 80 mg/dl, $p = 0.040$).

TABLE 1 Demographics and comorbidities of patients who underwent CTO-PCI.

Variable	Failed CTO-PCI (*N* = 48)		Successful CTO-PCI (*N* = 252)		*p*-value
Mean age (±SD)	67.0	±9.1	64.4	±10.3	0.11
	N	%	*N*	%	
Female	10	20.8	40	15.9	0.40
Smoking	26	54.2	133	52.8	0.86
Alcohol consumption	29	60.4	112	44.6	0.045*
Hypertension	36	75.0	186	74.1	0.90
Hyperlipidaemia	36	75.0	210	83.3	0.17
Familial hypercholesterolaemia	0	0.0	3	1.2	0.45
Diabetes mellitus	16	33.3	84	33.3	1.00
Diabetes status					1.00
Diet or no diabetes	33	68.8	173	69.2	
Insulin	4	8.3	21	8.4	
Oral	11	22.9	56	22.4	
Previous myocardial infarction	22	45.8	124	49.2	0.67
Previous PCI	39	81.3	209	82.9	0.78
Previous CABG	7	14.6	27	10.7	0.44
Peripheral artery disease	14	29.2	25	9.9	<0.001*
Cerebrovascular disease	8	16.7	32	12.7	0.46
Previous stroke or TIA	4	8.3	13	5.2	0.38
COPD	9	18.8	27	10.7	0.12
Malignancy	9	18.8	35	13.9	0.38
Atrial fibrillation	5	10.4	31	12.3	0.71
Heart failure	17	35.4	74	30.1	0.47

SD, standard deviation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease. *$p < 0.05$.

Clinical outcomes of interest are shown in Table 4. Figure 1 shows the Kaplan-Meier survival curve for patients with successful and failed CTO-PCI for the first 3-years of follow-up. Overall mortality was 9.9% and 12.5%, respectively ($p = 0.59$)). There were no significant differences observed with respect to in-hospital death, or MACE between the two groups (3.6% vs. 2.1%, $p = 0.60$, and 8.7% vs. 6.3%, $p = 0.57$, respectively). Additionally, the incidence of in-stent thrombosis, its subtypes, and associated complications did not differ significantly between the two groups.

Post-procedural assessments included a comprehensive evaluation of patient-reported outcomes and QoL measures (Table 5). A total of 177 patients provided informed consent and completed the questionnaire via telephone interview. The successful CTO-PCI group exhibited favorable outcomes in terms of angina relief and overall satisfaction. More specifically, CTO-PCI was associated with a significant improvement in several SAQ domains, as follows: angina with stressful activity ($p = 0.005$), angina frequency in the last 4 weeks ($p = 0.004$), use of nitrates ($p = 0.008$) and satisfaction of no anginal relief ($p = 0.002$).

TABLE 2 Angina class and lesion characteristics of patients who underwent CTO PCI.

Variable	Failed CTO-PCI (n = 48)		Successful CTO-PCI (n = 252)		p-value
	N	%	N	%	
CCS score					0.87
No angina	18	37.5	86	34.3	
1	2	4.2	22	8.8	
2	8	16.7	43	17.1	
3	9	18.8	44	17.5	
4	11	22.9	56	22.3	
No. of diseased vessels					0.018*
Single-vessel	9	18.8	48	19.1	
Two-vessel	10	20.8	83	32.9	
Three-vessel	18	37.5	103	40.9	
Single-vessel and left main	1	2.1	2	0.8	
Two-vessel and left main	0	0.0	1	0.4	
Three-vessel and left main	10	20.8	15	6.0	
Antegrade wiring	43	89.6	225	89.3	0.95
Rotablation	2	4.2	14	5.6	0.68
Mean no. of implanted stents (±SD)	0.8	±1.7	3.7	±2.2	<0.001*
Access site					ns
Right radial artery	8	17.8	37	14.9	
Left radial artery	2	4.4	21	8.5	
Right femoral artery	30	66.7	168	67.7	
Left femoral artery	2	4.4	5	2.0	
Left brachial artery	0	0.0	4	1.6	
Right femoral vein	2	4.4	12	4.8	
Left femoral vein	1	2.2	1	0.4	

SD, standard deviation.
*$p < 0.05$.

The change in CCS class for patients with successful CTO-PCI and failed CTO-PCI is shown in Figure 2. Patients with successful CTO-PCI exhibited a significant improvement in follow-up vs. baseline self-reported CCS angina grade ($p < 0.001$). On the other hand, there was no statistical difference in CCS angina grade at follow-up vs. baseline in the group of patients that had failed CTO-PCI ($p = 0.23$).

Femoral access (OR 6.67, 95%-CI 1.69–26.38, $p = 0.007$), peripheral artery disease (PAD) (OR 2.95, 95%-CI 1.14–7.59, $p = 0.025$), heart failure (OR 2.37, 95%CI 1.06–5.31, $p = 0.036$), number of diseased vessels (OR 2.20, 95%-CI 1.15–4.21, $p = 0.017$) and heart rate (OR 1.05, 95%-CI 1.02–1.09, $p = 0.002$) were independently associated with higher mortality. The presence of PAD was the only independent predictor for failing CTO-PCI (OR 0.30, 95%-CI 0.14–0.66, $p = 0.003$). However, unsuccessful CTO-PCI was not independently associated with higher mortality.

Discussion

The key finding of our study was that successful CTO-PCI significantly improved symptoms and quality of life during follow-up, among patients with chronic coronary syndrome.

Notably, one third of the investigated collective did not experience typical angina prior to undergoing PCI. Consequently, these patients were scheduled for revascularization to reduce ischemia in CCS (3) or to facilitate complete revascularization after ACS (23–25). This observed proportion is similar to previously published data from the OPEN-CTO by Sapontis and coworkers (26), where 72% underwent PCI with the primary indication to relief ischemic symptoms. Nevertheless, the proportion of patients with no angina at baseline was below 10% (26). However, some CTO patients may underestimate their daily symptom burden and perceive a significant improvement in quality of life after successful PCI that they may not have anticipated previously.

Widely, observational research and RCTs have provided substantial evidence indicating successful CTO-PCI is associated with improved angina relief and quality of life (27–29). Likewise, our study could demonstrate significantly improved angina measured by CCS following successful PCI in contradiction to failed PCI. Moreover, all but one parameter of SAQ were numerically better in patients with successful PCI compared to those with failed PCI in our study, In case of four variables (angina with stressful activity ($p = 0.005$), angina frequency in the last 4 weeks ($p = 0.004$), use of nitrates ($p = 0.008$) and satisfaction of no anginal relief ($p = 0.002$)) this difference reached statistical significance.

To this date, two randomized trials were published which compared the benefit of CTO-PCI vs. OMT in patients with stable angina (15, 28). The DECISION-CTO trial (15) enrolled 834 patients with stable angina including a CTO as one of their lesions. The results showed no difference between PCI vs. OMT regarding the primary endpoint of death, MI, stroke, or re-

TABLE 3 Medications of patients who underwent CTO-PCI.

Variable	Failed CTO-PCI (n = 48)		Successful CTO-PCI (n = 252)		p-value
	N	%	*N*	%	
Medications					
Adenosine	1	2.1	2	0.8	0.41
Aspirin	5	10.4	13	5.2	0.16
Atropine	1	2.1	6	2.4	0.90
Bivalirudin	1	2.1	0	0	0.022*
Ticagrelor	3	6.3	24	9.5	0.47
Piritramide	0	0.0	1	0.4	0.66
Urapidil	0	0.0	7	2.8	0.24
Prasugrel	0	0.0	7	2.8	0.24
Fentanyl	0	0.0	1	0.4	0.66
GP IIb/IIIa inhibitor	3	6.3	4	1.6	0.050
Isoptin	2	4.2	33	13.1	0.077
Furosemide	1	2.1	3	1.2	0.62
Nitroglycerine	9	18.8	138	54.8	<0.001*
Nitropohl infusion pump	1	2.1	1	0.4	0.19
Clopidogrel	7	14.6	41	16.3	0.77
Propofol	5	10.4	13	5.2	0.16
Protamine sulfate	2	4.2	0	0	<0.001*
PSP/Valium	2	4.2	3	1.2	0.14
Sedacorone	1	2.1	2	0.8	0.41
Epinephrine	1	2.1	3	1.2	0.62
Morphine	15	31.3	4	1.6	0.49*
Norepinephrine	4	8.3	0	0.0	0.008*
Mean heart rate (±SD)	69.4	±11.4	69.2	±12.2	0.90
Alpha-blocker	1	2.1	11	4.4	0.46
Beta-blocker	40	83.3	219	86.9	0.51
Calcium channel blocker	9	18.8	43	17.1	0.78
ACEi or ARB	42	87.5	203	80.6	0.25
Diuretic	20	41.7	93	36.9	0.53
Entresto	0	0	4	1.6	0.38
Aldosterone antagonist	4	8.3	39	15.5	0.20
Proton pump inhibitor	33	68.8	137	54.4	0.065
Statin					0.29
None	5	10.4	30	11.9	
Low/normal dose	20	41.7	76	30.2	
High dose	23	47.9	146	57.9	
Sedacoron	1	2.1	6	2.4	0.90
Antianginal drug	23	47.9	72	28.6	0.008*
Aspirin	46	95.8	250	99.2	0.062
DAPT medication					<0.001*
Clopidogrel	25	52.1	161	64.1	
Prasugrel	6	12.5	20	8.0	
Ticagrelor	10	20.8	68	27.1	
Other	7	14.6	2	0.8	
DAPT duration					<0.001*
1 month	0	0	1	0.4	
3 months	3	6.3	4	1.6	
6 months	3	6.3	12	4.8	
12 months	26	54.2	223	88.5	
24 months	2	4.2	3	1.2	
Other	14	29.0	9	3.5	
Triple therapy	5	10.4	30	12.0	0.76
Oral anticoagulant	6	12.5	34	13.5	0.85
Type of oral anticoagulant					
No anticoagulant	42	87.5	219	86.9	
Apixaban	1	2.1	8	3.2	
Dabigatran	0	0	2	0.8	

(*Continued*)

TABLE 3 Continued

Variable	Failed CTO-PCI (n = 48)		Successful CTO-PCI (n = 252)		p-value
Edoxaban	0	0	1	0.4	
Rivaroxaban	3	6.3	14	5.6	
VKA	2	4.2	8	3.2	

SD, standard deviation; DAPT, dual antiplatelet therapy; VKA, vitamin K antagonist.
*$p < 0.05$.

TABLE 4 Outcomes of patients who underwent CTO-PCI.

Variable	Failed CTO-PCI (n = 48)		Successful CTO-PCI (n = 252)		p-value
Mean follow up (±SD), days	1,152	±479	1,328	±512	0.12
	N	%	N	%	
Stent thrombosis	0	0	10	4.0	0.16
Stent thrombosis type					0.41
None	48	100	243	96.4	
Probable	0	0	1	0.4	
Definite	0	0	8	3.2	
Stent thrombosis time					0.62
None	48	100	243	96.4	
Acute	0	0	3	1.2	
Late	0	0	4	1.6	
Very late	0	0	2	0.8	
In-hospital death	1	2.1	9	3.6	0.60
All-cause death	6	12.5	25	9.9	0.59
MACE	3	6.3	22	8.7	0.57
MACE type					0.36
No MACE	45	93.8	230	91.3	
Cardiac death	0	0	6	2.4	
Myocardial infarction	3	6.3	7	2.8	
Revascularization	0	0	6	2.4	
Unknown	0	0	3	1.2	
Post intervention CCS class					0.20
No angina	11	45.8	72	56.7	
1	4	16.7	23	18.1	
2	3	12.5	16	12.6	
3	2	8.3	11	8.7	
4	4	16.7	5	3.9	

SD, standard deviation; MACE, major adverse cardiovascular event.

revascularization. Moreover, this trial also failed to show a significant difference for the secondary endpoint of symptomatic improvement measured by changes in the Seattle Angina Questionnaire (SAQ). However, several limitations need to be considered when interpreting the results of this trial. Most importantly, the study design predetermined that non-CTO lesions were treated after the baseline assessment in both groups. Given the fact that 77% of patients in DECISION-CTO have multi-vessel disease, around 70% of patients in the conservative arm received PCI, which could possibly explain the improvement in SAQ in the conservative arm. Furthermore, there was a high cross-over rate of about 20% from the conservative arm to the CTO-PCI group. Hence, when the results were reported in as per-treated analyses (rather than as per-protocol), there was a significant decrease in MACE and spontaneous MI (both $p = 0.01$), a strong trend to reduced all-cause mortality ($p = 0.06$) and cardiac mortality ($p = 0.08$) in the CTO-PCI treated group when compared to conservative treatment. In the EURO-CTO trial (28) with 448 randomized patients, CTO-PCI outperformed OMT in terms of symptomatic benefit. Contrary to DECISION-CTO, all patients in this study were randomized after treatment of concomitant relevant non-CTO lesions. Consistently, confounding effects of non-CTO-PCI were negligible in this study since a rather low cross-over rate of 7% from OMT in the intention-to-treat analysis was reported. The results showed significant differences in improvement in angina frequency and quality of life in SAQ subscales favoring CTO-PCI. Regarding major adverse cardiovascular and cerebrovascular events, no significant differences between the two groups were observed. Although the results of both studies may seem contradictory at first glance, DECISION-CTO does not disprove the results of the EURO-CTO study, because of the major differences in study

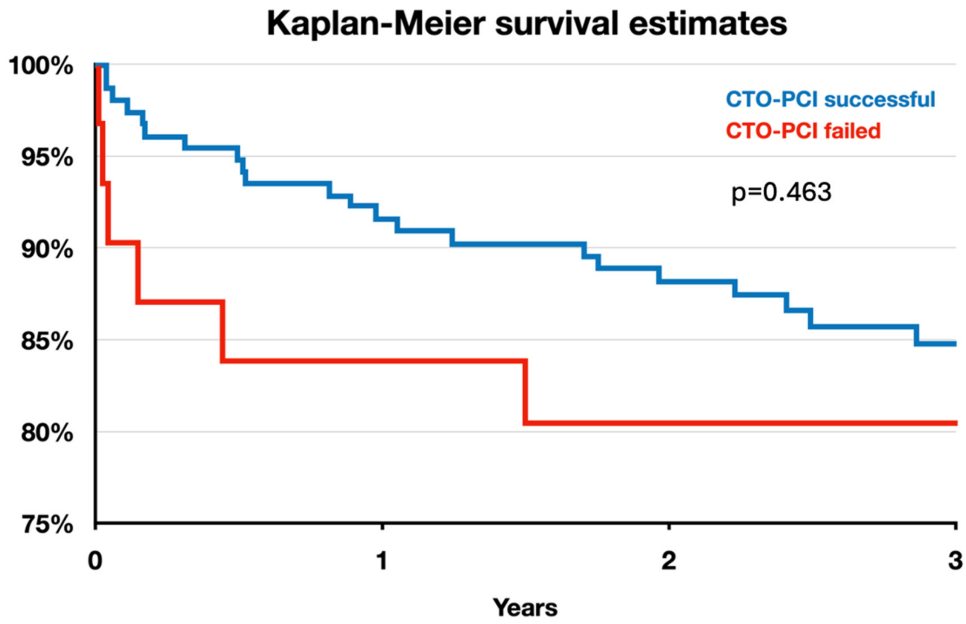

FIGURE 1
Kaplan meier survival curve for patients stratified by successful CTO-PCI.

TABLE 5 SAQ at follow up.

Variable	Failed CTO-PCI (n = 48)		Successful CTO-PCI (n = 252)		p-value
SAQ-quality of Life[a]	*N*	±SD	*N*	±SD	
Getting dressed	4.8	±0.6	4.8	±0.6	0.68
Walking on flat surface	4.8	±0.4	4.8	±0.6	0.55
Showering	4.9	±0.4	4.7	±0.8	0.14
Walking uphill/stairs	4.0	±1.4	4.1	±1.6	0.74
Gardening/carrying shopping bags	4.2	±1.1	4.3	±1.2	0.77
Fast walking 100 m	3.9	±1.3	4.1	±1.5	0.57
Jogging/running	2.5	±1.8	3.9	±1.6	0.053†
Lifting heavy things	4.0	±1.5	4.3	±1.3	0.52
Strenuous exercise	3.9	±1.6	4.2	±1.5	0.60
Angina with stressful activity	3.1	±0.5	3.7	±0.9	0.004*
Angina frequency in last 4 weeks	3.2	±1.1	3.8	±1.2	0.091†
Use of nitrates	3.0	±1.0	4.7	±0.5	0.005*
Medication burden	4.3	±1.0	4.4	±1.1	0.87
Whether patient is convinced everything done for chest pain	4.5	±0.8	4.7	±0.7	0.18
Explanation by doctors satisfactory	4.6	±0.8	4.7	±0.8	0.58
Treatment success/satisfaction	4.5	±0.8	4.7	±0.8	0.21
Quality of life	4.3	±1.1	4.6	±1.0	0.22
Satisfaction of angina relief	3.6	±1.4	4.4	±1.1	<0.001*
How often they worry if they could have heart attack	4.0	±1.1	4.2	±1.0	0.25

SD, standard deviation; SAQ, seattle angina questionnaire.
[a]Paired t-test.
*Significant ($p = 0.05$).
†Trend ($p < 0.10$).

design and the given limitations. Whereas DECISION-CTO failed to proof the benefit of CTO-PCI on top of Non-CTO-PCI, EURO-CTO identified the isolated benefit of CTO-PCI vs. OMT. Recently, at 3 years follow-up of the EURO-CTO trial observed no difference in the incidence of cardiovascular mortality or myocardial infarction between PCI or OMT. However, a higher MACE rate was observed in the OMT group, which was primarily due to ischemia driven revascularization (9).

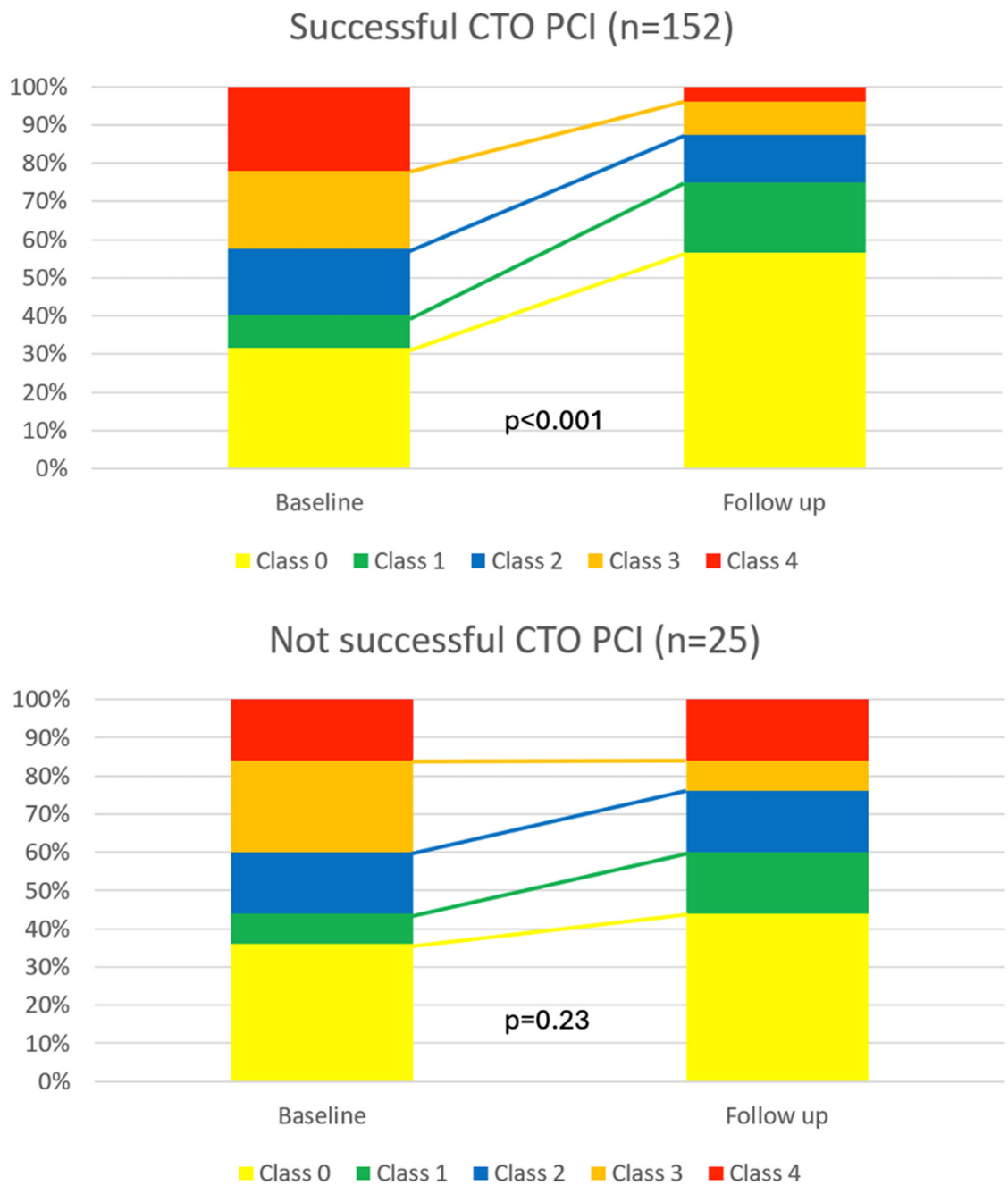

FIGURE 2
Change in CCS angina grade before and after follow-up for patients with chronic coronary syndrome and with successful vs. failed CTO-PCI.

Several research on the population of patients with CAD have emphasized the significant influence of CTOs on outcomes (18, 21, 30–33). Several underlying mechanisms have been reported for this phenomenon. Patients with CTOs may be prone to experience fatal cardiac events in the future. Notably, patients with STEMI who receive primary PCI experience a threefold rise in 30-day mortality if there is a bystander CTO in a non-culprit artery (21).

Occasionally, the culprit vessel in acute STEMI serves as donor artery for a myocardial CTO territory by providing collateral supply. In these cases of "double jeopardy" mortality increases up to 52%, because of a large area of threatened myocardium and a higher risk for cardiogenic shock (21).

This is attributed to the "double jeopardy" phenomenon, which occurs when the sudden blockage of a donor vessel supplying collateral blood flow beyond the CTO poses a threat to a larger myocardial area (21, 34). Additionally, non-revascularized CTOs may be associated with impaired left ventricular ejection fraction (LVEF), a well-established prognostic marker for MACE (4). Malignant arrhythmias also appear to play a significant role in causing cardiovascular fatalities among patients with CTOs (30, 35, 36).

Despite all these pathophysiological considerations, our study did not find a benefit of successful CTO-PCI on hard clinical endpoints. There was an absolute decrease in mortality by 2.6%, favoring successful CTO-PCI (9.9% vs. 12.5%), but likely due to small sample size this numerical difference did not reach statistical significance. In the event of a subtle effect size a rather small study like ours might fail to discern it. Moreover, the mean follow-up time of 3.4 years of our study may be too short to detect a significant difference in all-cause death since data by Park et al. (18) suggest later benefits of CTO revascularization.

Comparable to our study, Lee et al. (37) and Yamamoto et al. (38) conducted studies that found no significant difference in the survival rates of patients who underwent successful CTO-PCI at 3-year and 4.6-year follow-ups, respectively. However, both trials reported a TVR rate of 20% after failed CTO-PCI, suggesting that a considerable number of patients initially labeled as having an "unsuccessful" procedure were successfully revascularized later. However, meta-analyses have shown that successful CTO-PCI was associated with a lower risk of MACE and death compared with failed procedures (39, 40). Christakopoulos et al. (40) analyzed 25 observational studies and found successful CTO-PCI was associated with lower risk of death [odds ratio (OR), 0.52; 95% CI, 0.43–0.63] and MACE (OR 0.59; 95% CI, 0.44–0.79), but not TVR (OR, 0.66; 95% CI, 0.36–1.23) or MI (OR, 0.73; 95% CI, 0.52–1.03) compared with failed CTO-PCI, during a median follow-up of 3 years. In the report by Megaly et al. (39), which represents a contemporary CTO-PCI population since 2010, the risk of MACE and death was significantly lower at 12 months in patients who had successful CTO-PCI.

In conclusion, our analysis demonstrated a symptomatic benefit of successful CTO-PCI among patients with chronic coronary syndrome in a nationally representative tertiary medical center in Austria. Further research, including larger observational studies and randomized controlled trials, are necessary to investigate the effects of CTO-PCI on symptom relief and mortality rates.

Limitations

Our study has some limitations worth discussing. First, this is a retrospective single center experience.

Second, this study represents information obtained from PCIs carried out from 2016 to 2021. However, this data may be considered outdated as it does not reflect the current state of the art in CTO-PCI due to technological advancements and improvements that occurred in this field over the last several years. Consequently, any impact on mortality and symptom improvements may have been underestimated, however, this notion should be investigated in future studies.

Another limitation is the extremely limited sample size of the unsuccessful group of only 25 probands, which is inadequate for making definitive conclusions. Notably, the proportion of patients with three-vessel coronary disease was significantly higher in patients with failed CTO-PCI compared to those with successful CTO-PCI which might be a major confounder in this setting. Furthermore, it cannot be excluded that the improvement of symptoms may have been attributable to the revascularization of non-chronically occluded coronary arteries rather than the chronic total occlusion lesion itself in these patients.

Moreover, one-third of the patients did not report typical angina, which was the primary endpoint of the study, prior to receiving PCI. However, this observation becomes even more intriguing considering that a significant difference was observed for this outcome. Regrettably, baseline values for the SAQ - scores pre-PCI were not available, limiting our ability to compare post PCI values and thus reducing the significance of this analyzed parameter.

One further constraint of our study is the absence of detailed information about ischemia testing for all patients, restricting a thorough analysis concerning this important aspect.

This analysis was limited to patients who underwent percutaneous coronary intervention, excluding those initially managed with optimal medical therapy alone. Consequently, the ability to compare outcomes between optimal medical management and successful PCI was constrained, potentially introducing selection bias and neglecting the placebo effect.

Conclusions

Successful CTO-PCI significantly improved the symptoms of angina and quality of life during follow-up, among patients with chronic coronary syndrome. CTO-PCI should be considered in symptomatic patients alongside OMT. Prospective studies with larger sample size become are warranted to further address this important research question.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Commission on Ethics and Scientific Integrity - Karl Landsteiner University Krems. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MW: Conceptualization, Funding acquisition, Investigation, Project administration, Writing – original draft, Writing – review & editing. KS: Supervision, Writing – review & editing. SA: Data curation, Investigation, Writing – review & editing. GLe: Conceptualization, Supervision, Writing – review & editing. ES: Data curation, Investigation, Writing – review & editing. DM: Data curation, Investigation, Writing – review & editing. PV: Writing – review & editing. JB: Writing – review & editing. CK: Data curation, Formal Analysis, Methodology, Writing – review

& editing. GLa: Writing – review & editing. JM: Writing – review & editing. TW: Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2024.1447829/full#supplementary-material

References

1. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. (2018) 39:119–77. doi: 10.1093/eurheartj/ehx393

2. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. (2021) 42 (14):1289–367. doi: 10.1093/eurheartj/ehaa575

3. Neumann FJ, Sechtem U, Banning AP, Bonaros N, Bueno H, Bugiardini R, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. (2020) 41:407–77. doi: 10.1093/eurheartj/ehz425

4. Fefer P, Knudtson ML, Cheema AN, Galbraith PD, Osherov AB, Yalonetsky S, et al. Current perspectives on coronary chronic total occlusions: the Canadian multicenter chronic total occlusions registry. *J Am Coll Cardiol*. (2012) 59 (11):991–7. doi: 10.1016/j.jacc.2011.12.007

5. Konstantinidis NV, Werner GS, Deftereos S, Di Mario C, Galassi AR, Buettner JH, et al. Temporal trends in chronic total occlusion interventions in Europe. *Circ Cardiovasc Interv*. (2018) 11(10):e006229. doi: 10.1161/CIRCINTERVENTIONS.117.006229

6. Råmunddal T, Hoebers LP, Henriques JP, Dworeck C, Angerås O, Odenstedt J, et al. Chronic total occlusions in Sweden–a report from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). *PLoS One*. (2014) 9(8):e103850. doi: 10.1371/journal.pone.0103850. Erratum in: *PLoS One*. (2014) 9(10):e112370.

7. Grantham JA, Marso SP, Spertus J, House J, Holmes DR, Rutherford BD. Chronic total occlusion angioplasty in the United States. *JACC Cardiovasc Interv*. (2009) 2 (6):479–86. doi: 10.1016/j.jcin.2009.02.008

8. Habara M, Tsuchikane E, Muramatsu T, Kashima Y, Okamura A, Mutoh M, et al. Comparison of percutaneous coronary intervention for chronic total occlusion outcome according to operator experience from the Japanese retrograde summit registry. *Catheter Cardiovasc Interv*. (2016) 87(6):1027–35. doi: 10.1002/ccd.26354

9. Werner GS, Hildick-Smith D, Yuste VM, Boudou N, Sianos G, Gelev V, et al. Three-year outcomes of A randomized multicentre trial comparing revascularization and optimal medical therapy for chronic total coronary occlusions (EuroCTO). *EuroIntervention*. (2023) 19(7):571–9. doi: 10.4244/EIJ-D-23-00312

10. Werner GS, Martin-Yuste V, Hildick-Smith D, Boudou N, Sianos G, Gelev V, et al. A randomized multicentre trial to compare revascularization with optimal medical therapy for the treatment of chronic total coronary occlusions interventional cardiology. *Eur Heart J*. (2018) 39:2484–93. doi: 10.1093/eurheartj/ehy220

11. Brilakis ES, Mashayekhi K, Tsuchikane E, Abi Rafeh N, Alaswad K, Araya M, et al. Guiding principles for chronic total occlusion percutaneous coronary intervention: a global expert consensus document. *Circulation*. (2019) 140:420–33. doi: 10.1161/CIRCULATIONAHA.119.039797

12. Joyal D, Afilalo J, Rinfret S. Effectiveness of recanalization of chronic total occlusions: a systematic review and meta-analysis. *Am Heart J*. (2010) 160 (1):179–87. doi: 10.1016/j.ahj.2010.04.015

13. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *EuroIntervention*. (2020) 14(14):1435–534. doi: 10.4244/EIJY19M01_01

14. Galassi AR, Vadalà G, Werner GS, Cosyns B, Sianos G, Hill J, et al. Evaluation and management of patients with coronary chronic total occlusions considered for revascularisation. A clinical consensus statement of the European association of percutaneous cardiovascular interventions (EAPCI) of the ESC, the European association of cardiovascular imaging (EACVI) of the ESC, and the ESC working group on cardiovascular surgery. *EuroIntervention*. (2024) 20(3):e174–84. doi: 10.4244/EIJ-D-23-00749

15. Lee SW, Lee PH, Ahn JM, Park DW, Yun SC, Han S, et al. Randomized trial evaluating percutaneous coronary intervention for the treatment of chronic total occlusion: the DECISION-CTO trial. *Circulation*. (2019) 139(14):1674–83. doi: 10.1161/CIRCULATIONAHA.118.031313

16. Al-Lamee R, Thompson D, Dehbi HM, Sen S, Tang K, Davies J, et al. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *Lancet*. (2018) 391(10115):31–40. doi: 10.1016/S0140-6736(17)32714-9

17. Maron DJ, Hochman JS, Reynolds HR, Bangalore S, O'Brien SM, Boden WE, et al. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med*. (2020) 382(15):1395–407. doi: 101056/NEJMoa1915922

18. Park TK, Lee SH, Choi KH, Lee JM, Yang JH, Bin SY, et al. Late survival benefit of percutaneous coronary intervention compared with medical therapy in patients with coronary chronic total occlusion: a 10-year follow-up study. *J Am Heart Assoc*. (2021) 10(6):19022. doi: 10.1161/JAHA.120.019022

19. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. (2009) 360(10):961–72. doi: 101056/NEJMoa0804626

20. Farooq V, Serruys PW, Garcia-Garcia HM, Zhang Y, Bourantas C V, Holmes DR, et al. The negative impact of incomplete angiographic revascularization on clinical outcomes and its association with total occlusions: the SYNTAX (synergy between percutaneous coronary intervention with Taxus and cardiac surgery) trial. *J Am Coll Cardiol*. (2013) 61(3):282–94. doi: 10.1016/j.jacc.2012.10.017

21. van der Schaaf RJ, Vis MM, Sjauw KD, Koch KT, Baan J, Tijssen JGP, et al. Impact of multivessel coronary disease on long-term mortality in patients with ST-

elevation myocardial infarction is due to the presence of a chronic total occlusion. *Am J Cardiol*. (2006) 98(9):1165–9. doi: 10.1016/j.amjcard.2006.06.010

22. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med*. (2007) 4 (10):1623–7. doi: 10.1371/journal.pmed.0040296

23. Henriques JPS, Hoebers LP, Råmunddal T, Laanmets P, Eriksen E, Bax M, et al. Percutaneous intervention for concurrent chronic total occlusions in patients with STEMI: the EXPLORE trial. *J Am Coll Cardiol*. (2016) 68(15):1622–32. doi: 10.1016/j.jacc.2016.07.744

24. Villablanca PA, Olmedo W, Weinreich M, Gupta T, Mohananey D, Albuquerque FN, et al. Staged percutaneous intervention for concurrent chronic total occlusions in patients with ST-segment-elevation myocardial infarction: a systematic review and meta-analysis. *J Am Heart Assoc*. (2018) 7(8):e008415. doi: 10.1161/JAHA.117.008415

25. Mehta SR, Wood DA, Storey RF, Mehran R, Bainey KR, Nguyen H, et al. Complete revascularization with multivessel PCI for myocardial infarction. *N Engl J Med*. (2019) 381(15):1411–21. doi: 10.1056/NEJMoa1907775

26. Sapontis J, Salisbury AC, Yeh RW, Cohen DJ, Hirai T, Lombardi W, et al. Early procedural and health Status outcomes after chronic total occlusion angioplasty: a report from the OPEN-CTO registry (outcomes, patient health Status, and efficiency in chronic total occlusion hybrid procedures). *JACC Cardiovasc Interv*. (2017) 10(15):1523–34. doi: 10.1016/j.jcin.2017.05.065

27. Kucukseymen S, Iannaccone M, Grantham JA, Sapontis J, Juricic S, Ciardetti N, et al. Association of successful percutaneous revascularization of chronic total occlusions with quality of life: a systematic review and meta-analysis. *JAMA Netw Open*. (2023) 6(7):E2324522. doi: 10.1001/jamanetworkopen.2023.24522

28. Werner GS, Martin-Yuste V, Hildick-Smith D, Boudou N, Sianos G, Gelev V, et al. A randomized multicentre trial to compare revascularization with optimal medical therapy for the treatment of chronic total coronary occlusions. *Eur Heart J*. (2018) 39 (26):2484–93. doi: 10.1093/eurheartj/ehy220

29. Obedinskiy AA, Kretov EI, Boukhris M, Kurbatov VP, Osiev AG, Ibn Elhadj Z, et al. The IMPACTOR-CTO trial. *JACC Cardiovasc Interv*. (2018) 11(13):1309–11. doi: 10.1016/j.jcin.2018.04.017

30. Godino C, Giannattasio A, Scotti A, Baldetti L, Pivato CA, Munafò A, et al. Risk of cardiac and sudden death with and without revascularisation of a coronary chronic total occlusion. *Heart*. (2019) 105(14):1096–102. doi: 10.1136/heartjnl-2018-314076

31. Råmunddal T, Hoebers LP, Henriques JPS, Dworeck C, Angerås O, Odenstedt J, et al. Prognostic impact of chronic total occlusions: a report from SCAAR (Swedish coronary angiography and angioplasty registry). *JACC Cardiovasc Interv*. (2016) 9 (15):1535–44. doi: 10.1016/j.jcin.2016.04.031

32. Claessen BE, Dangas GD, Weisz G, Witzenbichler B, Guagliumi G, Möckel M, et al. Prognostic impact of a chronic total occlusion in a non-infarct-related artery in patients with ST-segment elevation myocardial infarction: 3-year results from the HORIZONS-AMI trial. *Eur Heart J*. (2012) 33(6):768–75. doi: 10.1093/eurheartj/ehr471

33. George S, Cockburn J, Clayton TC, Ludman P, Cotton J, Spratt J, et al. Long-term follow-up of elective chronic total coronary occlusion angioplasty: analysis from the U.K. Central cardiac audit database. *J Am Coll Cardiol*. (2014) 64 (3):235–43. doi: 10.1016/j.jacc.2014.04.040

34. Bataille Y, Déry JP, Larose É, Déry U, Costerousse O, Rodés-Cabau J, et al. Deadly association of cardiogenic shock and chronic total occlusion in acute ST-elevation myocardial infarction. *Am Heart J*. (2012) 164(4):509–15. doi: 10.1016/j.ahj.2012.07.008

35. Nombela-Franco L, Mitroi CD, Fernández-Lozano I, García-Touchard A, Toquero J, Castro-Urda V, et al. Ventricular arrhythmias among implantable cardioverter-defibrillator recipients for primary prevention: impact of chronic total coronary occlusion (VACTO primary study). *Circ Arrhythm Electrophysiol*. (2012) 5 (1):147–54. doi: 10.1161/CIRCEP.111.968008

36. Nombela-Franco L, Iannaccone M, Anguera I, Amat-Santos IJ, Sanchez-Garcia M, Bautista D, et al. Impact of chronic total coronary occlusion on recurrence of ventricular arrhythmias in ischemic secondary prevention implantable cardioverter-defibrillator recipients (VACTO secondary study): insights from coronary angiogram and electrogram analysis. *JACC Cardiovasc Interv*. (2017) 10(9):879–88. doi: 10.1016/j.jcin.2017.02.008

37. Lee PH, Lee SW, Park HS, Kang SH, Bae BJ, Chang M, et al. Successful recanalization of native coronary chronic total occlusion is not associated with improved long-term survival. *JACC Cardiovasc Interv*. (2016) 9(6):530–8. doi: 10.1016/j.jcin.2015.11.016

38. Yamamoto E, Natsuaki M, Morimoto T, Furukawa Y, Nakagawa Y, Ono K, et al. Long-term outcomes after percutaneous coronary intervention for chronic total occlusion (from the CREDO-Kyoto registry cohort-2). *Am J Cardiol*. (2013) 112 (6):767–74. doi: 10.1016/j.amjcard.2013.05.004

39. Megaly M, Khalil M, Basir MB, McEntegart MB, Spratt JC, Yamane M, et al. Outcomes of successful vs. Failed contemporary chronic total occlusion percutaneous coronary intervention. *Cardiovasc Interv Ther*. (2022) 37(3):483–9. doi: 10.1007/s12928-021-00819-x

40. Christakopoulos GE, Christopoulos G, Carlino M, Jeroudi OM, Roesle M, Rangan BV, et al. Meta-analysis of clinical outcomes of patients who underwent percutaneous coronary interventions for chronic total occlusions. *Am J Cardiol*. (2015) 115(10):1367–75. doi: 10.1016/j.amjcard.2015.02.038

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The association of coronary artery disease with heart rate at anaerobic threshold and respiratory compensatory point

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Background: There is limited knowledge regarding the association between heart rate (HR) during different exercise phases and coronary artery disease (CAD). This study aimed to evaluate the relationship between four exercise-related HR metrics detected by cardiopulmonary exercise testing (CPET) and CAD. These metrics include HR at the anaerobic threshold (HR_{AT}), HR at respiratory compensatory point (HR_{RCP}), maximal HR (HR_{max}), and HR 60 s post-exercise (HR_{Rec60s}).

Methods: The 705 participants included 383 with CAD and 322 without CAD in Beijing Hospital, who underwent CPET between January 2021 and December 2022. The Logistic regression analysis was applied to estimate the odds ratio and the 95% confidence interval. Additionally, the multivariable Logistic regression analyses with restricted cubic splines were conducted to characterize the dose-response association and explore whether the relationship was linear or nonlinear.

Results: Our primary finding indicates that for each one-beat increase in HR_{AT}, there is a 2.8% reduction in the adjusted risk of CAD in the general population. Similarly, a one-beat increase in HR_{RCP} corresponds to a 2.6% reduction in the adjusted risk of CAD. Subgroup analyses revealed significant interactions between HR_{AT} and factors such as sex, hypertension, and lung cancer, as well as between HR_{RCP} and sex and hypertension, in relation to CAD. The dose-response analysis further confirmed that higher HR_{AT} and HR_{RCP} are associated with a reduced risk of CAD.

Conclusion: These results are suggestive of a good association between HR_{AT}, HR_{RCP}, and CAD. The lower HR_{AT}, and HR_{RCP} are signs of poor HR response to exercise in CAD. HR_{AT} and HR_{RCP} are potentially good indicators of poor HR response to exercise without considering maximal effort.

KEYWORDS

heart rate, coronary artery disease, anaerobic threshold, respiratory compensatory point, cardiopulmonary exercise test

Abbreviations

AT, anaerobic threshold; CAD, coronary artery disease; CI, chronotropic incompetence; CPET, cardiopulmonary exercise test; ECG, electrocardiogram; HR, heart rate; RCP, respiratory compensatory point; RER, respiratory exchange ratio; VO_2, oxygen consumption.

1 Introduction

Coronary artery disease (CAD) is a leading cause of morbidity and mortality, posing a growing public health burden worldwide (1). Prediction and early diagnosis of CAD facilitates appropriate intervention in its early stages, aiming to improve the prognosis, delay the progression, and reduce the burden on patients and their families. In accordance with the latest guidelines from the American College of Cardiology and the American Heart Association, exercise stress testing was recommended as an initial diagnostic test for suspected CAD patients (2).

Cardiopulmonary exercise testing (CPET) is a non-invasive method of evaluating an individual's cardiovascular, muscular, respiratory, and metabolic responses to physical stress through exercise stress testing combined with expired gas analysis (3). Unlike the current "gold standard" for diagnosing CAD, which relies on invasive coronary angiography, CPET offers a safer, less expensive, and more psychologically comfortable alternative for patients. Although CPET involves a variety of complex indicators, each parameter provides distinct diagnostic and prognostic insights, making this area increasingly important in clinical practice.

We will emphasize the two vital lactic acid (LA)-related metabolism points during exercise in our study. As the incremental exercise testing proceeds, the LA in the circulation begins to accumulate eventually leading to hypercapnia at the end of the exercise (4). Once a working skeletal muscle cell begins to produce LA, the anaerobic threshold (AT) is reached. AT marks the transition to mixed aerobic-anaerobic metabolism (5). The work intensity increases continuously and gradually to go beyond a certain point called the respiratory compensation point (RCP), where LA production can no longer be compensated by circulating bicarbonate, then hyperventilation begins. RCP represents the transition to predominant anaerobic metabolism (5).

Heart rate (HR) is thought to have a broad and complex relationship with the cardiac function of CAD. However, the significance of HR, particularly exercise-induced HR, in understanding cardiovascular pathophysiology, prognosis, and treatment is often underestimated. This may be due to the complex nature of its effects, despite HR being a familiar and easily measurable parameter (6). Previous evidence has consistently shown that elevated resting heart rate (HR) is an independent predictor of both all-cause and cardiovascular mortality in patients with CAD (7–9). Additionally, poor exercise capacity and inadequate HR response during exercise and recovery are significant indicators of higher overall mortality and an increased risk of CAD (10–12). However, most previous studies have primarily focused on resting HR and HR recovery post-exercise in CAD patients, often neglecting the importance of HR at various stages of exercise.

In this study, we examined four specific HR metrics during different phases of CPET as potential predictors of CAD: HR at the anaerobic threshold (HR_{AT}), HR at the respiratory compensatory point (HR_{RCP}), maximal HR (HR_{max}), and HR 60 s post-exercise (HR_{Rec60s}). This cross-sectional, population-based study aimed to compare these exercise-related HR measurements to determine which one is most strongly associated with CAD in the general population.

2 Method

2.1 Ethics statements

This cross-sectional study conformed to the Declaration of Helsinki and was approved by the Committee of Beijing Hospital (2023BJYYEC-116-01).

2.2 Study population

This cross-sectional study included 705 patients, aged 18–60, who underwent CPET at Beijing Hospital between January 2021 and December 2022. The testing was conducted to screen for cardiopulmonary disease or to evaluate exercise capacity and/or the severity of CAD.

The diagnosis of coronary artery disease (CAD) was confirmed by reviewing each patient's inpatient and/or outpatient medical records. Documented CAD was defined by the presence of at least one of the following criteria: (1) ≥50% stenosis in at least one coronary artery trunk or major branch as demonstrated by percutaneous coronary angiography or computed tomography; (2) typical exertional angina symptoms with a positive stress test (electrocardiogram stress test, stress echocardiography, or nuclear myocardial stress imaging); (3) previously diagnosed myocardial infarction; (4) previously diagnosed unstable angina pectoris (typical ischemic chest pain + ECG changes + increased markers of muscle damage; or the dynamic changes of ST segment during ischemic attack, or coronary angiography confirmed the existence of severe lesions leading to symptoms) (13, 14). According to the history of CAD, there were 322 participants in the non-CAD group and 383 participants in the CAD group.

2.3 Data collection

Baseline characteristics for the target population were gathered from electronic medical records. These included demographics, comorbidities, chronic medications, past medical history, and biochemical data such as total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) or brain natriuretic peptide (BNP).

2.4 Cardiopulmonary exercise test

The cardiopulmonary function detector (MasterScreen CPX, Jaeger, Switzerland) was used to detect the changes of oxygen consumption (VO_2) and carbon dioxide (VCO_2) emission on an upright cycle ergometer (Ergoselect 100p, Ergoline, Germany) or

mechanical treadmill (T2100-ST2, GE, America). Meanwhile, a 12-lead ECG recorder (CASE, GE, America) and a dynamic blood pressure monitor (TangoM2, SunTech, America) records continuously the HR and blood pressure (BP).

CPET monitored the following parameters for each participant at resting, AT, RCP, and peak states, and 1, 2 and 3 min after exercise, including work load (WL), minute ventilation (VE), VO_2, oxygen consumption/kilogram (VO_2/kg; which is considered as the peak VO_2 at the maximal WL), VCO_2, HR, respiratory rate (RR), oxygen pulse (VO_2/HR), dead space (VD), tidal volume (VT), systolic blood pressure (SBP), diastolic blood pressure (DBP), breathing reserve (BR), respiratory quotient (RQ), end-tidal carbon dioxide pressure ($P_{ET}CO_2$), end-tidal oxygen pressure ($P_{ET}O_2$), and oxygen saturation (SpO_2). The VE/VCO_2 was calculated. The detailed CPET assessment protocol includes a 3-min rest and 3-min warm-up at 0 watts (W), followed by a continuous increase in the Work Rate (WR) by 10 W/min to 20 W/min until exhaustion. A respiratory exchange ratio (RER, ratio of VCO_2/VO_2 at peak exercise) of ≥1.05 was considered an objective indicator of peak effort during assessment (15). Borg Scale (scale 6–20) > 17 was regarded as a subjective index. Discontinue the exercise test if any of the following occurs: abnormal hemodynamic or ECG exercise response or other reasons such as dyspnea, angina, or lower extremity muscle fatigue (16, 17).

AT and RCP were located by visual inspection. AT is deemed reached when the following criteria are met: (1) the VE/VO_2 curve starts to rise with the VE/VCO_2 curve remaining constant, and (2) $P_{ET}O_2$ starts to rise with $P_{ET}CO_2$ remaining unchanged. RCP is deemed to be reached when the following criteria are met: (1) a decrease in $P_{ET}CO_2$ after reaching a maximal level; (2) a rapid nonlinear increase in VE (second deflection); (3) the VE/VCO_2 ratio reached a minimum and began to increase and (4) a nonlinear increase in VCO_2 vs. VO_2 (departure from linearity) (4, 18).

2.5 Heart rate

Continuous ambulatory electrocardiograms were recorded using a 12-lead ECG recorder (CASE, GE, America) during the maximum symptom-limited CPET. HR was recorded at AT and RCP, designated as HR_{AT} and HR_{RCP}, respectively. HR_{max} was defined as the highest HR achieved during the CPET. Additionally, HR 60 s after the exercise session, referred to as HR_{Rec60s}, was measured during the recovery period.

2.6 Statistical analysis

The random forest method was used to impute missing data (19). Based on their CAD history, participants were categorized into a CAD group and a non-CAD group. The distributions of variables in each group were assessed using the Kolmogorov-Smirnov test. Continuous variables that followed a normal distribution were reported as mean ± standard deviation and analyzed using Student's *t*-test. For variables that did not follow a normal distribution, data were presented as median and interquartile range (IQR), with the rank-sum test applied for comparison. Categorical variables were expressed as counts and percentages and compared using the Chi-square test.

Logistic regression analysis was used to estimate the odds ratios (OR) and 95% confidence intervals (CIs) for the continuous HR-related indices (HR_{RCP}, HR_{AT}, HR_{max}, and HR_{Rec60s}) in relation to the outcome of CAD. Additionally, we categorized the HR-related indices into tertiles and compared the associations between the medium and highest tertiles with the lowest tertile. Subgroup analysis was performed to determine whether the relationship between CAD and HR-related indices differed across various subgroups defined by covariates and comorbid conditions. We examined the interaction effects of CAD with HR-related indices in several participant subgroups (age grouping, sex, hypertension, diabetes mellitus, hyperlipidemia, and lung cancer status), and the Wald test determined the *P* for interaction. We constructed three multivariable Logistic regression models. Model 1 was unadjusted. The second and third adjustment models with robust adjustment for covariates are thought to be potential confounders of the associations of the HR-related indices with CAD. Thus, model 2 included age (Continuous), sex (male or female), and body mass index [normal (18.5–25 kg/m^2), overweight (≥25 kg/m^2) or low (<18.5 kg/m^2)]; model 3 further adjusted for hypertension, diabetes mellitus, hyperlipidemia, chronic kidney disease, and lung cancer status (yes or no).

The multivariable Logistic regression analyses with restricted cubic splines (RCS) were used to characterize the dose-response association and explore the potential linear or nonlinear relationship of the HR-related indices with the CAD. The Akaike information criterion (AIC) was used to identify the knots for the splines to balance best fit and overfitting in the RCS (20). The medians of the HR-related indices were assigned as the reference values. The test result for nonlinearity was checked first. If the test for nonlinearity was insignificant, the overall association test result was checked, with the considerable result indicating the linear association.

For statistical analysis, R (version 4.2.2; https://www.R-project.org) was utilized. A result with a two-sided *P* value < 0.05 was considered statistically significant when testing the hypotheses of the study.

3 Result

3.1 Comparison of baseline characteristics between CAD group and non-CAD group

A total of 705 eligible participants met all the inclusion and none of the exclusion criteria. The average age was 59.40 ± 11.44 years, and 408 (57.90%) were men. Compared with the non-CAD group, participants with CAD tended to be male, older, and have higher BMI, VO_2/HR in the period of resting, AT, RCP, and peak (all $P < 0.05$). The proportions of Co-morbid conditions, including hypertension, diabetes mellitus (DM), hyperlipidemia, chronic kidney disease (CKD), and stroke were higher in the CAD group. The participants in the non-CAD

TABLE 1 Baseline characteristics of 705 participants.

	non-CAD (*n* = 322)	CAD (*n* = 383)	*P*
Sex (%)			<0.0001
Female	164 (50.93)	133 (34.73)	
Male	158 (49.07)	250 (65.27)	
Age (year), mean (SD)	56.957 (12.534)	61.462 (9.987)	<0.0001
BMI, median (IQR)	24.340 (22.389, 26.943)	25.391 (23.405, 27.470)	0.0003
BMI (%)			0.0001
Normal	177 (54.97)	176 (45.95)	
Overweight	134 (41.61)	206 (53.79)	
Low	11 (3.42)	1 (0.26)	
Hypertension (%)	161 (50.00)	312 (81.46)	<0.0001
DM (%)	61 (18.94)	144 (37.60)	<0.0002
Hyperlipidemia (%)	126 (39.13)	332 (86.68)	<0.0004
CKD (%)	9 (2.80)	26 (6.79)	0.024
Lung cancer (%)	104 (32.30)	41 (10.70)	<0.0002
OSA (%)	14 (4.35)	24 (6.27)	0.339
COPD (%)	10 (3.11)	11 (2.87)	1
Stroke (%)	303 (94.10)	337 (87.99)	0.0078
Serum indexes			
NT-proBNP (pg/ml), mean (SD)	249.071 (590.978)	251.864 (792.218)	0.9584
BNP (pg/ml), mean (SD)	69.653 (62.369)	80.849 (124.174)	0.1421
TC (mmol/L), mean (SD)	4.606 (0.888)	4.148 (0.989)	<0.0001
TG (mmol/L), mean (SD)	1.574 (1.260)	1.542 (1.043)	0.7128
HDL-C (mmol/L), mean (SD)	1.226 (0.281)	1.155 (0.305)	0.0015
LDL-C (mmol/L), mean (SD)	2.779 (0.762)	2.400 (0.889)	<0.0001
Resting			
VO_2 (L/min), median (IQR)	309.500 (259.000, 378.000)	320.000 (265.000, 383.500)	0.2818
VO_2/kg (ml/kg/min), median (IQR)	4.600 (3.900, 5.575)	4.500 (3.800, 5.200)	0.068
HR (bpm), median (IQR)	81.000 (73.250, 88.000)	75.000 (67.000, 83.000)	<0.0001
VO_2/HR (ml/beat), median (IQR)	3.900 (3.200, 4.900)	4.400 (3.500, 5.300)	0.0001
AT			
VO_2 (L/min), median (IQR)	827.000 (679.500, 1,082.250)	837.000 (671.500, 1,061.000)	0.9156
VO_2/kg (ml/kg/min), median (IQR)	12.350 (10.400, 14.800)	11.500 (9.500, 14.700)	0.0033
HR (bpm), median (IQR)	108.000 (98.000, 118.000)	99.000 (88.500, 108.500)	<0.0001
VO_2/HR (ml/beat), median (IQR)	7.900 (6.300, 9.850)	8.600 (7.000, 10.600)	0.0007
$\Delta VO_2/\Delta WR$ (ml/min/Watt), median (IQR)	9.549 (8.032, 11.178)	9.920 (8.450, 11.815)	0.1095
Peak			
VO_2 (L/min), median (IQR)	1,291.500 (1,038.500, 1,618.000)	1,323.000 (1,052.000, 1,601.000)	0.9904
VO_2/kg (ml/kg/min), median (IQR)	19.200 (16.225, 22.875)	17.700 (15.000, 22.200)	0.0039
HR (bpm), median (IQR)	137.000 (123.500, 153.000)	125.000 (112.000, 141.000)	<0.0001
VO_2/HR (ml/beat), median (IQR)	9.400 (7.800, 12.075)	10.600 (8.500, 12.650)	0.0001
$\Delta VO_2/\Delta WR$ (ml/min/Watt), median (IQR)	9.785 (8.400, 11.035)	9.700 (8.435, 11.080)	0.9882
RCP			
VO_2 (L/min), median (IQR)	1,067.000 (859.250, 1,367.633)	1,090.000 (873.500, 1,354.000)	0.7092
VO_2/kg (ml/kg/min), median (IQR)	15.850 (13.404, 19.100)	15.100 (12.700, 18.533)	0.0144
HR (bpm), median (IQR)	126.000 (114.000, 139.000)	113.000 (101.000, 127.000)	<0.0001
VO_2/HR (ml/beat), median (IQR)	8.500 (7.100, 10.975)	9.600 (7.881, 11.600)	0.0001
$\Delta VO_2/\Delta WR$ (ml/min/Watt), median (IQR)	9.390 (8.110, 10.508)	9.330 (8.305, 10.698)	0.4039
Rec60 s			
VO_2 (L/min), median (IQR)	620.000 (506.250, 751.500)	653.000 (551.000, 789.500)	0.007
VO_2/kg (ml/kg/min), median (IQR)	11.900 (10.300, 13.900)	11.700 (10.200, 13.800)	0.731
HR (bpm), median (IQR)	119.000 (107.000, 136.000)	109.000 (96.500, 124.000)	<0.0001
VO_2/HR (ml/beat), median (IQR)	6.700 (5.600, 8.400)	7.900 (6.400, 9.550)	<0.0001
$\Delta VO_2/\Delta WR$ (ml/min/Watt), median (IQR)	36.085 (27.340, 45.245)	36.620 (28.860, 49.695)	0.1231

BMI, body mass index; DM, diabetes mellitus; CKD, chronic kidney disease; OSA, obstructive sleep apnea; COPD, chronic obstructive pulmonary disease; BNP, brain natriuretic peptide; TC, total cholesterol; TG, triglyceride; VO_2, oxygen consumption; VO_2/kg, oxygen consumption/kilogram; HR, heart rate; VO_2/HR, oxygen pulse; $\Delta VO_2/\Delta WR$, ratio of the increase in VO_2 to the increase in the work rate; AT, anaerobic threshold; RCP, respiratory compensation point; Rec60 s, post-exercise after 60 s; SD, standard deviation; IQR, interquartile range.

TABLE 2 Multivariable logistic regression analysis of HR_{AT} and HR_{RCP} associated with CAD.

	HR_{AT}				HR_{RCP}			
	Continuous	< 96	[96,110)	≥110	Continuous	<111	[111, 127)	≥127
Model 1								
OR	0.963 (0.953,0.973)	1.000 (R.)	0.516 (0.351,0.755)	0.248 (0.168,0.364)	0.966 (0.958,0.975)	1.000 (R.)	0.422 (0.286,0.619)	0.254 (0.172,0.373)
P values	<0.0001		<0.001	<0.0001	<0.0001		<0.0001	<0.0001
Model 2								
OR	0.971 (0.960,0.981)	1.000 (R.)	0.593 (0.399,0.878)	0.336 (0.223,0.503)	0.973 (0.964,0.982)	1.000 (R.)	0.482 (0.323,0.715)	0.350 (0.231,0.529)
P values	<0.0001		0.009	<0.0001	<0.0001		<0.001	<0.0001
Model 3								
OR	0.972 (0.960,0.984)	1.000 (R.)	0.618 (0.390,0.974)	0.368 (0.229,0.589)	0.974 (0.963,0.985)	1.000 (R.)	0.394 (0.244, 0.629)	0.336 (0.204, 0.546)
P values	<0.0001		0.039	<0.0001	<0.0001		<0.001	<0.0001

TABLE 3 Multivariable logistic regression analysis of hR_{max} and HR_{Rec60s} associated with CAD.

	HR_{max}				HR_{Rec60s}			
	Continuous	< 121	[121,142)	≥ 142	Continuous	< 105	[105,123)	≥ 123
Model 1								
OR	0.974 (0.966,0.981)	1.000 (R.)	0.503 (0.342,0.737)	0.261 (0.176,0.383)	0.978 (0.971,0.986)	1.000 (R.)	0.417 (0.284,0.609)	0.314 (0.213,0.458)
P values	<0.0001		<0.001	<0.0001	<0.0001		<0.0001	<0.0001
Model 2								
OR	0.979 (0.971,0.987)	1.000 (R.)	0.525 (0.353,0.778)	0.346 (0.227,0.524)	0.984 (0.976,0.992)	1.000 (R.)	0.450 (0.302,0.667)	0.412 (0.273,0.618)
P values	<0.0001		0.001	<0.0001	<0.0001		<0.0001	<0.0001
Model 3								
OR	0.980 (0.971,0.990)	1.000 (R.)	0.448 (0.279, 0.713)	0.317 (0.192, 0.518)	0.984 (0.975,0.993)	1.000 (R.)	0.375 (0.232, 0.597)	0.376 (0.231, 0.608)
P values	<0.0001		<0.001	<0.0001	<0.001		<0.0001	<0.0001

Model 1: unadjusted model; Model 2: adjusted for age (Continuous), sex (male or female), and body mass index [normal (18.5–25 kg/m^2), overweight (≥25 kg/m^2) or low (<18.5 kg/m^2)]; Model 3: Further adjusted for hypertension, diabetes mellitus, hyperlipidemia, chronic kidney disease, and lung cancer status (yes or no).
OR, odds ratio; R., reference; HR, heart rate; RCP, respiratory compensation point; AT, anaerobic threshold; max, maximum; Rec60 s, post-exercise after 60 s.

group had higher TC, HDL-C, LDL-C, and HR in the period of resting, AT, RCP, and peak, and VO_2/kg in the period of AT, RCP, and peak, and lower percentage of lung cancer, than in the CAD group (all $P < 0.05$) (Table 1). The baseline characteristics of participants grouped by HR-related indices tertiles were shown in the Supplementary Tables S1–S4.

3.2 Multivariable logistic regression analysis of HR-related indices associated with CAD

Tables 2, 3 shows the results of associations between HR-related indices and risk of CAD using the multivariable Logistic regression analysis. The fully multivariable-adjusted ORs (95% CIs) per 1 unit increase of HR_{AT}, HR_{RCP}, HR_{max}, and HR_{Rec60s} for CAD were 0.972 (0.960, 0.984), 0.974 (0.963, 0.985), 0.980 (0.971, 0.990), and 0.984 (0.975, 0.993), respectively. Compared with participants with HR_{AT} <96 bpm, the multivariable-adjusted ORs (95% CIs) were 0.618 (0.390, 0.974) and 0.368 (0.229, 0.589) for CAD in participants with HR_{AT} ranged from 96 to 110 bpm and ≥110 bpm. Compared with participants with $HR_{RCP} < 111$ beats per minute (bpm), the multivariable-adjusted ORs (odds ratio, 95% CIs) were 0.394 (0.244, 0.629) and 0.336 (0.204, 0.546) for CAD in participants with HR_{RCP} ranged from 111 to 127 bpm and ≥127 bpm. Compared with participants with $HR_{max} < 121$ bpm, the multivariable-adjusted ORs (95% CIs) were 0.448 (0.279, 0.713) and 0.317 (0.192, 0.518) for CAD in participants with HR_{max} ranged from 121 to 142 bpm and ≥142 bpm. Compared with participants with $HR_{Rec60s} <$ 105 bpm, the multivariable-adjusted ORs (95% CIs) were 0.375 (0.232, 0.597) and 0.376 (0.231, 0.608) for CAD in participants with $HR_{Rec60\ s}$ ranged from 105 to 123 bpm, and ≥123 bpm.

3.3 Subgroup analyses

Tables 4, 5 summarized the results of subgroup analysis between the HR-related indices and CAD according to different subgroups, including age, sex, hypertension, DM, hyperlipidemia, and lung cancer status, using multivariable Logistic regression analyses adjusting for age (continuous), sex (male or female), body mass index (BMI, normal [18.5–25 kg/m^2], overweight [≥25 kg/m^2] or low [<18.5 kg/m^2], hypertension, diabetes mellitus, hyperlipidemia, chronic kidney disease, and lung cancer status (yes or no).

In subgroup analyses, statistically significant interactions were not observed between HR_{Rec60s} and any study covariates in relation to CAD (all *P* for interaction > 0.05). The interactions between HR_{AT} and sex, hypertension status, and lung cancer in

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TABLE 4 Subgroup analysis of HR_{RCP} and HR_{AT} associated with CAD.

Characteristic	HR_{AT}				HR_{RCP}			
	<96	[96,110)	≥110	*P* for interaction	<111	[111, 127)	≥127	*P* for interaction
Age				0.467				0.527
<50years	1.000 (R.)	0.640 (0.148,2.774)	0.181 (0.039,0.834)		1.000 (R.)	0.266 (0.058,1.219)	0.291 (0.067,1.271)	
P value		0.551	0.028			0.088	0.101	
≥50years	1.000 (R.)	0.591 (0.362,0.965)	0.378 (0.227,0.629)		1.000 (R.)	0.384 (0.232,0.634)	0.284 (0.169,0.477)	
P value		0.035	<0.0001			<0.001	<0.0001	
Sex				0.001				0.001
Female	1.000 (R.)	0.434 (0.200,0.944)	0.152 (0.067,0.341)		1.000 (R.)	0.362 (0.161, 0.813)	0.167 (0.074, 0.380)	
P value		0.035	<0.0001			0.014	<0.0001	
Male	1.000 (R.)	0.707 (0.394,1.268)	0.623 (0.340,1.142)		1.000 (R.)	0.407 (0.225,0.737)	0.544 (0.288,1.025)	
P value		0.245	0.126			0.003	0.06	
Hypertension				0.036				0.021
Yes	1.000 (R.)	0.702 (0.405, 1.216)	0.314 (0.177, 0.555)		1.000 (R.)	0.349 (0.197, 0.619)	0.251 (0.138, 0.455)	
P value		0.207	<0.0001			<0.001	<0.0001	
No	1.000 (R.)	0.495 (0.201,1.215)	0.541 (0.227,1.288)		1.000 (R.)	0.625 (0.250,1.564)	0.746 (0.296,1.882)	
P value		0.125	0.165			0.316	0.535	
DM				0.475				0.52
Yes	1.000 (R.)	0.914 (0.376,2.223)	0.451 (0.197,1.029)		1.000 (R.)	0.572 (0.245,1.336)	0.441 (0.185,1.049)	
P value		0.843	0.059			0.197	0.064	
No	1.000 (R.)	0.543 (0.315,0.938)	0.338 (0.189,0.607)		1.000 (R.)	0.334 (0.187,0.598)	0.277 (0.150,0.509)	
P value		0.028	<0.001			<0.001	<0.0001	
Hyperlipidemia				0.104				0.718
Yes	1.000 (R.)	0.55 (0.315,0.961)	0.417 (0.230,0.757)		1.000 (R.)	0.376 (0.208,0.683)	0.322 (0.172,0.602)	
P value		0.036	0.004			0.001	<0.001	
No	1.000 (R.)	0.849 (0.376,1.918)	0.268 (0.111,0.651)		1.000 (R.)	0.462 (0.199,1.072)	0.342 (0.147,0.797)	
P value		0.694	0.004			0.072	0.013	
Lung Cancer				0.036				0.543
Yes	1.000 (R.)	1.639 (0.543,4.944)	0.357 (0.096,1.331)		1.000 (R.)	0.569 (0.190,1.708)	0.328 (0.104,1.036)	
P value		0.38	0.125			0.315	0.057	
No	1.000 (R.)	0.489 (0.290, 0.823)	0.342 (0.201, 0.581)		1.000 (R.)	0.373 (0.218, 0.637)	0.337 (0.193, 0.588)	
P value		0.007	<0.0001			<0.001	<0.001	

relation to CAD were statistically significant (*P* for interaction = 0.001, 0.036, and 0.036, respectively). Statistically meaningful interactions were noted between HR_{RCP} and sex and hypertension status in relation to CAD (*P* for interaction = 0.001 and 0.021, respectively). The interactions between HR_{max} and sex and hypertension status in relation to CAD were also statistically significant (*P* for interaction = 0.027 and 0.037, respectively).

3.4 Dose-response analysis of the HR-related indices with CAD

Multivariable-adjusted RCS analyses revealed a linear association of HR_{AT} and HR_{RCP} and with CAD (all *P* for nonlinear > 0.05; Figures 1B, D). With increasing HR, the risk of CAD is reduced sharply. Nonlinear relationships of HR_{max} and HR_{Rec60s} with CAD were observed (all *P* for nonlinear < 0.05; Figures 1F, H).

4 Discussion

This present study aimed to investigate the association of HR_{AT}, HR_{RCP}, HR_{max}, and HR_{Rec60s} assessed by CPET with CAD. Analyzing a robust sample of 705 participants—322 without CAD and 383 with CAD—we mainly found that each additional beat per minute in HR_{AT} was associated with a 2.8% lower adjusted risk of CAD, and each additional beat per minute

TABLE 5 Subgroup analysis of hR_{max} and HR_{Rec60s} associated with CAD.

Characteristic	HR_{max}				HRRec60s			
	<121	[121,142)	≥142	*P*	<105	[105,123)	≥123	*P*
Age				0.417				0.572
<50years	1.000 (R.)	0.209 (0.040,1.083)	0.201 (0.045,.0.898)		1.000 (R.)	0.206 (0.037,1.159)	0.175 (0.034,0.911)	
P value		0.062	0.036			0.073	0.038	
≥50years	1.000 (R.)	0.461 (0.282,0.753)	0.28 (0.166,0.475)		1.000 (R.)	0.373 (0.227,0.612)	0.352 (0.212,0.587)	
P value		0.002	<0.0001			<0.0001	<0.0001	
Sex				0.027				0.134
Female	1.000 (R.)	0.421 (0.195, 0.913)	0.209 (0.095, 0.459)		1.000 (R.)	0.327 (0.153, 0.700)	0.304 (0.143, 0.646)	
P value		0.028	<0.0001			0.004	0.002	
Male	1.000 (R.)	0.459 (0.251,0.840)	0.405 (0.211,0.780)		1.000 (R.)	0.421 (0.228,0.777)	0.428 (0.225,0.813)	
P value		0.012	0.007			0.006	0.01	
Hypertension				0.037				0.054
Yes	1.000 (R.)	0.386 (0.219, 0.680)	0.251 (0.137, 0.458)		1.000 (R.)	0.336 (0.189, 0.595)	0.300 (0.166, 0.541)	
P value		0.001	<0.0001			<0.001	<0.0001	
No	1.000 (R.)	0.767 (0.303,1.945)	0.600 (0.239,1.509)		1.000 (R.)	0.575 (0.231,1.428)	0.678 (0.280,1.642)	
P value		0.577	0.278			0.233	0.389	
DM				0.928				0.684
Yes	1.000 (R.)	0.481 (0.202,1.141)	0.357 (0.151,0.843)		1.000 (R.)	0.538 (0.224,1.293)	0.435 (0.188,1.007)	
P value		0.097	0.019			0.166	0.052	
No	1.000 (R.)	0.400 (0.225,0.710)	0.283 (0.152,0.525)		1.000 (R.)	0.32 (0.179,0.570)	0.326 (0.177,0.601)	
P value		0.002	<0.0001			<0.001	<0.001	
Hyperlipidemia				0.276				0.656
Yes	1.000 (R.)	0.376 (0.208,0.679)	0.306 (0.163,0.574)		1.000 R.)	0.363 (0.203,0.649)	0.405 (0.219,0.748)	
P value		0.001	<0.001			<0.001	0.004	
No	1.000 (R.)	0.69 (0.310,1.538)	0.273 (0.110,0.679)		1.000 (R.)	0.401 (0.170,0.944)	0.346 (0.151,0.792)	
P value		0.364	0.005			0.037	0.012	
Lung cancer				0.329				0.462
Yes	1.000 (R.)	0.551 (0.204,1.485)	0.213 (0.056,0.805)		1.000 (R.)	0.45 (0.150,1.349)	0.278 (0.080,0.960)	
P value		0.238	0.023			0.154	0.043	
No	1.000 (R.)	0.438 (0.257, 0.748)	0.332 (0.191, 0.578)		1.000 (R.)	0.367 (0.215, 0.627)	0.392 (0.228, 0.675)	
P value		0.003	<0.0001			<0.001	<0.001	

R., reference; DM, diabetes mellitus; HR, heart rate; RCP, respiratory compensation point; AT, anaerobic threshold; max, maximum; Rec60 s, post-exercise after 60 s.

in HR_{RCP} was linked to a 2.6% lower adjusted risk of CAD in the general population. Referring to participants with $HR_{AT} < 96$ bpm, the risk of CAD of the participants with HR_{AT} ranged from 96 to 110 bpm and ≥110 bpm lower 38.2% and 63.2%, respectively. Referring to participants with $HR_{RCP} < 111$ bpm, the risk of CAD of the participants with HR_{RCP} ranged from 111 to 127 bpm and ≥127 bpm lower 60.6% and 66.4%, respectively. Further subgroup analysis showed significant interactions between HR_{AT} and sex, hypertension and lung cancer; HR_{RCP} and sex and hypertension in relation to CAD. The Dose-Response Analysis revealed with increasing HR_{AT} and HR_{RCP}, the risk of CAD is reduced sharply. These results are suggestive of a good association between HR_{AT} and HR_{RCP} with CAD. Thus, it is necessary to fully exploit the potential clinic diagnostic value of HR_{AT} and HR_{RCP}.

Around the world, the prevalence of CAD has increased dramatically due to an aging population, unhealthy lifestyles, and environmental changes following decades of rapid economic development. According to the Report on Cardiovascular Health and Diseases in China 2022 (21): An Updated Summary, the number of current CAD patients in China is estimated to be 11.39 million. Early diagnosis and recognition of CAD is essential. Thoroughly exploring the clinical diagnostic value of CPET is required, as it is a more sensitive and comprehensive method of screening for CAD than resting electrocardiogram (ECG) and ECG-only cardiac stress testing in adults with suspected CAD, especially asymptomatic people (22). The gas analysis can detect myocardial ischemia with reduced pulse volume and cardiac output during exercise before ST-segment changes or chest pain develops (23).

The evidence base for CPET screening and diagnosing CAD has grown exponentially over the past few decades. The European Association for Cardiovascular Prevention and Rehabilitation (EACPR) and American Heart Association (AHA) recommended a diagnostic stratification chart for patients with suspected myocardial ischemia, applying primary CPET variables such as O_2 pulse trajectory, per cent-predicted Peak oxygen uptake (VO_{2peak}), and $\Delta VO_2/\Delta WR$ trajectory (24). In this chart, the progressive variables are indicative of poorer aerobic fitness and possibly increased CAD severity. Further, existing studies suggested respiratory equivalent during anaerobic threshold (VE/VCO_2) (25, 26), VO_{2peak} (27), time to reach the anaerobic threshold (TAT) (28), VO_2/HR (29), the ratio of the increase in VO_2 to the increase in work rate ($\Delta VO_2/\Delta WR$) (22, 23) can be abnormal for CAD patients thus them are also significant parameters supporting diagnosis of CAD. However, for most of

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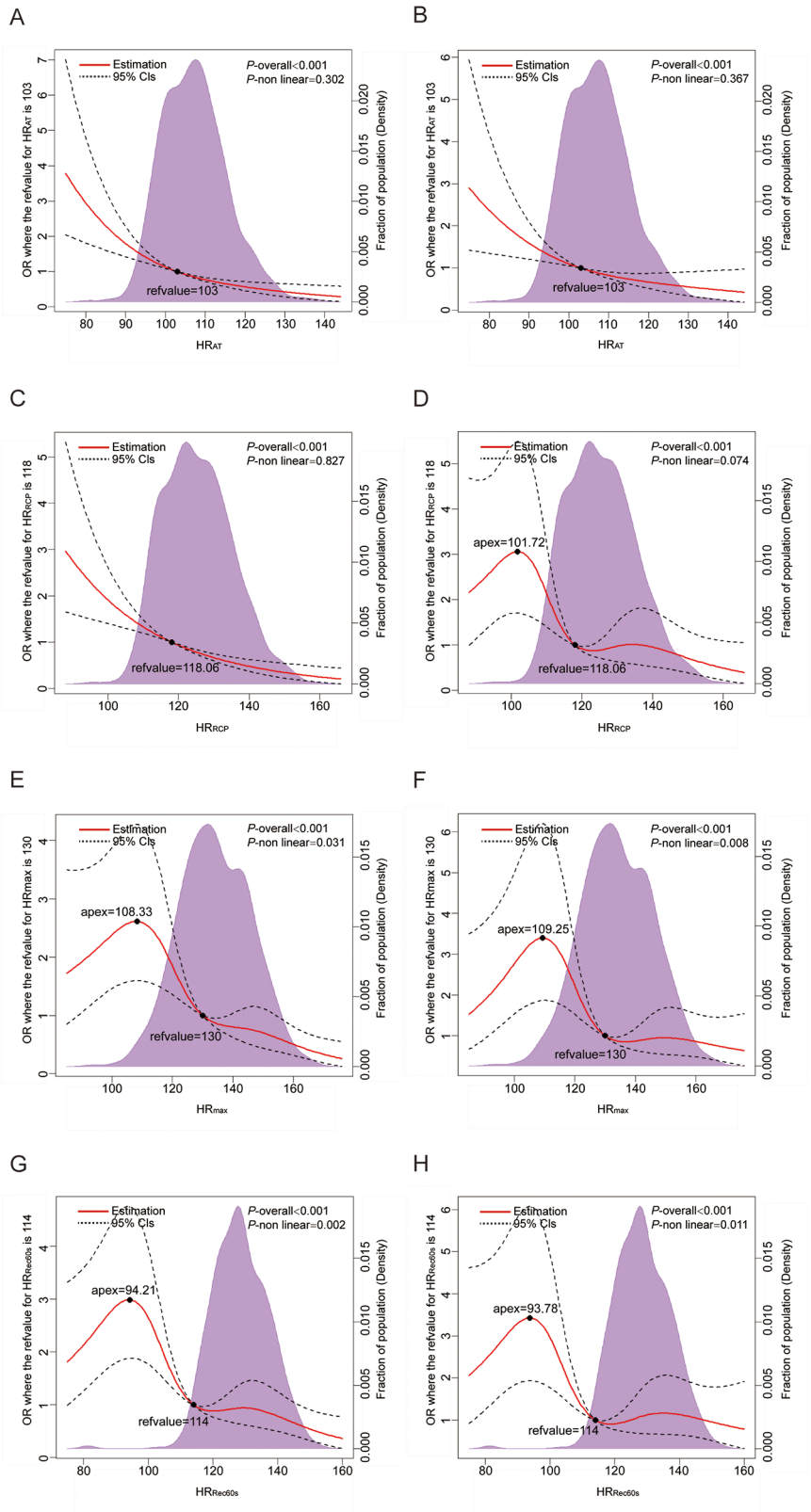

FIGURE 1
Dose–response analysis of the HR-related indices with CAD. **(A,C,E,G)** Dose–response analysis of HR_{AT}, HR_{RCP}, HR_{max}, and HR_{Rec60s} using model 1; **(B,D,F,H)** Dose–response analysis of HR_{AT}, HR_{RCP}, HR_{max}, and HR_{Rec60s} using model 3. Model 1: unadjusted model; Model 3: Further adjusted for hypertension, diabetes mellitus, hyperlipidemia, chronic kidney disease and lung cancer status (yes or no). HR, heart rate; RCP, respiratory compensation point; AT, anaerobic threshold; max, maximum; Rec60 s, post-exercise after 60 s.

these CPET variables, a prerequisite for their accuracy and suggestive value is that the patients reach peak exercise at or near maximum effort or have a RER greater than 1.05. In the clinical process, it was hard for CAD patients, especially those with severe symptoms or long-term no exercise, to perform the near-maximal effort in the cardiopulmonary exercise test. Approximately 4% to 22% of patients with cardiovascular disease fail to reach peak effort due to premature interruption of exercise testing for some motivational or emotional (anxiety) reason or medical reasons assessed by the supervisor (30).

During exercise with progressively increasing workload, ventilation follows three distinct domains regulated respectively by oxygen uptake, carbon dioxide production, and unbuffered acidosis. The entire progressive exercise is therefore divided into three domains in order: from beginning to AT, between AT and RCP, and from RCP to the end (31). AT is a submaximal index of exercise capacity, which signifies a metabolic transition toward increased glycolysis and raised lactate with an associated metabolic acidosis (32). The RCP is a point that marks the onset of hyperventilation during incremental exercise, which forms the boundary between the heavy and severe exercise intensity domains (33). Very few studies have reported the relationship between AT, RCP, and cardiovascular disease, especially CAD. Nakade et al. demonstrated that the duration between the RCP and AT (RCP-AT time) can predict the severity of cardiac disorders and prognosis in patients with heart failure with reduced fraction ejection (34). Alberto et al. found RCP-AT time significantly predicts CAD in patients with anginal chest pain and Left bundle branch block. Our study focused on the HR at AT and RCP in CAD patients for the first time (28).

The acute HR response to exercise, HR increase during exercise, and HR recovery after exercise provide unique insights into cardiac physiology compared to resting HR and can therefore be used to gain more information about cardiac function (35, 36). An impaired HR response to exercise (i.e., chronotropic incompetence, CI) has been shown to be predictive of all-cause mortality and risk of incident CAD, even after accounting for age, physical fitness, and standard cardiovascular risk factors (37). CI is commonly considered when (1) HR_{max} during exercise < 85% of the maximal age-predicted heart rate; or (2) failure to attain 80% of heart rate reserve (38). However, it is vital to consider the patient's level of effort and the reason for terminating the exercise test before diagnosing CI (39). That means the conclusion of CI requires that the patient perform near-maximal effort in CPET. For CAD patients who find it hard to reach peak effort, how do we properly find "poor HR response to exercise"? Our main finding of association between CAD and HR_{AT} or HR_{RCP} perhaps provide a potential clinic diagnostic value to find impaired chronotropic response upon heavy not severe intensity exercise.

The HR at any moment reflects the dynamic balance between sympathetic and parasympathetic nerves in the autonomic nervous system. Unlike resting HR, exercise HR is also largely influenced by cardiorespiratory fitness (40). The gradually increasing HR is the most significant contributor to the ability to sustain aerobic exercise. An intact HR response is essential to closely match a patient's cardiac output to the metabolic demands of exercise. Not only the inability to achieve maximal HR, submaximal HR insufficiency, or HR instability during exertion are all signs of an impaired chronotropic response (39). These complaints are relatively common in CAD, sick sinus syndrome, atrioventricular block, heart failure, and so on. Based on our analysis, the lower HR_{AT}, HR_{RCP}, and HR_{max} are signs of impaired chronotropic response in CAD. HR_{AT} and HR_{RCP} are potentially good indicators of impaired chronotropic response without considering maximal effort. In addition, the underlying mechanisms for CI in CAD and other cardiovascular disorders are incompletely understood. Referring to the mechanism of CI, we assumed that lower HR_{AT} and HR_{RCP} for CAD are related to autonomic nervous system dysfunction. These results are suggestive of a good association between HR_{AT}, HR_{RCP}, and CAD. Based on our analysis, the lower HR_{AT}, HR_{RCP}, and HR_{max} are signs of impaired chronotropic response in CAD. HR_{AT} and HR_{RCP} are potentially good indicators of impaired chronotropic response without considering maximal effort.

The study has potential limitation. First, the patients included in this study were all from Beijing Hospital and only represented a single-center study. The sample size of patients included was limited. Further confirmation clinic trials involving larger sample sizes and multiple centers are necessary. Second, this study was cross-sectional and does not allow for causal inferences; a longitudinal study is needed before forming any causal links. Third, the degree of stenosis of the coronary arteries in the included population should be graded to assess the association between HR and CAD further, but limited due to that not every participant had a result of invasive coronary angiography or coronary computer tomography angiography. Fourth, the diagnostic value of HR_{AT} and HR_{RCP} for suspected CAD is inappropriate for patients who cannot exercise and/or augment the HR response (advanced CAD, autonomic dysfunction, and HR-limiting medications causing CI).

5 Conclusion

These results are suggestive of a good association between HR_{AT}, HR_{RCP}, and CAD. The lower HR_{AT}, HR_{RCP}, and HR_{max} are signs of poor HR response to exercise in CAD. HR_{AT} and HR_{RCP} are potentially good indicators of poor HR response to exercise without considering maximal effort.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by Ethics Committee of Beijing Hospital (No.2023BJYYEC-116-01). The studies were conducted in accordance with the local legislation and institutional requirements. The Ethics Committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because this study is retrospective and involves analysis of existing medical records and data, so written informed consent is waived. This study poses minimal risk to participants as it does not involve any direct interaction or intervention. In addition, all personal and identifying information in this study is anonymized to protect the privacy of the patients and further reduce any potential risks.

Author contributions

YK: Conceptualization, Formal Analysis, Investigation, Methodology, Writing – original draft. RS: Conceptualization, Formal Analysis, Investigation, Methodology, Writing – original draft. TX: Data curation, Investigation, Writing – review & editing. JZ: Data curation, Investigation, Writing – review & editing. CX: Data curation, Writing – review & editing. TZ: Project administration, Writing – review & editing. FW: Funding acquisition, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2024.1442857/full#supplementary-material

References

1. Martin SS, Aday AW, Almarzooq ZI, Anderson CA, Arora P, Avery CL, et al. 2024 Heart disease and stroke statistics: a report of US and global data from the American Heart Association. *Circulation*. (2024) 149(8):e347–913. doi: 10.1161/CIR.0000000000001209

2. Otto C, Nishimura R, Bonow R, Carabello B, Erwin J, Gentile F, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. *Circulation*. (2021) 143(5):e35–71. doi: 10.1161/CIR.0000000000000932

3. Society. AT. ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med*. (2003) 167(2):211–77. doi: 10.1164/rccm.167.2.211

4. Beaver W, Wasserman K, Whipp B. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol*. (1986) 60(6):2020–7. doi: 10.1152/jappl.1986.60.6.2020

5. Glaab T, Taube C. Practical guide to cardiopulmonary exercise testing in adults. *Respir Res*. (2022) 23(1):9. doi: 10.1186/s12931-021-01895-6

6. Fox K, Ferrari R. Heart rate: a forgotten link in coronary artery disease? *Nat Rev Cardiol*. (2011) 8(7):369–79. doi: 10.1038/nrcardio.2011.58

7. Diaz A, Bourassa M, Guertin M, Tardif J. Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. *Eur Heart J*. (2005) 26(10):967–74. doi: 10.1093/eurheartj/ehi190

8. Zhang D, Wang W, Li F. Association between resting heart rate and coronary artery disease, stroke, sudden death and noncardiovascular diseases: a meta-analysis. *CMAJ*. (2016) 188(15):E384–E92. doi: 10.1503/cmaj.160050

9. Lang C, Gupta S, Kalra P, Keavney B, Menown I, Morley C, et al. Elevated heart rate and cardiovascular outcomes in patients with coronary artery disease: clinical evidence and pathophysiological mechanisms. *Atherosclerosis*. (2010) 212(1):1–8. doi: 10.1016/j.atherosclerosis.2010.01.029

10. Lauer M, Okin P, Larson M, Evans J, Levy D. Impaired heart rate response to graded exercise. Prognostic implications of chronotropic incompetence in the Framingham heart study. *Circulation*. (1996) 93(8):1520–6. doi: 10.1161/01.CIR.93.8.1520

11. Sandvik L, Erikssen J, Ellestad M, Erikssen G, Thaulow E, Mundal R, et al. Heart rate increase and maximal heart rate during exercise as predictors of cardiovascular mortality: a 16-year follow-up study of 1960 healthy men. *Coron Artery Dis*. (1995) 6(8):667–79. doi: 10.1097/00019501-199508000-00012

12. Johnson N, Goldberger J. Prognostic value of late heart rate recovery after treadmill exercise. *Am J Cardiol*. (2012) 110(1):45–9. doi: 10.1016/j.amjcard.2012.02.046

13. Pepine C, Handberg E, Cooper-DeHoff R, Marks R, Kowey P, Messerli F, et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The international verapamil-trandolapril study (INVEST): a randomized controlled trial. *JAMA*. (2003) 290(21):2805–16. doi: 10.1001/jama.290.21.2805

14. Liu Y, Zhu B, Zhou W, Du Y, Qi D, Wang C, et al. Triglyceride-glucose index as a marker of adverse cardiovascular prognosis in patients with coronary heart disease and hypertension. *Cardiovasc Diabetol*. (2023) 22(1):133. doi: 10.1186/s12933-023-01866-9

15. Mehra M, Canter C, Hannan M, Semigran M, Uber P, Baran D, et al. The 2016 international society for heart lung transplantation listing criteria for heart transplantation: a 10-year update. *J Heart Lung Transplant*. (2016) 35(1):1–23. doi: 10.1016/j.healun.2015.10.023

16. Guazzi M, Arena R, Halle M, Piepoli M, Myers J, Lavie C. 2016 focused update: clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Circulation*. (2016) 133(24):e694–711. doi: 10.1161/CIR.0000000000000406

17. Guazzi M, Arena R, Halle M, Piepoli M, Myers J, Lavie C. 2016 focused update: clinical recommendations for cardiopulmonary exercise testing data assessment in

specific patient populations. *Eur Heart J*. (2018) 39(14):1144–61. doi: 10.1093/eurheartj/ehw180

18. Price S, Wiecha S, Cieśliński I, Śliż D, Kasiak P, Lach J, et al. Differences between treadmill and cycle ergometer cardiopulmonary exercise testing results in triathletes and their association with body composition and body mass index. *Int J Environ Res Public Health*. (2022) 19(6):3557. doi: 10.3390/ijerph19063557

19. Shah A, Bartlett J, Carpenter J, Nicholas O, Hemingway H. Comparison of random forest and parametric imputation models for imputing missing data using MICE: a CALIBER study. *Am J Epidemiol*. (2014) 179(6):764–74. doi: 10.1093/aje/kwt312

20. Johannesen CDL, Langsted A, Mortensen MB, Nordestgaard BG. Association between low density lipoprotein and all cause and cause specific mortality in Denmark: prospective cohort study. *Br Med J*. (2020) 372:n422. doi: 10.1136/bmj.n422

21. The W. Report on cardiovascular health and diseases in China 2022: an updated summary. *Biomed Environ Sci*. (2023) 36(8):669–701. doi: 10.3967/bes2023.106

22. Belardinelli R, Lacalaprice F, Tiano L, Muçai A, Perna G. Cardiopulmonary exercise testing is more accurate than ECG-stress testing in diagnosing myocardial ischemia in subjects with chest pain. *Int J Cardiol*. (2014) 174(2):337–42. doi: 10.1016/j.ijcard.2014.04.102

23. Belardinelli R, Lacalaprice F, Carle F, Minnucci A, Cianci G, Perna G, et al. Exercise-induced myocardial ischaemia detected by cardiopulmonary exercise testing. *Eur Heart J*. (2003) 24(14):1304–13. doi: 10.1016/S0195-668X(03)00210-0

24. Guazzi M, Adams V, Conraads V, Halle M, Mezzani A, Vanhees L, et al. EACPR/AHA scientific statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Circulation*. (2012) 126(18):2261–74. doi: 10.1161/CIR.0b013e31826fb946

25. Mazaheri R, Shakerian F, Vasheghani-Farahani A, Halabchi F, Mirshahi M, Mansournia M. The usefulness of cardiopulmonary exercise testing in assessment of patients with suspected coronary artery disease. *Postgrad Med J*. (2016) 92(1088):328–32. doi: 10.1136/postgradmedj-2015-133576

26. Dominguez-Rodriguez A, Abreu-Gonzalez P, Gomez M, Garcia-Baute MC, Arroyo-Ucar E, Avanzas P, et al. Myocardial perfusion defects detected by cardiopulmonary exercise testing: role of VE/VCO_2 slope in patients with chest pain suspected of coronary artery disease. *Int J Cardiol*. (2012) 155(3):470–1. doi: 10.1016/j.ijcard.2011.12.063

27. Letnes J, Dalen H, Vesterbekkmo E, Wisløff U, Nes B. Peak oxygen uptake and incident coronary heart disease in a healthy population: the HUNT fitness study. *Eur Heart J*. (2019) 40(20):1633–9. doi: 10.1093/eurheartj/ehy708

28. Dominguez-Rodriguez A, Abreu-Gonzalez P, Gomez M, Garcia-Baute MC, Arroyo-Ucar E, Avanzas P, et al. Assessing coronary artery disease in patients with anginal chest pain and left bundle branch block: an emerging role for a new parameter of cardiopulmonary exercise testing. *Crit Pathw Cardiol*. (2012) 11(4):214–7. doi: 10.1097/HPC.0b013e31826298d6

29. Laukkanen J, Kurl S, Salonen J, Lakka T, Rauramaa R. Peak oxygen pulse during exercise as a predictor for coronary heart disease and all cause death. *Heart (British Cardiac Society)*. (2006) 92(9):1219–24. doi: 10.1136/hrt.2005.077487

30. Vanhees L, Stevens A, Schepers D, Defoor J, Rademakers F, Fagard R. Determinants of the effects of physical training and of the complications requiring resuscitation during exercise in patients with cardiovascular disease. *Eur J Cardiovasc Prev Rehabil*. (2004) 11(4):304–12. doi: 10.1097/01.hjr.0000136458.44614.a2

31. Binder R, Wonisch M, Corra U, Cohen-Solal A, Vanhees L, Saner H, et al. Methodological approach to the first and second lactate threshold in incremental cardiopulmonary exercise testing. *Eur J Cardiovasc Prev Rehabil*. (2008) 15(6):726–34. doi: 10.1097/HJR.0b013e328304fed4

32. Poole D, Rossiter H, Brooks G, Gladden L. The anaerobic threshold: 50+ years of controversy. *J Physiol (Lond)*. (2021) 599(3):737–67. doi: 10.1113/JP279963

33. Wasserman K, Whipp B, Koyl S, Beaver W. Anaerobic threshold and respiratory gas exchange during exercise. *J Appl Physiol*. (1973) 35(2):236–43. doi: 10.1152/jappl.1973.35.2.236

34. Nakade T, Adachi H, Murata M, Naito S. Relationship between respiratory compensation point and anaerobic threshold in patients with heart failure with reduced ejection fraction. *Circ J*. (2019) 84(1):76–82. doi: 10.1253/circj.CJ-19-0561

35. Fletcher G, Balady G, Amsterdam E, Chaitman B, Eckel R, Fleg J, et al. Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. *Circulation*. (2001) 104(14):1694–740. doi: 10.1161/hc3901.095960

36. van de Vegte Y, Tegegne B, Verweij N, Snieder H, van der Harst P. Genetics and the heart rate response to exercise. *Cell Mol Life Sci*. (2019) 76(12):2391–409. doi: 10.1007/s00018-019-03079-4

37. Dresing T, Blackstone E, Pashkow F, Snader C, Marwick T, Lauer M. Usefulness of impaired chronotropic response to exercise as a predictor of mortality, independent of the severity of coronary artery disease. *Am J Cardiol*. (2000) 86(6):602–9. doi: 10.1016/S0002-9149(00)01036-5

38. Azarbal B, Hayes S, Lewin H, Hachamovitch R, Cohen I, Berman D. The incremental prognostic value of percentage of heart rate reserve achieved over myocardial perfusion single-photon emission computed tomography in the prediction of cardiac death and all-cause mortality: superiority over 85% of maximal age-predicted heart rate. *J Am Coll Cardiol*. (2004) 44(2):423–30. doi: 10.1016/j.jacc.2004.02.060

39. Brubaker P, Kitzman D. Chronotropic incompetence: causes, consequences, and management. *Circulation*. (2011) 123(9):1010–20. doi: 10.1161/CIRCULATIONAHA.110.940577

40. Coote J. Recovery of heart rate following intense dynamic exercise. *Exp Physiol*. (2010) 95(3):431–40. doi: 10.1113/expphysiol.2009.047548

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Safety analysis of brachial artery sheath removal after heparin reversal with a half dose of protamine after percutaneous coronary intervention: a single-center experience

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Aim: To evaluate the safety of brachial artery (BA) sheath removal after heparin neutralization with a half dose of protamine immediately after percutaneous coronary intervention (PCI).

Methods: The clinical data of 209 consecutive patients who underwent PCI through the BA at Fu Wai Hospital between September 2019 and June 2024 were retrospectively collected. In group I, the brachial sheath was removed 4 h after the PCI procedure. In group II, circulating heparin was neutralized with a half dose of protamine sulfate, and the brachial sheath was removed immediately after the procedure.

Results: There were no cases of acute stent thrombosis, nonfatal myocardial infarction or in-hospital mortality in either group. In group II, there were two cases of pseudoaneurysm, one of which was transfer to surgery and the other was manually compressed. No severe puncture site-related bleeding occurred. The levels of hemoglobin were similar between the two groups before and after the PCI procedure ($p > 0.05$).

Conclusions: The BA sheath can be safely removed immediately after PCI by neutralizing heparin with a half dose of protamine. But we still need to be vigilant about the occurrence of pseudoaneurysms.

KEYWORDS

brachial artery, heparin, protamine, percutaneous coronary intervention, safety

Introduction

Coronary artery disease (CAD) is the leading cause of morbidity and mortality worldwide (1). Patients who undergo coronary catheterization (CC) via transradial access (TRA) are less likely to experience complications related to the access site and discomfort while walking in the early post-procedure period (2). According to the latest

Abbreviations
CAD, coronary artery disease; CC, coronary catheterization; TRA, transradial access; RAO, radial artery occlusion; FA, femoral artery; ACT, activated clotting time; PCI, percutanous coronary interventin; ST, stent thrombosis; MI, myocardial infarction; VCD, vascular closure device; MC, manual compression.

ESC guidelines, transradial access is recommended as the standard method for CC (3). However, TRA is also associated with several complications, such as hematoma, arteriovenous fistula, pseudoaneurysm, osteofascial compartment syndrome, and radial artery occlusion (RAO) (4). For patients with contraindications to puncture of the radial artery, routine puncture of the femoral artery (FA) is recommended. However, FA access may have more serious complications, such as retroperitoneal hematoma and pseudoaneurysm, as well as the need for bed rest after the procedure. FA puncture increases hospitalization time and is also uncomfortable for patients.

On occasion, neither the RA nor the FA can be safely accessed, such as in patients with severe peripheral vascular disease, an impalpable RA or unsuitable FA. Thus, a percutaneous brachial approach is often used in these patients.

In clinical practice, puncture of the BA often delays extubation to allow an activated clotting time (ACT) within 4 h after the percutanous coronary interventin (PCI) procedure. According to the literature, patients can be immediately and safely extubated after the administration of protamine (5). Therefore, the purpose of this study was to retrospectively analyze the safety of immediate BA sheath removal after heparin reversal with a half dose of protamine after PCI.

Materials and methods

Study population

A retrospective observational study of 215 continuously enrolled patients who underwent PCI through the BA at Fu Wai Hospital between September 2019 and June 2024 was performed. Six patients who received bivalirudin for anticoagulation therapy during the procedure were excluded. The remaining patients were divided into two groups: group I, which underwent brachial sheath removal 4 h after the PCI procedure without ACT, and group II, which underwent brachial sheath removal immediately after circulating heparin was neutralized with a half dose of protamine sulfate.

Procedural details

Before the procedure, all patients received sufficient oral doses of dual antiplatelet drugs (aspirin + clopidogrel or aspirin + ticagrelor). The patient was positioned flat on the bed with their palms facing up, and the puncture point was located at the strongest pulsation point on the inner lower one-third of the upper arm, 2 cm above the skin folds on the elbow. Local anesthesia with 2% lidocaine was applied to the puncture site, and the modified Seldinger method was used for nontransmural vascular puncture and extubation (Figure 1). During the procedure, unfractionated heparin (100 U/kg) was administered to all patients, and the use of glycoprotein IIb/IIIa inhibitors was based on the operator's judgment. The PCI strategy and stent type were selected by the treating physician. In group I, the BA sheath was removed in the ward by the cardiology resident four hours after the PCI procedure without assessing the ACT. In group II, according to the dosage of heparin, a half dose of protamine sulfate was administered immediately after the procedure. The sheath was subsequently removed by the operator who performed the PCI. After 15 min of local compression with elastic bandages (Figure 2), the patient could ambulate immediately.

Endpoints and definitions

The primary endpoints were in-hospital death, acute stent thrombosis (ST) and major bleeding complications. Myocardial infarction (MI) was defined according to the third universal definition of MI (6). ST was defined on the basis of the Academic Research Consortium definitions, and the level of certainty was regarded as definite or probable (7). Major bleeding was defined in accordance with the Bleeding Academic Research Consortium definitions and categorized into grades 3–5 (8). All endpoints were adjudicated centrally by two independent cardiologists, and any disagreements were resolved by consensus.

Statistical analysis

Statistical analysis was performed using SPSS 23.0 statistical software. The measurement data are presented as means ± standard deviations ($x \pm s$), and the Categorical variables are expressed as a percentages (%). A P-value < .05 was considered statistically significant.

Results

Baseline patient characteristics

The baseline characteristics of the study population are shown in Table 1. A total of 209 patients were included, and 104 patients were included in group I and 105 patients in group II. In Group II, there is a higher proportion of female patients(26% vs. 41%, $p = 0.022$). There was no significant difference in age, coexisting conditions, clinical presentation, or concomitant medication use between the two groups of patients.

Procedural characteristics

There was no significant difference in the type of intervention treatment between the two groups (emergency or elective PCI). There was no significant difference between the two groups of patients in terms of lesion type, target vessel intervention, number of drug boluses used, number of stents used, or proportion of f patients who underwent intravascular ultrasound ($p > 0.05$) (Table 2).

Patients in Group I received an average of 71.7 ± 13.0 mg of heparin. Patients in Group II received an average of 70.8 ± 12.7 mg

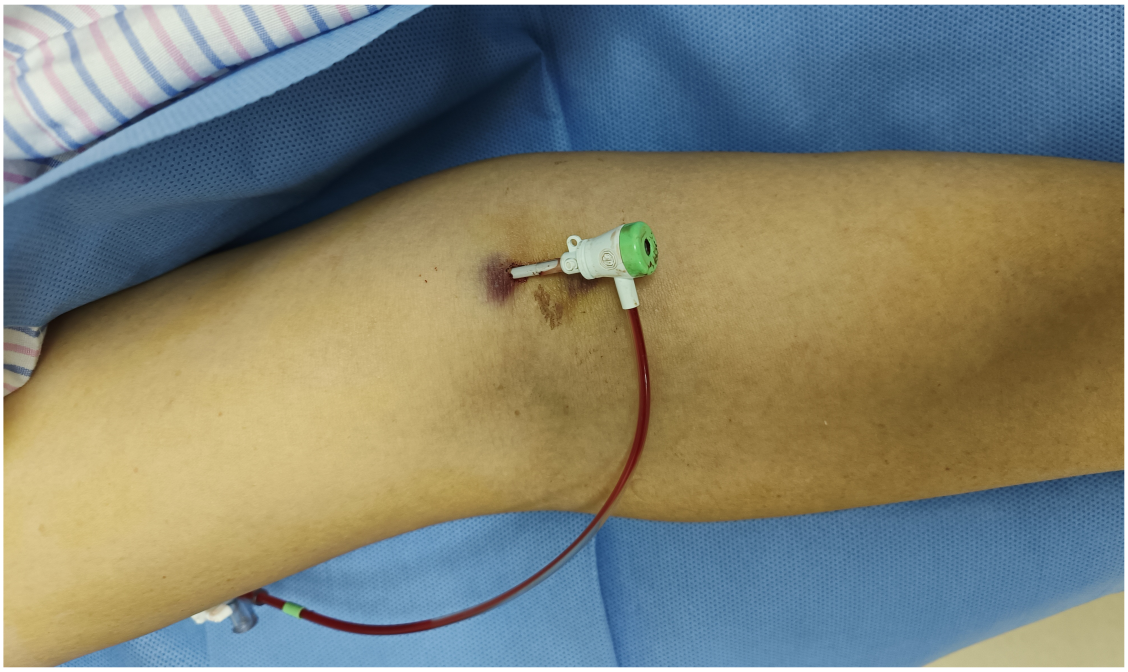

FIGURE 1
Implantation of sheath after brachial artery puncture.

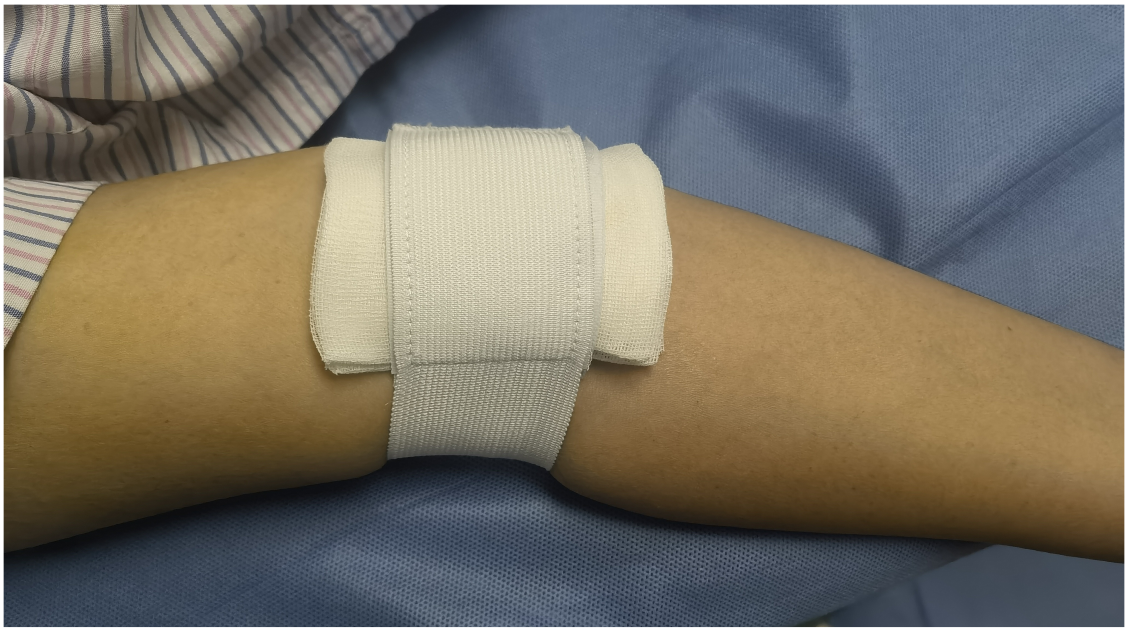

FIGURE 2
Wrap with elastic bandage at the puncture site of the brachial artery to stop bleeding.

of heparin and an average of 34.9 ± 8.8 mg of protamine for heparin neutralization immediately after the PCI procedure.

Only one patients had hematoma in group II, neither group of patients experienced severe bleeding, and there was no significant difference in hemoglobin or hematocrit between the two groups before and after the procedure. Two patients had pseudoaneurysm in group II, one patinet transfer to surgery and the other one had manual compression. Neither group of patients experienced acute stent thrombosis nor in-hospital mortality (Table 2).

TABLE 1 Clinical characteristics.

	Group I (n = 104)	Group II (n = 105)	P-value
Demographic characteristics			
Age; years	63 ± 6	60 ± 6	0.598
Female gender (%)	27 (26.0)	43 (41.0)	0.022
Co-existing conditions (%)			
Hypertension	57 (54.8)	69 (65.7)	0.107
T2DM	34 (32.7)	36 (34.3)	0.807
Dyslipidemia	64 (61.5)	69 (65.7)	0.530
Family history	5 (4.8)	9 (8.6)	0.276
Previous MI	29 (27.9)	21 (20.0)	0.182
Previous PCI	47 (45.2)	42 (40.0)	0.448
Previous CABG	7 (6.7)	6 (5.7)	0.761
CVD	11 (10.6)	10 (9.5)	0.800
PAD	6 (5.8)	4 (3.8)	0.507
Clinical presentation (%)			
ACS	62 (59.6)	61 (58.1)	0.823
Stable angina	34 (32.7)	35 (33.3)	0.922
Silent ischemia	6 (5.8)	7 (6.7)	0.788
Medication at discharge (%)			
Aspirin	102 (98.1)	102 (97.1)	0.659
Clopidogrel	80 (76.9)	88 (83.8)	0.210
Ticagrelor	23 (22.1)	12 (11.4)	0.039
Beta blocker	88 (84.6)	87 (82.9)	0.731
ACEI/ARB	59 (56.7)	59 (56.2)	0.937
Statin	104 (100.0)	102 (97.1)	0.083
Ezetimibe	60 (57.7)	65 (61.9)	0.535
PPI	59(56.7)	61(58.1)	0.842

T2DM, type 2diabetes mellitus; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CVD, cerebral vascular disease; PAD, peripheral vascular disease; ACS, acute coronary syndrome; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockade; PPI, proton pump inhibitor.
Data are expressed as mean ± standard deviation; or counts (percentage).

TABLE 2 Procedural characteristics and in-hospital complications.

	Group I (n = 104)	Group II (n = 105)	P-value
Procedural characteristics			
Emergency PCI (%)	4 (3.8)	3 (2.9)	0.691
Elective PCI (%)	100 (96.2)	102 (97.1)	0.691
Target vessel (%)			
LM	10 (9.6)	5 (4.8)	0.174
LAD	49 (47.1)	44 (41.9)	0.449
LCX	36 (34.6)	27 (25.7)	0.161
RCA	30 (28.8)	32 (30.5)	0.796
SVG	2 (1.9)	2 (1.9)	0.992
Type B2/C lesion (%)			
A	9 (8.7)	11 (10.5)	0.654
B1	13 (12.5)	13 (12.4)	0.979
B2	31 (29.8)	26 (24.8)	0.413
C	57 (55.9)	56 (53.8)	0.769
CTO (%)	15 (14.4)	17 (16.2)	0.723
IVUS application (%)	13 (12.5)	9 (8.6)	0.355
DCB (%)	41 (39.4)	42 (40.0)	0.932
Number of stents	1.2 ± 1.0	0.8 ± 1.0	0.862
Average diameter (mm)	2.27 ± 0.39	2.66 ± 0.38	0.135
Average length (mm)	21.8 ± 7.4	22.1 ± 8.4	0.139
Duration of PCI procedure (min)	44.0 ± 23.0	38.9 ± 20.3	0.553
Dosage of contrast (ml)	175.2 ± 32.6	177.0 ± 46.2	0.177
Heparin and protamine dosage			
Average weight (kg)	73.0 ± 13.0	71.0 ± 12.7	0.846
Heparin dosage (mg)	71.7 ± 13.0	70.8 ± 12.7	0.901
Protamine dosage (mg)	–	34.9 ± 8.8	–
In-hospital complications			
Puncture site hematoma (%)	0 (0)	1 (1.0)	0.318
Severe bleeding (%)			
HB before PCI (g/L)	144.3 ± 17.1	142.9 ± 15.7	0.422
Hematocrit before PCI (%)	43.0 ± 5.0	43.2 ± 5.6	0.547
HB after PCI (g/L)	131.2 ± 15.5	129.2 ± 16.0	0.751
Hematocrit after PCI (%)	39.2 ± 4.6	38.9 ± 6.0	0.483
Pseudoaneurysm (%)	0 (0)	2 (1.9)	0.157
		1 transfer to surgery 1 manual compression	
Acute stent thrombosis (%)	0	0	–
In-hospital mortality (%)	0	0	–

PCI, percutaneous coronary intervetion; LM, left main; LAD, left anterior descending artery; IVUS, intravascular ultrasound; LCX, left circumflex artery; RCA, right coronary artery; CTO, chronic total occlusion; DCB, drug coated balloon.

Discussion

This paper presents the results of heparin neutralization with a half dose of protamine after PCI and immediate removal of the BA sheath in a large cohort of consecutive, nonselected CAD patients. We found that this strategy was indeed safe and was associated with a very low risk of complications. But we still need to be vigilant about the occurrence of pseudoaneurysms.

Although the radial and femoral arteries are conventional accesses for intervention in most cases, they are also not suitable access sites in for some patients. Owing to extensive intervention through the RA, the incidence of RAO is reportedly between 1% and 10% (9). In addition, the rates of second puncture and intubation failure using the same RA were 3.5% (male) and 7.9% (female), respectively (10). FA puncture is associated with serious complications, such as retroperitoneal hematoma and pseudoaneurysm, and requires bed rest after the procedure, which increases the hospitalization time and increases patient discomfort. Therefore, for patients with contraindications to puncture of the radial and femoral arteries, the BA may be a good choice.

In the early stages of coronary angiography in the 1970s, PCI was performed through the BA. However, owing to the puncture strategies and operating instruments used at that time, once bleeding occurred, the patient would likely develop compartment syndrome of the bone fascia and experience compression of the median nerve, which often led to ischemia in the entire upper limb and subsequent hand disability (11). Earlier studies have shown that the incidence of complications, mainly bleeding complications and pseudoaneurysms, at the BA puncture site ranges from 7%–11% (12), whereas others have shown that the incidence of complications can reach as high as 36% (13). Therefore, its clinical application is greatly limited.

Concerns about using the BA are limited to compression hemostasis. A meta-analysis including fifteen articles published after 2008 revealed the rates of complications rates associated with percutaneous BA interventions. Seventy-five of 1,424 (5.27%)

patients experienced major complications at the access site. Thirteen of 309 (4.21%) patients who underwent hemostasis with a vascular closure device (VCD) experienced major complications, and 65 of 1,122 (5.79%) patients who underwent hemostasis with manual compression (MC) experienced major complications. The major access site complication rate associated with TBA was 5.27% (14). In recent years, owing to the extensive use of the BA in peripheral vascular intervention, the BA has once again become a focus of attention for interventional cardiologists. Owing to the development of technologically advanced surgical instruments, the incidence of complications associated with the BA has significantly decreased compared with that reported previously. Recent studies have shown that the BA can be a safe and effective alternative to the FA for access, with complication rates reportedly ranging between 1.3% and 3.4% (15, 16).

Unlike the radial route, there are no VCDs suitable for external arterial compression in China. Some studies have indicated that the BA sheath should not be removed until normal coagulability has been restored (ACT < 180 s) (17), so the BA sheath is usually removed 4 h after the procedure to allow heparin to metabolize, reducing the risk of bleeding, and then MC is used for hemostasis. This method is not very convenient for interventional cardiologists and also increases the workload of ward nurses. Therefore, we aimed to explore the safety of neutralizing heparin with protamine for immediate extubation.

Protamine was used to neutralize circulating heparin was in earlier studies. In 1997, Pan et al. randomly divided 228 consecutive patients whose stent implantation was successful into 2 groups, one of which received 2 mg/kg of protamine and underwent in-laboratory sheath removal and reported that heparin could be safely reversed with protamine immediately after stent implantation (18). Lin et al. consecutively enrolled 105 femoral PCI patients; 78 underwent stent implantation (1.3 ± 1.1 stents), and heparin was reversed with 0.5 mg/100 U of protamine. The ACT was checked before and after protamine administration, with the aim of removing the sheath when the ACT was less than 170 s. The average heparin dose was 5,076 ± 1,746 units, the peak ACT was 269 ± 68 s, and the postprotamine ACT was 165 ± 31 s. The average protamine dose administered was 24 ± 6 mg. No significant adverse events occurred except for a single hematoma that did not require surgical intervention (19). Ducas John et al. consecutively enrolled 429 eligible patients who underwent PCI. After the procedure, if the ACT was at or above 160 s, intravenous protamine was administered for 5 min according to the ACT. If the ACT was between 160 and 200, 15 mg of protamine was administered. If the ACT was between 200 and 250, 20 mg of protamine was administered. If the ACT was between 250 and 300 mg, 25 mg of protamine was administered. Repeated doses of protamine were administered if necessary. If the ACT was less than 160 s, the sheath was removed immediately in the catheterization laboratory, and hemostasis was achieved by manual compression or clamp compression. Minor groin bleeding occurred in six patients. One patient required femoral pseudoaneurysm repair. There were no deaths during the 30-day follow-up period. The results showed that immediate reversal of anticoagulation therapy is safe and feasible for immediate sheath removal after PCI (20). The above studies show that administering different doses of protamine to neutralize heparin after PCI is safe and effective.

This was a retrospective study, and all patients included had contraindications to radial and femoral artery puncture or were unwilling to undergo FA puncture. In this study, the BA sheath was quickly removed after the administration of protamine to neutralize heparin without assessing the ACT; owing to heparin metabolism, a half dose of protamine was given on the basis of experience and previous studies on the FA approach.

In the group II, 2 patients developed pseudoaneurysms, with a probability of 1.9%, which is lower than the reported probability in other literature. Reversal with protamine for early sheath removal in this single-center study appears to be efficacious and safe. The BA is located superficially, easily palpable, and has a thicker diameter, providing a thicker sheath. It is a simple and effective alternative to femoral closure devices and the RA approach to early ambulation after PCI. But we still need to be vigilant about the occurrence of pseudoaneurysms.

To our knowledge, this study is the first to explore the safety and effectiveness of immediate sheath removal after neutralization with protamine after BA puncture. This may be another good strategy for patients with contraindications to puncture of the radial and femoral arteries in clinical practice.

Limitations

This study was limited by its single-center retrospective nature, small sample size, lack of ultrasound examination, and lack of information regarding whether there were local vascular complications. Patient comfort, length of hospital stay, radiation exposure, and fluoroscopy use were not assessed. The procedures were performed by four cardiologists with varying levels of experience, and there was significant operator variability in both the selection criteria and experience in establishing BA access. A larger multicenter study investigating the safety and efficacy of this strategy is suggested, with the goal of reducing costs and expediting care.

Conclusion

A half-dose of protamine to reverse heparin for early BA sheath removal in this single-center study appears to be efficacious and safe, with no early adverse cardiac events. But we still need to be vigilant about the occurrence of pseudoaneurysms.

Data availability statement

The datasets presented in this article are not readily available due to privacy and ethical restrictions. Requests to access the datasets should be directed to Lijian Gao, gljxra0104@126.com.

Ethics statement

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Fuwai Hospital (Beijing, China). The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

HW: Writing – original draft, Writing – review & editing. CC: Writing – original draft, Writing – review & editing. DL: Data curation, Writing – original draft. HL: Data curation, Writing – original draft. TT: Methodology, Supervision, Writing – review & editing. ML: Data curation, Software, Formal Analysis, Writing – original draft. BZ: Data curation, Writing – original draft. TZ: Conceptualization, Data curation, Investigation, Software, Writing – review & editing. ZG: Resources, Supervision, Visualization, Writing – review & editing. LG: Funding acquisition, Project administration, Resources, Visualization, Writing – review & editing. HL: Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Rydén L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovasdular diseases developed in collaboration with the EASD—summary. *Diab Vasc Dis Res*. (2014) 11(3):133–73. doi: 10.1177/1479164114525548

2. Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. (2019) 40(2):87–165. doi: 10.1093/eurheartj/ehy394

3. Coomes EA, Haghbayan H, Cheema AN. Distal transradial access for cardiac catheterization: a systematic scoping review. *Catheter Cardiovasc Interv*. (2020) 96 (7):1381–9. doi: 10.1002/ccd.28623

4. Sheikh AR, Abdelaal E, Sastry S, Karim S, Zeb M. Novel distal left radial artery access in anatomical snufbox for recanalization of proximal radial artery total occlusion and percutaneous coronary intervention through left internal mammary artery. *Circulation*. (2018) 11(7):e006579. doi: 10.1161/CIRCINTERVENTIONS.118.006579

5. De Luca G, Parodi G, Antoniucci D. Safety and benefits of protamine administration to revert anticoagulation soon after coronary angioplasty. A meta-analysis. *J Thromb Thrombolysis*. (2010) 30(4):452–8. doi: 10.1007/s11239-010-0482-4

6. Jaffe AS. Third universal definition of myocardial infarction. *Clin Biochem*. (2013) 46(1-2):1–4. doi: 10.1016/j.clinbiochem.2012.10.036

7. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, Van Es GA, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. (2007) 115:2344–51. doi: 10.1161/CIRCULATIONAHA.106.685313

8. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the bleeding academic research consortium. *Circulation*. (2011) 123:2736–47. doi: 10.1161/CIRCULATIONAHA.110.009449

9. Sciahbasi A, Rigattieri S, Sarandrea A, Cera M, Di Russo C, Fedele S, et al. Radial artery occlusion and hand strength after percutaneous coronary procedures: results of the HANGAR study. *Catheter Cardiavac Interv*. (2016) 87:864–74. doi: 10.1002/ccd.26142

10. Sakai H, Ikeda S, Harada T, Yonashiro S, Ozumi K, Ohe H, et al. Limitations of successive transradial approach in the same arm: the Japanese experience. *Catheter Cardiovasc Interv*. (2001) 54(2):204–8. doi: 10.1002/ccd.1268

11. Stajic Z, Romanovic R, Tavciovski D. Forearm approach for percutaneous coronaty procedures. *Acta Inform Med*. (2013) 21:283–7. doi: 10.5455/aim.2013.21.283-287

12. Watkinson AF, Hartnell GG. Complications of direct brachial artery puncture for arteriography: a comparison of techniques. *Clin Radiol*. (1991) 44(3):189–91. doi: 10.1016/S0009-9260(05)80868-2

13. Armstrong PJ, Han DC, Elmore JR, Baxter JA, Franklin DP. Complication rates of percutaneous brachial artery access in peripheral vascular angiography. *Ann Vasc Surg*. (2003) 17(1):107–10. doi: 10.1007/s10016-001-0339-6

14. Mantripragada K, Abadi K, Echeverry N, Shah S, Snelling B. Transbrachial access site complications in endovascular interventions: a systematic review of the literature. *Cureus*. (2022) 14(6):e25894. doi: 10.7759/cureus.25894

15. Franz RW, Tanga CF, Herrmann JW. Treatment of peripheral arterial disease via percutaneous brachial artery access. *J Vasc Surg*. (2017) 66(2):461–5. doi: 10.1016/j.jvs.2017.01.050

16. Parviz Y, Rowe R, Vijayan S, Iqbal J, Morton AC, Grech ED, et al. Percutaneous brachial artery access for coronary artery procedures: feasible and safe in the current era. *Cardiovasc Revasc Med*. (2015) 16(8):447–9. doi: 10.1016/j.carrev.2015.08.004

17. Criado FJ, Wilson EP, Abul-Khoudoud O, Barker C, Carpenter J, Fairman R. Brachial artery catheterization to facilitate endovascular grafting of abdominal aortic aneurysm: safety and rationale. *J Vasc Surg*. (2000) 32(6):1137–41. doi: 10.1067/mva.2000.109335

18. Pan M, Suárez de Lezo J, Medina A, Romero M, Torres A. In-laboratory removal of femoral sheath following protamine administration in patients having intracoronary stent implantation. *Am J Cardiol*. (1997) 80:1336–8. doi: 10.1016/S0002-9149(97)00676-0

19. Lin J, Gaidhu N, Awan R, Kong W, Amlani S, Raco D, et al. Protamine reversal post heparin administration for immediate femoral sheath removal in coronary catheterization/intervention: vascular and cardiac safety and efficacy. *Can J Cardiol*. (2018) 34(10):S205. doi: 10.1016/j.cjca.2018.07.442

20. Ducas J, Chan MCY, Miller A, Kashour T. Immediate protamine administration and sheath removal following percutaneous coronary intervention: a prospective study of 429 patients. *Catheter Cardiovasc Interv*. (2002) 56(2):196–9. doi: 10.1002/ccd.10195

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Effect of ticagrelor combined with metoprolol extended-release tablets on cardiac function and clinical prognosis in elderly patients with acute coronary syndrome after percutaneous coronary intervention

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Background: Acute coronary syndrome (ACS) poses significant risks to older individuals. This study sought to assess the impact of combining ticagrelor and metoprolol extended-release tablets on clinical prognosis and cardiac function in elderly ACS patients following percutaneous coronary intervention (PCI).
Methods: From February 2022 to February 2023, 90 elderly ACS patients who underwent PCI at our institution were retrospectively enrolled and divided into two groups: an observation group (OG) and a control group (CG), with 45 patients in each group. The CG received oral metoprolol extended-release tablets, while the OG received both oral metoprolol extended-release tablets and ticagrelor. Prognostic indicators and cardiac function were evaluated before and after treatment.
Results: The treatment effectiveness rate in the OG was 97.78%, significantly higher than the CG's rate of 77.78% ($P < 0.05$). Post-treatment, the OG displayed notable improvements in cardiac function, including significantly higher left ventricular ejection fraction (LVEF), stroke volume (SV), cardiac output (CO), and cardiac index (CI) compared to the CG ($P < 0.05$). Both groups experienced enhanced exercise capacity, as evidenced by longer exercise duration (ED) and improved 6-min walking test (6MWT) results, with the OG showing superior gains ($P < 0.05$). Additionally, the OG had significantly higher serum levels of cardiac troponin T (cTnT) and creatine kinase isoenzyme (CK-MB) than the CG ($P < 0.05$). Decreases in serum levels of sICAM-1, MMP-9, and hs-CRP were observed in both groups, with more pronounced improvements in the OG ($P < 0.05$). The incidence of adverse prognostic events in the OG was significantly lower at 8.89%, compared to 37.78% in the CG ($P < 0.05$).
Conclusion: Ticagrelor combined with metoprolol extended-release tablets can significantly improve cardiac function, motor performance, and quality of life in ACS patients after PCI. Additionally, it effectively increases myocardial injury markers and reduces serum inflammatory factor levels.

KEYWORDS

ticagrelor, metoprolol extended-release tablets, acute coronary syndrome, percutaneous coronary intervention, cardiac function, clinical prognosis

1 Introduction

Acute coronary syndrome (ACS) is a cardiovascular condition caused by the rupture or erosion of coronary atherosclerotic plaques, leading to partial or complete obstruction of the artery by a thrombus. This condition significantly increases global mortality and morbidity. ACS is considered a severe form of coronary artery disease, encompassing acute ST-segment elevation myocardial infarction (STEMI), unstable angina (UA) pectoris, and non-ST segment elevation myocardial infarction (NSTEMI) (1, 2). Without timely and appropriate treatment, ACS can lead to shock or sudden death, posing a serious threat to the patient's life (3–5). The main therapeutic option for ACS is percutaneous coronary intervention (PCI), which helps clear stenotic or occluded coronary arteries, improving myocardial perfusion and reducing the risk for coronary heart disease. However, stent placement and mechanical expansion during PCI can damage vascular cells, leading to complications such as bleeding and inflammation. Therefore, careful attention must be given to antiplatelet therapy. Once administered, antiplatelet agents inhibit platelet aggregation and adhesion, thereby reducing thrombosis at the site of vascular injury (6). Antithrombotic therapy is administered not only after PCI but also as part of the standard treatment for ACS, as platelets play a central role in the pathogenesis of ACS. Antithrombotic therapy can also avoid further injury of endothelium and cardiomyocytes, which is beneficial for repairing and protecting blood vessels and myocardium (7).

Inflammatory response, platelet activation, and vascular endothelial cell injury after Percutaneous coronary intervention (PCI) can lead to adverse cardiovascular events in patients with ACS. Metoprolol extended-release tablets, a β-receptor blocker, competitively and reversibly bind to β-adrenoceptors, reducing sympathetic activity, myocardial oxygen consumption, and plasma catecholamine levels. It also prolongs the diastolic period, improves coronary blood supply, inhibits ventricular remodeling, and improves cardiac function, reducing the risk of major adverse cardiac events (MACEs). However, its long-term effects are less favorable, and patients often relapse after discontinuing the drug (8, 9).. Recent studies have shown that low-density lipoprotein (LDL) cholesterol and oxidized LDL are significant risk factors for unstable angina in coronary heart disease. These lipoproteins can also promote the migration of leukocytes to the arterial intima, leading to endothelial cell damage (10, 11).

Ticagrelor is a novel antiplatelet medication that belongs to non-thiophene pyridine, which can act on platelet receptors directly without liver activation after oral administration and can effectively regulate lipids by blocking platelet receptors (12, 13). Additionally, ticagrelor benefits from a quick onset of action, stable pharmacological effects, and significant platelet inhibition in clinical settings (14). Since both ticagrelor and extended-release metoprolol have demonstrated efficacy for treating ACS individually, some experts and scholars have hypothesized that their combination could further enhance clinical outcomes. However, there is limited literature on the combined use of these treatments for managing patients undergoing PCI who develop ACS. Therefore, further research is needed to determine their potential value. The current study aims to evaluate the therapeutic efficacy, impact on cardiac function, and clinical prognosis of administering this dual treatment after PCI in elderly individuals with ACS. The findings will contribute to the body of knowledge and provide valuable insights for clinical practitioners.

2 Materials and methods

2.1 General information

Between February 2022 and February 2023, we screened 142 patients diagnosed with ACS who underwent PCI at our institution for inclusion in this retrospective study. Figure 1 presents a schematic diagram illustrating the screening process of subjects into groups. The diagnosis of ACS in this study was based on the criteria outlined in the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines (15). After applying the inclusion and exclusion criteria, a total of 90 elderly patients with a diagnosis of ACS were enrolled in the study. Patients were divided into two groups: an observation group (OG) and a control group (CG), with 45 patients in each group. The flowchart of patient selection process is illustrated in Figure 2. The division into groups was based on the treatment received at the time of admission, with the CG receiving oral metoprolol extended-release tablets and the OG receiving ticagrelor in addition to metoprolol extended-release tablets. Due to the nature of the retrospective design, the physicians involved in the treatment were aware of the treatment modalities prescribed to the patients, as treatment decisions were made based on clinical judgment and standard care protocols. The demographic and clinical characteristics of the patients were collected from medical records to ensure comprehensive data analysis. The study received approval from the institutional review boards of Taizhou Jiangyan Hospital of Traditional Chinese Medicine (reference number: RJ-2022-19) and was conducted in line with the Declaration of Helsinki principles. Because the study was retrospective and observational, and the data were anonymized, the requirement for informed consent was waived.

Inclusion criteria were as follows: (a) Patients aged 65 years or older who met the diagnostic criteria for ACS as outlined by the AHA/ACC guidelines, including those with STEMI, NSTEMI, and UA subtypes (15); (b) Coronary artery stenosis was confirmed by coronary angiography with >50% stenosis; (c) Patients with good cardiac function, indicated by a left ventricular ejection fraction (LVEF) of ≥40%, and no history of hemorrhagic diseases, allergies to hematopoietic agents, or significant complications, as well as no severe liver or kidney dysfunction, coagulation disorders, or active major hemorrhage; (d) The patient's condition was stable; (e) Patients were classified as Grade II to III according to the American New York Heart Association (NYHA) classification (16). Exclusion criteria were as follows: (a) Patients who had received traditional Chinese medicine or physiotherapy in the past month; (b) Individuals with allergies or intolerance to the medications used in this

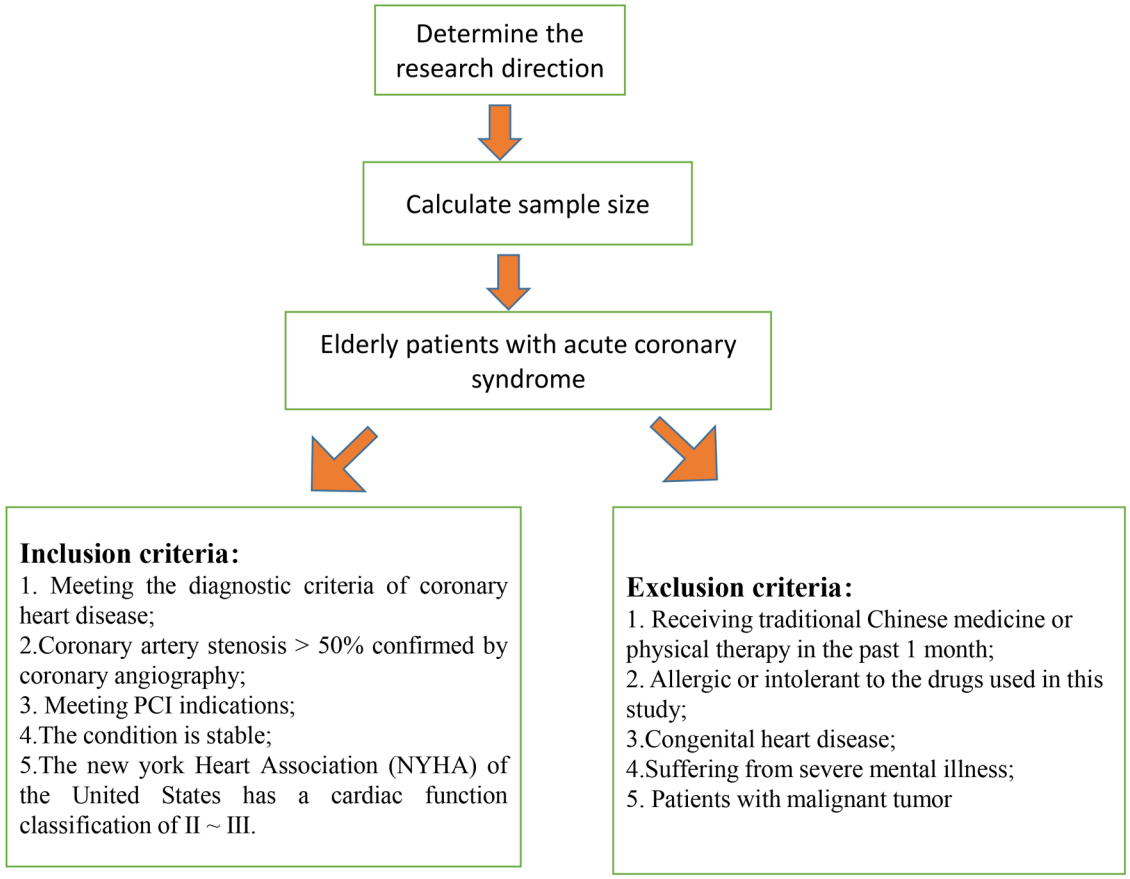

FIGURE 1
Schematic diagram of screening subjects into groups.

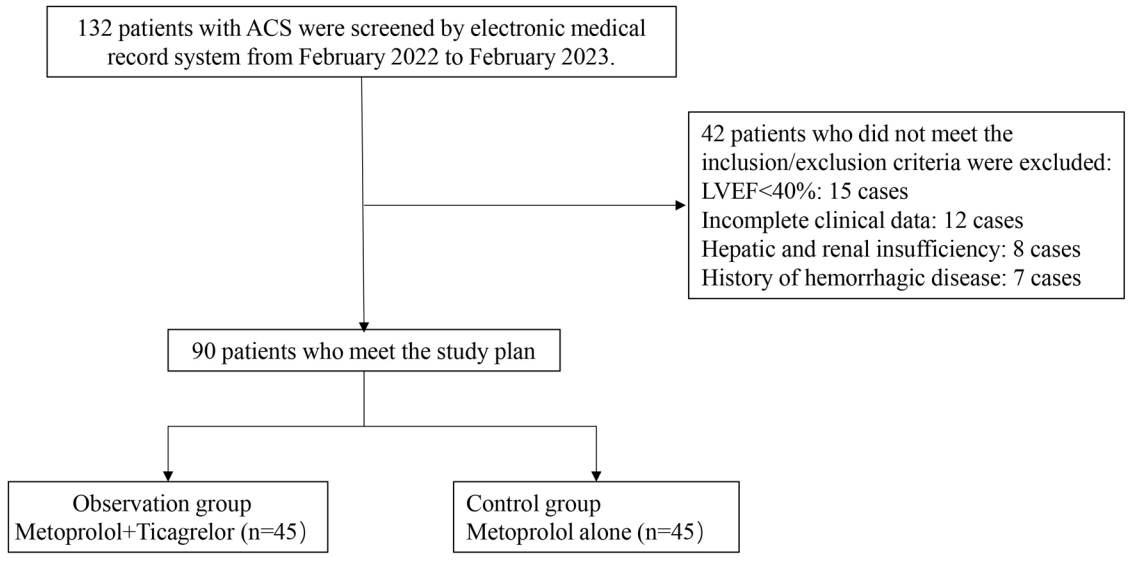

FIGURE 2
Flowchart depicting the patient selection process.

study; (c) Patients with congenital heart disease; (d) Individuals with severe mental illness; (e) Patients with malignant tumors; (f) Patients who required oral anticoagulants for comorbid conditions, such as atrial fibrillation or other thromboembolic disorders. We used the following formula to calculate the sample size:

$$n_1 = \frac{\left[Z_{\alpha/2}\sqrt{p(1-p)(1+c)/c} + Z_{\beta}\sqrt{p_1(1-p_1)+p_2(1-p_2)/c}\right]^2}{(p_1-p_2)^2}$$

Bilateral α was set at 0.05 and β at 0.20. The clinical efficacy (total effective rate) was used as the effect index, based on relevant literature and previous studies (17), with $P_1 = 0.95$ and $P_2 = 0.75$. According to the calculation, 41 cases were needed in each group. Considering a dropout rate of 10%, approximately 45 patients were required per group, resulting in a total of 90 patients.

2.2 Treatment methods

Both groups in this study underwent PCI and received aspirin (100 mg once daily) as part of their standard post-PCI treatment regimen. Patients requiring oral anticoagulation for atrial fibrillation were excluded from the study. The CG was additionally treated with oral metoprolol extended-release tablets (AstraZeneca Pharmaceutical Company, Chinese Medicine Registration Number H37023121, batch numbers: 201552933, 201642358) at a dosage of 50 mg twice daily. The OG received a combination therapy of oral metoprolol extended-release tablets, administered at the same dosage as in the CG (50 mg twice daily), and ticagrelor, administered orally at a dose of 90 mg twice daily. Dual antiplatelet therapy (DAPT) was not used in the CG, as the aim was to evaluate the impact of adding ticagrelor to standard metoprolol therapy in the intervention group. This approach allowed us to assess the impact of a more potent antiplatelet regimen compared to a conservative, aspirin-only strategy. DAPT was initiated in the OG according to current ACS management guidelines, ensuring that all eligible patients received both ticagrelor and aspirin unless contraindications were present. The rationale for selecting ticagrelor centered on its demonstrated superiority over clopidogrel in reducing thrombotic events, particularly in high-risk ACS patients. We considered the feasibility of ticagrelor use by carefully evaluating patient characteristics, including age, comorbidities, and bleeding risk. The safety and appropriateness of administering ticagrelor were ensured by excluding patients with significant bleeding risks or contraindications. Patients with known contraindications to ticagrelor, such as a history of hemorrhagic stroke, active bleeding, or hypersensitivity to the drug, were excluded. A thorough pre-enrollment screening process was conducted to identify and exclude such patients, maintaining the safety and integrity of the study. Both groups were observed over a four-week period to assess the impact of the treatment regimens on cardiac function and clinical outcomes.

2.3 Outcome measure

The primary outcome was the treatment effectiveness rate, defined as a significant improvement in cardiac function and exercise capacity. Secondary outcomes included measurements of cardiac function (left ventricular ejection fraction [LVEF], stroke volume [SV], cardiac output [CO], and cardiac index [CI]), exercise performance [exercise duration <ed > and 6-minute walking test (6MWT)], and serum biomarker levels (cardiac troponin T [cTnT], creatine kinase isoenzyme [CK-MB], soluble intercellular adhesion molecule-1 [sICAM-1], matrix metalloproteinase-9 [MMP-9], and high-sensitivity C-reactive protein [hs-CRP]). The incidence of adverse prognostic events was also recorded.

2.4 Observation index

2.4.1 Comparison of the clinical effectiveness between the two groups

The clinical efficacy of both groups was assessed after 4 weeks of therapy using the following evaluation criteria (17): (a) Significant Effect: ECG returned to normal or significantly improved, all symptoms disappeared, and there was an 80% reduction in cases of angina pectoris; (b) Effective: ECG and clinical symptoms improved, with a 50%–79% reduction in the occurrence of angina pectoris; (c) Invalid: Cases that did not meet the above criteria. The total effective rate is calculated as: (significant effect + effective cases)/total cases × 100%.

2.4.2 Cardiac function assessment

Echocardiographic examinations were performed before treatment and 4 weeks after treatment by two experienced sonographers independently (κ coefficient >0.8). A GE Vivid E95 ultrasound system equipped with an M5Sc-D probe (1.4–4.6 MHz) was used. Measurements included left ventricular ejection fraction (LVEF), stroke volume (SV), cardiac output (CO), and cardiac index (CI). All measurements were averaged over three cardiac cycles.

2.4.3 Exercise capacity assessment

Exercise capacity was evaluated using the six-minute walk test (6MWT) and exercise duration (ED) before and 4 weeks after treatment. The 6MWT was conducted in a standard 30-meter hospital corridor, recording the total walking distance covered within 6 min. Heart rate and oxygen saturation were monitored throughout the test. The test was terminated if the heart rate exceeded 85% of maximum, oxygen saturation fell below 90%, or patients experienced severe fatigue or chest pain.

2.4.4 Biomarker detection

Biomarker measurements were conducted before treatment and 4 weeks after treatment. Blood samples for these markers were collected at baseline (prior to treatment initiation) and again at the end of the 4-week treatment period to evaluate changes over time. These included myocardial injury markers such as cardiac troponin T (cTnT) and creatine kinase-MB isoenzyme (CK-MB),

as well as inflammatory factors like soluble intercellular adhesion molecule-1 (sICAM-1), matrix metalloproteinase-9 (MMP-9), and high-sensitivity C-reactive protein (hs-CRP). Blood samples were processed within 30 min of collection by centrifugation (3,000 rpm for 15 min), and the separated serum was stored at −80°C until analysis. All test kits were purchased from Shanghai JieYi Biotechnology Co., Ltd. (Shanghai, China) and were used strictly according to the manufacturer's instructions.

2.4.5 Quality of life assessment

Quality of life (18) was evaluated before treatment and 4 weeks after treatment using a quality-of-life questionnaire that assessed daily living function, psychological function, social function, and material living conditions. Each dimension was scored on a scale of 0–100 points, with higher scores indicating better quality of life in that dimension. Assessments were conducted by trained nurses through face-to-face interviews.

2.4.6 Prognosis

The incidence of adverse prognostic events, including angina pectoris, myocardial infarction, in-stent thrombosis, and death, was recorded in both treatment groups. The total incidence was calculated by dividing the total number of adverse events by the total number of cases and multiplying by 100%. Angina pectoris is characterized by paroxysmal, compressive chest pain, often accompanied by other symptoms (19). Myocardial infarction refers to the sudden necrosis of the myocardium caused by prolonged ischemia and hypoxia of the coronary artery, with chest pain as the primary symptom (20). In-stent thrombosis occurs when the endothelium is damaged, exposing subendothelial tissue after stent implantation (21). It can be triggered by stent rupture or the development of new atherosclerotic plaque within the stent, leading to rapid platelet aggregation and thrombus formation. Symptoms may include chest pain, chest tightness, and dyspnea.

2.5 Statistical analysis

The data were analyzed using the statistical software SPSS 22.0. Measurement data with a normal distribution and homogeneous variance were expressed as mean ± standard deviation ($\bar{x} \pm s$). Independent sample *t*-tests were used to compare data between groups, while paired *t*-tests were performed within each group. Categorical data, expressed as *n* (%), were analyzed using the chi-square (χ^2) test. A *P*-value of less than 0.05 was considered statistically significant.

3 Results

3.1 Baseline characteristics of the study population

The CG consisted of 22 females and 23 males, with an age range of 65–83 years and an average age of 72.71 ± 5.62 years. Regarding vessel involvement, 25 cases had single-vessel involvement, while 20 cases had double-vessel involvement. The average body mass index (BMI) was 22.87 ± 2.31 kg/m^2, ranging from 17.88 to 27.74 kg/m^2. Regarding education level, 20 participants had completed primary or junior high school, 10 had completed junior college or higher education, and 15 had graduated from senior high school or technical secondary school. The OG comprised 19 females and 26 males, with an average age of 73.89 ± 5.81 years, ranging from 65 to 83 years. Among the OG participants, 26 cases had single-vessel involvement, while 19 cases had double-vessel involvement. BMI values ranged from 17.90 to 27.80 kg/m^2. The education level distribution was as follows: 18 participants had completed primary or junior middle school, 11 had completed junior college or higher education, and 16 had graduated from senior high school or technical secondary school. There were no significant differences between the CG and OG in terms of gender distribution, age, vessel involvement, BMI, or education level ($p > 0.05$ for all comparisons) (Supplementary Table S1).

3.2 Comparison of clinical efficacy between the two groups

The treatment effectiveness rate in the OG was 97.78% (44/45 patients), which was significantly higher than the CG's rate of 77.78% (35/45 patients) ($P < 0.05$). Figure 3 displays the effectiveness rates for both groups.

3.3 Comparison of cardiac function indexes between the two groups before and after treatment

Before therapy, there were no discernible differences in cardiac function between the two groups ($P > 0.05$). After therapy, cardiac function indexes, including LVEF, SV, CO, and CI, were significantly higher in the observation group compared to the CG ($P < 0.05$). All outcomes are presented in detail in Table 1.

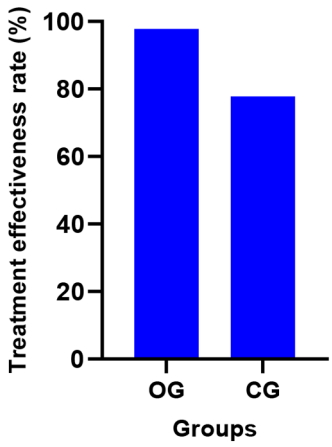

FIGURE 3
Comparison of clinical efficacy between the two groups (%). OG, Observation group; CG, Control group.

TABLE 1 Comparison of cardiac function indexes between the two groups before and after treatment ($\bar{x}\pm s$, $n = 45$).

Group	LVEF (%)		SV (ml)		CO (L/min)		CI (min·m^2)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
OG	44.12 ± 4.58	59.88 ± 5.06[a]	51.05 ± 5.82	68.83 ± 6.42[a]	3.41 ± 0.82	5.83 ± 1.05[a]	2.67 ± 0.58	3.92 ± 0.67[a]
CG	44.03 ± 4.19	53.24 ± 4.91[b]	50.89 ± 5.44	62.41 ± 5.28[b]	3.52 ± 0.59	5.04 ± 0.81[b]	2.83 ± 0.44	3.22 ± 0.55[b]
t	0.097	6.317	0.135	5.181	0.730	3.996	1.474	5.417
P	0.923	<0.001	0.893	<0.001	0.467	<0.001	0.149	<0.001

Values are presented as Mean ± SD. Compared with the OG before treatment.
OG, observation group; CG, control group.
[a]$P < 0.05$; compared with the CG before treatment.
[b]$P < 0.05$.

3.4 Comparison of motor assessment scale between the two groups before and after treatment

The two groups had no significant difference in baseline 6MWT and ED scores ($P > 0.05$). After therapy, the 6MWT and ED scores significantly improved in both groups, with the OG showing a notably better improvement than the CG ($P < 0.05$). All outcomes are detailed in Table 2.

3.5 Comparison of the levels of myocardial injury-related factors between the two groups before and after treatment

Before therapy, the two groups had no significant differences in serum CK-MB and cTnT levels ($P > 0.05$). After treatment, the OG showed significantly higher serum CK-MB and cTnT levels than the CG ($P < 0.05$). All results are presented in Figures 4, 5.

3.6 Comparison of serum levels of inflammatory factors between the two groups before and after treatment

Before therapy, the two groups had no significant differences in the concentrations of sICAM-1, MMP-9, and hs-CRP ($P > 0.05$). After treatment, serum levels of sICAM-1, MMP-9, and hs-CRP decreased in both groups, with the OG showing a significantly greater improvement than the CG ($P < 0.05$). All results are detailed in Table 3.

3.7 Comparison of quality of life scores between the two groups

Before therapy, there was no statistically significant difference between the two groups regarding daily, psychological, social, and material functioning ($P > 0.05$). After the intervention, scores for quality of life across all categories significantly improved in both groups, with the OG showing a more significant improvement than the CG ($P < 0.05$). The results are detailed in Table 4.

3.8 Comparison of adverse prognostic events between the two groups

The incidence of adverse prognostic events was significantly lower in the OG (8.89%) compared to the CG (37.78%) ($P < 0.05$). The detailed results of adverse prognostic events between the two groups are shown in Table 5.

4 Discussion

In recent years, the number of ACS cases has been rising as the aging population in China increases. The clinical treatment of ACS is based on the principles of restoring coronary blood flow, improving myocardial oxygen consumption, alleviating myocardial ischemia, and preventing coronary thrombosis to

TABLE 2 Comparison of motor function indexes between the two groups before and after treatment ($\bar{x} \pm s$, $n = 45$).

Group	6MWT (m)		ED (s)	
	Before treatment	After treatment	Before treatment	After treatment
OG	381.39 ± 44.23	409.52 ± 45.66[a]	360.49 ± 27.04	379.28 ± 27.09[a]
CG	380.84 ± 44.09	390.04 ± 44.21[b]	360.43 ± 26.55	365.05 ± 27.14[b]
t	0.059	2.056	0.007	2.489
P	0.953	0.045	0.995	0.018

Values are presented as Mean ± SD. Compared with the OG before treatment.
OG, observation group; CG, control group.
[a]$P < 0.05$; compared with the CG before treatment.
[b]$P < 0.05$.

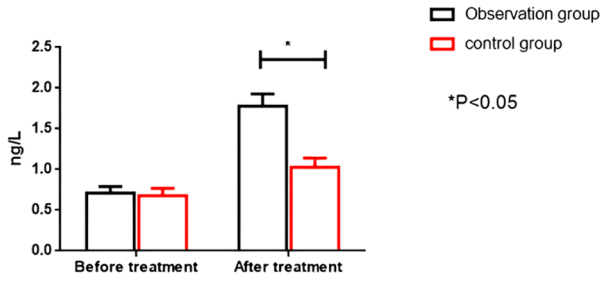

FIGURE 4
Comparison of CK-MB levels between the two groups before and after intervention. CK-MB; Creatine kinase MB isoform.

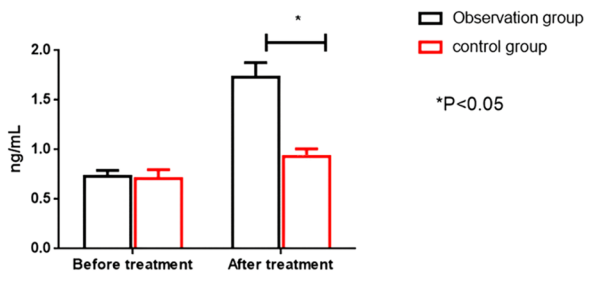

FIGURE 5
Comparison of cTnT levels between the two groups before and after intervention. cTnT; cardiac troponin I.

reduce complications and mortality (22). For elderly patients with ACS, it is difficult to tolerate revascularization due to declining body functions and organ dysfunction, making drug therapy the preferred choice.

ACS is primarily caused by intracoronary thrombosis, which leads to coronary artery occlusion and myocardial injury. Thrombosis occurs when the fibrous cap of an atherosclerotic plaque ruptures, releasing a highly thrombotic lipid core into the bloodstream. This triggers a series of signaling pathways that activate platelets, initiating the coagulation cascade and promoting thrombosis (23). Therefore, in conventional treatment, alongside coronary artery dilation and the use of angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACE inhibitors), anticoagulant and antiplatelet therapies play a significant role in managing ACS and are integral to the treatment process. However, long-term use of anticoagulants and antiplatelet agents increases the risk of bleeding. Furthermore, elderly patients with ACS often have multiple underlying conditions, and the adverse effects of prolonged medication can negatively impact adherence to the prescribed treatment regimen. As a result, the effectiveness of conventional treatment is often suboptimal due to various complex factors. Hence, there is an urgent need to identify a treatment for elderly ACS patients that is both effective and safe (24, 25).

Ticagrelor is a novel antiplatelet medication that can quickly and effectively inhibit adenosine diphosphate-mediated platelet aggregation, significantly reducing the incidence of adverse events such as myocardial infarction and cardiovascular death (26, 27).

TABLE 3 Comparison of serum indexes between the two groups before and after treatment ($\bar{x} \pm s$, $n = 45$).

Group	sICAM-1 (ng/ml)		MMP-9 (μg/L)		hs-CRP	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
OG	645.53 ± 109.91	439.91 ± 87.04[a]	182.42 ± 20.38	90.45 ± 11.34[a]	26.18 ± 5.03	18.81 ± 4.02[a]
CG	644.15 ± 115.03	347.22 ± 65.68[b]	181.94 ± 21.34	62.17 ± 7.53[b]	26.54 ± 5.19	13.15 ± 3.24[b]
t	0.058	5.702	0.109	13.936	0.334	7.354
P	0.954	<0.001	0.914	<0.001	0.740	<0.001

Values are presented as Mean ± SD. Compared with the OG before treatment.
OG, observation group; CG, control group.
[a]$P < 0.05$; compared with the CG before treatment.
[b]$P < 0.05$.

TABLE 4 Comparison of life quality scores between the two groups (points, $\bar{x} \pm s$).

Group	Daily life function		Psychological function		Social function		Material function	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
OG	32.24 ± 5.12	60.22 ± 9.14[a]	21.82 ± 2.41	67.48 ± 8.15[a]	30.46 ± 4.84	66.82 ± 7.11[a]	22.82 ± 8.12	69.67 ± 8.37[a]
CG	31.23 ± 5.07	47.31 ± 7.15[b]	21.13 ± 2.09	56.33 ± 8.24[b]	30.17 ± 4.78	52.51 ± 4.72[b]	22.71 ± 8.06	55.91 ± 8.23[b]
t	0.94	7.463	1.451	6.454	0.293	11.248	0.064	7.864
P	0.351	<0.001	0.152	<0.001	0.761	<0.001	0.949	<0.001

Values are presented as Mean ± SD. Compared with the OG before treatment.
OG, observation group; CG, control group.
[a]$P < 0.05$; compared with the CG before treatment.
[b]$P < 0.05$.

TABLE 5 Comparison of the incidence of adverse prognostic events involving both groups (n/%).

Group	*N*	Angina	Myocardial infarction	In-stent thrombus	Death	Total incidence rate（%）
OG	45	1（2.22）	2（4.44）	0（0.00）	1（2.22）	4（8.89）
CG	45	3（6.67）	5（11.11）	6（13.33）	3（6.67）	17（37.78）
$\chi 2$						10.497
P						0.003

Values are presented as count (percentage).
OG, observation group; CG, control group.

In the present study, the efficacy rate in the OG was 97.78%, which was statistically higher than that of the CG (77.78%). After treatment, cardiac function indicators such as LVEF, SV, CO, and CI were significantly higher in the OG compared to the CG, and both the 6MWT and ED were longer in the OG. These results suggest that metoprolol extended-release tablets can improve cardiac and motor functions, thereby enhancing the therapeutic effect. However, the therapeutic effect of combining metoprolol with ticagrelor was even better. Ticagrelor is a novel oral antiplatelet medication known for its potent antiplatelet effects. It works by inhibiting the P2Y12 receptor on platelets, binding to it reversibly, and effectively reducing platelet aggregation. This mechanism of action leads to significant anticoagulant effects, improving myocardial blood supply and enhancing coronary artery blood flow (28). Metoprolol extended-release tablets are widely used due to their rapid absorption, fast peak time, and short plasma half-life. In contrast, succinic acid, which has lower solubility than tartaric acid, allows for the sustained and controlled release of the drug over an extended period. This prolonged release leads to stable blood concentrations with minimal fluctuations between peak and trough levels (29). Additionally, metoprolol extended-release tablets utilize a multi-unit microcapsule-controlled release technique that ensures a slow and consistent release. The absorption process lasts over 20 h, resulting in a longer plasma half-life. Taken once daily, the tablets maintain stable 24-h blood concentrations, provide ideal β1-receptor blockade, enhance drug compliance, and improve cardiac function in patients (30). The combination of these two drugs can have a synergistic effect, further enhancing therapeutic outcomes.

While the myocardial infarction with non-obstructed coronary arteries (MINOCA) study (31) reported a high risk of adverse events during follow-up, especially reinfarction, with nearly half of the patients with re-AMI experiencing progression of atherosclerosis, our study found that PCI combined with dual antiplatelet therapy resulted in a lower rate of reinfarction, which may be attributed to more aggressive management strategies. Inflammation is a key factor influencing the prognosis of ACS patients, as it is strongly associated with adverse cardiovascular outcomes. Research on STEMI showed that elevated T2 values in the non-infarcted myocardium were correlated with larger infarct sizes, microvascular obstruction, and left ventricular dysfunction, emphasizing the role of inflammation at the tissue level (32). These findings suggest that inflammation, especially within the non-infarcted myocardium, could serve as an important predictor of reinfarction and other major adverse cardiac events in ACS patients. Previous research has shown that unstable coronary artery disease-related angina pectoris is associated with a low level of chronic inflammation in the body, and the inflammatory response within plaques is a key factor contributing to plaque instability (33). Adipose tissue in the body secretes various bioactive substances, including the immunoglobulin superfamily member sICAM-1, which is expressed and secreted by smooth muscle cells and endothelial cells in atherosclerotic plaques. sICAM-1 is currently recognized as an independent risk factor for predicting ACS. Previous literature has also indicated that elevated levels of MMPs serve as a separate risk factor for the progression of ACS (34). This increase is closely associated with plaque instability and can be used as a diagnostic marker for ACS, as well as for assessing the extent of infarction and predicting prognosis. Hepatocytes produce the acute phase protein hs-CRP, which can promote thrombosis and is a risk factor for unstable angina pectoris. Its serum level plays a crucial role in ACS's intervention and prognosis assessment. This research demonstrated that after therapy, serum levels of sICAM-1, MMP-9, and hs-CRP decreased in both groups, with the improvement in the OG being significantly better than in the CG. These results suggest that ticagrelor may more effectively inhibit the release of inflammatory factors. Mechanistically, metoprolol extended-release tablets can enhance the oxygen supply to myocardial cells, improve the aerobic metabolism of the myocardium, reduce the production of free fatty acids, and alleviate angina pectoris symptoms. Ticagrelor reversibly inhibits platelet aggregation, but it is effective only after biotransformation into active metabolites. To improve patient prognosis, excessive doses may lead to medication resistance. When myocardial injury occurs, serum levels of CK-MB and cTnT rise significantly, making CK-MB and cTnT commonly used indicators for diagnosing and predicting the prognosis of ACS. After treatment, the OG's serum CK-MB and cTnT levels were higher than those of the CG, with this difference being statistically significant. It is hypothesized that treating elderly ACS patients with a combination of ticagrelor and metoprolol extended-release tablets is beneficial. This combination may reduce inflammatory and oxidative stress responses, improve immune indexes, prevent cardiomyocyte damage, and enhance therapeutic outcomes. According to our findings, the quality of life scores in the OG were higher than those in the CG. This is because the combination of ticagrelor with metoprolol extended-release tablets was more effective than metoprolol extended-release tablets alone. This combination better improves the patient's condition and helps them return to their regular lives more quickly. The rate of adverse prognostic events was lower in the OG compared to the CG. The

daily blood concentration of metoprolol extended-release tablets remains within the therapeutic window, selectively blocking β1 receptors while avoiding adverse effects associated with β2 receptors.

There are several limitations to this study. First, as a retrospective observational analysis, we cannot eliminate the potential for bias and confounding factors. Second, being a single-center study limits its generalizability, and the small sample size may affect the reliability of the findings. Third, a limitation of the study is that the CG received only aspirin and metoprolol without DAPT. This conservative approach, in line with current ACS guidelines (35), was intentionally chosen to assess the added benefit of ticagrelor in the intervention group OG. Lastly, the dosages of ticagrelor and metoprolol used in this study are not universally recommended and may differ from standard guidelines in various regions. Future prospective studies involving multiple centers are needed to validate these findings.

5 Conclusion

In summary, using a combination of ticagrelor and metoprolol extended-release tablets after PCI can enhance the overall effectiveness and cardiac function in patients with coronary heart disease and reduce the occurrence of adverse prognostic events, compared to metoprolol extended-release tablets alone. However, prospective multi-center studies with larger sample sizes are required to validate our findings.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the study received approval from the institutional review boards of Taizhou Jiangyan Hospital of Traditional Chinese Medicine (reference number: RJ-2022-19) and was conducted in line with the Declaration of Helsinki principles. The studies were conducted in accordance with the local legislation and institutional requirements. The Ethics Committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because the study was retrospective and observational, and the data were anonymized, the requirement for informed consent was waived.

Author contributions

LW: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. LG: Data curation, Formal Analysis, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. QC: Conceptualization, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Validation, Writing – original draft, Writing – review & editing. LC: Conceptualization, Formal Analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. HX: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. LS: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. YH: Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing, Conceptualization.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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References

1. Bhatt DL, Lopes RD, Harrington RA. Diagnosis and treatment of acute coronary syndromes: a review. *JAMA*. (2022) 327:662–75. doi: 10.1001/jama.2022.0358

2. Palm DS, Drame A, Moliterno DJ, Aguilar D. Acute coronary syndromes among patients with prior coronary artery bypass surgery. *Curr Cardiol Rep*. (2022) 24:1755–63. doi: 10.1007/s11886-022-01784-4

3. Atwood J. Management of acute coronary syndrome. *Emerg Med Clin North Am*. (2022) 40:693–706. doi: 10.1016/j.emc.2022.06.008

4. Mehilli J, Presbitero P. Coronary artery disease and acute coronary syndrome in women. *Heart (British Cardiac Society)*. (2020) 106:487–92. doi: 10.1136/heartjnl-2019-315555

5. Bianco M, Mottola FF, Cerrato E, Giordana F, Cinconze S, Baralis G, et al. Acute coronary syndrome in very elderly patients-a real-world experience. *Heart Vessels*. (2023) 38:1019–27. doi: 10.1007/s00380-023-02260-x

6. Higuchi S, Kabeya Y, Nishina Y, Miura Y, Shibata S, Hata N, et al. Clinical impact of noncontrast percutaneous coronary intervention in patients with acute coronary syndrome. *J Med Investig JMI*. (2022) 69:57–64. doi: 10.2152/jmi.69.57

7. Jeremias A, Davies JE, Maehara A, Matsumura M, Schneider J, Tang K, et al. Blinded physiological assessment of residual ischemia after successful angiographic percutaneous coronary intervention: the DEFINE PCI study. *JACC Cardiovasc Interv*. (2019) 12:1991–2001. doi: 10.1016/j.jcin.2019.05.054

8. Bahuva R, Aoun J, Goel SS. Management of acute coronary syndrome in the COVID era. *Methodist Debakey Cardiovasc J*. (2021) 17:16–21. doi: 10.14797/mdcvj.1049

9. Schieffer B, Kreutz J, Markus B, Schäfer A-C. [Acute coronary syndrome (ACS) in preclinical emergency medicine]. *Anasthesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie: AINS*. (2021) 56:734–45. doi: 10.1055/a-1330-5226

10. Chandrasekhar J, Baber U, Sartori S, Aquino M, Moalem K, Kini AS, et al. Prasugrel use and clinical outcomes by age among patients undergoing PCI for acute coronary syndrome: from the PROMETHEUS study. *Clin Res Cardiol*. (2020) 109:725–34. doi: 10.1007/s00392-019-01561-4

11. Schnaubelt S, Oppenauer J, Bader M DUN, Eibensteiner F, Kienbacher CL, Baldi E, et al. Arterial stiffness in acute coronary syndrome as a potential triage tool: a prospective observational study. *Minerva Med*. (2023) 114:1–14. doi: 10.23736/S0026-4806.22.07909-5

12. Carande EJ, Brown K, Jackson D, Maskell N, Kouzaris L, Greene G, et al. Acute kidney injury following percutaneous coronary intervention for acute coronary syndrome: incidence, aetiology, risk factors and outcomes. *Angiology*. (2022) 73:139–45. doi: 10.1177/00033197211040375

13. McKnight AH, Katzenberger DR, Britnell SR. Colchicine in acute coronary syndrome: a systematic review. *Ann Pharmacother*. (2021) 55:187–97. doi: 10.1177/1060028020942144

14. Gorog DA, Geisler T. Platelet inhibition in acute coronary syndrome and percutaneous coronary intervention: insights from the past and present. *Thromb Haemostasis*. (2020) 120:565–78. doi: 10.1055/s-0040-1702920

15. Gulati M, Levy PD, Mukherjee D, Amsterdam E, Bhatt DL, Birtcher KK, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation*. (2021) 144:e368–454. doi: 10.1161/CIR.0000000000001029

16. Bredy C, Ministeri M, Kempny A, Alonso-Gonzalez R, Swan L, Uebing A, et al. New York Heart association (NYHA) classification in adults with congenital heart disease: relation to objective measures of exercise and outcome. *Eur Heart J Qual Care Clin Outcomes*. (2018) 4:51–8. doi: 10.1093/ehjqcco/qcx031

17. Qing-Yun H. Observation on clinical efficacy of ticagrelor combined with metoprolol in the treatment of acute coronary syndrome. *China Pract Med*. (2019).

18. Yingzi Z. Comparison of the clinical efficacy and safety of different doses of progesterone in the treatment of functional uterine bleeding. *J Clin Ration Drug Use*. (2021) 14:117–8.

19. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: executive summary: a report of the American College of Cardiology foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. (2012) 126:3097–137. doi: 10.1161/CIR.0b013e3182776f83

20. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol*. (2018) 72:2231–64. doi: 10.1016/j.jacc.2018.08.1038

21. Klein LW, Nathan S, Maehara A, Messenger J, Mintz GS, Ali ZA, et al. SCAI Expert consensus statement on management of in-stent restenosis and stent thrombosis. *J Soc Cardiovasc Angiograp Interv*. (2023) 2:100971. doi: 10.1016/j.jscai.2023.100971

22. Biccirè FG, Barillà F, Sammartini E, Dacierno EM, Tanzilli G, Pastori D. Relationship between non-invasively detected liver fibrosis and in-hospital outcomes in patients with acute coronary syndrome undergoing PCI. *Clin Res Cardiol*. (2023) 112:236–46. doi: 10.1007/s00392-022-02078-z

23. Thiele H, Jobs A. [ESC guidelines 2020: acute coronary syndrome without persistent ST-segment elevation: what is new?]. *Herz*. (2021) 46:3–13. doi: 10.1007/s00059-020-05002-1

24. Brown RM. Acute coronary syndrome in women. *Emerg Med Clin North Am*. (2022) 40:629–36. doi: 10.1016/j.emc.2022.06.003

25. Alblaihed L. Huis In 't Veld MA. Allergic acute coronary syndrome-Kounis syndrome. *Immunol Allergy Clin North Am*. (2023) 43:503–12. doi: 10.1016/j.iac.2022.10.010

26. Leopoulou M, Mistakidi VC, Oikonomou E, Latsios G, Papaioannou S, Deftereos S, et al. Acute coronary syndrome with non-ruptured plaques (NONRUPLA): novel ideas and perspectives. *Curr Atheroscler Rep*. (2020) 22:21. doi: 10.1007/s11883-020-00839-7

27. Kakizaki S, Otake H, Seike F, Kawamori H, Toba T, Nakano S, et al. Optical coherence tomography fractional flow reserve and cardiovascular outcomes in patients with acute coronary syndrome. *JACC Cardiovascular Interventions*. (2022) 15:2035–48. doi: 10.1016/j.jcin.2022.08.010

28. Fernández-Ortiz A, Bas Villalobos MC, García-Márquez M, Bernal Sobrino JL, Fernández-Pérez C, Del Prado González N, et al. The effect of weekends and public holidays on the care of acute coronary syndrome in the Spanish national health system. *Revista Espanola de Cardiologia (English ed)*. (2022) 75:756–62. doi: 10.1016/j.rec.2021.10.022

29. Akbar MR, Pranata R, Wibowo A, Irvan ST, Martha JW. The association between triglyceride-glucose index and major adverse cardiovascular events in patients with acute coronary syndrome—dose-response meta-analysis. *Nutr Metab Cardiovasc Dis*. (2021) 31:3024–30. doi: 10.1016/j.numecd.2021.08.026

30. Piccolo R, Esposito G. Percutaneous coronary intervention in patients with COVID-19 and acute coronary syndrome: what if the old normal became the new normal? *Catheter Cardiovasc Interv*. (2021) 97:199–200. doi: 10.1002/ccd.29480

31. Ciliberti G, Guerra F, Pizzi C, Merlo M, Zilio F, Bianco F, et al. Characteristics of patients with recurrent acute myocardial infarction after MINOCA. *Prog Cardiovasc Dis*. (2023) 81:42–7. doi: 10.1016/j.pcad.2023.10.006

32. Bergamaschi L, Landi A, Maurizi N, Pizzi C, Leo LA, Arangalage D, et al. Acute response of the noninfarcted myocardium and surrounding tissue assessed by T2 mapping after STEMI. *JACC Cardiovasc Imaging*. (2024) 17:610–21. doi: 10.1016/j.jcmg.2023.11.014

33. Mahmood MM, Nawaz MJ. Prescription of statins after acute coronary syndrome; a single-centre observational study. *J Pak Med Assoc*. (2023) 73:646–9. doi: 10.47391/JPMA.4328

34. Higuchi S, Kabeya Y, Nishina Y, Miura Y, Yoshino H. Feasibility and safety of noncontrast percutaneous coronary intervention in patients with complicated acute coronary syndrome. *Catheter Cardiovasc Interv*. (2020) 96:E666–73. doi: 10.1002/ccd.28958

35. Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: executive summary: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation*. (2022) 145:e4–e17. doi: 10.1161/CIRCULATIONAHA.121.058519

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Risk factors and clinical consequences of side branch occlusion in left anterior descending bifurcation percutaneous coronary intervention: a validation study of the V-RESOLVE score

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Background/purpose: Side branch occlusion (SBO) remains a prevalent and clinically significant complication during percutaneous coronary intervention (PCI) for bifurcation lesions, particularly those involving the left anterior descending (LAD) artery. This retrospective study aimed to assess the incidence, identify independent predictors, and evaluate the clinical consequences of SBO in the context of LAD bifurcation PCI.

Methods: We conducted a retrospective analysis of 553 patients who underwent PCI targeting LAD bifurcation lesions between 2018 and 2023. Comprehensive data encompassing clinical characteristics, angiographic findings, and procedural details were collected. The primary outcome was the occurrence of SBO, defined as a reduction in side branch TIMI flow following stent implantation. Multivariate logistic regression was applied to determine independent risk factors.

Results: SBO occurred in 41 cases (7.4%). Multivariate analysis identified true bifurcation lesions (OR 1.221, $P < 0.001$), an increased main vessel to side branch (MV/SB) diameter ratio (OR 1.431, $P < 0.001$), and higher Visual estimation-based Risk prEdiction of Side branch OccLusion in coronary bifurcation interVEntion (V-RESOLVE) scores (OR 3.736, $P = 0.001$) as significant independent predictors. Patients with SBO showed reduced procedural success rates (82.9% vs. 94.7%, $P = 0.007$), a higher incidence of periprocedural myocardial infarction (14.6% vs. 3.5%, $P = 0.003$), and increased rates of in-hospital major adverse cardiovascular events (MACE) (17.1% vs. 5.3%, $P = 0.007$).

Conclusions: SBO is a clinically impactful yet partially preventable event in LAD bifurcation PCI. Key contributors include anatomical complexity, suboptimal protection strategies, and underutilization of intracoronary imaging. The V-RESOLVE score proved to be a robust predictor and may serve as a valuable tool for pre-procedural risk stratification, facilitating more tailored and effective intervention strategies.

KEYWORDS

left anterior descending artery, percutaneous coronary intervention, side branch occlusion, V-RESOLVE score, coronary bifurcation lesions

Introduction

Coronary bifurcation sites are particularly prone to atherosclerotic plaque accumulation due to disturbed hemodynamics and turbulent shear forces, which elevate oscillatory shear stress in these regions. Consequently, bifurcation lesions are commonly identified during coronary angiography (CAG) (1). The intricate morphology and distinctive anatomical structure of bifurcation coronary lesions (BCL) present considerable technical difficulties during percutaneous coronary intervention (PCI), resulting in higher procedural risk and complication rates. As such, BCLs are recognized as one of the most challenging subsets in interventional cardiology, accounting for approximately 15%–20% of all coronary interventions (2).

Side branch occlusion (SBO) is one of the most concerning complications encountered during bifurcation PCI (3). Following stent deployment in the main vessel (MV), the reported incidence of SBO ranges between 7.4% and 16.7% (4, 5). This event can result in perioperative myocardial infarction (MI) and stent thrombosis, significantly elevating the risk of major adverse cardiovascular events (MACE) and adversely affecting patient outcomes (6, 7). Multiple procedural and anatomical factors contribute to SBO during bifurcation PCI, including side branch (SB) diameter stenosis greater than 50%, extended lesion length within the SB, MV proximal stenosis over 50%, thrombus displacement at the SB ostium, vasospasm, dissection, an elevated MV/SB diameter ratio, and a wide carina angle (5, 8).

Among bifurcation lesions, those involving the left anterior descending artery (LAD) are the most prevalent, typically affecting diagonal and septal branches. Compared with lesions in the left circumflex (LCX) or right coronary artery (RCA), interventions in the LAD region are more likely to compromise SB flow (9). Prior studies have reported severe outcomes associated with SB occlusion in LAD lesions, including ventricular septal rupture and cardiac rupture (10). However, dedicated research focusing specifically on LAD bifurcation lesions remains limited. This single-center cohort study aims to investigate the incidence and predictors of SBO during PCI in patients with LAD bifurcation lesions.

2 Materials and methods

2.1 Study participants

This retrospective study enrolled patients who were admitted to the Department of Cardiology at Xiangtan Central Hospital between October 2018 and June 2023 for elective or urgent PCI targeting bifurcation lesions in the LAD artery, including presentations such as stable angina, unstable angina, non–ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI). Prior to undergoing PCI, all participants provided written informed consent. The research protocol was approved by the Ethics Committee of Xiangtan Central Hospital and complied with the principles outlined in the Declaration of Helsinki (2013 revision). Ethical approval number: X201807352-1. Inclusion criteria were as follows: patients who underwent PCI for LAD bifurcation lesions with CAG confirming ≥70% diameter stenosis and a vessel diameter ≥2.5 mm; in addition, the implanted stent in the MV had to extend across the ostium of the SB. CBL were defined as atherosclerotic narrowing involving or located adjacent to the origin of a functionally significant SB. Exclusion criteria included: left main coronary bifurcation lesions; chronic total occlusion (CTO) of the LAD; isolated septal branch lesions; bifurcation lesions in the LCX-OM (obtuse marginal), RCA-RV (right ventricular), or PDA-PL (posterior descending artery- posterolateral branch) regions; procedures where SB stenting was performed electively before MV stenting; SB with pre-stenting TIMI (thrombolysis in myocardial infarction) flow grade ≤2; and patients with a known allergy to contrast media (Figure 1).

2.2 Data collection

Baseline demographic data, comorbid conditions, and laboratory parameters were systematically documented in a dedicated research database. The choice of vascular access for PCI (either radial or femoral), procedural strategy, device selection, and application of intracoronary imaging were left to the discretion of the interventional cardiologist, guided by current clinical practice guidelines and expert recommendations (11). All main vessel stents implanted were second-generation drug-eluting stents (DES), including everolimus-eluting and zotarolimus-eluting stents. Bare metal stents were not used in this cohort. Provisional stenting was the primary strategy utilized in this cohort, with SB stenting performed only if there was significant compromise following MV stenting. All participants received a loading dose of clopidogrel (300 mg) and aspirin (300 mg) within 24 h prior to the intervention. For P2Y12 inhibitor therapy, the majority of patients received clopidogrel (300 mg loading dose followed by 75 mg/day maintenance), while ticagrelor (180 mg loading dose followed by 90 mg twice daily maintenance) was administered to some acute coronary syndrome patients at the discretion of the treating physician. Prasugrel was not used in this cohort. During the procedure, unfractionated heparin was administered to maintain an activated clotting time within the therapeutic range of 250–300 s. Post-PCI, patients were prescribed dual antiplatelet therapy for at least 12 months, consisting of clopidogrel (75 mg once daily) or ticagrelor (90 mg twice daily) in combination with lifelong aspirin (100 mg/day).

2.3 Angiographic analysis

CAG was independently reviewed by two experienced investigators selected from a larger pool of qualified analysts. Offline assessment of the baseline angiographic images, obtained prior to PCI, was conducted using the QAngio software system (version 2.1.9, Medis, Leiden, the Netherlands). Quantitative coronary angiography (QCA) of both the MV and SB was performed according to standardized protocols previously reported in the literature (12).

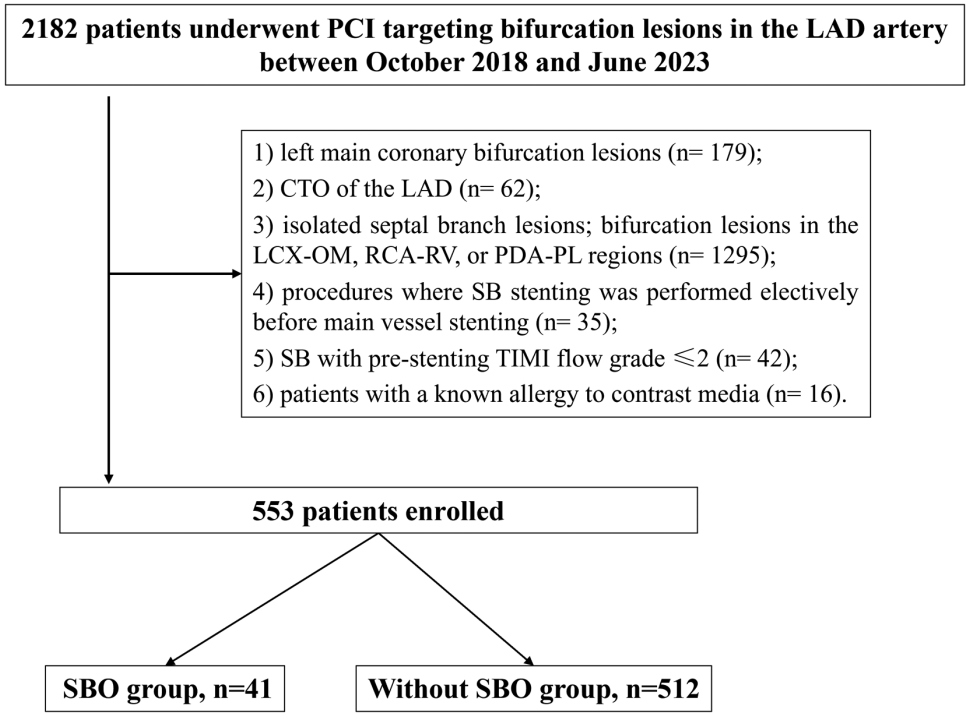

FIGURE 1
Study flow. PCI, percutaneous coronary intervention; LAD, left anterior descending artery; CTO, chronic total occlusion; LCX, left circumflex; RCA, right coronary artery; SBO, side branch occlusion.

The variables collected in this study encompassed four major categories: (1) Angiographic and procedural characteristics of the target bifurcation lesion, including the lesion's location within the main vessel lesion (ML), Medina classification, identification of true bifurcation lesions, stenosis severity at the bifurcation core, baseline bifurcation angle prior to PCI, and the total length of implanted stents. (2) ML–specific angiographic and procedural parameters, such as reference vessel diameter (RVD), degree of stenosis before the procedure, presence of moderate-to-severe calcification or angulation, evidence of thrombus, pre-PCI TIMI flow grade, plaque irregularity, dissection following pre-dilation, lesion preparation strategy (e.g., semi-compliant or non-compliant balloon use, with no systematic use of scoring balloons, cutting balloons, or intravascular lithotripsy recorded), post-dilation TIMI flow grade, and residual stenosis after pre-dilation. (3) SB–related angiographic and procedural characteristics, including reference diameter, pre-procedural stenosis severity, presence of moderate-to-severe calcification or angulation, thrombus involvement, TIMI flow grade before PCI, plaque irregularity, whether balloon pre-dilation was performed, use of the jailed wire technique, and residual stenosis after pre-dilation. (4) Primary outcome, defined as the occurrence of SBO following MV stent implantation.

2.4 Side branch occlusion management

In cases of SBO without a jailed wire in place, the side branch was first rewired, followed by balloon dilatation using semi-compliant or non-compliant balloons to restore flow. In cases with a jailed wire in place, the jailed wire was removed after the side branch was then rewired prior to balloon dilatation. If flow could not be adequately restored despite these measures, bailout side branch stenting was performed as a final strategy.

2.5 Definitions

Bifurcation classification: Among the various classification systems available for CBL, the Medina classification remains the most commonly adopted due to its simplicity, consistency, and ease of clinical application (13). A true bifurcation lesion was defined as one that met any of the following Medina criteria: 1,1,1; 1,0,1; or 0,1,1. MV plaque location: When atherosclerotic plaque was confined to the side of the MV opposite the SB ostium, it was classified as plaque opposite to the SB. If the plaque was situated on the same side as the SB ostium or simultaneously present on both sides, it was categorized as plaque on the SB side. Assessment of coronary artery calcification: The extent of calcification was evaluated based on standardized criteria previously established in the literature (14). Bifurcation angulation: The angle at the bifurcation site was categorized as follows: mild (<45°), moderate (>45° and <90°), or severe (>90°), based on the measured angle between the MV and SB. Coronary blood flow evaluation: Coronary perfusion was assessed using the TIMI flow grading system, in accordance with the definitions outlined by Gibson et al. (15). Coronary

dissection was classified according to the criteria established by the National Heart, Lung, and Blood Institute (NHLBI) (16). SB pre-dilation referred to the use of balloon angioplasty in the SB prior to the implantation of the MV stent. Jailed wire technique was defined as the placement of a guidewire in the SB during MV stenting to safeguard patency at the SB ostium (2). The bifurcation core (carina region) was defined as the anatomical zone located within 5 mm proximal to the carina point, where the distal MV and SB intersect; this region was evaluated visually. Diameter stenosis (%): calculated as [RVD−minimal lumen diameter(MLD)]/RVD, representing the most severe luminal narrowing within the analyzed segment. MV/SB RVD ratio: calculated as (proximal MV reference diameter + distal MV reference diameter)/(2× SB reference diameter). Bifurcation angle (°) was defined as the angle formed between the central axis of the distal MV and that of the SB. RVD was visually estimated based on the dimensions of the proximal and distal artery segments not affected by atherosclerotic plaque, representing the presumed normal vessel caliber. SBO was defined as a complete or significant reduction in SB blood flow—either temporary or persistent—following MV stent implantation, characterized by a decline in TIMI flow grade (17). A SB was considered significant if its RVD, as assessed by QCA, was ≥1.5 mm. The Visual estimation-based Risk prEdiction of Side branch OccLusion in coronary bifurcation interVEntion (V-RESOLVE) score for each patient was calculated in accordance with the methodology and criteria established in prior studies (5). Derived from the Risk prEdiction of Side branch OccLusion in coronary bifurcation intervention (RESOLVE) study, the V-RESOLVE score is a simplified angiographic-based scoring system incorporating six bifurcation lesion characteristics to predict the risk of SOB during PCI. This scoring system was originally designed to estimate the likelihood of SBO in BCL. Technical success was defined by achieving TIMI grade 3 flow and a residual stenosis of less than 30% in both the MV and SB when SB stenting was performed. In cases where no SB stent was attempted, technical success was defined as TIMI grade 3 flow in the MV with residual stenosis <30%, and in the SB either (1) TIMI 3 flow with residual stenosis less than or equal to its baseline severity, (2) residual stenosis <50%, or (3) physiologically normal flow parameters. Procedural success was defined as the attainment of technical success without the occurrence of in-hospital MACE.

2.6 In-hospital major adverse cardiovascular events

In-hospital MACE included any of the following events occurring before discharge: cardiac death, MI, acute stent thrombosis, recurrence of symptoms requiring urgent repeat target-vessel revascularization (TVR) via PCI or coronary artery bypass grafting (CABG), and cardiac tamponade necessitating either pericardiocentesis or surgical intervention. All clinical endpoints and adverse outcomes were defined based on criteria provided by the Academic Research Consortium (18).

2.7 Statistical analysis

Statistical analyses were conducted using SPSS software version 26.0 (IBM Corp., Armonk, NY, USA). Categorical variables were summarized as frequencies and percentages, and intergroup comparisons were assessed using either the chi-square test or Fisher's exact test, depending on data distribution and sample size. Continuous variables were reported as mean ± standard deviation (SD) for normally distributed data, and as median with interquartile range (IQR) for data not following a normal distribution. For comparisons involving continuous variables, the independent samples *t*-test was applied when the assumption of normality was met; otherwise, the Mann–Whitney *U*-test was employed. To identify independent predictors of SBO, multivariate logistic regression analysis was performed. Variables included in the multivariate model were those demonstrating statistical significance in univariate analysis or deemed clinically important based on prior literature. A *P*-value less than 0.05 was considered to indicate statistical significance.

3 Results

3.1 Baseline clinical characteristics

A total of 2,182 patients were initially screened, of whom 553 met the inclusion criteria and were included in the final analysis (Figure 1). Among these, 41 cases (7.4%) experienced SBO. As presented in Table 1, baseline demographic characteristics and comorbid conditions were comparable between the SBO and without-SBO groups. The mean age did not differ significantly between the groups (57.3 ± 10.6 vs. 58.1 ± 11.6 years, $P = 0.674$), and the majority of patients in both cohorts were male (95.1% vs. 86.1%, $P = 0.162$). No statistically significant differences were observed in other clinical parameters, including body mass index, presence of diabetes mellitus, hypertension, dyslipidemia, smoking history, previous MI, stroke, peripheral artery disease, or left ventricular ejection fraction(LVEF) (all $P > 0.05$). Similarly, the distribution of clinical presentations—such as stable angina, unstable angina, STEMI, and NSTEMI—did not show a significant difference between the groups ($P = 0.469$).

3.2 Lesion and procedural characteristics

As shown in Table 2, the SBO group demonstrated significantly greater lesion complexity and procedural difficulty. True bifurcation lesions were markedly more prevalent among patients who developed SBO (68.3% vs. 35.5%, $P < 0.001$), with a higher incidence of Medina 1,1,1 configurations (53.7% vs. 25.4%, $P = 0.004$). Baseline angiographic assessments of both the MV and SB revealed notable disparities between the groups, particularly in terms of calcification severity, bifurcation geometry, and degree of ostial

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TABLE 1 Baseline clinical characteristics.

Variables	All (n = 553)	SBO group (n = 41)	Without SBO group (n = 512)	P-value
Age, years	58.1 ± 11.5	57.3 ± 10.6	58.1 ± 11.6	0.674
Male sex, n (%)	480 (86.8)	39 (95.1)	441 (86.1)	0.162
BMI, kg/m^2	24.6 ± 3.5	23.6 ± 2.9	24.6 ± 3.6	0.070
Diabetes mellitus, n (%)	127 (23.0)	13 (31.7)	114 (22.3)	0.234
Hypertension, n (%)	312 (56.4)	27 (65.9)	285 (55.7)	0.270
Dyslipidemia, n (%)	161 (29.1)	15 (36.6)	146 (28.5)	0.359
MI in 1 month, n (%)	100 (18.1)	8 (19.5)	92 (18.0)	0.971
Previous MI (>1 month), n (%)	125 (22.6)	7 (17.1)	118 (23.0)	0.492
Previous PCI, n (%)	152 (27.5)	9 (22.0)	143 (27.9)	0.520
Previous stroke, n (%)	70 (12.7)	4 (9.8)	66 (12.9)	0.736
Current smoking, n (%)	251 (45.4)	21 (51.2)	230 (44.9)	0.537
Previous peripheral vascular disease, n (%)	77 (13.9)	5 (12.2)	72 (14.1)	0.922
CAD presentation				0.469
Stable angina, n (%)	178 (32.2)	10 (24.4)	168 (32.8)	
Unstable angina, n (%)	216 (39.1)	15 (36.6)	201 (39.3)	
STEMI, n (%)	70 (12.7)	7 (17.1)	63 (12.3)	
NSTEMI, n (%)	89 (16.1)	9 (22.0)	80 (15.6)	
LVEF, %	59.8 ± 8.8	58.4 ± 5.7	60.0 ± 9.0	0.280

Continuous variables were expressed as mean ± SD. Categorical variables were expressed as number (percentage).
SBO, side branch occlusion; MI, myocardial infarction; PCI, percutaneous coronary intervention; NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST segment elevation myocardial infarction; LVEF, left ventricular ejection fraction.

narrowing (Table 2). Within the MV, patients in the SBO group exhibited a higher frequency of moderate-to-severe calcification (41.5% vs. 29.5%, $P = 0.034$), thrombus-laden lesions (9.8% vs. 4.7%, $P = 0.029$), and irregular plaque morphology (14.6% vs. 6.1%, $P = 0.028$). Atherosclerotic plaque was significantly more likely to be situated on the same side as the SB ostium in these patients (90.2% vs. 35.2%, $P < 0.001$). Additionally, greater stenosis was observed in the bifurcation core (median 51.7% vs. 35.5%, $P = 0.027$), alongside narrower bifurcation angles (57.1° vs. 62.8°, $P = 0.015$), and elevated MV/SB reference diameter ratios (1.72 vs. 1.35, $P = 0.041$). In terms of SB characteristics, patients with SBO had smaller reference diameters (2.28 mm vs. 2.36 mm, $P = 0.018$) and more severe ostial stenosis (43.4% vs. 15.2%, $P = 0.032$). However, there were no significant group differences in SB calcification, angulation, thrombus presence, or pre-procedural TIMI flow grade (all $P > 0.05$). Procedural data further underscored the technical challenges associated with SBO. Dissection prior to MV stent implantation was more frequent in the SBO group (7.3% vs. 1.2%, $P = 0.023$). Notably, balloon pre-dilation of the SB was performed significantly less often in this group (4.9% vs. 25.4%, $P = 0.005$), and use of the jailed wire technique was considerably lower (14.6% vs. 43.0%, $P < 0.001$). Furthermore, patients who developed SBO had significantly higher V-RESOLVE scores (median 20.7 vs. 10.1, $P < 0.001$), and were substantially less likely to undergo pre-stenting intravascular imaging with intravascular ultrasound (IVUS) or optical coherence tomography (OCT) (2.4% vs. 33.2%, $P < 0.001$). Among the 41 cases defined as SBO, 39 patients (95.1%) successfully achieved TIMI grade 3 flow following side branch balloon dilatation. Bailout side branch stenting was required in 4 cases (9.8%) due to persistent flow compromise despite balloon dilatation, and 2 patients (4.9%) did not achieve full restoration of TIMI 3 flow even after stenting or balloon dilatation.

3.3 In-hospital clinical outcomes

As detailed in Table 3 and Figure 2, the occurrence of SBO was significantly associated with a reduced rate of procedural success (82.9% vs. 94.7%, $P = 0.007$) and a higher incidence of in-hospital MACE (17.1% vs. 5.3%, $P = 0.007$). The increased MACE rate in the SBO group was primarily driven by a significantly elevated incidence of periprocedural MI (14.6% vs. 3.5%, $P = 0.003$). Other complications, including cardiac tamponade, acute stent thrombosis, and TVR, were observed infrequently and did not differ significantly between the two groups.

3.4 Predictors of side branch occlusion

Univariate logistic regression analysis (Table 4) identified several factors significantly associated with the occurrence of SBO, including the presence of a true bifurcation lesion ($P < 0.001$), a higher MV/SB diameter ratio ($P < 0.001$), absence of jailed wire technique ($P = 0.037$), lack of SB pre-dilation ($P = 0.022$), and an elevated V-RESOLVE score ($P = 0.001$). Subsequent multivariate logistic regression analysis confirmed that three variables remained independent predictors of SBO: true bifurcation lesion [odds ratio [OR] 1.221, 95% confidence interval [CI] 1.052–1.522, $P < 0.001$], MV/SB reference diameter ratio (OR 1.431, 95% CI 1.333–2.727, $P < 0.001$), and V-RESOLVE score (OR 3.736, 95% CI 1.227–8.665, $P = 0.001$). These results emphasize the critical role of anatomical complexity and the importance of strategic procedural planning in reducing the risk of SBO during bifurcation PCI.

TABLE 2 Lesion and procedural characteristics.

Variables	All (*n* = 553)	SBO group (*n* = 41)	Without SBO group (*n* = 512)	*P*-value
Medina classification, *n* (%)				0.004
1,1,1	152 (27.5)	22 (53.7)	130 (25.4)	
1,1,0	175 (31.6)	7 (17.1)	168 (32.8)	
1,0,1	19 (3.4)	2 (4.9)	17 (3.3)	
0,1,1	39 (7.1)	4 (9.8)	35 (6.8)	
1,0,0	63 (11.4)	3 (7.3)	60 (11.7)	
0,1,0	91 (16.5)	2 (4.9)	89 (17.4)	
0,0,1	14 (2.5)	1 (2.4)	13 (2.5)	
True bifurcation lesion, *n* (%)	210 (40.0)	28 (68.3)	182 (35.5)	<0.001
Pre-procedural angiographic characteristics of MV				
RVD, mm	3.50 (3.36, 3.63)	3.50 (3.35, 3.67)	3.50 (3.36, 3.63)	0.628
Moderate to severe calcification, *n* (%)	168 (30.4)	17 (41.5)	151 (29.5)	0.034
Moderate to severe angulation, *n* (%)	145 (26.2)	13 (31.7)	132 (25.8)	0.336
Thrombus containing, *n* (%)	28 (5.1)	4 (9.8)	24 (4.7)	0.029
Pre-procedural TIMI flow grade, *n* (%)				0.984
TIMI 1 grade	24 (4.3)	2 (4.9)	22 (4.3)	
TIMI 2 grade	54 (9.8)	4 (9.8)	50 (9.8)	
TIMI 3 grade	475 (85.9)	35 (85.4)	440 (85.9)	
Irregular plaque, *n* (%)	37 (6.7)	6 (14.6)	31 (6.1)	0.028
Plaque location of MV, *n* (%)				<0.001
Opposite side of SB	336 (60.8)	4 (9.8)	332 (64.8)	
Same side of SB	217 (39.2)	37 (90.2)	180 (35.2)	
Stenosis of the diameter of the bifurcation core, (%)	36.30 (28.80–43.80)	51.70 (45.80–60.30)	35.50 (28.30–42.50)	0.027
Bifurcation angle,°	62.60 (53.90–71.10)	57.10 (45.00–66.80)	62.80 (54.30–71.80)	0.015
MV/SB reference vessel diameter ratio	1.37 (1.22–1.50)	1.72 (1.51–1.82)	1.35 (1.20–1.48)	0.041
Pre-procedural angiographic characteristics of SB				
RVD, mm	2.34 (2.17, 2.53)	2.28 (2.15, 2.35)	2.36 (2.17, 2.55)	0.018
Stenosis of the diameter of ostial SB, %	16.20 [7.60, 24.90]	43.40 [34.70, 52.60]	15.15 [7.10, 22.70]	0.032
Moderate to severe calcification, *n* (%)	1 (0.2)	0 (0.0)	1 (0.2)	0.619
Moderate to severe angulation, *n* (%)	26 (4.7)	2 (4.9)	24 (4.7)	0.545
Thrombus containing, *n* (%)	1 (0.2)	0 (0.0)	1 (0.2)	0.884
Pre-procedural TIMI flow grade, *n* (%)				0.236
TIMI 1 grade	0 (0.0)	0 (0.0)	0 (0.0)	
TIMI 2 grade	19 (3.4)	2 (4.9)	17 (3.3)	
TIMI 3 grade	534 (96.6)	39 (95.1)	495 (96.7)	
Irregular plaque, *n* (%)	10 (1.8)	1 (2.4)	9 (1.8)	0.764
Procedural characteristics				
MV				
Dissection before MV stenting, *n* (%)	9 (1.6)	3 (7.3)	6 (1.2)	0.023
TIMI flow grade after MV stenting, *n* (%)				0.268
TIMI 1 grade	0 (0.0)	0 (0.0)	0 (0.0)	
TIMI 2 grade	12 (2.2)	1 (2.4)	11 (2.1)	
TIMI 3 grade	541 (97.8)	40 (97.6)	501 (97.9)	
SB				
SB pre-dilation, *n* (%)	132 (23.9)	2 (4.9)	130 (25.4)	0.005
Jailed wire in SB, *n* (%)	226 (40.9)	6 (14.6)	220 (43.0)	<0.001
V-RESOLVE score	10.30 [9.20, 11.30]	20.70 [18.20, 21.70]	10.10 [9.10, 11.10]	<0.001
Pretreatment IVUS/OCT, *n* (%)	171 (30.9)	1 (2.4)	170 (33.2)	<0.001

Continuous variables were expressed as mean ± SD, or median (interquartile range). Categorical variables were expressed as number (percentage).
SBO, side branch occlusion; RVD, reference vessel diameter; TIMI, thrombolysis in myocardial infarction; MV, main vessel; SB, side branch; OCT, optical coherence tomography; IVUS, intravascular ultrasound.

4 Discussion

In this retrospective cohort study evaluating PCI for LAD artery bifurcation lesions, SBO was observed in 7.4% of cases. The results indicate that both anatomical and procedural variables play a crucial role in the development of SBO. Specifically, the presence of true bifurcation lesions, elevated MV/SB diameter ratios, and atherosclerotic plaques located on

TABLE 3 Clinical outcomes and SBO-related in-hospital outcomes.

Variables	All (n = 553)	SBO group (n = 41)	Without SBO group (n = 512)	P-value
Procedural success, n (%)	519 (93.9%)	34 (82.9%)	485 (94.7%)	0.007
In-hospital MACE, n (%)	34 (6.1%)	7 (17.1%)	27 (5.3%)	0.007
Cardiac death, n (%)	0 (0)	0 (0)	0 (0)	-
MI, n (%)	24 (4.3%)	6 (14.6%)	18 (3.5%)	0.003
TVR, n (%)	11 (2.0%)	1 (2.4%)	10 (2.0%)	1.000
Tamponade, n (%)	1 (0.2%)	1 (2.4%)	0 (0.0%)	0.103
Acute stent thrombosis, n (%)	13 (2.4%)	1 (2.4%)	12 (2.3%)	1.000

Categorical variables were expressed as number (percentage).
SBO, side branch occlusion; MACE, major adverse cardiovascular event; TVR, target-vessel revascularization; MI, myocardial infarction.

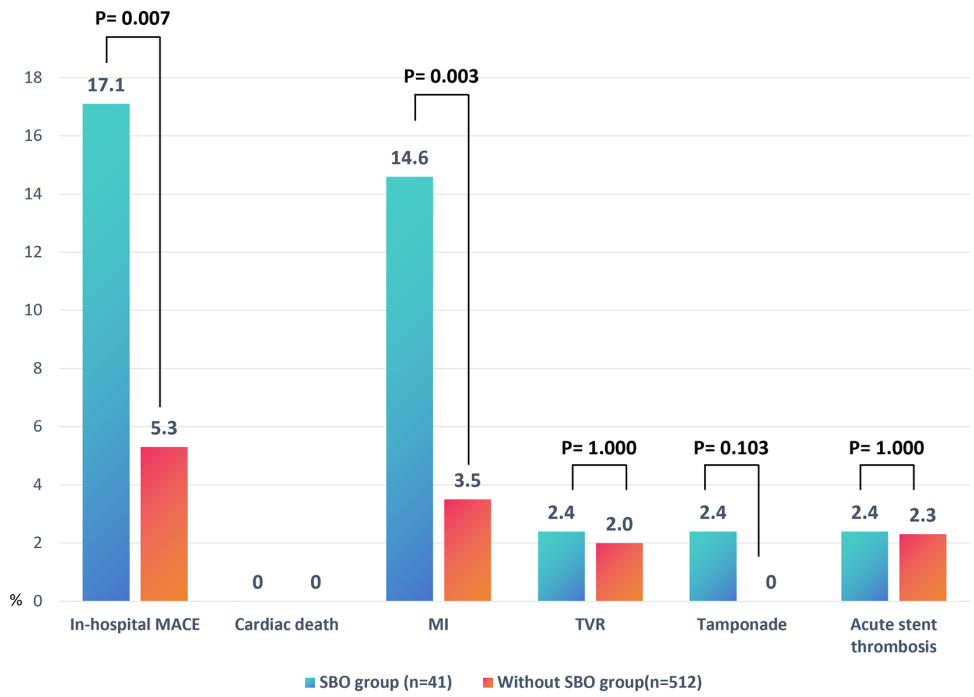

FIGURE 2
Comparison of in-hospital outcomes between patients with and without SBO. Bar chart illustrates the incidence rates (%) of MACE components, including cardiac death, MI, TVR, cardiac tamponade, and acute stent thrombosis, in the SBO group (n = 41) vs. the without-SBO group (n = 512). Significant differences were observed in the rates of overall in-hospital MACE (P = 0.007) and MI (P = 0.003). Data are presented as percentages. P-values were derived from chi-square or Fisher's exact tests as appropriate. SOB, side branch occlusion; MACE, major adverse cardiovascular events; MI, myocardial infarction; TVR, target vessel revascularization.

the same side as the SB ostium were significantly associated with increased SBO risk—highlighting the influence of lesion geometry on procedural outcomes. Additionally, insufficient SB protection strategies, including limited application of balloon pre-dilation and the jailed wire technique, as well as underuse of intravascular imaging modalities, emerged as modifiable technical contributors. Of particular note, the V-RESOLVE score demonstrated strong predictive capability for SBO, reinforcing its potential value as a pre-procedural risk assessment tool. SBO was also linked to a substantially higher incidence of in-hospital MACE, predominantly driven by periprocedural MI. These findings underscore the necessity for comprehensive anatomical evaluation and meticulous procedural planning to mitigate the risk of SBO and improve clinical outcomes.

4.1 Prevalence and anatomical determinants of side branch occlusion

In this single-center cohort study evaluating PCI for LAD artery bifurcation lesions, the incidence of SBO was 7.4%, consistent with previous studies such as the V-RESOLVE trial (7.4%) (5) and the COBIS II registry (8.4%) (8). These findings reinforce the reproducibility and clinical relevance of SBO as a

TABLE 4 Univariable and multivariable logistic analyses to predict side branch occlusion.

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Medina classification	1.302	0.640–3.179	0.455			
True bifurcation lesion	1.125	1.082–1.289	<0.001	1.221	1.052–1.522	<0.001
Moderate to severe calcification in pre-procedural of MV	1.233	0.737–3.824	0.327			
Thrombus containing in pre-procedural of MV	1.234	0.737–2.837	0.843			
Irregular plaque in pre-procedural of MV	1.622	0.737–2.827	0.528			
Plaque location of MV	1.624	0.729–4.521	0.178			
Stenosis of the diameter of the bifurcation core	1.410	0.736–1.730	0.631			
Bifurcation angle	1.672	0.836–3.626	0.073			
MV/SB reference vessel diameter ratio	1.626	1.466–2.771	<0.001	1.431	1.333–2.727	<0.001
RVD of SB	1.138	0.720–2.001	0.534			
Stenosis of the diameter of ostial SB	1.355	0.941–2.011	0.146			
Dissection before MV stenting	1.037	0.551–4.221	0.933			
SB pre-dilation	2.153	1.142–4.152	0.022	3.441	0.204–16.829	0.346
Jailed wire in SB	1.054	1.032–1.064	0.037	1.186	0.151–11.533	0.893
V-RESOLVE score	2.323	1.640–5.737	0.001	3.736	1.227–8.665	0.001
Pretreatment IVUS/OCT	1.023	0.445–2.335	0.602			

OR, odds ratio; CI, confidence interval; MV, main vessel; SB, side branch; OCT, optical coherence tomography; IVUS, intravascular ultrasound; RVD, reference vessel diameter.

common complication in bifurcation interventions. Although the PROGRESS-BIFURCATION registry reported a higher SBO incidence of 13%, the variation likely reflects differences in lesion complexity and inclusion criteria, with broader anatomical patterns represented in that cohort (19).

Several anatomical characteristics were found to be significantly associated with SBO in our study. True bifurcation lesions—especially those classified as Medina 1,1,1—were notably more common among patients who experienced SBO (68.3% vs. 35.5%, $P < 0.001$). This observation is consistent with prior research suggesting that true bifurcations are more vulnerable to plaque or carina shift during stent implantation in the MV (20). Additionally, atherosclerotic plaques positioned on the same side as the SB ostium were significantly more prevalent in the SBO group (90.2% vs. 35.2%, $P < 0.001$), a finding supported by OCT study showing that layered or bulky plaques at the SB origin increase the likelihood of occlusion (21).

Geometrical considerations also played a key role. A narrower bifurcation angle was independently associated with SBO in our population (57.1° vs. 62.8°, $P = 0.015$), likely due to increased susceptibility to carina displacement during stent expansion. Although the impact of bifurcation angle on SB outcome remains a topic of debate, several investigations support the notion that narrower angles elevate the risk of carina shift and subsequent SB occlusion (22). Conversely, some studies have suggested that wider bifurcation angles may also compromise SB outcomes by reducing ostial area or shortening ostial length (23). One analysis even found that the SBO group exhibited larger bifurcation angles than non-SBO counterparts (23). Nonetheless, our results align more closely with studies that highlight mechanical carina shift—more pronounced at narrower angles—as a key mechanism of SBO development (21).

Another important predictor was the MV/SB reference diameter ratio, which was significantly higher in the SBO group (1.72 vs. 1.35, $P = 0.041$). This metric reflects the relative vessel size mismatch and has been implicated in plaque redistribution and hemodynamic compromise at the SB ostium during stent deployment, as documented in IVUS-based investigations (24). Furthermore, a higher degree of stenosis within the bifurcation core was observed in SBO cases (51.7% vs. 35.5%, $P = 0.027$), emphasizing the contribution of lesion burden at the carina to impaired SB perfusion (20). Taken together, these anatomical risk factors highlight the critical importance of thorough preprocedural angiographic assessment in bifurcation PCI. They also provide a mechanistic framework suggesting that SBO is not merely a procedural mishap, but rather a foreseeable event stemming from adverse bifurcation geometry and complex plaque distribution.

4.2 Procedural factors and operator-dependent risk contributors

Beyond anatomical complexity, procedural techniques and operator-driven decisions play a pivotal role in determining the risk of SBO during bifurcation PCI. Our findings highlight several procedural characteristics that were significantly associated with SBO and may be amenable to optimization through refined interventional strategies.

Notably, SB pre-dilation was performed far less frequently in the SBO group compared to patients without SBO (4.9% vs. 25.4%, $P = 0.005$). Pre-dilation may enhance ostial lesion compliance and facilitate favorable plaque redistribution, thereby improving SB preservation during MV stenting. This protective role has been emphasized in prior studies, particularly for lesions with high plaque burden or tight ostial narrowing (20, 24). Similarly, use of the jailed wire technique—an established and technically straightforward approach to maintain SB access—was significantly lower in the SBO cohort (14.6% vs. 43.0%, $P < 0.001$). The presence of a jailed wire enables re-access and bailout maneuvers

in cases of SB flow compromise and has been shown to lower the incidence of complete SB occlusion in high-risk bifurcation anatomy (24, 25).

Procedural complications also appeared to influence SBO risk. Dissections occurring prior to MV stent deployment were significantly more common among SBO cases (7.3% vs. 1.2%, $P = 0.023$), potentially contributing to altered flow dynamics or formation of a false lumen that impairs SB perfusion. These observations reinforce the importance of meticulous lesion preparation and conservative balloon sizing during pre-dilation and modification procedures (20, 24). A particularly striking finding was the markedly low rate of intravascular imaging use in the SBO group. Only 2.4% of these patients underwent IVUS or OCT guidance, compared to 33.2% in the without-SBO group ($P < 0.001$). Intravascular imaging provides valuable insights into lesion morphology, plaque eccentricity, and carina shift potential—factors that are critical in guiding stent deployment and minimizing SB compromise. Several studies have advocated for routine use of IVUS/OCT in complex bifurcation interventions to enhance procedural precision and outcomes (20, 24, 26). Taken together, these data suggest that SBO is not solely determined by anatomical constraints but is also significantly influenced by modifiable, operator-dependent factors. Inadequate SB preparation, failure to employ protective techniques, and underutilization of intravascular imaging are all preventable contributors. These findings support the need for greater procedural standardization and broader integration of evidence-based bifurcation techniques to reduce the incidence of SBO in contemporary practice.

4.3 Risk stratification with the V-RESOLVE score

Our study demonstrated a strong and statistically significant association between the V-RESOLVE score and the occurrence of SBO in patients undergoing PCI for LAD bifurcation lesions. Patients who experienced SBO had substantially higher V-RESOLVE scores compared to those without SBO (median 20.7 vs. 10.1, $P < 0.001$). Furthermore, multivariate logistic regression confirmed the V-RESOLVE score as an independent predictor of SBO (OR 3.736, 95% CI: 1.227–8.665, $P = 0.001$). These results support the V-RESOLVE scoring system's discriminatory power and validate its clinical applicability for peri-procedural risk stratification in real-world settings. This finding is consistent with the original V-RESOLVE study, which demonstrated that visual estimation of lesion characteristics could effectively substitute for QCA in predicting SBO, with a c-statistic of 0.76 (95% CI: 0.71–0.80)—a performance nearly equivalent to that of the QCA-based RESOLVE score (c-statistic: 0.77, 95% CI: 0.72–0.81) (5). Simulation analyses from the original study further showed acceptable inter-observer consistency (c-statistic range: 0.65–0.77), highlighting the score's robustness across different operators and institutions (5). Importantly, our analysis extends the validation of V-RESOLVE specifically to LAD bifurcation lesions—a subset characterized by higher SBO risk due to frequent involvement of critical diagonal or septal branches. While earlier studies have evaluated bifurcation PCI in general, few have focused exclusively on LAD-specific anatomy or validated risk assessment tools in this context. Our findings thus address a notable gap in the current evidence base. Given its predictive strength and practical simplicity, we advocate incorporating the V-RESOLVE score into routine pre-procedural assessments for bifurcation PCI. The score offers a rapid, visually assessed, and non-QCA-dependent tool to identify high-risk patients. This early stratification could inform the use of protective strategies—such as jailed wire or balloon techniques—or prompt the deployment of intravascular imaging to better characterize lesion morphology. When employed proactively, these measures have the potential to mitigate SBO risk and improve procedural outcomes (20).

Incorporating the V-RESOLVE score into standardized clinical workflows—potentially as part of a consensus-driven PCI decision-making pathway—could enhance both individualized treatment planning and institutional protocol consistency. While prior expert consensus documents have advocated for structured bifurcation PCI strategies, few have formally integrated validated predictive scores into these frameworks (20). Nevertheless, despite its utility, the V-RESOLVE score is subject to variability due to its reliance on visual assessment. To ensure consistency, operator training and standardized interpretation protocols are essential. Prospective, multicenter trials are warranted to further validate the prognostic impact of the V-RESOLVE score on long-term outcomes and to explore its integration within algorithmic, guideline-based approaches to bifurcation PCI.

4.4 Prognostic impact of SBO and clinical outcomes

SBO during PCI for bifurcation lesions carries significant clinical consequences and should no longer be viewed as a minor angiographic inconvenience. In our cohort of 553 patients undergoing PCI for LAD bifurcation lesions, SBO occurred in 7.4% of cases and was associated with notably lower procedural success (82.9% vs. 94.7%, $P = 0.007$), higher rates of periprocedural MI (14.6% vs. 3.5%, $P = 0.003$), and increased in-hospital MACE (17.1% vs. 5.3%, $P = 0.007$). These results highlight the immediate prognostic significance of SBO, even when the affected SB appears angiographically small or non-dominant.

Pathophysiologically, SBO impairs myocardial perfusion in the territory supplied by the occluded SB, potentially leading to ischemia, infarction, and microvascular dysfunction—particularly in cases involving functionally important branches such as diagonals or septals. Furthermore, the abrupt cessation of flow can result in endothelial damage and activate inflammatory cascades, exacerbating myocardial injury (11). Our findings align with previous research by Strepkos et al., who examined 933 bifurcation PCI cases across six centers. Their analysis demonstrated that SBO was linked to significantly lower procedural success (73.5% vs. 92.2%,

$P < 0.001$), a greater need for unplanned two-stent strategies (24.8% vs. 6.0%, $P < 0.001$), and higher rates of dissection and plaque modification interventions (19). Importantly, patients with untreated SBO exhibited increased long-term MACE and mortality, emphasizing the enduring consequences of unaddressed SB compromise (19). Similarly, Guo et al. reported that in a cohort of 245 patients with chronic total occlusion and bifurcation lesions (CTO-BFL), SBO- defined as post-recanalization TIMI flow <3—was significantly associated with periprocedural MI and composite procedural complications. Key independent predictors included the absence of SB protection, ostial stenosis of the SB, and use of dissection-reentry techniques (27). Although some literature has suggested that occlusion of small or non-dominant SBs may be clinically inconsequential, our results and those from large registries challenge this assumption. Even SBs with reference diameters ≥1.5 mm can supply critical myocardial territories—particularly in LAD bifurcations—and their occlusion may initiate a cascade of ischemic injury (27). These findings reinforce the view that SBO is a clinically meaningful complication with both procedural and prognostic implications. Furthermore, periprocedural MI itself has been shown to be independently associated with increased short- and long-term all-cause mortality in patients undergoing PCI, underscoring its prognostic importance (28). It not only reflects underlying anatomical complexity but also acts as a direct mediator of myocardial injury and adverse outcomes. As such, prevention, early detection, and effective management of SBO should be prioritized in bifurcation PCI. Further prospective, large-scale studies are needed to investigate the long-term effects of SBO, including its role in target vessel failure, progression of heart failure, and mortality. Incorporating SBO risk assessment into pre-procedural planning and post-PCI surveillance protocols may contribute to improved short- and long-term cardiovascular outcomes.

4.5 Limitations

Several limitations of this study should be acknowledged. First, this was a single-center, retrospective cohort study, which may introduce inherent selection bias and limit the generalizability of our findings. Although multivariate analyses were performed to adjust for confounding variables, residual confounders cannot be fully excluded. Second, the assessment of lesion characteristics and V-RESOLVE scoring was based on angiographic visual estimation, which, despite standardization and operator training, is subject to inter-observer variability. Third, our study focused exclusively on LAD bifurcation lesions and may not be fully extrapolatable to left main or other coronary bifurcations. Fourth, the lack of long-term follow-up data precludes definitive conclusions regarding the chronic impact of SBO on clinical outcomes such as mortality, target vessel failure, or late stent thrombosis. Finally, although intravascular imaging was underused in the SBO group, its limited overall usage prevented subgroup analysis regarding its potential protective role. Future multicenter, prospective studies with comprehensive imaging and long-term outcome data are warranted to validate and extend these findings.

5 Conclusion

In this retrospective analysis of LAD bifurcation PCI, SOB occurred in 7.4% of patients and was significantly associated with adverse procedural and in-hospital outcomes, including increased rates of periprocedural MI and MACE. True bifurcation anatomy, high MV/SB diameter ratios, carina-adjacent plaque distribution, and lack of procedural protection emerged as key contributors to SBO. The V-RESOLVE score proved to be a powerful and independent predictor of SBO, supporting its integration into pre-procedural risk stratification workflows. Collectively, these findings highlight the need for meticulous anatomical assessment, risk-based planning, and adoption of evidence-based procedural strategies to minimize SBO risk. Future prospective studies are needed to validate imaging-guided and AI-assisted approaches for personalized bifurcation intervention planning.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of Xiangtan Central Hospital (The Affiliated Hospital of Hunan University). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

XW: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Writing – original draft. MW: Writing – review & editing. HaH: Writing – review & editing. ZL: Writing – review & editing. HeH: Writing – review & editing. LW: Writing – review & editing.

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References

1. Pyle AL, Young PP. Atheromas feel the pressure: biomechanical stress and atherosclerosis. *Am J Pathol*. (2010) 177(1):4–9. doi: 10.2353/ajpath.2010.090615

2. Lefèvre T, Louvard Y, Morice MC, Loubeyre C, Piéchaud JF, Dumas P. Stenting of bifurcation lesions: a rational approach. *J Interv Cardiol*. (2001) 14(6):573–85. doi: 10.1111/j.1540-8183.2001.tb00375.x

3. Iannaccone F, Chiastra C, Karanasos A, Migliavacca F, Gijsen FJH, Segers P, et al. Impact of plaque type and side branch geometry on side branch compromise after provisional stent implantation: a simulation study. *EuroIntervention*. (2017) 13(2):e236–e45. doi: 10.4244/EIJ-D-16-00498

4. Dou K, Zhang D, Xu B, Yang Y, Yin D, Qiao S, et al. An angiographic tool for risk prediction of side branch occlusion in coronary bifurcation intervention: the RESOLVE score system (risk prEdiction of Side branch OccLusion in coronary bifurcation interVEntion). *JACC Cardiovasc Interv*. (2015) 8(1 Pt A):39–46. doi: 10.1016/j.jcin.2014.08.011

5. Dou K, Zhang D, Xu B, Yang Y, Yin D, Qiao S, et al. An angiographic tool based on visual estimation for risk prEdiction of Side branch OccLusion in coronary bifurcation interVEntion: the V-RESOLVE score system. *EuroIntervention*. (2016) 11(14):e1604–11. doi: 10.4244/EIJV11I14A311

6. Naganuma T, Latib A, Basavarajaiah S, Chieffo A, Figini F, Carlino M, et al. The long-term clinical outcome of T-stenting and small protrusion technique for coronary bifurcation lesions. *JACC Cardiovasc Interv*. (2013) 6(6):554–61. doi: 10.1016/j.jcin.2013.01.137

7. Park TK, Park YH, Song YB, Oh JH, Chun WJ, Kang GH, et al. Long-term clinical outcomes of true and non-true bifurcation lesions according to medina classification-results from the COBIS (COronary BIfurcation stent) II registry. *Circ J*. (2015) 79(9):1954–62. doi: 10.1253/circj.CJ-15-0264

8. Hahn JY, Chun WJ, Kim JH, Song YB, Oh JH, Koo BK, et al. Predictors and outcomes of side branch occlusion after main vessel stenting in coronary bifurcation lesions: results from the COBIS II registry (COronary BIfurcation stenting). *J Am Coll Cardiol*. (2013) 62(18):1654–9. doi: 10.1016/j.jacc.2013.07.041

9. Kralev S, Poerner TC, Basorth D, Lang S, Wolpert C, Haghi D, et al. Side branch occlusion after coronary stent implantation in patients presenting with ST-elevation myocardial infarction: clinical impact and angiographic predictors. *Am Heart J*. (2006) 151(1):153–7. doi: 10.1016/j.ahj.2005.01.034

10. Asakura K, Homma T, Akutsu N, Fukamachi D, Ozaki S, Ohta H, et al. Cardiac rupture due to Side branch occlusion after stent implantation—the crime of jailed stent. *Circ J*. (2020) 84(2):295. doi: 10.1253/circj.CJ-19-0510

11. Banning AP, Lassen JF, Burzotta F, Lefèvre T, Darremont O, Hildick-Smith D, et al. Percutaneous coronary intervention for obstructive bifurcation lesions: the 14th consensus document from the European bifurcation club. *EuroIntervention*. (2019) 15(1):90–8. doi: 10.4244/EIJ-D-19-00144

12. Muramatsu T, Grundeken MJ, Ishibashi Y, Nakatani S, Girasis C, Campos CM, et al. Comparison between two- and three-dimensional quantitative coronary angiography bifurcation analyses for the assessment of bifurcation lesions: a subanalysis of the TRYTON pivotal IDE coronary bifurcation trial. *Catheter Cardiovasc Interv*. (2015) 86(3):E140–9. doi: 10.1002/ccd.25925

13. Medina A, Suárez de Lezo J, Pan M. A new classification of coronary bifurcation lesions. *Rev Esp Cardiol*. (2006) 59(2):183. doi: 10.1157/13084649

14. Mintz GS, Nissen SE, Anderson WD, Bailey SR, Erbel R, Fitzgerald PJ, et al. American College of Cardiology Clinical expert consensus document on standards for acquisition, measurement and reporting of intravascular ultrasound studies (IVUS). A report of the American College of Cardiology task force on clinical expert consensus documents. *J Am Coll Cardiol*. (2001) 37(5):1478–92. doi: 10.1016/s0735-1097(01)01175-5

15. Gibson CM, Murphy SA, Rizzo MJ, Ryan KA, Marble SJ, McCabe CH, et al. Relationship between TIMI frame count and clinical outcomes after thrombolytic administration. Thrombolysis in myocardial infarction (TIMI) study group. *Circulation*. (1999) 99(15):1945–50. doi: 10.1161/01.CIR.99.15.1945

16. Goldstein JA, Casserly IP, Katsiyiannis WT, Lasala JM, Taniuchi M. Aortocoronary dissection complicating a percutaneous coronary intervention. *J Invasive Cardiol*. (2003) 15(2):89–92.

17. Mohsin M, Khan HS, Saleem M, Afzal A. Assessment of predictors of Side branch occlusion after main vessel stenting in coronary bifurcation lesions in patients undergoing percutaneous coronary intervention. *J Coll Phys Surgeons–Pakistan: JCPSP*. (2018) 28(10):744–7.

18. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. (2007) 115(17):2344–51. doi: 10.1161/CIRCULATIONAHA.106.685313

19. Strepkos D, Alexandrou M, Mutlu D, Carvalho PEP, Ser OS, Jalli S, et al. Impact of Side branch occlusion on patient outcomes after bifurcation percutaneous coronary intervention. *Catheter Cardiovasc Interv*. (2025) 105(5):1142–8. doi: 10.1002/ccd.31439

20. Li D, Dai H, Gao C, Liu H, Yang A, Guo W. Review of techniques for protecting Side branch from occlusion during provisional stenting in coronary bifurcation lesions. *Rev Cardiovasc Med*. (2023) 24(11):323. doi: 10.31083/j.rcm2411323

21. Cao Y, Mintz GS, Matsumura M, Zhang W, Lin Y, Wang X, et al. The relation between optical coherence tomography-detected layered pattern and acute Side branch occlusion after provisional stenting of coronary bifurcation lesions. *Cardiovasc Revasc Med*. (2019) 20(11):1007–13. doi: 10.1016/j.carrev.2018.12.021

22. Vassilev D, Gil R. Clinical verification of a theory for predicting side branch stenosis after main vessel stenting in coronary bifurcation lesions. *J Interv Cardiol*. (2008) 21(6):493–503. doi: 10.1111/j.1540-8183.2008.00400.x

23. Zhang D, Xu B, Yin D, Li Y, He Y, You S, et al. How bifurcation angle impacts the fate of side branch after main vessel stenting: a retrospective analysis of 1,200 consecutive bifurcation lesions in a single center. *Catheter Cardiovasc Interv*. (2015) 85(Suppl 1):706–15. doi: 10.1002/ccd.25858

24. Sakamoto N, Hoshino Y, Mizukami H, Sugimoto K, Yamaki T, Kunii H, et al. Intravascular ultrasound predictors of acute side branch occlusion in coronary artery bifurcation lesions just after single stent crossover. *Catheter Cardiovasc Interv*. (2016) 87(2):243–50. doi: 10.1002/ccd.26021

25. Yang H, Song Y, Cao J, Weng X, Zhang F, Dai Y, et al. Double kissing inflation outside the stent secures the patency of small side branch without rewiring. *BMC Cardiovasc Disord*. (2021) 21(1):232. doi: 10.1186/s12872-021-02028-z

26. Hong MK, Mintz GS, Lee CW, Park DW, Choi BR, Park KH, et al. Intravascular ultrasound predictors of angiographic restenosis after sirolimus-eluting stent implantation. *Eur Heart J*. (2006) 27(11):1305–10. doi: 10.1093/eurheartj/ehi882

27. Guo Y, Peng H, Zhao Y, Liu J. Predictors and complications of side branch occlusion after recanalization of chronic total occlusions complicated with bifurcation lesions. *Sci Rep*. (2021) 11(1):4460. doi: 10.1038/s41598-021-83458-9

28. Armillotta M, Bergamaschi L, Paolisso P, Belmonte M, Angeli F, Sansonetti A, et al. Prognostic relevance of type 4a myocardial infarction and periprocedural myocardial injury in patients with non-ST-segment-elevation myocardial infarction. *Circulation*. (2025) 151(11):760–72. doi: 10.1161/CIRCULATIONAHA.124.070729

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Impact of myocardial bridge on lesion morphology and clinical outcomes in patients undergoing IVUS-guided PCI for LAD CTO

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Introduction: Myocardial bridge (MB) is increasingly recognized for its potential role in coronary artery disease. However, its impact on lesion morphology and clinical outcomes in patients with left anterior descending (LAD) chronic total occlusion (CTO) undergoing intravascular ultrasound (IVUS)-guided percutaneous coronary intervention (PCI) remains unclear.
Methods: This single-center retrospective study analyzed 256 patients who underwent IVUS-guided PCI for LAD CTO between 2016 and 2022. Patients were divided into MB ($n = 61$) and non-MB ($n = 195$) groups based on IVUS findings. Lesion characteristics, stent strategy, and 2-year clinical outcomes were compared.
Results: MB was identified in 23.8% of patients. Compared with the non-MB group, MB patients had significantly shorter CTO length (17.71 mm vs. 21.31 mm, $P < 0.001$), less calcification (29.5% vs. 47.7%, $P = 0.018$), and more proximal lesion distribution (41.0% vs. 20.0%, $P = 0.001$). Despite these favorable anatomical features, the MB group had higher rates of major adverse cardiovascular events (MACE) (19.7% vs. 8.7%, $P = 0.033$) and clinically driven target lesion revascularization (18.0% vs. 6.7%, $P = 0.016$). MB was an independent predictor of MACE (HR = 2.173, P = 0.021).
Discussion: MB is associated with distinct morphological features and worse clinical outcomes in LAD CTO patients undergoing PCI. Its presence may require careful procedural planning and personalized revascularization strategies to reduce long-term risks.

KEYWORDS

myocardial bridge, chronic total occlusion, left anterior descending artery, percutaneous coronary intervention, intravascular ultrasound

1 Introduction

Coronary arteries conventionally traverse the epicardial surface of the heart, embedded within subepicardial connective tissue. However, in certain individuals, a segment of a coronary artery courses intramyocardially and becomes surrounded by myocardial fibers—a configuration identified as a myocardial bridge (MB), with the embedded portion referred to as a "tunneled artery" (1). The left anterior descending artery (LAD), especially its mid-to-distal segments, is most commonly involved, with MB reported in as many as 67%–98% of cases (2).

Historically regarded as a benign anatomical variant, MBs have reemerged as clinically significant due to accumulating evidence linking them to unfavorable cardiovascular outcomes. These include myocardial ischemia, acute coronary syndromes (ACS), coronary

vasospasm, arrhythmogenic events, and even sudden cardiac death (3, 4). The proposed pathophysiological mechanism involves dynamic compression of the bridged segment during systole, which may alter coronary flow dynamics and impair endothelial function in adjacent arterial regions (1). Interestingly, MBs exhibit a paradoxical role in the context of atherosclerosis: while the tunneled segment tends to be protected from plaque formation due to mechanical shielding, the arterial region proximal to the MB frequently demonstrates enhanced plaque burden and vulnerability. This is likely attributable to altered shear stress and flow turbulence (5). This duality—simultaneously protective and predisposing—has led to MBs being described as a "double-edged sword" in coronary artery disease (6).

The observed prevalence of MBs varies substantially across different diagnostic modalities. Postmortem examinations have reported prevalence rates approaching 86% (1), whereas imaging techniques such as intravascular ultrasound (IVUS) and computed tomography have identified MBs in approximately 22%–40% of individuals (7). Conversely, coronary angiography is less sensitive in detecting MBs, with detection rates often below 5% (2). Recent retrospective analyses have highlighted the potential relevance of MBs in patients presenting with chronic total occlusion (CTO) of the LAD. Preliminary data indicate that MBs may be more prevalent in LAD CTO lesions compared to non-occlusive counterparts, with implications for procedural planning and long-term outcomes after percutaneous coronary intervention (PCI) (8). Importantly, stenting within MB-involved segments has been associated with increased risks of target lesion failure (TLF), possibly due to factors such as mechanical compliance mismatch, elastic recoil, or inadequate stent deployment (8). Despite these findings, direct comparative investigations of LAD CTO lesions with and without MBs are sparse. It remains unclear whether significant anatomical or procedural differences exist between these two groups, or how the presence of MBs influences intravascular imaging interpretation, stent strategy, and clinical outcomes following PCI. This study, therefore, seeks to conduct a comparative evaluation of LAD CTO lesions with and without MB, emphasizing distinctions in lesion architecture, stent deployment characteristics, and post-intervention outcomes. Through this analysis, we aim to enhance procedural planning and advance understanding of the complex interaction between MBs and severe coronary artery occlusions.

2 Materials and methods

2.1 Study participants

This was a single-center, retrospective observational study conducted at the Department of Cardiology, Xiangtan Central Hospital. A total of 256 consecutive patients who underwent IVUS-guided successful PCI for CTO lesions in the LAD artery between January 2016 and August 2022 were included. For patients without documented clinical evidence of occlusion duration, the chronicity of the lesion was assessed based on angiographic features indicative of long-standing occlusion (9). To ensure adequate assessment of MB, only patients with >40 mm analyzable IVUS image length distal to the LAD ostium were included (10). Inclusion criteria: successful PCI for *de novo* LAD CTO lesions; use of IVUS during the procedure; analyzable IVUS pullbacks with adequate segment length for MB detection. Patients were excluded if they had in-stent restenosis-related CTO, a history of heart transplantation, or significant comorbidities that could confound the analysis or affect outcomes. These included severe hepatic or renal dysfunction, hyperthyroidism, active malignancy with extensive metastatic spread, and bleeding disorders (Figure 1). All patients presented with symptoms consistent with myocardial ischemia, predominantly effort-induced angina pectoris or angina-equivalent symptoms such as dyspnea on exertion. Objective evidence of ischemia was evaluated prior to PCI decision-making based on a combination of clinical presentation, resting or stress electrocardiography, and echocardiographic assessment of regional wall motion abnormalities when clinically indicated. In addition, coronary angiography demonstrated LAD chronic total occlusion with impaired distal perfusion, supporting the diagnosis of significant myocardial ischemia. Demographic characteristics, clinical comorbidities, laboratory parameters, angiographic and IVUS imaging data, procedural details, and long-term clinical outcomes were retrospectively collected from the hospital's electronic medical records and imaging archives. The study complied with the ethical principles outlined in the Declaration of Helsinki (2013 revision) and was approved by the Ethics Committee of Xiangtan Central Hospital (Approval No. X201853). Written informed consent was obtained from all participants. For certain cases where written consent was not feasible, verbal consent was documented in accordance with institutional policy.

2.2 CTO procedures

All CTO procedures were conducted by experienced interventionalists, with procedural strategies determined individually at the operator's discretion. Upon successful guidewire crossing, balloon predilation was initially performed under angiographic guidance. IVUS imaging was then utilized to verify the intraluminal position of the guidewire distally, evaluate the lesion architecture, and delineate optimal stent landing zones. Lesion preparation was undertaken when indicated. Stents were deployed in reference vessel segments demonstrating a plaque burden of less than 50%, as assessed by IVUS. In cases where an MB was located distal to the lesion, stent placement into the MB segment was generally avoided. Exceptions were made in the presence of significant dissection involving the MB or when critical disease existed just proximal to the MB, necessitating extension of the stent into the bridged segment. Technical success was defined by restoration of antegrade TIMI grade 3 flow and achieving residual diameter stenosis <30% in the treated segment. Total procedure time was recorded from the initiation of vascular access to the withdrawal of the final catheter. In this study cohort, all lesions were treated with second-generation DES implantation, and neither bioresorbable scaffolds nor drug-coated balloon strategies were utilized.

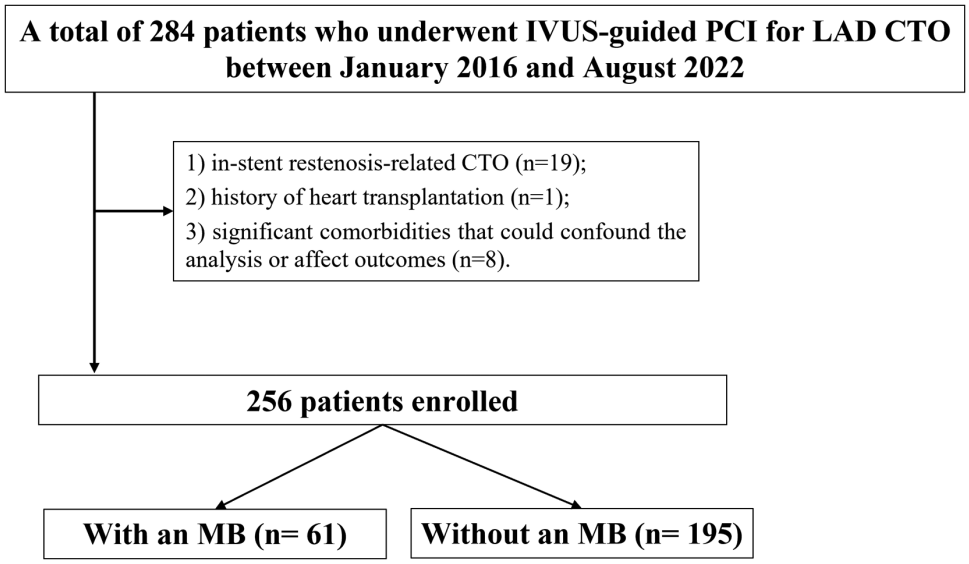

FIGURE 1
Study flowchart. MB, myocardial bridge; CTO, chronic total occlusion; LAD, left anterior descending; IVUS, intravascular ultrasound; PCI, percutaneous coronary intervention.

2.3 Periprocedural pharmacotherapy

All patients received dual antiplatelet therapy (DAPT) consisting of aspirin (100 mg/day) and clopidogrel (75 mg/day). For patients who had not been on chronic DAPT for at least 7 days prior to the procedure, a loading dose was administered 24 h before the intervention, consisting of aspirin (300 mg) and either clopidogrel (300 mg) or ticagrelor (180 mg), in accordance with current guideline recommendations. Post-procedurally, patients continued DAPT with aspirin (100 mg/ day) and clopidogrel (75 mg/day) for 12 months. Additional pharmacotherapy—including statins, beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), and nitrates—was prescribed as clinically indicated.

2.4 Angiographic analysis strategy and assessment

Coronary angiographic evaluation was conducted by an experienced interpreter (H.H.) who was blinded to all clinical and IVUS data. Quantitative analysis was performed using the QAngioXA software (Medis Medical Imaging Systems, Leiden, the Netherlands). The length of the CTO lesion was determined based on contrast opacification of the distal vessel using either antegrade or retrograde approaches, including simultaneous bilateral injections when appropriate. Lesion complexity was assessed utilizing the J-CTO score, as defined by the Multicenter CTO Registry of Japan (11). The extent of collateral circulation was graded according to the Rentrop classification system (12).

2.5 IVUS imaging and analysis

Following successful guidewire advancement, all CTO lesions underwent balloon predilation prior to prestenting IVUS imaging. To reduce the risk of vasospasm, an intracoronary dose of 100–200 μg nitroglycerin was routinely administered before image acquisition. Two IVUS catheters were used during the study period: the 40 MHz Atlantis SR catheter (Boston Scientific, USA) from 2016 to 2019, and the OptiCross catheter (Boston Scientific, USA) from 2019 to 2022. Both devices were compatible with the iLab IVUS system and provided similar image quality and acquisition characteristics. The IVUS catheter was positioned distally beyond the lesion and withdrawn proximally toward the aorta under fluoroscopy at a consistent speed of 0.5 mm/s or 1.0 mm/s. Imaging sequences were digitally stored. Offline interpretation was performed using QIvus® software (Medis, Leiden, the Netherlands), a dedicated IVUS analysis platform. Quantitative and qualitative measurements were independently performed by two trained reviewers blinded to clinical data. In the event of disagreement, a third senior analyst adjudicated the final value. Identical analysis protocols and scoring criteria were employed for both catheter systems to maintain methodological uniformity.

All analyses were conducted according to contemporary recommendations for IVUS imaging acquisition, interpretation, and reporting, as outlined in expert consensus guidelines (13) on intravascular imaging and physiologic assessment. An MB was identified as a segment of epicardial coronary artery showing systolic compression surrounded by echolucent muscular tissue on IVUS (14) (Figure 2). Within this segment, the following parameters were evaluated: minimum lumen area (MLA), plaque burden at the MLA, maximum MB thickness, total MB length,

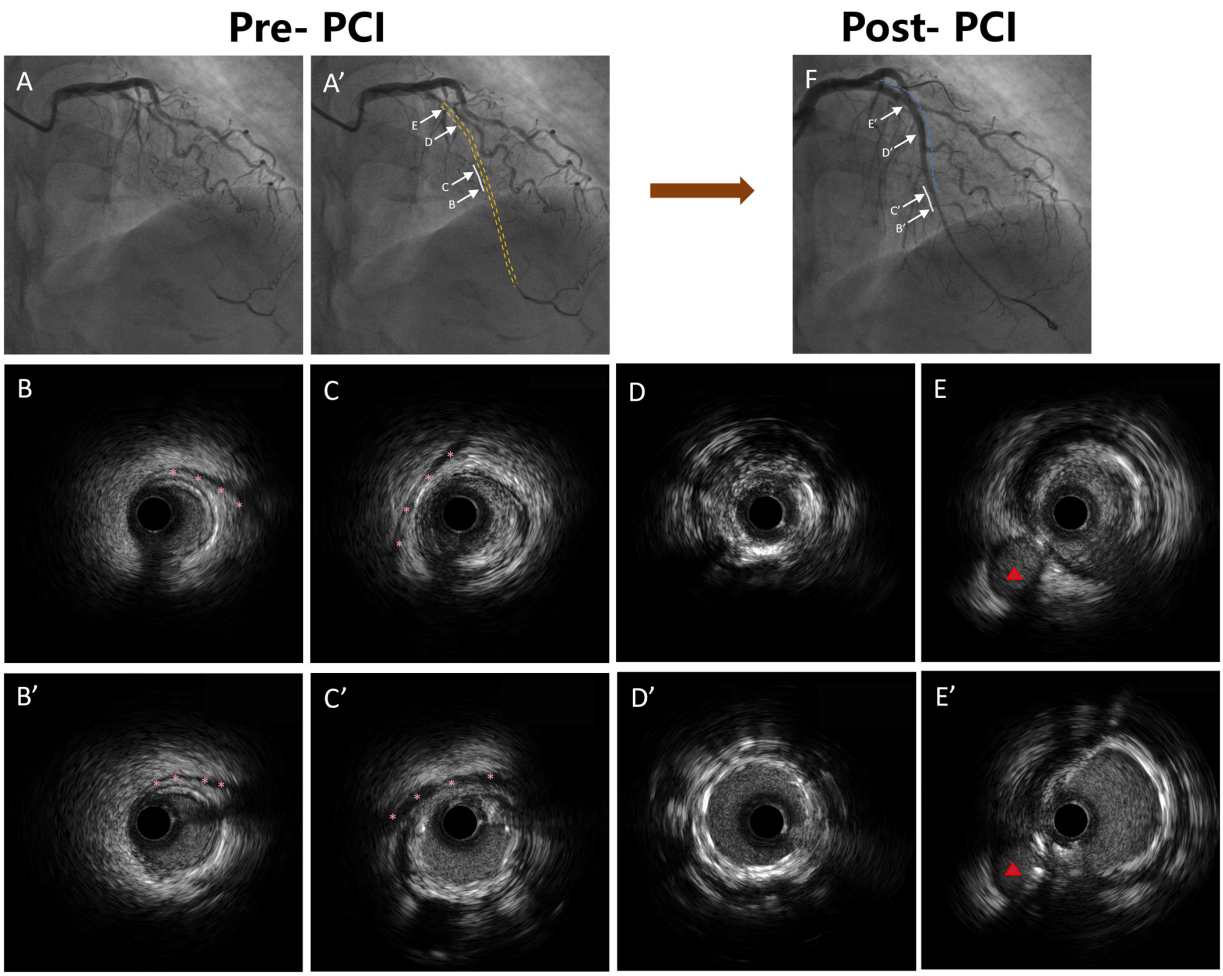

FIGURE 2
Representative coronary angiography and IVUS images demonstrating MB morphology and stent implantation strategy. **(A)** A′: Coronary angiography demonstrating the LAD with MB segments marked. The white solid lines indicate MB segments, and the yellow dashed line indicates the occluded segment identified by angiography. **(B)** B′: IVUS image showing the distal segment of the MB without any plaque formation. The pink asterisks indicate the stent edges. **(C)** C′: IVUS image showing plaque formation in the proximal segment of the MB, with the stent extending into the bridged segment. The pink asterisks indicate the stent edges. **(D)** D′: IVUS image showing stent implantation within the CTO segment without MB. **(E)** E′: IVUS image showing stent implantation in the proximal LAD segment outside of the CTO lesion. The red triangles indicate the diagonal branch. **(F)** Coronary angiography image showing the LAD after stent implantation. The blue dashed lines indicate the stented segments, and the white solid lines indicate the MB segments. IVUS, intravascular ultrasound; MB, myocardial bridge; LAD, left anterior descending; PCI, percutaneous coronary intervention.

and diastolic vessel restriction, calculated as (1—diastolic vessel area/interpolated reference vessel area) (14). True CTO length was determined by coregistering IVUS images with angiography via fiduciary landmarks. The IVUS-defined CTO segment was characterized by cross-sections lacking a smooth, concave lumen contour, distinguishing it from adjacent reference regions. CTO length was then calculated based on the pullback speed and duration. For manually withdrawn catheters, measurements were derived from the coregistered angiogram. Extraplaque tracking was defined as guidewire passage outside the plaque but within the adventitia, recognized by the absence of the classic three-layer vessel wall pattern (15). Stent expansion was defined as the ratio of minimum stent area (MSA) to the average lumen area of the proximal and distal reference segments. All IVUS measurements were obtained during phases of maximal vessel diameter, presumed to correspond with diastole. Anatomical assessments from both IVUS and angiographic data were independently reviewed by two experienced interventional cardiologists (X.W. and L.W.) blinded to patient presentation and laboratory data. Inter-observer and intra-observer agreement were excellent, with κ coefficients of 0.90 and 0.93, respectively.

2.6 Follow-up and clinical outcomes

Patients were followed up at 1, 6, and 12 months post-discharge and annually thereafter. Follow-up data were collected via outpatient visits, hospital records, telephone interviews, and verification through referring physicians or national mortality databases. The primary outcome was the occurrence of major adverse cardiovascular events

(MACE), defined as a composite of cardiac death, target vessel myocardial infarction (MI), clinically driven target lesion revascularization (TLR), or in-stent thrombosis (IST), as per the Academic Research Consortium definitions (16). Clinically driven TLR was defined as revascularization performed in the presence of recurrent ischemic symptoms or objective evidence of myocardial ischemia, in combination with angiographic restenosis of ≥50% within the target lesion, in accordance with guideline recommendations.

2.7 Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov–Smirnov test was employed to assess the distributional normality of continuous variables. Variables following a normal distribution were presented as mean ± standard deviation (SD) and compared between groups using independent-samples t-tests. For variables not normally distributed, data were expressed as median and interquartile range [M (P25, P75)] and compared using the Mann–Whitney *U* test. Categorical variables were summarized as frequencies and percentages [*n* (%)] and analyzed using either Pearson's χ^2 test or Fisher's exact test, depending on cell counts. All statistical evaluations were two-sided, and a p-value < 0.05 was considered to indicate statistical significance. Variables identified as potential predictors of MACE in univariate analysis were subsequently entered into a multivariate Cox proportional hazards regression model using backward stepwise selection to determine independent predictors of adverse outcomes. The cumulative incidence of MACE was estimated using Kaplan–Meier survival curves, and differences between groups were assessed with the log-rank test. A two-tailed *P* value < 0.05 was defined as the threshold for statistical significance.

3 Results

A total of 256 patients with LAD CTO were included, of whom 61 (23.8%) had coexisting MB. As shown in Table 1, baseline demographic characteristics, cardiovascular risk factors, and

TABLE 1 Baseline characteristics.

Variable	All (*n* = 256)	With an MB (*n* = 61)	Without an MB (*n* = 195)	*P* value
Age, years	65.00 (61.00, 71.00)	63.00 (59.00, 70.00)	67.00 (64.00, 71.00)	0.123
Male, *n* %	158 (61.7%)	37 (60.7%)	121 (62.1%)	0.842
Prior hypertension, *n* %	128 (50.0%)	30 (49.2%)	98 (50.3%)	0.887
Prior hyperlipidemia, *n* %	99 (38.7%)	21 (34.4%)	78 (40.0%)	0.504
Prior diabetes mellitus, *n* %	70 (27.3%)	20 (32.8%)	50 (25.6%)	0.293
Prior stroke, *n* %	14 (5.5%)	4 (6.6%)	10 (5.1%)	0.915
Smoking, *n* %	124 (48.4%)	31 (50.8%)	93 (47.7%)	0.779
Chronic kidney disease[a], *n* %	9 (3.5%)	5 (8.2%)	4 (2.1%)	0.060
Peripheral artery disease, *n* %	34 (13.3%)	9 (14.8%)	25 (12.8%)	0.863
Prior myocardial infarction, *n* %	77 (30.1%)	16 (26.2%)	61 (31.3%)	0.554
Prior PCI, *n* %	27 (10.5%)	7 (11.5%)	20 (10.3%)	0.974
Laboratory biomarkers				
Platelet count, 10^9/L	251.12 (235.24, 272.83)	249.75 (234.98, 268.73)	252.98 (236.02, 274.49)	0.445
TG, mmol/L	1.93 (1.69, 2.17)	1.94 (1.75, 2.16)	1.93 (1.69, 2.17)	0.709
TC, mmol/L	5.36 (5.04, 5.66)	5.34 (5.04, 5.78)	5.38 (5.05, 5.66)	0.886
HDL, mmol/L	1.24 (1.16, 1.35)	1.22 (1.16, 1.37)	1.25 (1.16, 1.35)	0.728
LDL, mmol/L	3.32 (3.09, 3.63)	3.33 (3.11, 3.60)	3.32 (3.09, 3.63)	0.766
Lp(a), mg/L	203.21 (168.46, 250.59)	201.62 (171.11, 254.71)	204.15 (167.33, 248.94)	0.697
AST, U/L	112.71 (89.65, 133.21)	120.45 (97.93, 138.11)	110.45 (88.57, 130.92)	0.051
ALT, U/L	49.35 (38.34, 63.60)	49.37 (41.34, 64.36)	49.32 (37.39, 63.05)	0.467
TBIL, μmol/L	16.34 (15.13, 18.00)	16.37 (15.14, 18.33)	16.28 (15.13, 17.96)	0.634
Uric acid, μmol/L	482.89 (433.10, 541.59)	466.49 (414.73, 514.59)	489.27 (441.03, 550.92)	0.070
Scr, μmol/L	88.92 (84.51, 95.77)	88.46 (84.35, 94.20)	89.21 (84.65, 96.04)	0.731
eGFR, ml/min per 1.732 m^2	99.07 (91.64, 107.72)	102.92 (90.93, 114.04)	98.28 (91.77, 107.03)	0.476
Pharmacologic therapy				
DAPT, *n* %	256 (100.0%)	61 (100.0%)	195 (100.0%)	1.000
Statins, *n* %	237 (92.6%)	59 (96.7%)	178 (91.3%)	0.256
ACEI or ARB, *n* %	190 (74.2%)	42 (68.9%)	148 (75.9%)	0.352
Beta-blockers, *n* %	150 (58.6%)	38 (62.3%)	112 (57.4%)	0.601
Aldosterone antagonists, *n* %	48 (18.8%)	12 (19.7%)	36 (18.5%)	0.981
Nitrates, *n* %	67 (26.2%)	15 (24.6%)	52 (26.7%)	0.876
Calcium channel blockers, *n* %	36 (14.1%)	7 (11.5%)	29 (14.9%)	0.649

Continuous variables were expressed as median (interquartile range). Categorical variables were expressed as number (percentage).
MB, myocardial bridge; PCI, percutaneous coronary intervention; DAPT, dual antiplatelet therapy; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; TG, triglycerides; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); AST, aspartate aminotransferase; ALT, alanine aminotransferase; TBIL, total bilirubin; Scr, serum creatinine; eGFR, estimated glomerular filtration rate.
[a]Estimated glomerular filtration rate <60 ml/min/1.73 m^2 using the Modification of Diet in Renal Disease study equation.

laboratory indices were generally balanced between the MB and non-MB groups, with no statistically significant differences observed.

Angiographic and procedural characteristics are summarized in Table 2. The MB group exhibited a significantly shorter lesion length (19.36 ± 2.31 mm vs. 20.37 ± 2.58 mm, $P = 0.004$), more frequent ostial-proximal location (41.0% vs. 20.0%, $P = 0.001$), and shorter calcium arc length (11.55 ± 0.41 mm vs. 12.39 ± 0.52 mm, $P < 0.001$). The total stent length was also significantly reduced in MB patients (69.17 ± 2.93 mm vs. 71.46 ± 4.13 mm, $P < 0.001$). Other parameters including device diameter, retrograde approach rate, and procedural time were comparable between groups.

IVUS analysis (Table 3) revealed that MB patients had significantly shorter CTO lesion lengths (17.71 ± 3.21 mm vs. 21.31 ± 2.44 mm, $P < 0.001$) and a lower prevalence of calcification within the CTO segment (29.5% vs. 47.7%, $P = 0.018$). No significant intergroup differences were observed in minimum stent area, stent expansion percentage, or other IVUS-derived procedural outcomes.

During the 2-year follow-up (Table 4), the incidence of MACE was significantly higher in the MB group compared to the control group (19.7% vs. 8.7%, $P = 0.033$). Similarly, the rate of clinically driven TLR was increased in patients with MB (18.0% vs. 6.7%, $P = 0.016$). No significant differences were found in cardiac death, target vessel myocardial infarction (TVMI), or in-stent thrombosis.

Univariate logistic regression analysis (Table 5) demonstrated that MB was significantly associated with MACE. In the multivariate model, after adjustment for age, sex, hypertension, dyslipidemia, diabetes mellitus, and chronic kidney disease, MB remained an independent predictor of 2-year MACE (HR: 2.173, 95% CI: 1.031–4.667, $P = 0.021$).

Kaplan–Meier survival analysis revealed that patients with MB exhibited a significantly higher cumulative incidence of both MACE and clinically driven TLR over the 2-year follow-up period compared to those without MB (Figure 3). Specifically, the incidence of MACE was significantly elevated in the MB group (log-rank $P = 0.018$), with a hazard ratio (HR) of

TABLE 2 Angiographic and procedural findings.

Variable	All (*n* = 256)	With an MB (*n* = 61)	Without an MB (*n* = 195)	*P* value
Multivessel disease[a], *n* %	88 (34.4%)	19 (31.1%)	69 (35.4%)	0.650
Reattempt CTO PCI, *n* %	15 (5.9%)	4 (6.6%)	11 (5.6%)	1.000
CTO length, mm	20.13 ± 2.55	19.36 ± 2.31	20.37 ± 2.58	0.004
CTO length >20 mm, *n* %	111 (43.4%)	24 (39.3%)	87 (44.6%)	0.563
Ostial to proximal lesion location, *n* %	64 (25.0%)	25 (41.0%)	39 (20.0%)	0.001
Lesion length, mm	43.35 ± 3.38	42.60 ± 3.77	43.58 ± 3.22	0.069
Calcification, *n* %	71 (27.7%)	13 (21.3%)	58 (29.7%)	0.262
Calcium length, mm	12.19 ± 0.61	11.55 ± 0.41	12.39 ± 0.52	<0.001
Abrupt proximal cap, *n* %	129 (50.4%)	29 (47.5%)	100 (51.3%)	0.716
Lesion bend, *n* %	29 (11.3%)	6 (9.8%)	23 (11.8%)	0.849
J-CTO score ≥2, *n* %	114 (44.5%)	26 (42.6%)	88 (45.1%)	0.844
Rentrop classification grade 3, *n* %	128 (50.0%)	33 (54.1%)	95 (48.7%)	0.557
Post-PCI in-segment[b]				
Reference vessel diameter, mm	3.19 ± 0.47	3.16 ± 0.41	3.20 ± 0.48	0.498
Minimum lumen diameter, mm	2.52 ± 0.20	2.51 ± 0.11	2.52 ± 0.22	0.853
Diameter stenosis, %	23.17 ± 4.97	23.22 ± 5.38	23.15 ± 4.85	0.929
Post-PCI distal vessel				
Reference vessel diameter, mm	1.58 ± 1.29	1.39 ± 1.10	1.64 ± 1.34	0.143
Minimum lumen diameter, mm	1.13 ± 0.60	1.11 ± 0.45	1.14 ± 0.63	0.678
Diameter stenosis, %	30.05 ± 4.59	30.12 ± 4.12	30.03 ± 4.74	0.887
Procedural findings				
Final guidewire crossing technique				0.268
Antegrade guidewire escalation, *n* %	130 (50.8%)	28 (45.9%)	102 (52.3%)	
Antegrade dissection reentry, *n* %	25 (9.8%)	7 (11.5%)	18 (9.2%)	
Retrograde guide wire escalation, *n* %	26 (10.2%)	10 (16.4%)	16 (8.2%)	
Retrograde dissection reentry, *n* %	75 (29.3%)	16 (26.2%)	59 (30.3%)	
Retrograde attempt, *n* %	88 (34.4%)	19 (31.1%)	69 (35.4%)	0.650
Total stent length, mm	70.92 ± 3.99	69.17 ± 2.93	71.46 ± 4.13	<0.001
Maximum device diameter, mm	3.30 ± 2.58	3.41 ± 2.62	3.27 ± 2.57	0.708
Maximum balloon inflation pressure, atm	18.43 ± 2.91	18.59 ± 3.26	18.37 ± 2.80	0.632
Procedure time, min	50.39 ± 5.87	48.84 ± 7.83	50.87 ± 5.03	0.061
Radiation exposure dose, Gy	2.1 (1.5, 2.7)	2.1 (1.6, 2.6)	2.1 (1.4, 2.8)	0.944
Contrast media volume, ml	272.94 ± 13.57	270.51 ± 12.03	273.70 ± 13.95	0.085

Continuous variables were expressed as mean ± SD, or median (interquartile range). Categorical variables were expressed as number (percentage).
MB, myocardial bridge; PCI, percutaneous coronary intervention; CTO, chronic total occlusion.
[a]Defined as the presence of >50% diameter stenosis in 2 or more major epicardial arteries.
[b]In-segment includes stent and 5 mm proximal and distal reference from each stent edge.

TABLE 3 Intravascular ultrasound findings.

Variable	All (n = 256)	With an MB (n = 61)	Without an MB (n = 195)	P value
CTO length, mm	20.45 ± 3.05	17.71 ± 3.21	21.31 ± 2.44	<0.001
CTO length >20 mm, n %	106 (41.4%)	18 (29.5%)	88 (45.1%)	0.044
Extraplaque tracking, n %	59 (23.0%)	15 (24.6%)	44 (22.6%)	0.877
Extraplaque length, mm	31.70 ± 3.53	31.78 ± 3.05	31.67 ± 3.67	0.816
Lesion length, mm	49.67 ± 5.53	48.77 ± 5.62	49.95 ± 5.48	0.150
Maximum plaque burden, %	84.26 ± 5.48	84.56 ± 5.03	84.16 ± 5.62	0.602
Calcification in CTO lesion, n %	111 (43.4%)	18 (29.5%)	93 (47.7%)	0.018
Maximum arc of calcium,°	125.34 ± 21.30	125.90 ± 22.77	125.16 ± 20.88	0.822
Dissection, n %	102 (39.8%)	24 (39.3%)	78 (40.0%)	1.000
Dissection extended into an MB, n %	–	6 (9.8)	–	–
Reference minimum lumen area, mm^2	3.52 ± 1.33	3.56 ± 1.33	3.51 ± 1.33	0.799
Reference maximum plaque burden, %	58.32 ± 3.41	58.74 ± 3.22	58.19 ± 3.47	0.262
MB segment				
Distance from LAD ostium to MB, mm	–	38.52 ± 6.43	–	–
Total MB length, mm	–	9.53 ± 2.52	–	–
Maximum thickness of MB, mm	–	0.49 ± 0.09	–	–
Diastolic vessel area at max compression site, mm^2	–	4.41 ± 0.53	–	–
Diastolic vessel restriction, %	–	19.47 ± 4.43	–	–
Minimum lumen area, mm^2	–	2.39 ± 0.64	–	–
Plaque burden at minimum lumen area site, %	–	41.02 ± 4.32	–	–
Postprocedure findings				
MSA, mm^2	5.18 ± 3.11	5.09 ± 2.91	5.21 ± 3.17	0.780
Stent expansion, %	70.51 ± 3.82	70.70 ± 2.97	70.45 ± 4.06	0.606
Rate of MSA in the MB, when stented, n %	–	31 (50.8)	–	–

Continuous variables were expressed as mean ± SD. Categorical variables were expressed as number (percentage).
MB, myocardial bridge; CTO, chronic total occlusion; MSA, minimum stent area; LAD, left anterior descending artery.

TABLE 4 2-year clinical outcomes.

Variable	All (n = 256)	With an MB (n = 61)	Without an MB (n = 195)	P value
MACE, n %	29 (11.3%)	12 (19.7%)	17 (8.7%)	0.033
Cardiac death, n %	1 (0.4%)	1 (1.6%)	0 (0.0%)	0.538
Target vessel MI, n %	5 (2.0%)	1 (1.6%)	4 (2.1%)	1.000
Clinically driven TLR, n %	24 (9.4%)	11 (18.0%)	13 (6.7%)	0.016
In-stent thrombosis, n %	3 (1.2%)	2 (3.3%)	1 (0.5%)	0.284

Categorical variables were expressed as number (percentage).
MB, myocardial bridge; MACE, major adverse cardiovascular events; MI, myocardial infarction; TLR, target lesion revascularization.

TABLE 5 Univariate and multivariate Cox regression analyses showing independent predictors of MACE in patients with LAD CTO.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age	1.847	1.155–2.953	0.018	1.122	0.623–2.012	0.704
Hypertension	1.008	0.561–1.811	0.977			
Diabetes mellitus	1.251	0.695–2.246	0.455			
MB	2.072	1.168–3.674	0.012	2.173	1.031–4.667	0.021
Prior MI	1.065	0.588–1.929	0.833			
LDL	1.125	0.626–2.022	0.693			

MB, myocardial bridge; MACE, major adverse cardiovascular events; HR, hazard ratios; CI, confidence interval; CTO, chronic total occlusion; LAD, left anterior descending artery; MI, myocardial infarction.

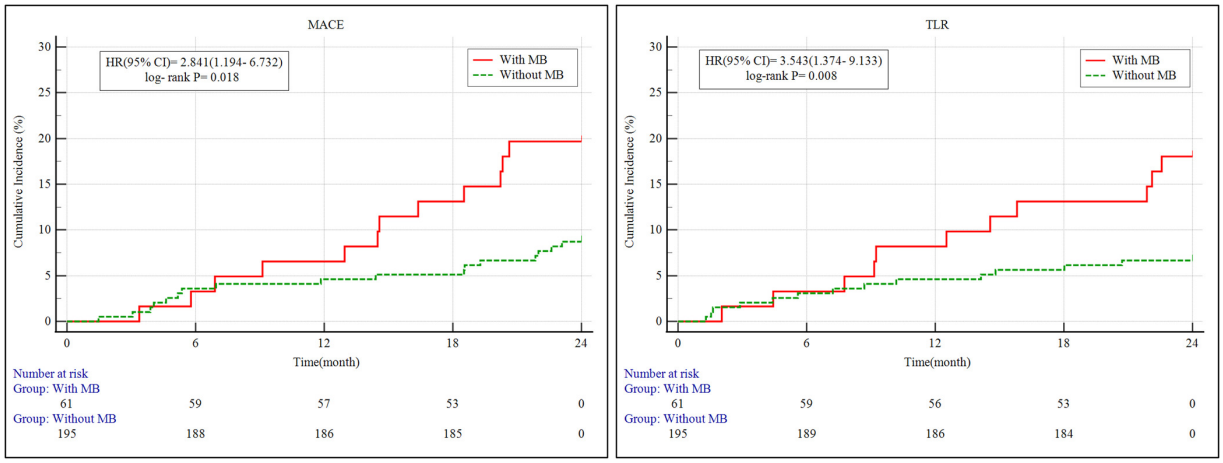

FIGURE 3
Kaplan–Meier survival curves of MACE and clinically driven TLR for 2 years. MB, myocardial bridge; MACE, major adverse cardiovascular events; TLR, target lesion revascularization; 95% CI, 95% confidence intervals; HR, hazard ratio.

2.841 [95% confidence interval (CI): 1.194–6.732]. Likewise, the risk of clinically driven TLR was significantly higher in the MB group, with an HR of 3.543 (95% CI: 1.374–9.133; log-rank $P = 0.008$).

4 Discussion

In this retrospective study utilizing IVUS to evaluate patients undergoing PCI for CTO of the LAD, MB was identified in 23.8% of cases. Compared to patients without MB, those with MB demonstrated unique anatomical and imaging features, including shorter true CTO segment lengths, reduced calcification within the occluded region, and a higher prevalence of lesions located proximally. Despite these ostensibly more favorable lesion morphologies, the presence of MB was significantly correlated with worse long-term clinical outcomes. During a median follow-up period of two years, the MB group experienced a significantly elevated rate of MACE and clinically driven TLR relative to those without MB. Multivariate Cox proportional hazards analysis further substantiated MB as an independent predictor of 2-year MACE (hazard ratio: 2.173; 95% confidence interval: 1.031–4.667; $P = 0.021$), even after controlling for traditional cardiovascular risk factors. These results indicate that MB not only modifies lesion morphology in the setting of LAD CTO but also carries independent prognostic significance, with a potentially deleterious impact on both procedural success and clinical prognosis.

4.1 Mechanistic insights into the preferential localization of CTO proximal to myocardial bridge

While MB has traditionally been regarded as a benign anatomical variation, accumulating evidence suggests it plays a pivotal role in modifying local coronary hemodynamics. This alteration predisposes the segment proximal to the bridge to the development of atherosclerosis and CTO, rather than the tunneled or distal segments of the artery.

4.1.1 Pathophysiological mechanisms linking MB to CTO formation

CTO development in the context of MB does not typically arise from disease within the bridged segment itself. Instead, the pre-bridge (proximal) portion of the artery is affected, largely due to hemodynamic disruptions instigated by MB. During systole, the mural coronary artery (MCA) undergoes dynamic compression by the MB, leading to retrograde flow, decelerated blood velocity, and disruption of laminar shear patterns upstream of the bridge (17). These hemodynamic perturbations result in regions of low or oscillatory wall shear stress (WSS), conditions well known to impair endothelial homeostasis and facilitate atherosclerotic development (18). In areas of diminished shear, endothelial nitric oxide synthase (eNOS) activity is suppressed, reducing the bioavailability of nitric oxide (NO), a critical molecule for maintaining vascular tone and endothelial function. The resultant deficiency in NO promotes vascular inflammation, platelet adhesion, and smooth muscle cell (SMC) proliferation (18). Simultaneously, enhanced generation of reactive oxygen species (ROS) contributes to oxidative stress, facilitating lipid accumulation, foam cell transformation, and extracellular matrix breakdown—hallmark processes in chronic occlusive disease (19).

4.1.2 Why CTO localizes proximally, rather than within or distal to MB

In contrast to the hemodynamic profile of the proximal segment, the bridged and distal portions of the artery are subjected to elevated shear stress levels. These conditions have atheroprotective effects, including enhanced NO production,

reduced platelet activation, and suppression of pro-inflammatory signaling pathways (1, 20). Both histological examinations and advanced imaging modalities have consistently shown that atherosclerotic lesions are seldom observed within the MB segment. Instead, plaques predominantly form just proximal to the MB and often exhibit eccentric morphologies (1).

Furthermore, the mechanical forces exerted by MB during repetitive systolic compression may induce chronic endothelial injury in the proximal segment. This mechanical trauma is associated with the release of potent vasoactive mediators such as endothelin-1 (ET-1) and activation of the angiotensin-converting enzyme (ACE) system (21, 22). Such alterations foster a local vascular milieu that is increasingly pro-thrombotic and pro-inflammatory, predisposing the segment to plaque destabilization and thrombotic occlusion, thereby culminating in CTO formation.

Collectively, MB serves not as the site of direct pathology but as a biomechanical trigger that generates a vulnerable upstream vascular environment conducive to atherogenesis and total occlusion. These mechanistic insights offer a plausible and evidence-supported rationale for the anatomical predilection of CTO lesions proximal to MB, as consistently observed in both our current analysis and prior research findings.

4.2 Reduced coronary calcification in MB-associated CTO lesions

In our analysis, IVUS demonstrated that patients with MB-related LAD CTO lesions exhibited a lower prevalence of calcified plaques and a reduced extent of calcification within the occluded segment compared to those without MB. This observation underscores a key structural divergence between the two patient cohorts and may reflect the distinct hemodynamic conditions imposed by the presence of MB. The repetitive systolic compression characteristic of MB alters local vascular wall mechanics and generates unique shear stress distributions that are less favorable to chronic arterial remodeling and calcific plaque development.

Specifically, the bridged region and its upstream segment—particularly the pre-bridge area—are subjected to disturbed flow patterns and diminished shear stress, a combination that is more commonly associated with non-calcified or mixed plaque morphologies (18, 23). Unlike calcified lesions, non-calcified plaques—often termed soft or vulnerable plaques—are defined by a large lipid-rich core, a thin fibrous cap, and an abundance of inflammatory cell infiltration, characteristics that render them susceptible to rupture (24). Although coronary artery calcification is traditionally considered a surrogate marker of chronic plaque stability and burden, its relative paucity in MB-associated CTO lesions does not equate to clinical quiescence. On the contrary, the predominance of non-calcified, unstable plaque—particularly proximal to the MB where adverse hemodynamic influences are concentrated—may signal a higher risk profile. This insight urges caution in interpreting low calcific burden in such lesions; although it may suggest technical ease in lesion crossing or reduced stent length, the underlying plaque vulnerability increases the likelihood of peri-procedural complications during PCI. Therefore, meticulous imaging assessment and vigilant post-intervention surveillance are essential when managing these patients.

4.3 Shorter CTO and stent length in MB-associated lesions

In our investigation, both the IVUS-assessed length of CTO lesions and the total stent length were significantly reduced in patients with MB compared to those without. This finding likely reflects the distinct anatomical and pathophysiological profile associated with MB, particularly its capacity to shield the tunneled segment from atherosclerotic involvement, thereby localizing disease predominantly to the proximal LAD.

Multiple mechanisms have been proposed to explain this relative resistance to plaque accumulation within MB segments. Firstly, the bridged arterial portion is anatomically segregated from surrounding perivascular adipose tissue, which is a recognized contributor to atherogenesis via pro-inflammatory paracrine signaling (25). Secondly, advanced imaging modalities such as optical coherence tomography (OCT) have revealed an absence of adventitial vasa vasorum in MB regions (26), potentially limiting the transvascular infiltration of inflammatory stimuli. Moreover, the cyclical systolic compression exerted on the tunneled artery may promote enhanced lymphatic drainage, thereby facilitating the removal of lipids and inflammatory cytokines from the vessel wall (27). Lastly, elevated or physiologically favorable wall shear stress within the MB region has been implicated in the upregulation of atheroprotective genes and maintenance of endothelial function (20).

While these factors may account for the shorter lesion length and reduced stent requirement, they also pose procedural complexities. Stenting into MB segments is generally avoided due to the risks of inadequate expansion under systolic compression and the potential for mechanical complications such as stent fracture or malapposition. As a result, the selection of appropriate landing zones becomes more constrained, particularly in MB-associated CTOs characterized by focal disease (8). Thus, although MB appears to offer a form of anatomical protection against extended atherosclerotic development, this benefit is offset by technical challenges in PCI planning.

The observed reduction in lesion and stent lengths in the MB cohort should not be viewed purely as a procedural advantage. Rather, it underscores a set of anatomical limitations that necessitate careful pre-procedural imaging, strategic lesion preparation, and individualized stenting approaches to minimize the risk of incomplete lesion coverage or geographic miss.

4.4 Clinical implications and revascularization strategy for MB-associated LAD CTO lesions

Our study demonstrates that the presence of MB in LAD CTO lesions is significantly associated with higher incidences of MACE

(19.7% vs. 8.7%, $P = 0.033$) and TLR (18.0% vs. 6.7%, $P = 0.016$) at the 2-year mark. Moreover, MB was identified as an independent prognostic factor for MACE in multivariate analysis (HR = 2.173, $P = 0.021$). These results underscore the clinical importance of tailoring PCI strategies for this distinct anatomical and hemodynamic subgroup.

While earlier studies have reported favorable long-term survival in patients with isolated MB—approximately 98% over 11 years (28)—the outcomes are markedly less favorable when MB coexists with coronary artery disease (CAD), particularly in individuals undergoing PCI. Our findings align with growing evidence that stent implantation within MB segments may be associated with adverse outcomes, including increased neointimal hyperplasia, elevated rates of in-stent restenosis, and higher incidence of TLR (10, 29). Tsujita et al. observed a significant rise in TLR (from 3% to 24%) when stent deployment extended into MB regions (10). Additional studies using OCT and IVUS have revealed substantial neointimal tissue proliferation and even mechanical complications, such as stent fracture, within bridged segments (1).

These unfavorable outcomes are likely a result of the unique biomechanical environment inherent to MB. Stents positioned within MB segments are subjected to repetitive systolic compression, non-physiological shear stress patterns, and the so-called "sandwich effect", in which the device is compressed between the coronary artery wall and the overlying myocardium (1, 30). This dynamic stress environment promotes the release of vasoactive substances, activates local inflammatory pathways, and may accelerate mechanical fatigue of the stent, thereby contributing to maladaptive remodeling and subsequent clinical complications.

From a technical perspective, the reduced CTO lesion length and the clinical preference to avoid stenting within MB segments result in limited options for stent landing zones. This constraint may elevate the risk of incomplete lesion coverage or geographic miss. Therefore, the presence of MB should be carefully evaluated during pre-procedural planning—ideally with high-resolution imaging modalities such as IVUS or CT—to facilitate accurate landing zone selection and optimal stent deployment strategy. Collectively, these findings suggest that conventional PCI algorithms may be insufficient for managing MB-associated LAD CTO lesions. Instead, a customized revascularization approach should be considered—one that aims to mitigate mechanical strain on the stent, avoid unnecessary implantation within bridged segments, and explore alternative therapies such as drug-coated balloon (DCB) angioplasty or ultrashort stent platforms. Additionally, rigorous post-PCI monitoring and extended follow-up are warranted to identify and manage potential TLR events or stent-related complications.

4.5 Limitations

This study has several noteworthy limitations that should be acknowledged. First, it was conducted as a single-center, retrospective observational study, which inherently introduces potential selection bias and limits the generalizability of the findings to other centers, populations, and practice settings. Second, various procedural decisions—including selection of stents, lesion preparation techniques, and strategy choice (antegrade vs. retrograde)—were made at the discretion of individual operators. This operator-dependent variability may have introduced heterogeneity that influenced clinical outcomes. Third, the analysis was confined to CTO lesions of the LAD, limiting the extrapolation of the results to CTO lesions in other coronary vessels such as the RCA or LCX, where the presence of MB is uncommon but may still be clinically relevant. Fourth, referral bias may have influenced the composition of the study population, complicating efforts to determine the true prevalence of MB in either LAD CTO or non-CTO scenarios. Fifth, no routine angiographic or intravascular imaging follow-up was performed after the index procedure, limiting our ability to evaluate stent-related complications such as in-stent restenosis, stent fracture, or neoatherosclerosis, and to correlate imaging findings with clinical outcomes. Sixth, although multivariate analysis was feasible for MACE, the relatively small number of events related to both MACE and TLR constrained the statistical power of the Cox regression models, resulting in wide confidence intervals and necessitating cautious interpretation of these findings. Seventh, subgroup analyses comparing clinical outcomes between patients with stenting within MB segments vs. those without, and interaction analyses incorporating clinical modifiers such as CTO score or lesion calcification, could not be performed due to limited sample size and low event rates in these subgroups. Lastly, although critical anatomical variables such as plaque burden and stent length are known to impact long-term clinical outcomes, these were not consistently matched or adjusted in subgroup comparisons. Despite these limitations, our findings are consistent with prior literature suggesting that stent placement within MB segments may predispose patients to unfavorable outcomes, including neointimal proliferation and restenosis (29, 31). Future multicenter, prospective studies with larger sample sizes are warranted to validate and extend these findings to broader patient populations.

5 Conclusion

In this IVUS-guided observational analysis of patients undergoing PCI for LAD CTO lesions, MB was associated with distinct anatomical characteristics, including shorter occlusion length, reduced calcific burden, and a higher prevalence of proximally located lesions. Although these morphological features may initially appear favorable, the presence of MB was independently linked to increased rates of MACE and TLR at two years. These results underscore the dualistic role of MB—as a structural feature that may shield against atherosclerosis within the bridged segment, yet simultaneously introduce procedural complexity and heightened clinical risk. Given the biomechanical constraints posed by MB, particularly in the setting of stent implantation, intervention within MB segments warrants a cautious and individualized approach. The risk of adverse

outcomes such as stent malapposition, fracture, and restenosis necessitates careful pre-procedural planning and intravascular imaging to guide optimal landing zone selection and stent deployment. Overall, our findings emphasize the importance of treating MB-associated LAD CTO lesions as a distinct clinical entity, rather than applying conventional revascularization algorithms. Future investigations should aim to further elucidate the prognostic implications of MB in CTO interventions and to develop tailored treatment strategies that mitigate procedural risks while ensuring durable and effective revascularization.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Ethics Committee of Xiangtan Central Hospital (The Affiliated Hospital of Hunan University). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

XW: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Supervision, Writing – original draft. MW: Conceptualization, Formal analysis, Investigation, Methodology, Writing – review & editing. HaH: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Writing – review & editing. ZL: Conceptualization, Investigation, Methodology, Writing – review & editing. HeH: Conceptualization, Investigation, Writing – review & editing. LW: Conceptualization, Data curation, Formal analysis, Validation, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

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Publisher's note

References

1. Sternheim D, Power DA, Samtani R, Kini A, Fuster V, Sharma S. Myocardial bridging: diagnosis, functional assessment, and management: JACC state-of-the-art review. *J Am Coll Cardiol.* (2021) 78(22):2196–212. doi: 10.1016/j.jacc.2021.09.859

2. Rajendran R, Hegde M. The prevalence of myocardial bridging on multidetector computed tomography and its relation to coronary plaques. *Pol J Radiol.* (2019) 84: e478–e83. doi: 10.5114/pjr.2019.90370

3. Kikuchi S, Okada K, Hibi K, Maejima N, Matsuzawa Y, Konishi M, et al. Myocardial infarction caused by accelerated plaque formation related to myocardial bridge in a young man. *Can J Cardiol.* (2018) 34(12):1687.e13–.e15. doi: 10.1016/j.cjca.2018.08.023

4. Nam P, Choi BG, Choi SY, Byun JK, Mashaly A, Park Y, et al. The impact of myocardial bridge on coronary artery spasm and long-term clinical outcomes in patients without significant atherosclerotic stenosis. *Atherosclerosis.* (2018) 270:8–12. doi: 10.1016/j.atherosclerosis.2018.01.026

5. Tarantini G, Migliore F, Cademartiri F, Fraccaro C, Iliceto S. Left anterior descending artery myocardial bridging: a clinical approach. *J Am Coll Cardiol.* (2016) 68(25):2887–99. doi: 10.1016/j.jacc.2016.09.973

6. Ishii T, Ishikawa Y, Akasaka Y. Myocardial bridge as a structure of "double-edged sword" for the coronary artery. *Ann Vasc Dis.* (2014) 7(2):99–108. doi: 10.3400/avd.ra.14-00037

7. Hostiuc S, Negoi I, Rusu MC, Hostiuc M. Myocardial bridging: a meta-analysis of prevalence. *J Forensic Sci.* (2018) 63(4):1176–85. doi: 10.1111/1556-4029.13665

8. Yamamoto K, Sugizaki Y, Karmpaliotis D, Sato T, Matsumura M, Narui S, et al. Presence and relevance of myocardial bridge in LAD-PCI of CTO and non-CTO lesions. *JACC Cardiovasc Interv.* (2024) 17(4):491–501. doi: 10.1016/j.jcin.2023.12.017

9. Galassi AR, Werner GS, Boukhris M, Azzalini L, Mashayekhi K, Carlino M, et al. Percutaneous recanalisation of chronic total occlusions: 2019 consensus document from the EuroCTO club. *EuroIntervention.* (2019) 15(2):198–208. doi: 10.4244/EIJ-D-18-00826

10. Tsujita K, Maehara A, Mintz GS, Doi H, Kubo T, Castellanos C, et al. Impact of myocardial bridge on clinical outcome after coronary stent placement. *Am J Cardiol.* (2009) 103(10):1344–8. doi: 10.1016/j.amjcard.2009.01.340

11. Morino Y, Abe M, Morimoto T, Kimura T, Hayashi Y, Muramatsu T, et al. Predicting successful guidewire crossing through chronic total occlusion of native coronary lesions within 30 min: the J-CTO (multicenter CTO registry in Japan)

score as a difficulty grading and time assessment tool. *JACC Cardiovasc Interv*. (2011) 4(2):213–21. doi: 10.1016/j.jcin.2010.09.024

12. Rentrop KP, Cohen M, Blanke H, Phillips RA. Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. *J Am Coll Cardiol*. (1985) 5(3):587–92. doi: 10.1016/S0735-1097(85)80380-6

13. Lotfi A, Jeremias A, Fearon WF, Feldman MD, Mehran R, Messenger JC, et al. Expert consensus statement on the use of fractional flow reserve, intravascular ultrasound, and optical coherence tomography: a consensus statement of the society of cardiovascular angiography and interventions. *Catheter Cardiovasc Interv*. (2014) 83(4):509–18. doi: 10.1002/ccd.25222

14. Hashikata T, Honda Y, Wang H, Pargaonkar VS, Nishi T, Hollak MB, et al. Impact of diastolic vessel restriction on quality of life in symptomatic myocardial bridging patients treated with surgical unroofing: preoperative assessments with intravascular ultrasound and coronary computed tomography angiography. *Circ Cardiovasc Interv*. (2021) 14(10):e011062. doi: 10.1161/CIRCINTERVENTIONS.121.011062

15. Muramatsu T, Tsuchikane E, Oikawa Y, Otsuji S, Fujita T, Ochiai M, et al. Incidence and impact on midterm outcome of controlled subintimal tracking in patients with successful recanalisation of chronic total occlusions: J-PROCTOR registry. *EuroIntervention*. (2014) 10(6):681–8. doi: 10.4244/EIJV10I6A119

16. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. (2007) 115(17):2344–51. doi: 10.1161/CIRCULATIONAHA.106.685313

17. Ge J, Erbel R, Rupprecht HJ, Koch L, Kearney P, Görge G, et al. Comparison of intravascular ultrasound and angiography in the assessment of myocardial bridging. *Circulation*. (1994) 89(4):1725–32. doi: 10.1161/01.CIR.89.4.1725

18. Puri R, Leong DP, Nicholls SJ, Liew GY, Nelson AJ, Carbone A, et al. Coronary artery wall shear stress is associated with endothelial dysfunction and expansive arterial remodelling in patients with coronary artery disease. *EuroIntervention*. (2015) 10(12):1440–8. doi: 10.4244/EIJV10I12A249

19. Lee MS, Chen CH. Myocardial bridging: an up-to-date review. *J Invasive Cardiol*. (2015) 27(11):521–8.

20. White SJ, Hayes EM, Lehoux S, Jeremy JY, Horrevoets AJ, Newby AC. Characterization of the differential response of endothelial cells exposed to normal and elevated laminar shear stress. *J Cell Physiol*. (2011) 226(11):2841–8. doi: 10.1002/jcp.22629

21. Leber AW, Knez A, Becker A, Becker C, von Ziegler F, Nikolaou K, et al. Accuracy of multidetector spiral computed tomography in identifying and differentiating the composition of coronary atherosclerotic plaques: a comparative study with intracoronary ultrasound. *J Am Coll Cardiol*. (2004) 43(7):1241–7. doi: 10.1016/j.jacc.2003.10.059

22. Aparci M, Ozturk C, Balta S, Okutucu S, Isilak Z. Hypercholesterolemia is accounted for atherosclerosis at the proximal arterial segments of myocardial bridging: a pilot study. *Clin Appl Thromb Hemost*. (2016) 22(3):297–302. doi: 10.1177/1076029614554995

23. Nakaura T, Nagayoshi Y, Awai K, Utsunomiya D, Kawano H, Ogawa H, et al. Myocardial bridging is associated with coronary atherosclerosis in the segment proximal to the site of bridging. *J Cardiol*. (2014) 63(2):134–9. doi: 10.1016/j.jjcc.2013.07.005

24. Koesbandono LA, Muljadi R, Yuniarti M, Sindunata NA, Sarikie A, Pratama TA, et al. High prevalence of myocardial bridging detected in an Indonesian population using multi-detector computed tomography. *Medicina (Kaunas Lithuania)*. (2024) 60(5):794. doi: 10.3390/medicina60050794

25. Verhagen SN, Rutten A, Meijs MF, Isgum I, Cramer MJ, van der Graaf Y, et al. Relationship between myocardial bridges and reduced coronary atherosclerosis in patients with angina pectoris. *Int J Cardiol*. (2013) 167(3):883–8. doi: 10.1016/j.ijcard.2012.01.091

26. Nishimiya K, Matsumoto Y, Wang H, Piao Z, Ohyama K, Uzuka H, et al. Absence of adventitial vasa vasorum formation at the coronary segment with myocardial bridge—an optical coherence tomography study. *Int J Cardiol*. (2018) 250:275–7. doi: 10.1016/j.ijcard.2017.09.211

27. Alsoufi B. Do not miss the bridge. *J Thorac Cardiovasc Surg*. (2018) 156(4):1627–8. doi: 10.1016/j.jtcvs.2018.02.082

28. Darabont RO, Vișoiu IS, Magda ȘL, Stoicescu C, Vintilă VD, Udroiu C, et al. Implications of myocardial bridge on coronary atherosclerosis and survival. *Diagnostics (Basel)*. (2022) 12(4):948. doi: 10.3390/diagnostics12040948

29. Xu T, You W, Wu Z, Meng P, Ye F, Wu X, et al. Retrospective analysis of OCT on MB characteristics and 1-year follow-up of the ISR incidence after the DES implantation in patients with MB. *Sci Rep*. (2022) 12(1):534. doi: 10.1038/s41598-021-04579-9

30. Kursaklioglu H, Barcin C, Iyisoy A, Kose S, Amasyali B, Isik E. Angiographic restenosis after myocardial bridge stenting. *Jpn Heart J*. (2004) 45(4):581–9. doi: 10.1536/jhj.45.581

31. Tsujita K, Maehara A, Mintz GS, Lansky AJ, Kubo T, Doi H, et al. Serial intravascular ultrasound analysis of the impact of myocardial bridge on neointimal proliferation after coronary stenting in patients with acute myocardial infarction. *J Interv Cardiol*. (2010) 23(2):114–22. doi: 10.1111/j.1540-8183.2010.00531.x

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Comparison of intravascular imaging, physiological assessment and angiography for coronary revascularization in acute coronary syndrome: a systematic review and network meta-analysis

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Background: The optimal percutaneous coronary intervention (PCI) technique to treat acute coronary syndrome (ACS) requires further investigation. This network meta-analysis evaluated the effects of physiological assessment and intravascular imaging techniques on the prevalence of adverse cardiac outcomes following PCIs.
Methods: We reviewed PubMed, Cochrane, and EMBASE databases for the purpose of identifying all randomized control trials published up to October 30, 2024, comparing the impact of intravascular imaging, physiology assessment, or angiography techniques on outcomes. The primary outcome for this research was major adverse cardiovascular events (MACE) occurrences. Each PCI strategy was ranked *as per* the risk ratio (RR) at the 95% confidence interval (95% CI) for developing MACE.
Results: Twenty-eight RCTs with 18,221 patients were identified. Compared with angiography, intravascular ultrasound (IVUS)- (RR: 0.62; 95%CI: 0.46–0.85) and fractional flow reserve (FFR)-guided PCI (RR: 0.62; 95%CI: 0.46–0.85) reduced the risk of MACE. Patients who received quantitative flow ratio (QFR)-guided PCI experienced lower all-cause mortality (RR: 0.25; 95%CI: 0.07–0.92) vs. those receiving angiography. Similarly, the RR decreased to 0.64 after using FFR-guided PCI vs. angiographic procedures (95% CI: 0.44–0.91). Compared to angiography, the subgroup analysis showed inconsistent results for IVUS-guided PCI in preventing MACE for both the optimization (RR: 0.60; 95%CI: 0.49–0.74) and decision-making (RR: 0.55; 95%CI: 0.05–6.18). The likelihood of developing MACE was lower for FFR-guided CR than for angiography-guide culprit-only PCIs (RR-0.72; 95%CI: 0.53–0.97), as confirmed by sensitivity assessment results. The research unveiled no statistically significant differences between FFR-guided culprit-only PCIs and culprit-only PCIs or angiography-guided CR.
Conclusion: IVUS- and FFR-guided PCI lowers the MACE risk in patients with ACS. In addition, IVUS achieved the best results in ACS patients undergoing PCI.

Systematic Review Registration: INPLASY (inplasy.com), INPLASY202420092.

KEYWORDS

intravascular imaging, physiology assessment, angiography, acute coronary syndrome, coronary revascularization

Introduction

The high prevalence of coronary artery disease (CAD) presents a considerable worldwide health burden, contributing to significant mortality and morbidity rates while exacerbating economic strain globally (1, 2). Coronary angiography is essential both for the diagnosis of CAD and for guiding revascularization (3). Despite its widespread use, the visual assessment of plaques on coronary angiography is subjective and cannot be used to reliably assess the function and impact of plaque burden on the coronary lesions (4). Several physiological assessment tools and advanced imaging techniques, such as fractional flow reserve (FFR), optical coherence tomography (OCT), and intravascular ultrasound (IVUS) could provide valuable information into ischemia-causing lesions and plaque composition (5). The current clinical evidence shows that integrating intravascular imaging and physiological assessment technologies with coronary angiography could improve diagnostic accuracy and outcomes in percutaneous coronary interventions (PCIs). Moreover, in cases of intermediate stenosis, these tools can simplify the selection of the optimal PCI technique (6, 7). However, the effect of imaging- and physiology-guided revascularization on the likelihood of developing adverse reactions in cases of acute coronary syndrome (ACS) remains unclear.

The network meta-analysis by Iannaccone et al. compared outcome data of four PCI techniques including coronary angiography, FFR, IVUS, and OCT, and the meta-regression analysis found that these techniques could improve outcomes in ACS patients (8). The subgroup analysis of a recently network meta-analysis demonstrated that the guiding of PCI for ACS patients with intravascular imaging and functional assessment is superior to using angiography alone (9). However, the outcomes of these techniques on the ACS group were derived from studies where the majority, but not necessarily all, of the patients had ACS. In addition, the impact of various intravascular imaging or physiological-based strategies on the outcomes of the PCI procedure has not been well established. These limitations may limit the generalization of the conclusions. Therefore, the benefits of physiology- and imaging-guided revascularization in ACS patients are not well established. This network meta-analysis aimed at evaluating the adverse events of various different imaging- and physiology-guided angiography techniques commonly used for coronary revascularization in ACS patients.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (10) to perform this study, which was also registered at The International Database to Register Systematic Reviews (INSPLASY) with reference number INPLASY202420092.

Ethical considerations

Since this study depended on published studies and the data extracted from them or their Supplementary Material, no ethical approval or informed consent was needed.

Search strategy

An electronic database search across PubMed, Cochrane, and EMBASE yielded all eligible randomized controlled trials (RCTs) published up to 30 October 2024 using the keywords "acute coronary syndrome," "intravascular imaging," "physiology assessment," and "coronary revascularization" (Supplementary Table 1). We also examined references from all qualified studies to uncover additional studies.

Selection criteria

Patients with any form of ACS, including unstable angina, T-segment elevation myocardial infarction (STEMI), and non-STEMI (NSTEMI) were qualified for this study. Only studies comparing angiography with physiological assessment or intravascular imaging vs. physiology assessment, and those that reported composite of clinical cardiovascular outcomes or major adverse cardiovascular events (MACE) were included. Papers with duplicated data from the same population that had an extended follow-up duration and comprehensive information were included. All eligible studies were reviewed by 2 researchers. Any differences in opinion between the two researchers were reviewed and an additional expert was consulted if necessary.

Data collection

Two researchers extracted and appraised the data individually. The study characteristics and randomization technique, patient characteristics (age and gender), clinical presentation, revascularization strategies, the purpose for the intravascular imaging guidance and physiology assessment, cut-off for stent implantation, the clinical outcomes, and study follow-up duration were extracted.

Outcomes

MACE was defined as the primary outcome measure while all-cause mortality, cardiac mortality, the number of repeat revascularizations, incidence of myocardial infarction (MI), and stent thrombosis were identified as secondary outcomes (Supplementary Table 2).

Abbreviations

PCI, coronary artery disease; IVUS, intravascular ultrasound; OCT, optical coherence tomography; FFR, fractional flow reserve; PCI, percutaneous coronary interventions; ACS, acute coronary syndrome; RCTs, randomized control trials; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; RRs, risk ratios; Cis, confidence intervals; SUCRA, surface under the cumulative ranking curve; CT, complete revascularization; QFR, quantitative flow ratio; OFDI, optical frequency domain imaging.

Bias evaluation

We used the revised Cochrane risk-of-bias tool (ROB2) for assessing bias by evaluating the following five items: randomization process, missing outcome data, deviations from intended interventions, selection of the reported result, and measurement of the outcome (11). Two researchers independently categorized the studies based on the ROB2 criteria as low, some concern, or high risk.

Data analysis

The data were analyzed with the Stata version 17 software as follows. The random-effects model was utilized to compare the risk ratios (RR) and 95% confidence intervals (95%CIs) between various angiography techniques. A continuity correction of 0.5 was added to the analysis for outcomes with zero events in any group (12). The I-squared (I^2) value was calculated to determine heterogeneity. Values under 25% indicate minimal heterogeneity, 25%–50% moderate heterogeneity, and above 50% substantial heterogeneity (13). We used comparison-adjusted funnel plots to evaluate publication bias and design-by-treatment interaction model to evaluate the network-wide inconsistency (14). We checked direct and indirect evidence consistency by applying the node-splitting method to evaluate any local inconsistencies in network closed loops. The ranking of each intervention node and its relative effectiveness was calculated using cumulative probabilities as determined by surface under the cumulative ranking curve (SUCRA) values. Additionally, Visual representation of results was achieved by use of cumulative ranking plots.

Subgroup analysis

The treatment arms were divided according to the purpose of the physiological assessment and the intravascular imaging guidance method. The studies were categorized as a decision-making trial or a PCI intervention optimization trial. The two treatments were analyzed in a separate network meta-analysis.

Sensitivity analysis

To address any potential discrepancies between complete revascularization (CR) and culprit-only PCI, an additional sensitivity analysis was conducted by reclassifying each treatment arm into CR or culprit-only PCI. We then recalculated the pooled RR and SUCRA values for all outcomes and generated the corresponding cumulative rankograms.

Results

Search results

Twenty-eight RCTs were eligible for this study (Supplementary Figure 1) (15–42). The RCTs included 18,221 patients (range 63–3,505 per trial) with ACS. These trials compared a total of six interventions; angiography, FFR, IVUS, OCT, quantitative flow ratio (QFR), and optical frequency domain imaging (OFDI). The average follow-up duration varied from 6 months to 5 years. Eight RCTs (20, 25, 27, 31, 32, 34, 35, 39) conducted subgroup analysis based on ACS or non-ACS cohorts. The results of these subgroup analyses were also included. Ten trials involved patients with ACS, nine focused on patients with STEMI, five included those with NSTEMI, three targeted individuals with MI, and one trial included cases with NSTEMI or unstable angina. Supplementary Table 3 outlines the baseline characteristics of the patient.

Bias evaluation

Inadequate allocation concealment ($n = 16$), lack of blinding ($n = 5$), and missing outcome data ($n = 7$) were identified as the most common causes of bias (Supplementary Figure 2). Eight trials were classified as low risk, fourteen studies were identified as some concern, and six were categorized as high risk. The visual funnel plot analysis revealed no publication bias for MACE, all-cause and cardiac mortality, and MI. However, asymmetrical funnel plots were noted for repeat revascularization and stent thrombosis, indicating potential publication bias for these categories (Supplementary Figures 3–8).

Primary outcome

Out of the 28 RCTs, 25 ($n = 17{,}720$) were incorporated in the MACE network meta-analysis (Figure 1). The closed-loop evaluation did not reveal any global or local inconsistency ($P > 0.05$). High heterogeneity was observed for studies comparing FFR and angiography. No substantial heterogeneity was found for all other comparators (Supplementary Table 4). The forest plot showed that compared with angiography both IVUS- (RR: 0.62; 95%CI 0.46–0.85) and FFR-guided PCIs (RR: 0.62; 95%CI: 0.46–0.85) were associated with a lower MACE incidence (Figure 2). In addition, there was a reduction trend in MACE for OCT (RR: 0.85; 95%CI: 0.62–1.17) and QFR (RR: 0.77; 95%CI: 0.51–1.16) compared with angiography. However, no significant difference emerged between any of the intravascular imaging and physiological strategies. The probability analysis ranked IVUS-guided PCI as the most effective strategy in reducing MACE (SUCRA 88.6%) followed by FFR-guided PCI (SUCRA 67.3%), QFR-guided PCI (SUCRA 60%), OCT-guided PCI (SUCRA 47.8%), angiography (SUCRA 22%) and OFDI-guided PCI (SUCRA 14.3%) (Figure 3).

Secondary outcomes

The secondary outcome network plots are highlighted in Supplementary Figures 9–13. The heterogeneity between studies for each secondary outcome was calculated as shown in

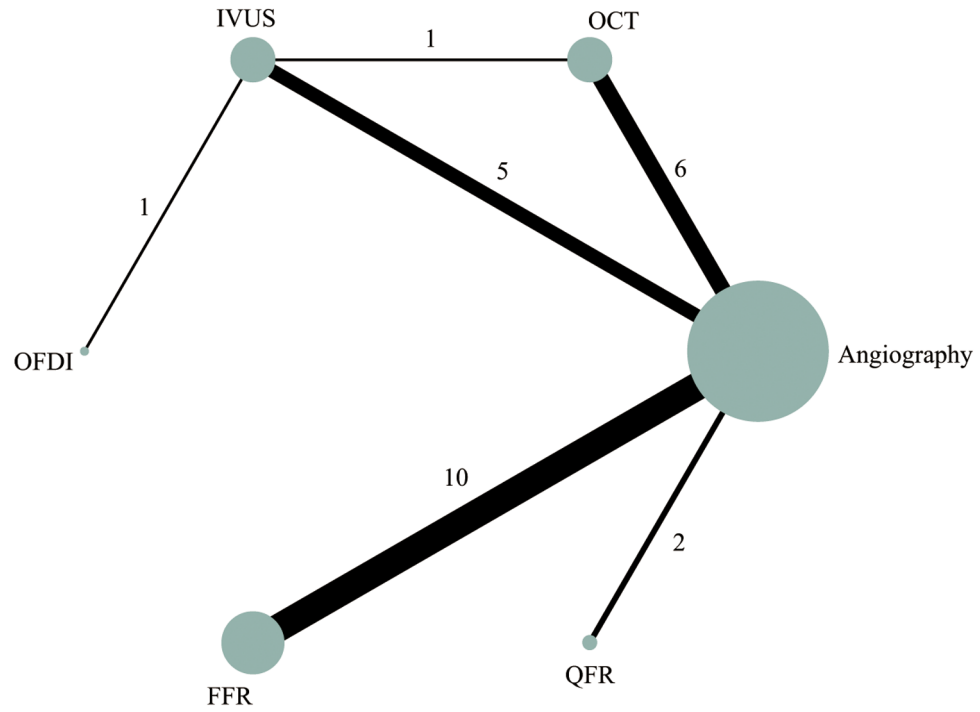

FIGURE 1
Network plot of intravascular imaging-guided, physiology-guided, and angiography-guided PCI for MACE.

Supplementary Table 4. High heterogeneity was found when comparing FFR-guided PCI with angiography for the repeat revascularization and stent thrombosis outcomes, but no substantial heterogeneity was detected in other outcomes. PCIs guided by QFR led to decreased all-cause mortality vs. angiography (RR: 0.25; 95%CI: 0.07–0.92, Supplementary Figure 14) and FFR-guided PCI (RR: 0.26; 95%CI: 0.07–0.96) (Supplementary Figure 14). In addition, compared with angiography, FFR-guided PCI was associated with a lower risk of repeat revascularization (RR: 0.64; 95%CI: 0.44–0.91, Supplementary Figure 17). No significant difference between the six techniques was noted for all other secondary outcomes (Supplementary Figure 14–18). In the cumulative rankograms, QFR-guided PCI was identified as the best intervention in reducing all-cause mortality (SUCRA 85.3%, Supplementary Figure 19) and repeat revascularization (SUCRA 81.8%, Supplementary Figure 22). IVUS-guided PCI was identified as the best approach to prevent cardiac mortality (SUCRA 75.1%), MI (SUCRA 82.6%), and stent thrombosis (SUCRA 66.6%) Supplementary Figures 20–23).

Subgroup analysis

A total of 14 RCTs were classified as decision-making or optimization trials. The revascularization strategies varied in the two MACE subgroups. FFR- and QFR-guided PCI was only used for decision-making purposes, whereas OCT- and OFDI-guided PCI were used solely to optimize the PCI procedure. IVUS-guided PCI helped lower the RR for MACE (RR: 0.60; 95%CI: 0.49–0.74, Table 1), cardiac mortality (RR: 0.45; 95%CI: 0.21–0.98, Supplementary Table 6), and MI (RR: 0.64; 95%CI: 0.45–0.93, Supplementary Table 7) in optimization subgroup when compared with the angiography. The outcomes between angiography and IVUS-guided PCI in the decision-making subgroup did not differ significantly. The subgroup analysis results for all other interventions for all outcome measures revealed similar results as those reported in the main analysis (Table 1 and Supplementary Tables 5–9).

Sensitivity analysis

Three interventions (angiography, FFR, and QFR) made use of culprit-only PCI and CR and were included in the sensitivity analysis. Compared with angiography, both IVUS-guided culprit-only PCI (RR: 0.63; 95%CI: 0.45–0.88) and FFR-guided CR (RR: 0.72; 95%CI: 0.53–0.97, Figure 4) had a lower MACE risk. Patients receiving angiography-guided CR experienced greater likelihood of death from all causes (RR: 2.64; 95%CI: 1.11–6.27 and cardiac conditions (RR: 5.64; 95%CI: 1.46–21.75) vs. IVUS-guided culprit-only PCI. The rate of all-cause mortality turned out higher for patients receiving angiography-guided CR than for those receiving QFR-guided CR (RR: 3.97; 95%CI: 1.08–14.54) (Supplementary Figures 24, 25). FFR-guided CR demonstrated lower cardiac mortality rates vs. angiography-guided CR (RR: 0.31; 95%CI: 0.11–0.88) (Supplementary Figure 25). Furthermore, angiography-guided CR produced fewer repeat revascularization

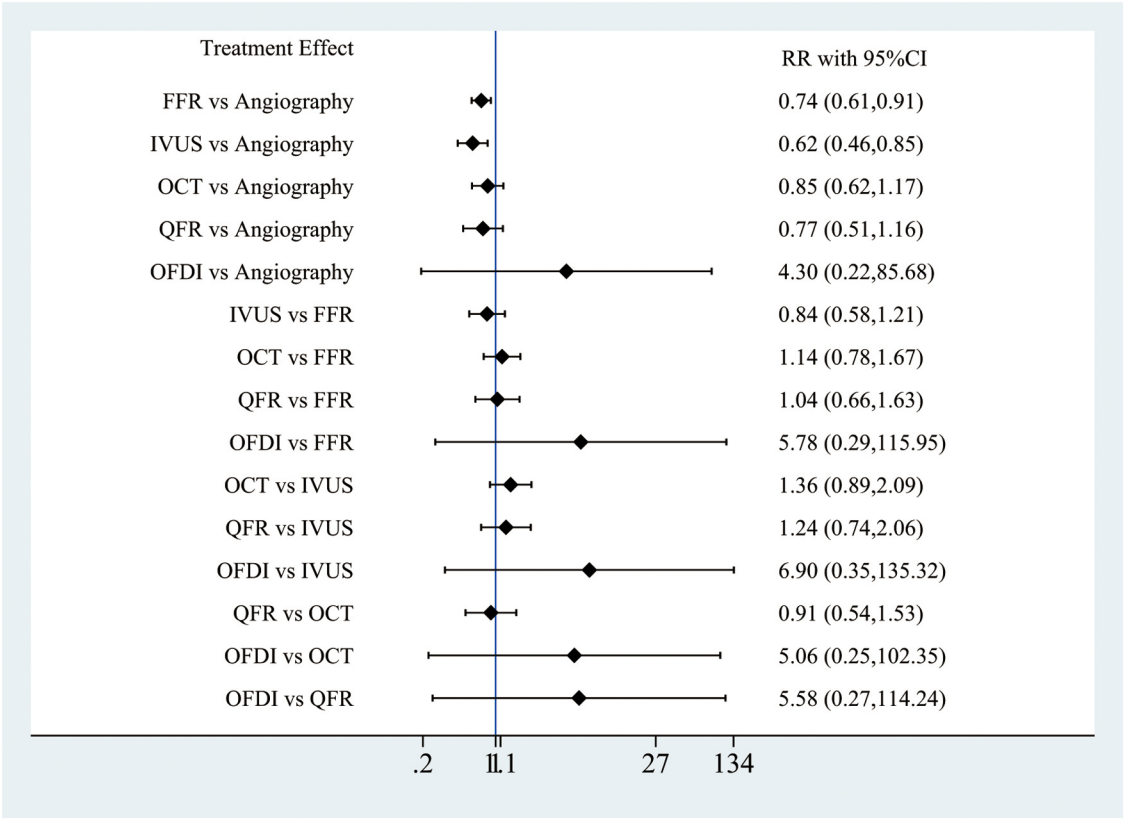

FIGURE 2
Network meta-analysis for MACE.

events than culprit-only PCIs guided by angiography (RR: 0.57; 95%CI: 0.37–0.88, Supplementary Figure 27). For stent thrombosis, FFR-guided culprit-only PCI showed higher risks than angiography-guided culprit-only PCI, IVUS-guided culprit-only PCI, and FFR-guided CR (Supplementary Figure 28). The other results did not differ significantly between all other revascularization strategies (Figure 4 and Supplementary Figure 24–28). The cumulative rankograms showed that IVUS-guided culprit-only PCI had the lowest MACE risk (SUCRA 81.5%, Supplementary Figures 29–34).

Discussion

The impact of physiology- and imaging-guided revascularization techniques on the incidence of MACE in ACS patients remains unclear. While several meta-analyses have evaluated these techniques, they often included mixed populations, limiting their applicability to ACS patients. In contrast, our study specifically focuses on ACS, providing more clinically relevant insights. Additionally, subgroup and sensitivity analyses were implemented to further assess the effectiveness of intravascular imaging and physiological assessment across different revascularization strategies (CR vs. culprit-only PCI) and intervention purposes (decision-making vs. optimization).

When PCI procedures integrated IVUS and FFR, MACE occurrence decreased vs. standard angiography. Analysis using QFR as a guidance method for PCI procedures revealed lower RR of all-cause mortality than angiography and FFR-guided PCI. Additionally, the use of FFR led to fewer cases of repeat revascularization vs. angiography. However, different revascularization methods showed similar results regarding cardiac mortality, MI, or stent thrombosis. Furthermore, IVUS-guided PCI was ranked the most effective for reducing MACE, cardiac mortality, MI, and stent thrombosis, while QFR-guided PCI ranked highest for lowering all-cause mortality and repeat revascularization. Despite these findings, the advantages of performing QFR-guided PCI remain uncertain due to restricted trial inclusion.

Another Bayesian network meta-analysis evaluated the effectiveness of intravascular imaging-guided PCI vs. angiography (43). The study outcomes demonstrated that all investigated intravascular imaging interventions (IVUS and OCT/OFDI) reduced MACE incidence compared to angiography. A recent network meta-analysis evaluating the outcomes of RCTs comparing intravascular image-guided PCI with angiography also found similar results (44). Our analysis of IVUS on MACE risk was consistent with the results observed in previously published meta-analyses (43, 44). Nevertheless, no significant effect on MACE was observed for OCT or OFDI in the present analysis.

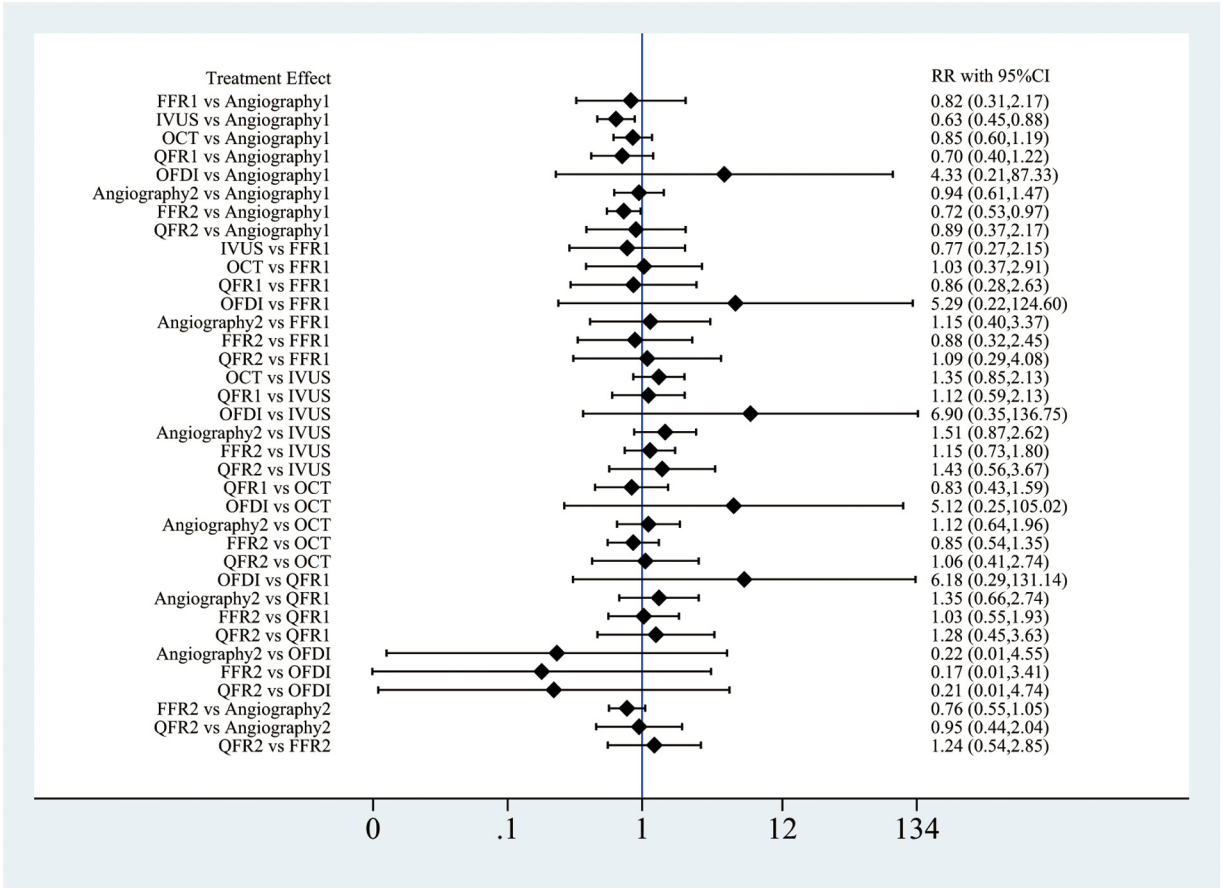

FIGURE 3
Rankogram of the six strategies for MACE.

Besides, our study only evaluated the revascularization strategies for patients with ACS. The results of our meta-analysis on IVUS align with current guidelines, which recommend intravascular imaging as a valuable tool for assisting coronary stent implantation (45). Nevertheless, results from our subgroup analysis demonstrated that IVUS-guided PCI optimization during PCI procedures decreased MACE risk levels than angiography alone, but with no significant difference was found in patients receiving IVUS for decision-making. This discrepancy was attributed to the different situations IVUS used for optimization or decision-making. IVUS is widely recommended for optimizing coronary stent implantation since it provides detailed visualization of the lumen and vessel wall. Moreover, the assessment of lesion length and external elastic lamina diameter through IVUS enables physicians to choose proper stent sizes and detect stent under expansion, malposition, tissue protrusion, edge dissection, and intramural hematoma following the PCI (46). IVUS is also commonly used as a diagnostic tool for ACS patients without significant coronary obstruction on angiography or in cases where the culprit lesion remains unclear (1). However, the RCT by Wang et al. (21) evaluated in our study, used IVUS for decision-making and only included STEMI patients. These patients tend to have severe coronary stenosis and often need stent implantation. Therefore, the subgroup analysis results regarding IVUS-guided PCI for decision-making should be interpreted with caution.

Our results indicate that relative to angiography, the implementation of FFR-guided PCI presents a significantly decrease the likelihood of developing MACE. However, the sensitivity analysis for the CR and culprit-only PCI demonstrated that the cardiovascular benefits of FFR-guided PCI were mainly driven by the effect of FFR-guided CR. Consistent with previous studies, no difference in the MACE morbidity was noted between the FFR-guided culprit-only PCI and angiography-guided CR or culprit-only PCI in our study (47). The FFR findings are in line with the recommendations of the European Society of Cardiology and American College of Cardiology guidelines (1, 45), which recommended FFR for angiographically intermediate stenoses in ACS patients with stable CAD or mild non-infarction-related artery (IRA) stenoses to assess the hemodynamic significance of the culprit or non-culprit lesion measurement. Accordingly, we assume that the MACE risk reduction in FFR-guided CR observed in our study was mainly attributed to the clinical cardiovascular outcome benefits generated by the revascularization of non-culprit vessels in ACS with multivessel disease.

Kuno et al. compared ACS and non-ACS patients separately and found that although intravascular-imaging-guided PCI

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TABLE 1 Network meta-analysis for MACE in decision-making or optimization cohorts.

Purpose	Decision-making					
Optimization	**OFDI**	NA	NA	NA	NA	NA
	NA	**QFR**	NA	1.41 (0.12,16.41)	1.05 (0.63,1.73)	0.78 (0.49,1.23)
	4.73 (0.25,91.33)	NA	**OCT**	NA	NA	NA
	6.90 (0.36,131.17)	NA	1.46 (1.08,1.97)	**IVUS**	0.74 (0.07,8.39)	0.55 (0.05,6.18)
	NA	NA	NA	NA	**FFR**	0.74 (0.60,0.92)
	4.15 (0.22,79.45)	NA	0.88 (0.69,1.11)	0.60 (0.49,0.74)	NA	**Angiography**

The bold text means intervention strategies.

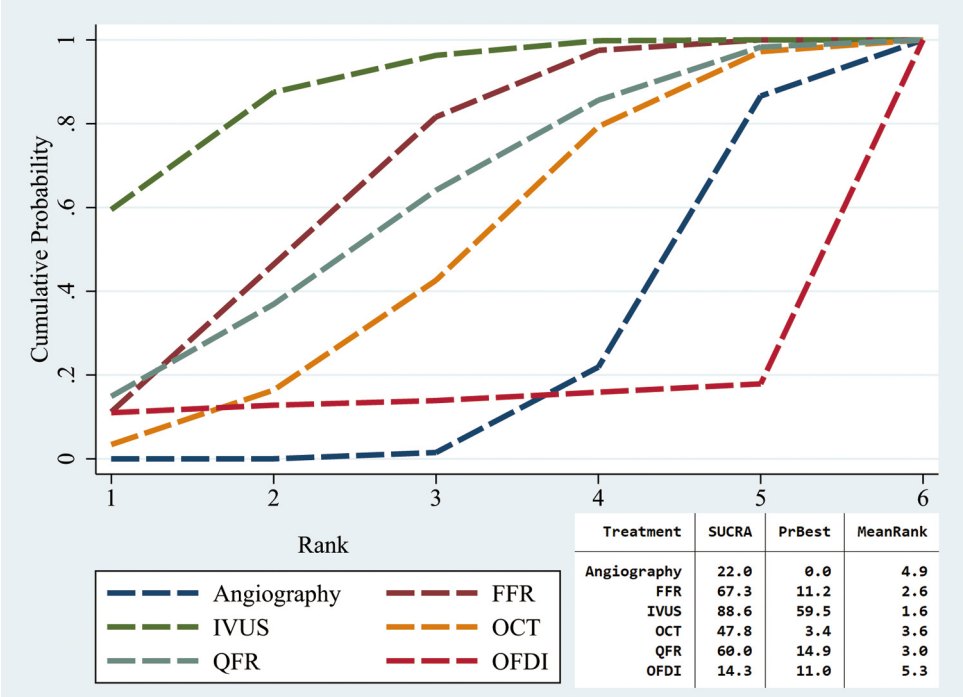

FIGURE 4
Network meta-analysis for MACE in sensitivity analysis. Angiography1, angiography-guided CR; Angiography2, Angiography-guided culprit-only PCI; FFR1, FFR-guided CR; FFR2, FFR-guided culprit-only PCI; QFR1, QFR-guided CR; QFR2, QFR-guided culprit-only PCI.

lowered the likelihood of developing MACE and other adverse events vs. angiography, no significant difference was found in the risk of developing adverse events in patients with physiology-guided PCI (9). However, this study did not examine the effects of specific intravascular imaging or physiology assessment techniques. A similar meta-analysis of RCTs evaluated the effects of IVUS-, FFR-, and OCT-guided PCI, as well as angiography, on MACE risk and found that IVUS-guided PCI was superior to angiography, while FFR-guided PCI slightly reduced the risks of adverse events following PCI (8). Additionally, the MACE reduction rate showed a direct positive correlation with the number of ACS patients who received PCIs under IVUS and FFR guidance through meta-regression analysis. Our network meta-analysis findings for IVUS-guided PCI were consistent with these studies; however, the outcomes for FFR-guided PCI differed. Notably, three of the RCTs (20, 48, 49) included in Iannaccone et al. (8) were derived from the same trial with varying follow-up durations. Furthermore, the imprecise classification of intervention strategies for FFR and angiography may have contributed to discrepancies between our analysis and prior studies.

Our findings highlight the cardiovascular benefits of IVUS-guided PCI for optimizing stent implantation and FFR-guided CR in ACS patients with multivessel disease. These results further support the application of IVUS and FFR in ACS patients. Additional large-scale trials with rigorous study designs are essential to confirm these results and establish definitive clinical guidelines provide definitive conclusions.

Limitations

Due to the lack of trials comparing intravascular imaging and physiology assessment, the findings of this study are based on indirect estimates. Additionally, limited overlap between intervention strategies in the two subgroups led to inadequate

comparisons of each intervention's effect for different purposes. Variability in the definitions of MACE and repeat revascularization across trials may have led to the introduction of bias. Furthermore, due to the limited availability of patient data, we could not analyze the temporal relationships between intravascular imaging and physiology assessment on clinical outcomes. In addition, we could not evaluate the effect of clinical and lesion type characteristics on the incidence of adverse events for each of the imaging and physiological procedures.

Conclusion

The application of IVUS- and FFR-guided PCI could improve outcomes and reduce the incidence of MACE than angiography. IVUS-guided PCI yielded the optimal results in lowering the risk of MACE, cardiac mortality, stent thrombosis, and MI while QFR-guided PCI ranked as the best modality for lowering all-cause mortality and repeat revascularization. Advanced intravascular imaging and physiological assessment exhibit clear benefits in optimizing PCI outcomes.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

X-YL: Writing – original draft, Writing – review & editing. B-HY: Writing – original draft, Writing – review & editing. X-DW: Writing – original draft. YL: Writing – review & editing. XL: Writing – review & editing. Y-YL: Writing – original draft. J-CS: Writing – original draft, Writing – review & editing.

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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References

1. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, et al. 2023 ESC guidelines for the management of acute coronary syndromes. *Eur Heart J Acute Cardiovasc Care*. (2024) 13(1):55–161. doi: 10.1093/ehjacc/zuad107 Erratum in: Eur Heart J Acute Cardiovasc Care. 2024 May 28;13(5):455. doi: 10.1093/ehjacc/zuad156.

2. Damluji AA, Forman DE, Wang TY, Chikwe J, Kunadian V, Rich MW, et al. Management of acute coronary syndrome in the older adult population: a scientific statement from the American Heart Association. *Circulation*. (2023) 147(3):e32–62. doi: 10.1161/CIR.0000000000001112

3. van Zandvoort LJC, Ali Z, Kern M, van Mieghem NM, Mintz GS, Daemen J. Improving PCI outcomes using postprocedural physiology and intravascular imaging. *JACC Cardiovasc Interv*. (2021) 14(22):2415–30. doi: 10.1016/j.jcin.2021.08.069

4. Shin DH, Hong SJ, Mintz GS, Kim JS, Kim BK, Ko YG, et al. Effects of intravascular ultrasound-guided versus angiography-guided new-generation drug-eluting stent implantation: meta-analysis with individual patient-level data from 2,345 randomized patients. *JACC Cardiovasc Interv*. (2016) 9(21):2232–9. doi: 10.1016/j.jcin.2016.07.021

5. Yang S, Koo BK. Physiology versus imaging-guided revascularization. *Where Are We in 2023? JACC Asia*. (2023) 3(3):521–5. doi: 10.1016/j.jacasi.2023.03.009

6. Koo BK, Hu X, Kang J, Zhang J, Jiang J, Hahn JY, et al. Fractional flow reserve or intravascular ultrasonography to guide PCI. *N Engl J Med*. (2022) 387(9):779–89. doi: 10.1056/NEJMoa2201546

7. Yang S, Kang J, Hwang D, Zhang J, Jiang J, Hu X, et al. Physiology- or imaging-guided strategies for intermediate coronary stenosis. *JAMA Netw Open*. (2024) 7(1): e2350036. doi: 10.1001/jamanetworkopen.2023.50036

8. Iannaccone M, Abdirashid M, Annone U, Saint-Hilary G, Meier P, Chieffo A, et al. Comparison between functional and intravascular imaging approaches guiding percutaneous coronary intervention: a network meta-analysis of randomized and propensity matching studies. *Catheter Cardiovasc Interv*. (2020) 95(7):1259–66. doi: 10.1002/ccd.28410

9. Kuno T, Kiyohara Y, Maehara A, Ueyama HA, Kampaktsis PN, Takagi H, et al. Comparison of intravascular imaging, functional, or angiographically guided coronary intervention. *J Am Coll Cardiol*. (2023) 82(23):2167–76. doi: 10.1016/j.jacc.2023.09.823

10. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Br Med J*. (2021) 372:n71. doi: 10.1136/bmj.n71

11. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. Rob 2: a revised tool for assessing risk of bias in randomised trials. *Br Med J*. (2019) 366: l4898. doi: 10.1136/bmj.l4898

12. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med*. (2004) 23(9):1351–75. doi: 10.1002/sim.1761

13. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Br Med J*. (2003) 327(7414):557–60. doi: 10.1136/bmj.327.7414.557

14. Spineli LM. Local inconsistency detection using the kullback-leibler divergence measure. *Syst Rev*. (2024) 13(1):261. doi: 10.1186/s13643-024-02680-4

15. Jakabcin J, Spacek R, Bystron M, Kvasnák M, Jager J, Veselka J, et al. Long-term health outcome and mortality evaluation after invasive coronary treatment using drug eluting stents with or without the IVUS guidance. Randomized control trial. HOME DES IVUS. *Catheter Cardiovasc Interv*. (2010) 75(4):578–83. doi: 10.1002/ccd.22244

16. Ghani A, Dambrink JH, van 't Hof AW, Ottervanger JP, Gosselink AT, Hoorntje JC. Treatment of non-culprit lesions detected during primary PCI: long-term follow-up of a randomised clinical trial. *Neth Heart J*. (2012) 20(9):347–53. doi: 10.1007/s12471-012-0281-y

17. Antonsen L, Thayssen P, Maehara A, Hansen HS, Junker A, Veien KT, et al. Optical coherence tomography guided percutaneous coronary intervention with nobori stent implantation in patients with non-ST-segment-elevation myocardial infarction (OCTACS) trial: difference in strut coverage and dynamic malapposition patterns at 6 months. *Circ Cardiovasc Interv*. (2015) 8(8):e002446. doi: 10.1161/CIRCINTERVENTIONS.114.002446

18. Engstrøm T, Kelbæk H, Helqvist S, Høfsten DE, Kløvgaard L, Holmvang L, et al. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3—pRIMULTI): an open-label, randomised controlled trial. *Lancet*. (2015) 386(9994):665–71. doi: 10.1016/s0140-6736(15)60648-1

19. Layland J, Oldroyd KG, Curzen N, Sood A, Balachandran K, Das R, et al. Fractional flow reserve vs. angiography in guiding management to optimize outcomes in non-ST-segment elevation myocardial infarction: the British heart foundation FAMOUS-NSTEMI randomized trial. *Eur Heart J*. (2015) 36(2):100–11. doi: 10.1093/eurheartj/ehu338

20. van Nunen LX, Zimmermann FM, Tonino PA, Barbato E, Baumbach A, Engstrøm T, et al. Fractional flow reserve versus angiography for guidance of PCI in patients with multivessel coronary artery disease (FAME): 5-year follow-up of a randomised controlled trial. *Lancet*. (2015) 386(10006):1853–60. doi: 10.1016/S0140-6736(15)00057-4

21. Wang HX, Dong PS, Li ZJ, Wang HL, Wang K, Liu XY. Application of intravascular ultrasound in the emergency diagnosis and treatment of patients with ST-segment elevation myocardial infarction. *Echocardiography*. (2015) 32(6):1003–8. doi: 10.1111/echo.12794

22. Meneveau N, Souteyrand G, Motreff P, Caussin C, Amabile N, Ohlmann P, et al. Optical coherence tomography to optimize results of percutaneous coronary intervention in patients with non-ST-elevation acute coronary syndrome: results of the multicenter, randomized DOCTORS study (does optical coherence tomography optimize results of stenting). *Circulation*. (2016) 134(13):906–17. doi: 10.1161/CIRCULATIONAHA.116.024393

23. Zhang Z, Li K, Tian J. Efficacy and safety outcomes of fractional flow reserve in guiding clinical therapy of non-ST-segment elevation myocardial infarction compared with angiography alone in elderly Chinese patients. *Clin Interv Aging*. (2016) 11:1751–4. doi: 10.2147/CIA.S123735

24. Kala P, Cervinka P, Jakl M, Kanovsky J, Kupec A, Spacek R, et al. OCT guidance during stent implantation in primary PCI: a randomized multicenter study with nine months of optical coherence tomography follow-up. *Int J Cardiol*. (2018) 250:98–103. doi: 10.1016/j.ijcard.2017.10.059

25. Hong SJ, Mintz GS, Ahn CM, Kim JS, Kim BK, Ko YG, et al. Effect of intravascular ultrasound-guided drug-eluting stent implantation: 5-year follow-up of the IVUS-XPL randomized trial. *JACC Cardiovasc Interv*. (2020) 13(1):62–71. doi: 10.1016/j.jcin.2019.09.033

26. Smits PC, Laforgia PL, Abdel-Wahab M, Neumann FJ, Richardt G, Boxma-de Klerk B, et al. Fractional flow reserve-guided multivessel angioplasty in myocardial infarction: three-year follow-up with cost benefit analysis of the compare-acute trial. *EuroIntervention*. (2020) 16(3):225–32. doi: 10.4244/EIJ-D-20-00012

27. Gao XF, Ge Z, Kong XQ, Kan J, Han L, Lu S, et al. 3-year outcomes of the ULTIMATE trial comparing intravascular ultrasound versus angiography-guided drug-eluting stent implantation. *JACC Cardiovasc Interv*. (2021) 14(3):247–57. doi: 10.1016/j.jcin.2020.10.001

28. Puymirat E, Cayla G, Simon T, Steg PG, Montalescot G, Durand-Zaleski I, et al. Multivessel PCI guided by FFR or angiography for myocardial infarction. *N Engl J Med*. (2021) 385(4):297–308. doi: 10.1056/NEJMoa2104650

29. Fallesen CO, Antonsen L, Maehara A, Noori M, Hougaard M, Hansen KN, et al. Optical coherence tomography- versus angiography-guided magnesium bioresorbable scaffold implantation in NSTEMI patients. *Cardiovasc Revasc Med*. (2022) 40:101–10. doi: 10.1016/j.carrev.2021.12.003

30. Jia H, Dai J, He L, Xu Y, Shi Y, Zhao L, et al. EROSION III: a multicenter RCT of OCT-guided reperfusion in STEMI with early infarct artery patency. *JACC Cardiovasc Interv*. (2022) 15(8):846–56. doi: 10.1016/j.jcin.2022.01.298

31. Song L, Xu B, Tu S, Guan C, Jin Z, Yu B, et al. 2-year outcomes of angiographic quantitative flow ratio-guided coronary interventions. *J Am Coll Cardiol*. (2022) 80(22):2089–101. doi: 10.1016/j.jacc.2022.09.007

32. Ali ZA, Landmesser U, Maehara A, Matsumura M, Shlofmitz RA, Guagliumi G, et al. Optical coherence tomography-guided versus angiography-guided PCI. *N Engl J Med*. (2023) 389(16):1466–76. doi: 10.1056/NEJMoa2305861

33. Barauskas M, Žiubrytė G, Jodka N, Unikas R. Quantitative flow ratio vs. angiography-only guided PCI in STEMI patients: one-year cardiovascular outcomes. *BMC Cardiovasc Disord*. (2023) 23(1):136. doi: 10.1186/s12872-023-03153-7 Erratum in: BMC Cardiovasc Disord. 2023 March 30;23(1):174. doi: 10.1186/s12872-023-03189-9.

34. Holm NR, Andreasen LN, Neghabat O, Laanmets P, Kumsars I, Bennett J, et al. OCT or angiography guidance for PCI in complex bifurcation lesions. *N Engl J Med*. (2023) 389(16):1477–87. doi: 10.1056/NEJMoa2307770

35. Kang DY, Ahn JM, Yun SC, Hur SH, Cho YK, Lee CH, et al. Optical coherence tomography-guided or intravascular ultrasound-guided percutaneous coronary intervention: the OCTIVUS randomized clinical trial. *Circulation*. (2023) 148(16):1195–206. doi: 10.1161/CIRCULATIONAHA.123.066429

36. Lee JM, Kim HK, Park KH, Choo EH, Kim CJ, Lee SH, et al. Fractional flow reserve versus angiography-guided strategy in acute myocardial infarction with multivessel disease: a randomized trial. *Eur Heart J*. (2023) 44(6):473–84. doi: 10.1093/eurheartj/ehac763

37. Zhang J, Yao M, Jia X, Feng H, Fu J, Tang W, et al. The efficacy and safety of quantitative flow ratio-guided complete revascularization in patients with ST-segment elevation myocardial infarction and multivessel disease: a pilot randomized controlled trial. *Cardiol J*. (2023) 30(2):178–87. doi: 10.5603/CJ.a2021.0111

38. Böhm F, Mogensen B, Engstrøm T, Stankovic G, Srdanovic I, Lønborg J, et al. FFR-guided complete or culprit-only PCI in patients with myocardial infarction. *N Engl J Med*. (2024) 390(16):1481–92. doi: 10.1056/NEJMoa2314149

39. Hong SJ, Lee SJ, Lee SH, Lee JY, Cho DK, Kim JW, et al. Optical coherence tomography-guided versus angiography-guided percutaneous coronary intervention for patients with complex lesions (OCCUPI): an investigator-initiated, multicentre, randomised, open-label, superiority trial in South Korea. *Lancet*. (2024) 404(10457):1029–39. doi: 10.1016/S0140-6736(24)01454-5

40. Li X, Ge Z, Kan J, Anjum M, Xie P, Chen X, et al. Intravascular ultrasound-guided versus angiography-guided percutaneous coronary intervention in acute coronary syndromes (IVUS-ACS): a two-stage, multicentre, randomised trial. *Lancet*. (2024) 403(10439):1855–65. doi: 10.1016/S0140-6736(24)00282-4

41. Otake H, Kubo T, Hibi K, Natsumeda M, Ishida M, Kataoka T, et al. Optical frequency domain imaging-guided versus intravascular ultrasound-guided percutaneous coronary intervention for acute coronary syndromes: the OPINION ACS randomised trial. *EuroIntervention*. (2024) 20(17):e1086–97. doi: 10.4244/EIJ-D-24-00314

42. Ullrich-Daub H, Olschewski M, Schnorbus B, Belhadj KA, Köhler T, Vosseler M, et al. Quantitative flow ratio or angiography for the assessment of non-culprit lesions in acute coronary syndromes, a randomized trial. *Clin Res Cardiol*. (2025) 114 (6):729–37. doi: 10.1007/s00392-024-02484-5

43. Buccheri S, Franchina G, Romano S, Puglisi S, Venuti G, D'Arrigo P, et al. Clinical outcomes following intravascular imaging-guided versus coronary angiography-guided percutaneous coronary intervention with stent implantation: a systematic review and Bayesian network meta-analysis of 31 studies and 17,882 patients. *JACC Cardiovasc Interv*. (2017) 10(24):2488–98. doi: 10.1016/j.jcin.2017.08.051

44. Stone GW, Christiansen EH, Ali ZA, Andreasen LN, Maehara A, Ahmad Y, et al. Intravascular imaging-guided coronary drug-eluting stent implantation: an updated network meta-analysis. *Lancet*. (2024) 403(10429):824–37. doi: 10.1016/S0140-6736(23)02454-6

45. Writing Committee Members, Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *J Am Coll Cardiol*. (2022) 79(2):e21–e129. doi: 10.1016/j.jacc.2021.09.006 Erratum in: J Am Coll Cardiol. 2022 April 19;79(15):1547. doi: 10.1016/j.jacc.2022.03.330. Erratum in: J Am Coll Cardiol. 2024 August 20;84(8):771. doi: 10.1016/j.jacc.2024.07.010.

46. Räber L, Mintz GS, Koskinas KC, Johnson TW, Holm NR, Onuma Y, et al. Clinical use of intracoronary imaging. Part 1: guidance and optimization of coronary interventions. An expert consensus document of the European association of percutaneous cardiovascular interventions. *Eur Heart J*. (2018) 39(35):3281–300. doi: 10.1093/eurheartj/ehy285 Erratum in: Eur Heart J. 2019 January 14;40(3):308. doi: 10.1093/eurheartj/ehy460.

47. Elbadawi A, Dang AT, Hamed M, Eid M, Prakash Hiriyur Prakash M, Saleh M, et al. FFR- versus angiography-guided revascularization for nonculprit stenosis in STEMI and multivessel disease: a network meta-analysis. *JACC Cardiovasc Interv*. (2022) 15(6):656–66. doi: 10.1016/j.jcin.2022.01.002

48. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med*. (2009) 360(3):213–24. doi: 10.1056/NEJMoa0807611

49. Sels JW, Tonino PA, Siebert U, Fearon WF, Van't Veer M, De Bruyne B, et al. Fractional flow reserve in unstable angina and non-ST-segment elevation myocardial infarction experience from the FAME (fractional flow reserve versus angiography for multivessel evaluation) study. *JACC Cardiovasc Interv*. (2011) 4(11):1183–9. doi: 10.1016/j.jcin.2011.08.008

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Reserve of global constructive work for early diagnosis of myocardial ischemia and risk stratification in chronic coronary syndrome

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Background: In chronic coronary syndrome (CCS), assessing myocardial ischemia is difficult due to its variable severity. Myocardial mechanical parameters are helpful in ischemia detection. This study investigates the use of non-invasive myocardial work (MW) for ischemia detection and risk assessment in CCS patients.

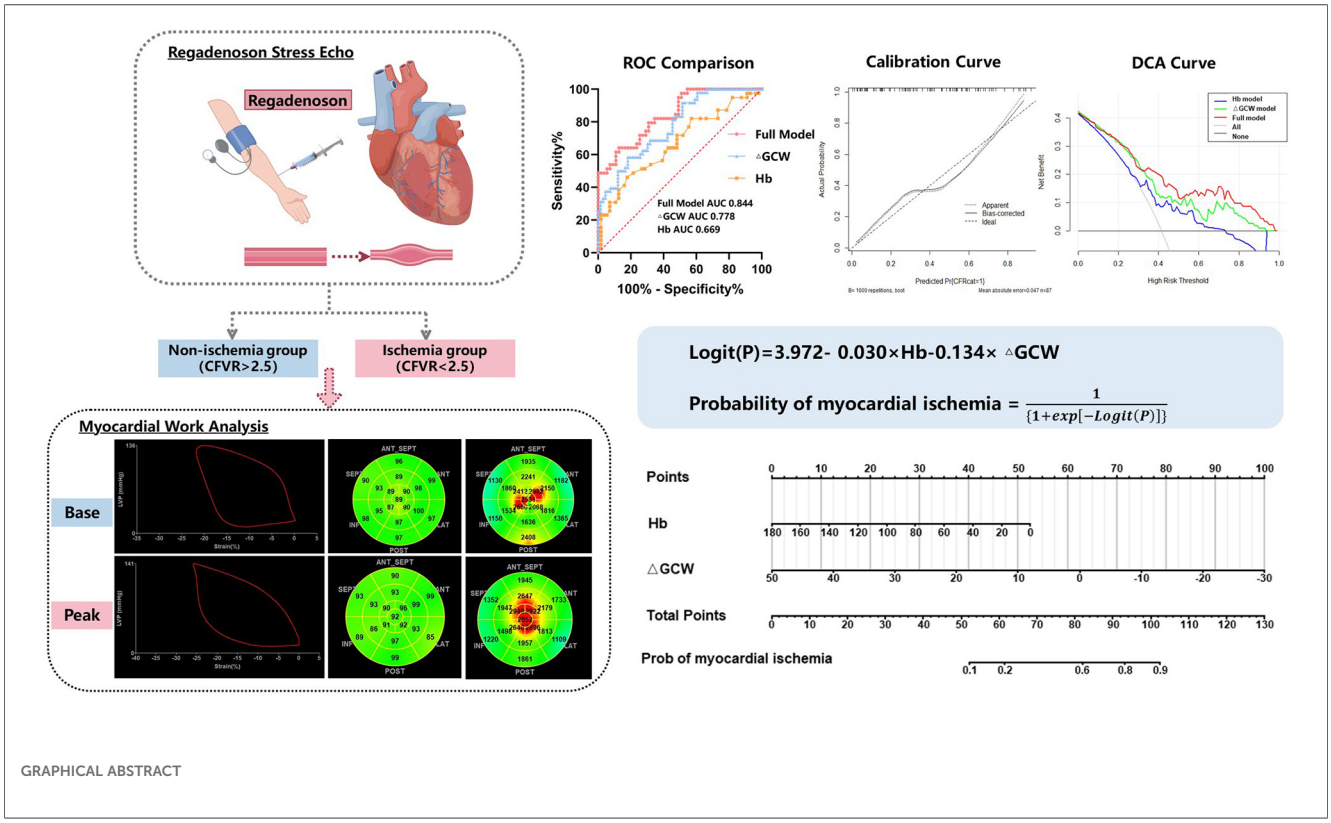
Method: The study included 115 patients (70 men, mean age 61 years) with suspected or diagnosed CCS in the derivation cohort and 62 patients in the validation cohort. All patients underwent regadenoson stress echocardiography, with early ischemia indicated by coronary flow velocity reserve (CFVR) <2.5. The patients were categorized based on CFVR, and logistic regression was used to assess the association between myocardial work (MW) and ischemia. Model performance was evaluated for accuracy, prediction, and practicality. The risk stratification thresholds were set by sensitivity and specificity.

Results: Of the 115 patients, 48 (41.74%) had myocardial ischemia. MW was more sensitive in detecting ischemia than global longitudinal strain. Multivariate analysis showed that global constructive work reserve (△GCW) was independently correlated with CFVR, with the highest AUC (0.777). A model including △GCW and hemoglobin identified ischemia with a C-index of 0.844 in the derivation cohort and 0.82 in the validation cohort, allowing calculation of the probability of ischemia in CCS. Risk levels were defined by probabilities of 20% (low) and 70% (high).

Conclusion: The incorporation of △GCW and hemoglobin into the prediction model enhances its ability to estimate myocardial ischemia risk. △GCW offered higher sensitivity and incremental diagnostic value in detecting myocardial ischemia in the heterogeneous CCS population.

KEYWORDS

chronic coronary syndrome, myocardial ischemia, myocardial work, stress echocardiography, coronary flow velocity reserve



GRAPHICAL ABSTRACT

1 Introduction

Chronic coronary syndromes (CCS) encompass a range of coronary issues such as microvascular dysfunction and vessel stenosis, leading to significant clinical diversity (1, 2). Current CCS guidelines emphasize myocardial ischemia as a critical factor in decision-making and prognosis assessment (3–7). However, due to the pathophysiological diversity of coronary lesions in CCS, the extent of myocardial ischemia in patients with CCS is highly heterogeneous and complex. Early and accurate identification of myocardial ischemia is challenging in the evaluation of CCS.

Reduced coronary flow velocity reserve (CFVR) is an early indicator of ischemia in both obstructive and non-obstructive CCS (8). The CFVR acquisition rate is lower in exercise/dobutamine SE and in the unskilled compared with vasodilator SE and in the skilled (9, 10).

Myocardial ischemia would induce myocardial mechanical alterations. However, the presentation of myocardial mechanical alteration in different extents of myocardial ischemia may vary. The positivity of regional wall motion abnormality (RWMA) is now declining in SE (11, 12). Thus, it presents a challenge in screening for the most sensitive index of myocardial mechanics in the context of myocardial ischemia. Myocardial work (MW) is a novel index of myocardial mechanics derived from a proprietary left ventricular pressure–strain loop (LV PSL) (13). In comparison to global longitudinal strain (GLS), MW is a superior option in SE. The latter incorporates aspects such as afterload, energy metabolism, and multiparameter analysis, which contribute to its superiority (14, 15). Thus, our study aimed to investigate whether MW was suitable to be applied in the identification of early myocardial ischemia in the context of heterogenous CCS.

2 Method

2.1 Study population

2.1.1 Derivation cohort

The study prospectively enrolled patients suspected of or diagnosed with CCS in Wuhan Union Hospital, Tongji Medical College, Huazhong University of Science and Technology from January 2022 to December 2023. Other inclusion criteria included successful acquisition of mid-distal left anterior descending coronary (LAD) blood flow and Doppler spectrum; apical four-chamber, three-chamber, and two-chamber views; and age over 18 years. The exclusion criteria were as follows: (1) left ventricular ejection fraction (LVEF) $\leq 50\%$, significant valvular disease, congenital heart disease, and inherited or acquired cardiomyopathy; (2) patients with contradictions to regadenoson—second-degree/third-degree atrioventricular block, sick sinus syndrome, acute coronary syndrome, decompensated heart failure, excessive low blood pressure, asthma, chronic obstructive pulmonary disease; (3) inadequate acoustic window; and (4) significant cardiac arrhythmia.

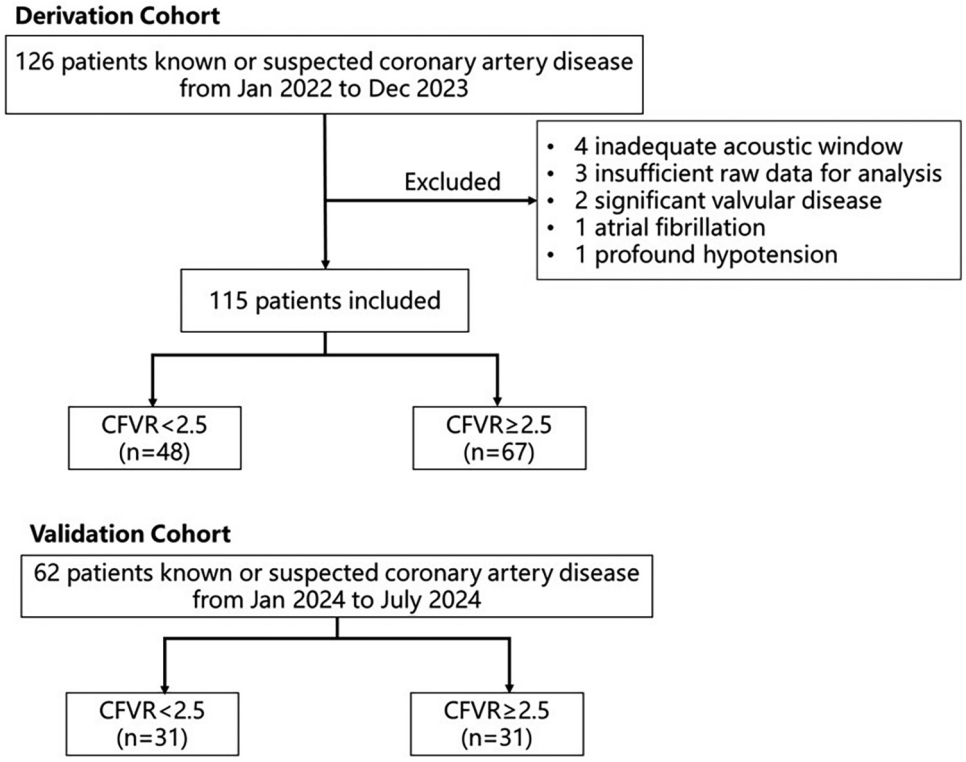


FIGURE 1
Patient flowchart in the study.

All patients underwent transthoracic echocardiography (TTE), including speckle-tracking analysis imaging, MW analysis, and regadenoson SE with an assessment of coronary flow velocity reserve (CFVR) of mid-distal LAD. Myocardial ischemia was defined as CFVR < 2.5 (16). The patients were divided into two groups based on CFVR. All the patients were processed to either coronary angiography or coronary CT angiography after completion of regadenoson SE. The trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Institutional Ethics Board of Wuhan Union Hospital, Tongji Medical College, Huazhong University of Science and Technology. All patients provided written informed consent.

2.1.2 Validation cohort

The validation cohort consisted of prospectively enrolled patients who were suspected to have CCS from January 2024 to July 2024. During this period, 62 subjects who met the inclusion and exclusion criteria mentioned above were included in the final analysis to validate the ischemia model (Figure 1).

2.2 Conventional echocardiography

Comprehensive conventional TTE at rest was performed using a commercially available ultrasound machine (Vivid E95, GE HealthCare, Horten, Norway), based on the latest guideline (17). Left ventricular ejection fraction (LVEF) was calculated by the biplane Simpson's method. The left atrial volume index (LAVI) was calculated as left atrial volume divided by body surface area. In the apical four-chamber view, Doppler ultrasound was applied to measure mitral valve inflow. Accordingly, mitral valve septal annulus movement was recorded by tissue Doppler imaging.

2.3 Regadenoson stress echocardiography and CFVR

Baseline two-dimensional grayscale images were initially recorded from the apical four-chamber, three-chamber, and two-chamber views at frame rates ranging from 50 to 80 fps to facilitate speckle-tracking and myocardial work analysis. We then used Doppler mapping with a 0.25 m/s velocity scale to find the baseline LAD. The scale was actively modified to provide optimal images. The mid-distal LAD was searched in modified apical two- and three-chamber views or modified parasternal short- and long-axis views. A sample volume (1.5–2 mm) was placed on the color signal in the mid-distal LAD to obtain pulse-wave Doppler flowmetry. Finally, the patients underwent regadenoson SE under a dose of 0.4 mg bolus injection according to the latest guideline (18). Pulse-wave Doppler flowmetry of mid-distal LAD and cine loop of apical four-chamber, three-chamber, and two-chamber views at hyperemic peak were recorded for CFVR analysis or stress myocardial work analysis. The interruption criteria were

severe, intolerable chest pain, intolerable dyspnea, marked electrocardiography positivity, significant arrhythmia, excessive hypotension [systolic blood pressure (SBP) ≤ 90 mmHg, diastolic blood pressure (DBP) ≤ 60 mmHg], or hypertension (SBP ≥ 220 mmHg, DBP ≥ 120 mmHg). Blood pressure was recorded at baseline and 1 min intervals after regadenoson injection. CFVR was defined as the ratio between hyperemic peak and baseline diastolic coronary flow velocities. CFVR < 2.5 was defined as ischemia. The examination was performed under continuous electrocardiography and blood pressure monitoring. The aminophylline was prepared to reverse regadenoson in necessity.

2.4 Speckle-tracking analysis and myocardial work analysis

Left ventricular global longitudinal strain (GLS) was analyzed on a vendor-specific workstation (Echopac version 204; GE Vingmed Ultrasound AS, GE Medical Systems). Following the initiation of the Q-analysis module and manual adjustment of the LV endocardium, the workstation tracked the LV endocardium automatically. The GLS was calculated from the average longitudinal strain of all the LV segments.

MW was calculated on the same workstation. In the dynamic video of the apical three-chamber view, the first frame of the opening and closure of the aortic and mitral valves was selected as the time point of valve switching. After calculating the strain, inputting the stored branchial blood pressure, and identifying the opening and closure of the mitral valve and aortic valve, we could obtain the non-invasive LV pressure–strain loop (LV PSL). Global work index (GWI) is the total work done by the ventricle during mechanical systole (area within the LV PSL curve). Global contractive work (GCW) is positive work performed by a segment in systole and negative work (segment lengthening) during isovolumic relaxation. Global waste work (GWW) is negative work (segment lengthening) during systole and positive work (segment shortening) during isovolumic relaxation. Global work efficiency (GWE) is equal to GCW/(GCW + GWW).

GLS and MW were measured both at baseline and at hyperemic peak. The reserve of LVEF, GLS, or MW is defined as the difference between the peak state and baseline state divided by the baseline state, recorded as Δ.

2.5 Coronary angiography or coronary CT angiography

All the patients underwent either coronary angiography or coronary CT angiography. The interval between coronary angiography/coronary CT and SE should be no more than 3 months. Obstructive coronary artery disease (CAD) was defined as ≥50% stenosis in one or more major epicardial vessels.

2.6 Statistical analysis

The statistical analysis was performed by SPSS version 25.0 (IBM Corp., Armonk, NY, USA), Medcalc 18.2.1 (MedCalc Software, Ltd., Ostend, Belgium), GraphPad Prism 8.0 (GraphPad Software, Boston, MA, USA), and R version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria). According to a normal distribution, continuous variables were presented as mean ± SD or median (Q1, Q3). Categorical variables were expressed as number (%). Accordingly, continuous variables were compared either by Student's *t*-test or Mann–Whitney *U* test. Parameters of pre- and post-stress were compared by paired rank sum tests or *t*-tests. The categorical data were analyzed by chi-squared tests or Fisher's exact tests. To avoid problems of overfitting and collinearity, multicollinearity was assessed using collinearity diagnostics (i.e., variance inflation factor >10). The correlation between continuous variables was tested using Spearman's or Pearson's correlation. The independent correlation with CFVR was tested with multivariate stepwise logistic regression. The diagnostic performance of the model and variables was reflected by the receiver operating characteristic (ROC) curve and the area under the curve (AUC). The calibration of the model was reflected by the calibration curve. The model was validated in the validation cohort. All tests were two-sided, and $P < 0.05$ was statistically significant.

3 Results

3.1 Demographic data and clinical data

The study prospectively included 126 patients with known or suspected coronary artery disease. Eleven patients were excluded (four with inadequate acoustic window, three with insufficient raw data for analysis, two with significant valvular disease, one with atrial fibrillation, one with extensive hypotension), and 115 patients were included in the study. There were 48 patients with CFVR < 2.5, accounting for 41.74% of the study (Figure 1). All the demographic data, clinical characteristics, coronary status, laboratory results, and current medication treatment were compared between the two groups in Table 1. The average age of the enrolled population was 61.00 (56–66.5) years; 61.40% of the subjects were male. As shown in Table 1, there are 64 (55.65%) patients with obstructive CAD. Of these patients, 25% had coronary stenosis between 50% and 70%, and 35.4% had coronary stenosis of 70% or more. Approximately 55.65% of patients' culprit vessel was LAD. There were no significant differences between the two groups in the culprit vessels, stenosis rate, and the number of coronary arteries involved. Patients with CFVR < 2.5 tended to be older ($P = 0.016$) and have lower hemoglobin ($P = 0.005$) than those in patients with CFVR > 2.5. In addition, the baseline characteristics of the two groups were not statistically different.

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TABLE 1 Clinical characteristics of the patients.

Variable	Total (n = 115)	CFVR ≥ 2.5 (n = 67)	CFVR < 2.5 (n = 48)	P
Gender/male, n (%)	70 (61.4)	40 (59.7)	30 (62.5)	0.656
Age/year, M (Q_1, Q_3)	61.00 (56, 66.5)	60.00 (54, 65)	63.50 (58.5, 70.25)	0.016
Height/cm, M (Q_1, Q_3)	166.00 (160, 170.5)	165.50 (158, 170)	167.00 (161, 173)	0.158
Weight/kg, M (Q_1, Q_3)	68.00 (60, 74.25)	67.27 (60.25, 73.75)	68.00 (60, 74.50)	0.973
BMI/kg/m^2, M (Q_1, Q_3)	24.39 (22.31, 26.50)	24.75 (22.5, 26.93)	23.53 (22.04, 25.06)	0.175
HR/bpm, Mean ± SD	71.27 ± 10.83	70.22 ± 10.42	72.73 ± 11.32	0.223
SBP/mmHg, Mean ± SD	129.97 ± 12.26	128.45 ± 11.63	132.08 ± 12.91	0.117
DBP/ mmHg, M (Q_1, Q_3)	80.00 (74.00, 87.5)	80.00 (74, 86)	79.00 (73.75, 89.5)	0.952
HBP, n (%)	59 (51.3)	33 (49.25)	26 (54.17)	0.603
DM, n (%)	27 (23.68)	17 (25.37)	10 (21.28)	0.613
CCS score				0.135
I	87 (75.65)	54 (80.60)	33 (68.75)	
II	26 (22.61)	13 (19.40)	13 (27.08)	
III	2 (1.74)	0 (0)	2 (4.17)	
IV	0 (0)	0 (0)	0 (0)	
Coronary status				
Obstructive CAD, n (%)	64 (55.65)	35 (52.24)	29 (60.42)	0.384
Culprit vessel, n (%)				0.700
Non	23 (20.00)	12 (17.91)	11 (22.92)	
LM	1 (0.87)	0 (0)	1 (2.08)	
LAD	64 (55.65)	39 (58.21)	25 (52.08)	
RCA	14 (12.17)	8 (11.94)	6 (12.5)	
LCX	13 (11.3)	8 (11.94)	5 (10.42)	
Vessel involved, n (%)				0.832
Single vessel	32 (27.83)	17 (25.37)	15 (31.25)	
Two-vessel	19 (16.52)	11 (16.42)	8 (16.67)	
Three-vessel	13 (11.3)	7 (10.45)	6 (12.5)	
Stenosis rate, %	50 (20,7)	50 (20,7)	50 (14,77.5)	0.587
Stenosis rate classification				0.520
0%–50%	52 (45.2)	33 (49.3)	19 (39.6)	
50%–70%	24 (20.9)	12 (17.9)	12 (25.0)	
70%–100%	39 (33.9)	22 (32.8)	17 (35.4)	
Gensini score	12.75 (3.12,26)	12 (3.12,25.75)	13 (3.12,29.25)	0.543
MI, n (%)	8 (6.96)	3 (4.48)	5 (10.42)	0.388
History of PCI, n (%)	15 (13.04)	11 (16.42)	4 (8.33)	0.204
Laboratory results				
Hb/g/L, M (Q_1, Q_3)	130.00 (122, 144)	139.00 (125, 146)	125.00 (112, 140)	0.005
Fglu/mmol/L, M (Q_1, Q_3)	5.30 (4.8, 6.1)	5.20 (4.65, 6.05)	5.45 (4.9, 6.2)	0.139
TC/mmol/L, M (Q_1, Q_3)	3.69 (3.18, 4.58)	3.74 (3.38, 4.54)	3.66 (3.13, 4.64)	0.267
TG/mmol/L, M (Q_1, Q_3)	1.17 (0.92, 1.72)	1.29 (0.96, 1.78)	1.09 (0.77, 1.46)	0.128
HDL-c/mmol/L, M (Q_1, Q_3)	1.09 (0.88, 1.37)	1.12 (0.88, 1.3)	1.05 (0.88, 1.39)	0.906
LDL-c/mmol/L, M (Q_1, Q_3)	1.94 (1.53, 2.87)	2.01 (1.53, 2.98)	1.93 (1.53, 2.55)	0.497
NT-proBNP/pg/L, M (Q_1, Q_3)	72.50 (32.5, 104)	73.10 (48.25, 107.75)	65.00 (32.70, 77.8)	0.459
cTNI/ng/L, M (Q_1, Q_3)	2.90 (1.8, 4.5)	2.80 (1.63, 4.27)	3.00 (2.25, 7.6)	0.138
HsCRP/mg/L, M (Q_1, Q_3)	1.20 (0.46, 3.41)	1.24 (0.48, 3.41)	1.13 (0.44, 3.24)	0.814
Medications				
ACEI/ARB, n (%)	42 (36.84)	24 (36.36)	18 (37.5)	0.901
Antiplatelet, n (%)	73 (64.04)	40 (60.61)	33 (68.75)	0.371
β-blocker, n (%)	46 (40.35)	23 (34.85)	23 (47.92)	0.16
Calcium channel blocker, n (%)	30 (26.32)	20 (30.3)	10 (20.83)	0.257
Statin, n (%)	71 (62.28)	39 (59.09)	32 (66.67)	0.41
Nicorandil, n (%)	29 (25.44)	17 (25.76)	12 (25)	0.927

BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; HBP, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; LM, left main artery; LAD, left anterior descending artery; RCA, right coronary artery; LCX, left circumflex artery; MI, myocardial infarction; PCI, percutaneous coronary intervention; Hb, hemoglobin; Fglu, fasting glucose; TC, total cholesterol; TG, triglyceride; HDL-c, high density lipoprotein; LDL-c, low density lipoprotein; NT-proBNP, N-terminal B-type natriuretic peptide; cTNI, cardiac troponin I; HsCRP, high-sensitivity C-reactive protein; ACEI, angiotensin-converting enzyme inhibitor; ARB, Angiotensin II Receptor Blocker.

TABLE 2 Conventional echocardiographic parameters in the two groups.

Variable	Total (n = 115)	CFVR ≥ 2.5 (n = 67)	CFVR < 2.5 (n = 48)	P
LAVI/ml/m^2, M (Q_1, Q_3)	23.08 (18.18, 26.62)	21.90 (18.08, 26.03)	24.07 (19.05, 27.3)	0.523
LVEDVI/ml/m^2, Mean ± SD	41.51 ± 11.83	43.1 ± 13.2	39.55 ± 9.64	0.135
LVESVI/ml/m^2, M (Q_1, Q_3)	14.93 ± 5.30	15.79 ± 5.31	13.81 ± 5.14	0.060
IVSd/cm, M (Q_1, Q_3)	1.00 (0.9, 1.1)	1.00 (0.9, 1.1)	1.00 (0.9, 1.02)	0.323
RA/cm, M (Q_1, Q_3)	3.40 (3.05, 3.65)	3.30 (3, 3.6)	3.40 (3.1, 3.7)	0.272
RV/cm, Mean ± SD	3.21 ± 0.44	3.18 ± 0.43	3.26 ± 0.44	0.39
LVEF/%, Mean ± SD	65.09 ± 6.25	64.72 ± 5.92	65.61 ± 6.71	0.45
E/A	0.91 ± 0.32	0.92 ± 0.33	0.89 ± 0.32	0.721
E/e′	11.09 ± 3.63	10.91 ± 3.75	11.34 ± 3.47	0.532

LAVI, left atrial volume index; RA, right atrial transversal diameter; RV, right ventricular transversal diameter; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; IVSd, interventricular septal end-diastolic diameter; RA, right atrium; RV, right ventricle; LVEF, left ventricular ejection fraction; E, E velocity of mitral valve; A, A velocity of mitral valve; e′, early diastolic mitral annular tissue velocity.

3.2 Conventional echocardiographic data

The cardiac chamber quantification, left ventricular systolic function, and diastolic function were compared between the two groups, shown in Table 2. There was no statistical difference in any of the conventional echocardiographic parameters between the two groups.

3.3 Stress echocardiography and myocardial work analysis

3.3.1 Characterizing the response to regadenoson

In both groups, compared with the baseline, the heart rate (HR), SBP, DBP, LADV, LVEF, GLS, and GWW increased after regadenoson stress, while GWE decreased after stress. However, the responses of GWI and GCW to stress were different in the two groups. GWI and GCW tend to increase upon stress in CFVR > 2.5, while they tend to decrease significantly or with preserved efficiency in CFVR < 2.5 (Figure 2).

3.3.2 Comparison between the CFVR < 2.5 and CFVR ≥ 2.5 group

The ΔSBP and ΔLVEF were lower in the CFVR < 2.5 group. The patients with myocardial ischemia had higher LAD velocity at baseline. All the baseline MW parameters were not statistically different in the two groups. The ΔGWI, peak GCW, and ΔGCW were lower in the CFVR < 2.5 group, as shown in Table 3. The GWI, GWW, and GWE at the peak were not significantly different in the two groups, as shown in Table 3.

3.4 Predictors of myocardial ischemia and modeling

We assessed multicollinearity by collinearity diagnosis (tolerance < 0.1, variance inflation factor >10). Firstly, univariate logistic regression was performed. The parameters with $P < 0.1$ were selected for multivariate logistic regression. The diagnostic value of the parameters was evaluated by receiver operating characteristic (ROC) curves, and the area under the curve (AUC) was calculated (Supplementary Table S1). ΔGCW was the single index with the highest diagnostic value (Supplementary Table S1). Age, Hb, △SBP, △LVEF, △GWI, Peak GCW, and △GCW were all included in the multivariate logistic regression. Hb (OR = 0.971, $P = 0.008$) and △GCW (OR = 0.894, $P = 0.002$) were independent predictors of CFVR abnormality after adjusting for confounders (Table 4).

We then developed a full model integrating Hb and ΔGCW. The ROC curve of the model had an AUC of 0.844, and ΔGCW contributed most to the discrimination of myocardial ischemia (Table 5, Figure 3A, Supplementary Table S1). ΔGCW was moderately related to CFVR (rho = 0.467, $P < 0.001$) (Supplementary Figure S1). The calibration ability of the model was evaluated by the Hosmer–Lemeshow goodness of fit ($\chi^2 = 4.7337$, $P = 0.785$) and calibration curve (Figure 3B). The decision curve analysis reflects the benefits of the full model compared with a single indicator for the identification of high-risk populations and further clinical management (Figure 3C). The CFVR < 2.5 probability developed by the logistic regression was expressed as follows: probability of CFVR < 2.5 = $\frac{1}{\{1+exp[-Logit(P)]\}}$, Logit ($P$) = 3.972 − 0.03 × Hb − 0.134 × ΔGCW. A personal myocardial ischemia could be conveniently calculated using nomography (Figure 3D). The different sensitivity and specificity of the model at different cutoff points were displayed in Supplementary Table S2. We defined the probability of 20% and 70% as the cutoff value of low, medium, and high risk. Among 22 patients classified into the high-risk group, 19 patients (86.36%) were proven to have myocardial ischemia. However, in 30 patients with a probability of <20%, only 2 patients (6.67%) had myocardial ischemia (Figure 3E).

Finally, the predictive ability of the model was validated in a group of 62 patients. In this cohort, 31 patients (50%) had CFVR < 2.5. Of these 62 patients, 20 patients were defined as low risk, 16 (80%) of whom had true-negative diagnoses. In contrast, 10 patients were classified as high risk and were then totally

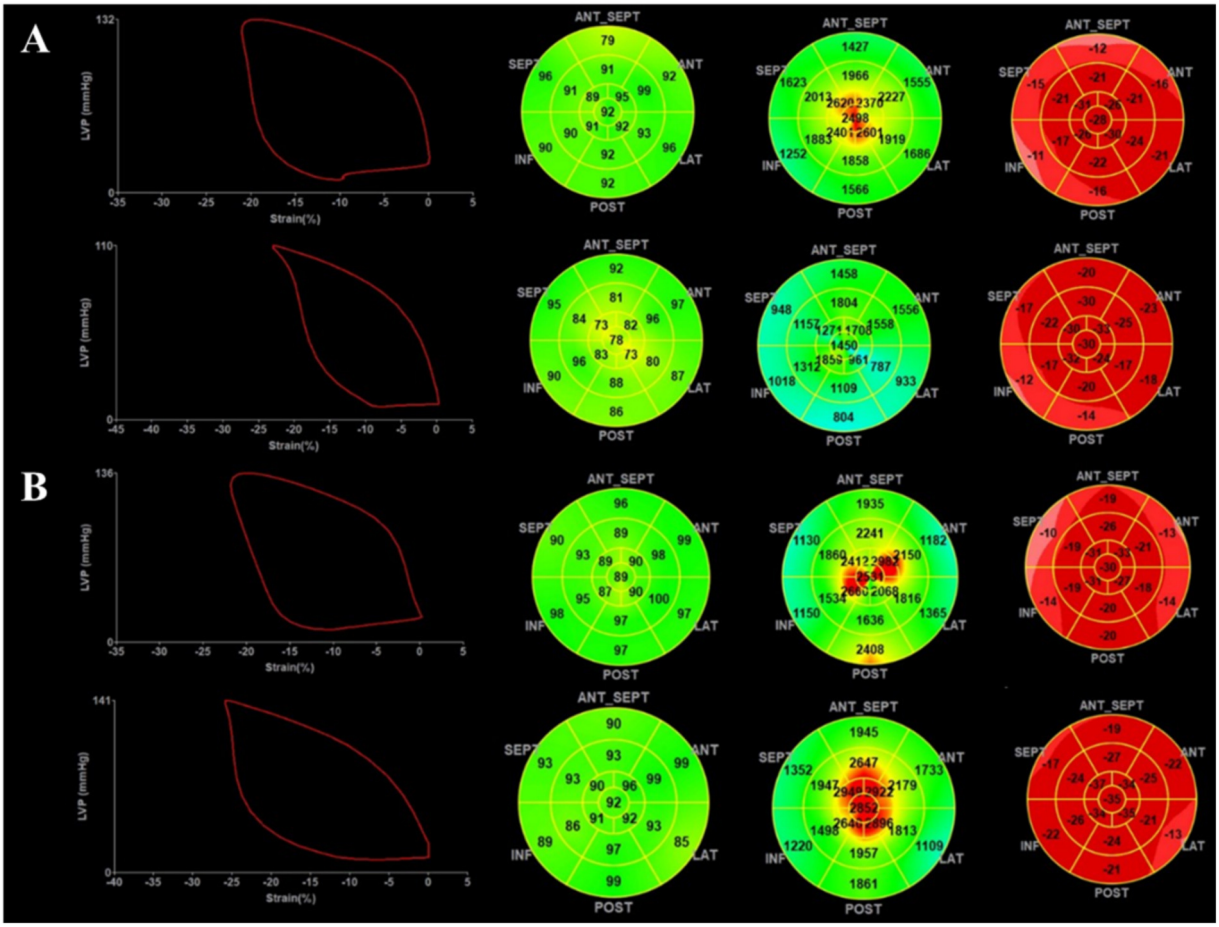

FIGURE 2
Demonstration of myocardial work during regadenoson stress. (A) Data from a patient with myocardial ischemia: the top shows myocardial work before stress, and the bottom shows myocardial work after stress. (B) Data from a patient without myocardial ischemia: the top shows myocardial work before stress, and the bottom shows myocardial work after stress.

confirmed as CFVR < 2.5 (Supplementary Figures S2A,B). The model showed good discrimination between patients with high risk and low risk of ischemia (AUC = 0.82) in the validation cohort (Supplementary Figure 2C).

3.5 Reproducibility

The reproducibility of MW was tested in 20 patients. Excellent intra-observer and inter-observer variabilities were observed in the measurement of MW parameters, which were demonstrated by intra-class correlation (ICC) (Supplementary Table S3) and Bland–Altman plots (Supplementary Figure S3).

4 Discussion

In this study, we analyzed the response of MW to regadenoson in CCS patients and subsequently, the feasibility of MW for predicting ischemia in CCS. We found that: (1) compared to the baseline status, GLS absolute value and GWW increased significantly by stress, and GWE decreased after stress. GWI and GCW would increase by stress in the CFVR ≥ 2.5 group but tend to decrease significantly or with preserved efficiency in the CFVR < 2.5 group. (2) After adjusting for confounding factors, ΔGCW and Hb are independent correlation factors for myocardial ischemia in CCS. (3) The novel full model integrating ΔGCW and Hb could be used in the estimation and risk stratification of ischemia. Non-invasive identification of high-risk patients has an important role in reducing unnecessary invasive coronary investigation and excessive revascularization.

4.1 MW outperforms GLS and RWMA in stress echocardiography for CCS

In the present study, general myocardial mechanical indices such as RWMA and GLS at rest and stress were not statistically significant between the two groups (19–22). Peak GLS only achieved an AUC of 0.581 (0.473–0.690) to predict CFVR

TABLE 3 Comparison of stress echocardiography in the two groups.

Variable	Total (n = 115)	CFVR ≥ 2.5 (n = 67)	CFVR < 2.5 (n = 48)	P
CFVR, M (Q_1, Q_3)	2.75 (2.23, 3.15)	3.07 (2.84, 3.58)	2.12 (1.94, 2.32)	**<0.001**
Base HR/bpm, Mean ± SD	71.27 ± 10.83	70.22 ± 10.42	72.73 ± 11.32	0.223
Peak HR/bpm, M (Q_1, Q_3)	92 (85, 103)[a]	89 (83.5, 102)[a]	94 (87, 103.5)[a]	0.191
ΔHR/%, Mean ± SD	31.47 ± 15.97	31.98 ± 17.47	30.76 ± 13.75	0.687
Base SBP/mmHg, Mean ± SD	129.97 ± 12.26	128.45 ± 11.63	132.08 ± 12.91	0.117
Peak SBP/mmHg, M (Q_1, Q_3)	123 (116, 136)[a]	124.00 (119, 136)[a]	121.5 (114, 136.25)[a]	0.28
ΔSBP/mmHg, Mean ± SD	−3.31 ± 7.92	−1.27 ± 7.54	−6.15 ± 7.62	**<0.001**
Base DBP/mmHg, M (Q_1, Q_3)	80 (74, 87.5)	80 (74, 86)	79 (73.75, 89.5)	0.952
Peak DBP/mmHg, Mean ± SD	75.82 ± 11.85[a]	76.72 ± 12.28[a]	74.56 ± 11.23[a]	0.339
ΔDBP/%, M (Q_1, Q_3)	−5.71 (−11.76, 0.65)	−4.65 (−10, 1.35)	−9.5 (−12.25, −2.49)	0.06
Base WMSI, M (Q_1, Q_3)	1 (1,1.2)	1 (1,1.12)	1 (1,1.25)	0.58
Peak WMSI, M (Q_1, Q_3)	1 (1,1.3)	1 (1,1.21)	1 (1,1.28)	0.34
Base LADV/m/s, Mean ± SD	0.25 ± 0.09	0.22 ± 0.06	0.29 ± 0.1	**<0.001**
Peak LADV/m/s, M (Q_1, Q_3)	0.64 (0.52, 0.76)[a]	0.64 (0.55, 0.76)[a]	0.6 (0.47, 0.74)[a]	0.052
Base LVEF/%, Mean ± SD	65.09 ± 6.25	64.72 ± 5.92	65.61 ± 6.71	0.45
Peak LVEF/%, Mean ± SD	69.62 ± 6.55[a]	70.23 ± 6.39[a]	68.79 ± 6.74[a]	0.25
ΔLVEF/%, Mean ± SD	7.29 ± 8.63	8.79 ± 8.54	5.22 ± 8.4	**0.029**
Base GLS/%, Mean ± SD	−19.84 ± 3.27	−19.86 ± 3.08	−19.81 ± 3.56	0.928
Peak GLS/%, M (Q_1, Q_3)	−22.5 (−24.05 −20)[a]	−22.90 (−24.15 −21.25)[a]	−21.70 (−24 −19.5)[a]	0.138
ΔGLS/%, M (Q_1, Q_3)	10.96 (4.55, 19.25)	12.65 (4.82, 21.66)	9.38 (2.17, 18.06)	0.088
Base GWI/mmHg%, Mean ± SD	1,951.94 ± 396.37	1,897.81 ± 340.35	2,027.5 ± 456.51	0.1
Peak GWI/mmHg%, Mean ± SD	1,964.87 ± 453.97[a]	1,999.85 ± 418.05[a]	1,916.77 ± 499.72[a]	0.337
ΔGWI/%, Mean ± SD	0.99 ± 15.7	5.79 ± 16.15	−5.61 ± 12.45	**<0.001**
Base GCW/mmHg%, Mean ± SD	2,359.83 ± 426.95	2,317.12 ± 414.12	2,419.44 ± 441.68	0.206
Peak GCW/mmHg%, Mean ± SD	2,487.42 ± 473.19[a]	2,573.52 ± 437.3[a]	2,369.04 ± 499.14	**0.022**
ΔGCW/%, Mean ± SD	5.81 ± 14.12	11.60 ± 13.66	−2.15 ± 10.47	**<0.001**
Base GWW/mmHg%, M (Q_1, Q_3)	109 (67, 159)	119.00 (70, 167)	97.00 (66.75, 152.25)	0.335
Peak GWW/mmHg%, M (Q_1, Q_3)	143.5 (82.5, 222)[a]	150.5 (87, 245.5)[a]	133.5 (73.75,202.5)[a]	0.238
ΔGWW/%, M (Q_1, Q_3)	28.18 (−24.9, 100)	30.06 (−33.07, 101.4)	25.90(−16.35, 82.11)	0.979
Base GWE/mmHg%, M (Q_1, Q_3)	95 (93, 96)	95 (93, 96)	95 (94, 96)	0.633
Peak GWE/mmHg%, M (Q_1, Q_3)	94 (91, 96)[a]	94 (90.25, 96)[a]	93.50 (91.75, 96)[a]	0.809
ΔGWE/%, M (Q_1, Q_3)	−1.05 (−3.22, 1.04)	−0.51 (−4.19, 1.04)	−1.06 (−3.13, 0.26)	0.965

[a]Statistically different between baseline and peak status.
CFVR, coronary flow velocity reserve; SBP, systolic blood pressure; DBP, diastolic blood pressure; LADV, velocity of left anterior descending artery; HR, heart rate; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; GWI, global work index; GCW, global constructive work; GWW, global waste work; GWE, global work efficiency.
The bold values mean $P < 0.05$.

TABLE 4 Logistic regression of the CFVR < 2.5 predictor.

Parameters	Univariate logistic regression		Multivariate logistic regression	
	OR (95% CI)	P	OR (95% CI)	P
Age	1.058 (1.010, 1.101)	**0.017**	1.018 (0.952, 1.088)	0.608
Hb	0.977 (0.956, 0.998)	**0.033**	0.971 (0.949, 0.992)	**0.008**
LVESV	0.966 (0.924, 1.009)	0.120		
ΔSBP	0.918 (0.871, 0.968)	**0.002**	0.978 (0.890, 1.075)	0.978
ΔLVEF	0.950 (0.907, 0.996)	**0.032**	0.964 (0.908, 1.024)	0.239
ΔGWI	0.947 (0.919, 0.976)	**0.001**	0.984 (0.939, 1.031)	0.507
Peak GCW	0.999 (0.998, 1.000)	**0.026**	1.000 (0.998, 1.001)	0.651
ΔGCW	0.902 (0.863, 0.944)	**0.001**	0.894 (0.833, 0.959)	**0.002**

The bold values mean $P < 0.05$.

abnormality, while ΔGCW achieved 0.777 (0.694–0.861) (Supplementary Table S1). MW is superior in the following aspects: Firstly, LV PSL is measured during the whole cardiac cycle, reflecting the energy utilization throughout the cardiac cycle (15). The use of multiple MW indices allows for quantitative evaluation of positive and negative output (23). Secondly, MW could overcome the afterload-dependent limitation of strain (24–26). Our study further demonstrates that the reserve of MW (ΔGCW) is a more accurate predictor of myocardial ischemia in CCS the absolute values of MW. In the ischemia group, the vasodilator would induce horizontal and vertical steel in the blood supply, resulting in uncoordinated local myocardial motion, impaired cardiac output. The GCW has precisely quantified the energy consumed by the myocardium that effectively contributes to cardiac output. Our study is consistent with the studies of Guo et al. (19) and Leitman et al. (27); GCW was sensitive to functional myocardial ischemia. But it is not consistent with Liu et al.'s (22) study that peak GLS differs in the coronary microvascular disease (CMD) group and the non-CMD group. It is possible that Liu et al.'s study was established in angina with non-obstructive coronary arteries rather than in heterogenous CCS. Consequently, the utilization of MW reserve in the diagnosis of myocardial ischemia may

TABLE 5 The performance of ΔGCW, Hb, and the new model combining ΔGCW and Hb for detecting myocardial ischemia.

Model variables	Discrimination		Reclassification				Goodness of fit
	AUC (95% CI)	*P*	NRI (95% CI)	*P*	IDI (95% CI)	*P*	AIC
Hb	0.668 (0.564, 0.762)	/	/	/	/	/	125.27
ΔGCW (%, vs. Hb)	0.777 (0.690, 0.850)	0.062	0.625 (0.349,0.902)	<0.001	0.187 (0.072,0.302)	0.001	130.41
ΔGCW + Hb (vs. ΔGCW)	0.844 (0.755, 0.911)	0.153	0.162 (−0.024, 0.346)	0.087	0.063 (0.007, 0.119)	0.028	97.55
ΔGCW + Hb (vs. Hb)	0.844 (0.755, 0.911)	0.004	0.787 (0.532, 1.042)	<0.001	0.250 (0.153,0.346)	<0.001	97.55

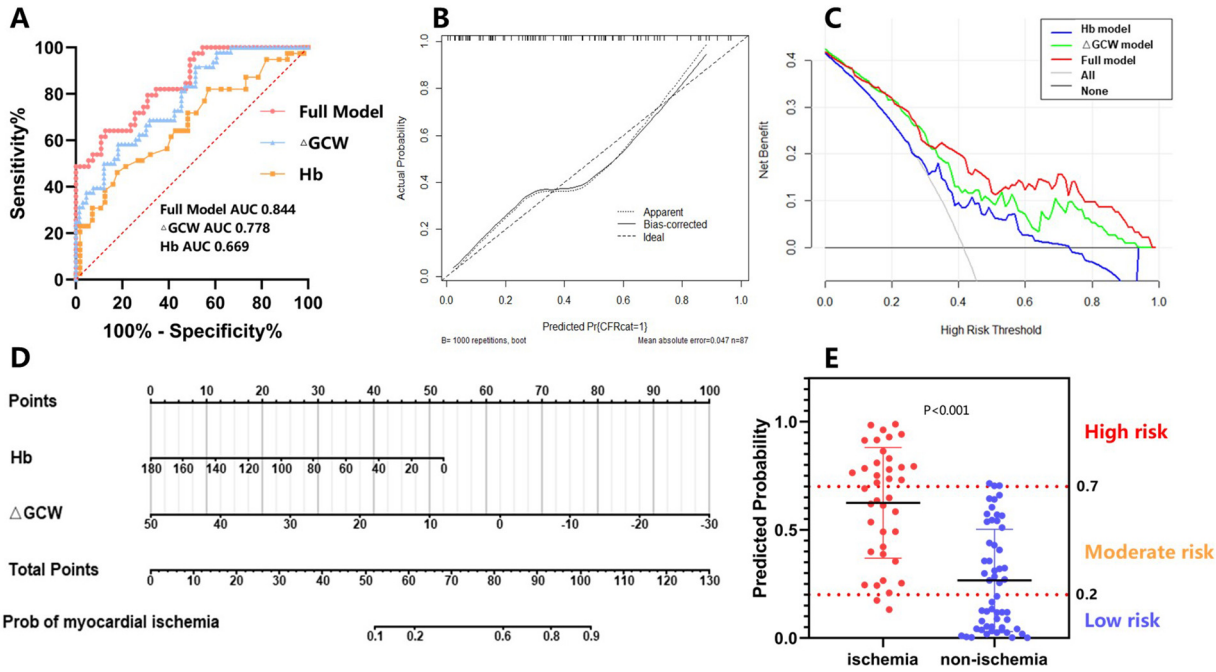

FIGURE 3
Evaluation of the model. (A) ROC curve analysis; (B) calibration analysis; (C) decision curve analysis; (D) nomograph; (E) risk stratification of the model.

circumvent the intricacies and heterogeneities of CCS, offering a comparatively objective indicator of how diverse subtypes of CCS respond to stressors.

4.2 Multivariate diagnostic model in predicting myocardial ischemia

Moreover, we conduct a novel diagnostic model to predict myocardial ischemia in CCS, which is currently lacking. In the multivariate diagnostic model, we include ΔGCW and Hb to increase the diagnostic value from 0.777 to 0.844. Our study demonstrated that Hb is an independent risk factor for myocardial ischemia (OR = 0.971, 95% CI: 0.949–0.992), which is consistent with the ARIC cohort study. The ARIC study may be the first to suggest that anemia is an independent risk factor for ischemia-related cardiovascular outcomes in the general population (HR = 1.41, 95% CI: 1.01–1.95) (28). Numerous studies have also shown that anemia is associated with poor outcomes in patients with cardiovascular disease due to chronic inflammation, inhibition of the renin–angiotensin–aldosterone system, and renal dysfunction (29–31). The degree of anemia is therefore associated with myocardial ischemia.

A combination of clinical data and stress MW indices in a multivariate model might rectify the overlap of a single factor between the two groups. A further invasive investigation into coronary physiology could be more costly and technically challenging. With a probability calculator in this study, the probability of myocardial ischemia is very low if the probability is below 20%. Of the 30 participants in this study with a probability below 20%, only 2 had myocardial ischemia. These patients could be free from further invasive coronary physiology investigation. Those with a probability of >70% were classified into the high-risk category. The probability of myocardial ischemia is relatively high among 22 patients at high risk. Only three did not have myocardial ischemia. Tight control of lipid levels, the use of anti-angina

therapy, and outpatient follow-up are essential if additional testing is not preferred. Additional testing is needed for those with moderate-risk (probability 20%–70%). The model was also applied in the validation cohort, which also showed good discrimination. The algorithm provides a framework that can be used to determine identified probability in the diagnosis of myocardial ischemia, based on a clinical and an echocardiographic parameter, rather than a binary category (present or absent).

4.3 Potential clinical implication

Reserve of MW could help us infer the probability of CFVR abnormality in vasodilator SE. Although this study was based on vasodilator stress, it also suggests that myocardial work reserve might be used to predict CFVR in situations with low CFVR success rates. The probability of myocardial ischemia in CCS could be calculated through the nomogram. The calculated likelihoods can assist clinicians in making clinical decisions.

4.4 Limitation

There are several potential limitations of the study. Firstly, this study was conducted at a single center with a small sample size, which may lead to statistical error. Further large-scale and multicenter studies need to verify the preliminary results. Secondly, the definition of myocardial ischemia was a CFVR abnormality. However, we merely measured CFVR in LAD. Myocardial ischemia in other coronary territories may be misdiagnosed. However, a study has shown that the LAD supplies approximately half of the myocardium, and ischemia in the region of LAD is strongly associated with prognosis (8). In the following study, we will validate the relation between MW and myocardial ischemia by SPECT or PET. Thirdly, only the response of MW to regadenoson was studied, and it remains unclear how MW in CCS changes under other stress modalities.

5 Conclusion

The incorporation of Hb and ΔGCW into the novel prediction model offers incremental value in estimating the likelihood of myocardial ischemia. The reserve of MW demonstrates predictive efficacy in identifying early myocardial ischemia.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Wuhan Union Hospital, Tongji Medical College, Huazhong University of Science and Technology. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

RZ: Writing – review & editing, Conceptualization, Investigation, Methodology, Writing – original draft, Software, Data curation, Project administration. JZ: Formal analysis, Writing – review & editing, Writing – original draft, Data curation, Conceptualization, Resources, Project administration, Investigation. YX: Formal analysis, Data curation, Writing – review & editing. YT: Data curation, Writing – review & editing. BQ: Writing – review & editing, Project administration, Resources, Visualization. LB: Resources, Visualization, Project administration, Writing – review & editing. JW: Project administration, Writing – review & editing, Visualization, Resources. MC: Project administration, Visualization, Writing – review & editing, Resources. XW: Project administration, Supervision, Writing – review & editing, Resources. QL: Resources, Writing – review & editing, Supervision, Validation. JW: Validation, Resources, Project administration, Writing – review & editing, Funding acquisition, Supervision. MX: Supervision, Validation, Writing – review & editing, Visualization, Project administration, Resources.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2025.1598453/full#supplementary-material

References

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart Disease and Stroke Statistics—2016 update. *Circulation*. (2016) 133(4): e38–360. doi: 10.1161/CIR.0000000000000350

2. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. (2020) 41(3):407–77. doi: 10.1093/eurheartj/ehz425

3. Tonino PAL, Fearon WF, De Bruyne B, Oldroyd KG, Leesar MA, Ver Lee PN, et al. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. *J Am Coll Cardiol*. (2010) 55(25):2816–21. doi: 10.1016/j.jacc.2009.11.096

4. Zimmermann Frederik M., Ding Victoria Y., Pijls Nico H. J., Piroth Zsolt, van Straten Albert H. M., Szekely Laszlo, Davidavicius Giedrius, et al. 2023. Fractional flow reserve-guided PCI or coronary bypass surgery for 3-vessel coronary artery disease: 3-year follow-up of the FAME 3 trial. *Circulation* 148 (12): 950–58. doi: 10.1161/CIRCULATIONAHA.123.065770

5. Ciampi Q, Zagatina A, Cortigiani L, Wierzbowska-Drabik K, Kasprzak JD, Haberka M, et al. Prognostic value of stress echocardiography assessed by the ABCDE protocol. *Eur Heart J*. (2021) 42(37):3869–78. doi: 10.1093/eurheartj/ehab493

6. Budoff MJ, Mayrhofer T, Ferencik M, Bittner D, Lee KL, Lu MT, et al. Prognostic value of coronary artery calcium in the PROMISE study (prospective multicenter imaging study for evaluation of chest pain). *Circulation*. (2017) 136(21):1993–2005. doi: 10.1161/CIRCULATIONAHA.117.030578

7. Shaw LJ, Berman DS, Maron DJ, John Mancini GB, Hayes SW, Hartigan PM, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the clinical outcomes utilizing revascularization and aggressive drug evaluation (COURAGE) trial nuclear substudy. *Circulation*. (2008) 117(10):1283–91. doi: 10.1161/CIRCULATIONAHA.107.743963

8. Picano E, Pierard L, Peteiro J, Djordjevic-Dikic A, Sade LE, Cortigiani L, et al. The clinical use of stress echocardiography in chronic coronary syndromes and beyond coronary artery disease: a clinical consensus statement from the European Association of Cardiovascular Imaging of the ESC. *Eur Heart J Cardiovasc Imaging*. (2024) 25(2):e65–90. doi: 10.1093/ehjci/jead250

9. Dagianti A, Penco M, Agati L, Sciomer S, Dagianti A, Rosanio S, et al. Stress echocardiography: comparison of exercise, dipyridamole and dobutamine in detecting and predicting the extent of coronary artery disease. *J Am Coll Cardiol*. (1995) 26(1):18–25. doi: 10.1016/0735-1097(95)00121-f

10. Wierzbowska-Drabik K, Picano E, Cortigiani L, Kasprzak JD. Comparison of coronary flow reserve feasibility in different stress echocardiography protocols: dobutamine, dipyridamole, exercise, and rapid pacing. *Pol Arch Int Med*. (2021) 131(9):830–9. doi: 10.20452/pamw.16035

11. Gaibazzi N, Ciampi Q, Cortigiani L, Wierzbowska-Drabik K, Zagatina A, Djordjevic-Dikic A, et al. Multiple phenotypes of chronic coronary syndromes identified by ABCDE stress echocardiography. *J Am Soc Echocardiogr*. (2023) 37(5):477–85. doi: 10.1016/j.echo.2023.12.003

12. Cortigiani L, Urluescu M-L, Coltelli M, Carpeggiani C, Bovenzi F, Picano E. Apparent declining prognostic value of a negative stress echocardiography based on regional wall motion abnormalities in patients with normal resting left ventricular function due to the changing referral profile of the population under study. *Circulation*. (2019) 12(6):e008564. doi: 10.1161/CIRCIMAGING.118.008564

13. Russell K, Eriksen M, Aaberge L, Wilhelmsen N, Skulstad H, Remme EW, et al. A novel clinical method for quantification of regional left ventricular pressure–strain loop area: a non-invasive Index of myocardial work. *Eur Heart J*. (2012) 33(6):724–33. doi: 10.1093/eurheartj/ehs016

14. Roemer S, Jaglan A, Santos D, Umland M, Jain R, Jamil Tajik A, et al. The utility of myocardial work in clinical practice. *J Am Soc Echocardiogr*. (2021) 34(8):807–18. doi: 10.1016/j.echo.2021.04.013

15. Edwards NFA, Scalia GM, Shiino K, Sabapathy S, Anderson B, Chamberlain R, et al. Global myocardial work is superior to global longitudinal strain to predict significant coronary artery disease in patients with normal left ventricular function and wall motion. *J Am Soc Echocardiogr*. (2019a) 32(8):947–57. doi: 10.1016/j.echo.2019.02.014

16. Chen W, Ni M, Huang H, Cong H, Fu X, Gao W, et al. Chinese expert consensus on the diagnosis and treatment of coronary microvascular diseases (2023 edition). *MedComm*. (2023) 4(6):e438. doi: 10.1002/mco2.438

17. Mitchell C, Rahko PS, Blauwet LA, Canaday B, Finstuen JA, Foster MC, et al. Guidelines for performing a comprehensive transthoracic echocardiographic examination in adults: recommendations from the American Society of Echocardiography. *J Am Soc Echocardiogr*. (2019) 32(1):1–64. doi: 10.1016/j.echo.2018.06.004

18. Pellikka PA, Arruda-Olson A, Chaudhry FA, Chen MH, Marshall JE, Porter TR, et al. Guidelines for performance, interpretation, and application of stress echocardiography in ischemic heart disease: from the American Society of Echocardiography. *J Am Soc Echocardiogr*. (2020) 33(1):1–41.e8. doi: 10.1016/j.echo.2019.07.001

19. Guo Y, Yang C, Wang X, Pei Z, Zhu H, Meng X, et al. Regional myocardial work measured by echocardiography for the detection of myocardial ischemic segments: a comparative study with invasive fractional flow reserve. *Front Cardiovasc Med*. (2022) 9:813710. doi: 10.3389/fcvm.2022.813710

20. Boe E, Russell K, Eek C, Eriksen M, Remme EW, Smiseth OA, et al. Non-invasive myocardial work Index identifies acute coronary occlusion in patients with non-ST-segment elevation-acute coronary syndrome. *European Heart Journal. Cardiovascular Imaging*. (2015) 16(11):1247–55. doi: 10.1093/ehjci/jev078

21. Clemmensen TS, Eiskjær H, Mikkelsen F, Granstam S-O, Flachskampf FA, Sørensen J, et al. Left ventricular pressure-strain-derived myocardial work at rest and during exercise in patients with cardiac amyloidosis. *J Am Soc Echocardiogr*. (2020) 33(5):573–82. doi: 10.1016/j.echo.2019.11.018

22. Liu Q, Li Q, Wan X, Xu M, Pan J, Zhang Y, et al. The value of myocardial work in the estimation of left ventricular systolic function in patients with coronary microvascular disease: a study based on adenosine stress echocardiography. *Front Cardiovasc Med*. (2023) 10:1119785. doi: 10.3389/fcvm.2023.1119785

23. Moya A, Buytaert D, Penicka M, Bartunek J, Vanderheyden M. State-of-the-art: noninvasive assessment of left ventricular function through myocardial work. *J Am Soc Echocardiogr*. (2023) 36(10):1027–42. doi: 10.1016/j.echo.2023.07.002

24. Reant P, Metras A, Detaille D, Reynaud A, Diolez P, Jaspard-Vinassa B, et al. Impact of afterload increase on left ventricular myocardial deformation indices. *J Am Soc Echocardiogr*. (2016) 29(12):1217–28. doi: 10.1016/j.echo.2016.09.006

25. Donal E, Bergerot C, Thibault H, Ernande L, Loufoua J, Augeul L, et al. Influence of afterload on left ventricular radial and longitudinal systolic functions: a two-dimensional strain imaging study. *Eur J Echocardiogr*. (2009) 10(8):914–21. doi: 10.1093/ejechocard/jep095

26. Marzlin N, Hays AG, Peters M, Kaminski A, Roemer S, O'Leary P, et al. Myocardial work in echocardiography. *Circulation. Cardiovascular Imaging*. (2023) 16(2):e014419. doi: 10.1161/CIRCIMAGING.122.014419

27. Leitman M, Balboul Y, Burgsdorf O, Tyomkin V, Fuchs S. Myocardial work index during normal dobutamine stress echocardiography. *Sci Rep*. (2022) 12:6813. doi: 10.1038/s41598-022-10903-8

28. Sarnak MJ, Tighiouart H, Manjunath G, MacLeod B, Griffith J, Salem D, et al. Anemia as a risk factor for cardiovascular disease in the Atherosclerosis Risk in Communities (ARIC) study. *J Am Coll Cardiol*. (2002) 40(1):27–33. doi: 10.1016/s0735-1097(02)01938-1

29. Sabatine MS, Morrow DA, Giugliano RP, Burton PBJ, Murphy SA, McCabe CH, et al. Association of hemoglobin levels with clinical outcomes in acute coronary syndromes. *Circulation*. (2005) 111(16):2042–49. doi: 10.1161/01.CIR.0000162477.70955.5F

30. McClellan WM, Dana Flanders W, Langston RD, Jurkovitz C, Presley R. Anemia and renal insufficiency are independent risk factors for death among patients with congestive heart failure admitted to community hospitals: a population-based study. *J Am Soc Nephrol*. (2002) 13(7):1928–36. doi: 10.1097/01.asn.0000018409.45834.fa

31. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Borenstein J. Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure. *J Am Coll Cardiol*. (2002) 39(11):1780–86. doi: 10.1016/s0735-1097(02)01854-5

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The incidence of coronary in-stent restenosis and the rate of reaching the standard of low-density lipoprotein cholesterol in patients with type 2 diabetes mellitus and unstable angina pectoris treated with ezetimibe and rosuvastatin

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Background: Diabetes is closely associated with the occurrence and development of coronary atherosclerotic heart disease. Coronary atherosclerosis is often severe and diffuse in patients with diabetes. We investigated the incidence of coronary in-stent restenosis (ISR) and the rate of reaching the standard of low-density lipoprotein cholesterol (LDL-C) in patients with type 2 diabetes mellitus (T2DM) and unstable angina pectoris (UAP) treated with ezetimibe and rosuvastatin one year later.

Materials and methods: We selected the first pair of UAP patients with T2DM who underwent coronary artery stent implantation at our hospital between October 2018 and February 2022. According to drug use, the patients were divided into the rosuvastatin group [61 cases, rosuvastatin 10 mg/qn (every night)] and the combined group [60 cases, ezetimibe 10 mg/qd (once daily) and rosuvastatin 10 mg/qn]. Biochemical indices, left ventricular ejection fraction, and left ventricular end-diastolic diameter were collected before and one year after the first percutaneous coronary intervention. We collected data on the incidence of ISR and the rate of reaching the standard of LDL-C one year after surgery. Emergency PCI or coronary artery bypass grafting, cardiac death, and non-fatal acute myocardial infarction due to unstable angina pectoris 30 days after coronary stent implantation and lipid-lowering treatment were regarded as the primary endpoints.

Results: After one year of follow-up, the incidence of in-stent restenosis(ISR), total cholesterol(TC), and LDL-C levels in the combined group[ISR, 3.33%; TC, 3.19 ± 0.75; LDL-C, 1.38(1.18–1.64)] were lower than those in the rosuvastatin group[ISR, 16.39% TC,C 3.84 ± 1.15; LDL-C, 1.92(1.52–2.61)] ($P < 0.05$). The rate of reaching the standard of LDL-C in the combined group (65%, 95% CI 0.560–0.809) was higher than that in the rosuvastatin group(31%, 95% CI 0.210–0.446) ($P < 0.05$). No significant difference in safety was observed between the two groups ($P > 0.05$). No endpoints were observed in the combined group.

Conclusion: Resuvastatin combined with ezetimibe can better prevent ISR and reduce the incidence of cardiovascular adverse events. In addition, ezetimibe combined with rosuvastatin better reduced LDL-C levels.

KEYWORDS

T2DM, unstable angina, in-stent restenosis (ISR), ezetimibe, rosuvastatin

Background

Percutaneous coronary intervention (PCI) has ushered in a new era of treatment for coronary artery disease. However, in-stent restenosis (ISR) remains a potential post-PCI complication (1, 2). Despite the fact that drug-eluting stent (DES) implantation significantly lowers the clinical incidence of ISR compared to bare-metal stents, ISR still occurs in 3% to 20% of cases, primarily influenced by patient pathological characteristics, risk factors (especially diabetes), and the type of DES used (3, 4).

The incidence and prevalence of type 2 diabetes mellitus (T2DM) have surged in both developed and developing countries (5). There is a strong correlation between the development of cardiovascular disease and abnormal glucose metabolism (6). Among individuals with diabetes, the prevalence of coronary heart disease can reach as high as 55% (7).

The 2019 ESC and EAC guidelines for blood lipid management recommend that patients with T2DM at very high risk should aim to reduce their low-density lipoprotein cholesterol (LDL-C) levels by 50% from baseline and maintain LDL-C levels below 1.4 mmol/L (55 mg/dl) (8).

The primary objective of this study was to assess the incidence of ISR and the rate of achieving LDL-C targets in patients with T2DM and unstable angina pectoris (UAP) one year after treatment with ezetimibe and rosuvastatin.

Materials and methods

Study population

Patients with UAP and T2DM who underwent coronary stent implantation at Wenzhou People's Hospital between October 2018 and February 2022 were enrolled in the study. The inclusion criteria were as follows: (1) meeting the diagnostic criteria for T2DM and UA and (2) not having received statins or any other lipid-modulating drugs in the past 15 days. The exclusion criteria were as follows: (1) allergy to statins or ezetimibe; (2) active liver disease or liver dysfunction (alanine aminotransferase [ALT] level >1.5 times the upper limit of normal [ULN), as statins can exacerbate liver damage; (3) hypothyroidism, as statins may increase the risk of rhabdomyolysis in this condition; (4) history of alcohol or drug abuse, which can lead to liver damage; (5) homozygous familial hypercholesterolemia or familial dyslipoproteinemia, due to extremely high LDL-C levels that may be refractory to treatment, potentially biasing results; (6) myalgia or myasthenia of unknown cause, or creatine kinase (CK) level >1.5 times ULN, as atorvastatin can exacerbate muscle damage; (7) rheumatic immunologic diseases or tumors, as treatments for these conditions can affect blood lipids and bias results; and (8) resistance to aspirin and clopidogrel, as determined by platelet aggregation function tests (AA and ADP).

Based on the treatment regimen, the patients were divided into two groups: the rosuvastatin group ($n = 61$), who received rosuvastatin 10 mg/qn (every night), and the combination group ($n = 60$), who received rosuvastatin 10 mg/qn combined with ezetimibe 10 mg/qd (once daily). Both groups took their medications regularly for one year and received standard therapy, including aspirin, clopidogrel, nitrates, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β-blockers, and oral hypoglycemic drugs.

Anthropometric measurements and biochemical tests

Total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and LDL-C levels were assessed before PCI and one year after the first coronary stent implantation. Hemoglobin A1c (HbA1c), fasting blood glucose (FBG), ALT, creatinine (Cr), and CK were also measured. Left ventricular ejection fraction (LVEF) and left ventricular end-diastolic dimension (LVDD) were recorded using transthoracic echocardiography. One year post-treatment, coronary angiography was repeated to evaluate the stent stenosis. The criterion for achieving LDL-C targets after one year of treatment was based on the 2019 ESC and EAC blood lipid management guidelines, which stipulate that LDL-C levels should be <1.4 mmol/L or reduced by >50% from baseline.

The rate of achieving LDL-C targets was calculated as follows: (number of patients meeting the criteria/total number of patients) × 100%. ISR was defined as recurrent stenosis with a stent segment diameter >50% of the intravascular diameter. Adverse reactions were monitored throughout the treatment period, and the study was terminated if ALT exceeded 3 times ULN or CK levels exceeded three or five times the ULN, respectively.

Endpoint event

The primary endpoints included emergency percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), cardiac death, and non-fatal acute myocardial

infarction attributable to unstable angina pectoris occurring within 30 days of coronary stent implantation during lipid-lowering therapy. The study enrollment flow chart is shown in Figure 1.

Ethics approval and consent to participate

This study complied with the Declaration of Helsinki and was approved by the Medical Ethics Committee of Wenzhou People's

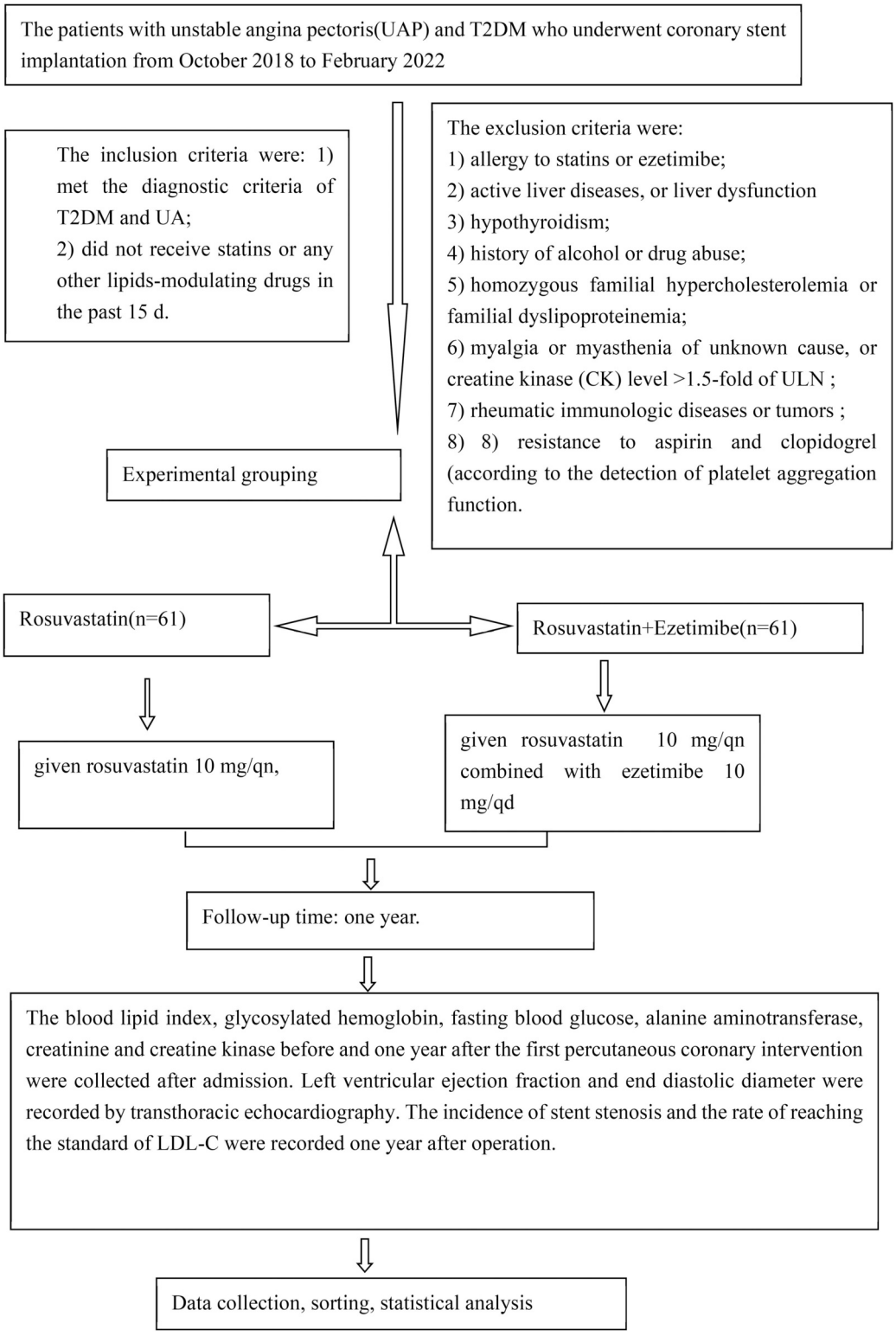

FIGURE 1
The study enrollment flow chart.

Hospital. Written informed consent was obtained from all participants prior to their enrollment in the study (clinical trial number: 2018196).

Statistical analysis

Statistical analyses were performed using SPSS version 23.0 for Windows (IBM Corp.; Armonk, NY). Categorical variables are presented as frequencies and percentages. Normally distributed continuous variables were expressed as mean ± standard deviation and analyzed using Student's *t*-test, while non-normally distributed data were reported as median (interquartile range) and analyzed using the Mann–Whitney *U*-test. Comparisons of categorical variables were conducted using either the chi-squared test or Fisher's exact test, with a *P*-value <0.05 considered statistically significant.

Results

Comparison of preoperative clinical characteristics between the two groups

No statistically significant differences were observed between the rosuvastatin group and the combination therapy group in terms of age, sex distribution, history of hypertension, severity of coronary artery disease, HbA1c levels, fasting blood glucose (FBG), alanine aminotransferase (ALT), creatinine (Cr), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), non-HDL-C levels, or preoperative left ventricular end-diastolic diameter (LVDD) and left ventricular ejection fraction (LVEF) (all $P > 0.05$). The clinical characteristics of the patients in the two groups are presented in Table 1.

Comparison of biochemical indexes and in stent restenosis results between the two groups one year after operation.

There was no significant difference in baseline data such as HbA1c, FBG, ALT, Cr, TG, HDL-C, preoperative LVDD and preoperative LVEF between rosuvastatin group and combined group ($P > 0.05$). After one year of follow-up, the incidence of ISR, TC and LDL-C levels in the combined group[ISR 3.33%,TC 3.19 ± 0.75, LDL-C 1.38(1.18–1.64)] were lower than those in the rosuvastatin group[ISR 16.39%, TC 3.84 ± 1.15, LDL-C 1.92 (1.52–2.61)]. The rate of reaching the standard of LDL-C in the combined group(65%, 95% CI 0.560–0.809) was higher than that in the rosuvastatin group(31%, 95% CI 0.210–0.446) ($P < 0.05$). The clinical characteristics of the patients in the two groups are shown in Table 2.

Comparison of adverse events

After one year of follow-up, no lipid-lowering drugs were stopped in either group due to impaired liver function, elevated creatine kinase levels, or myalgia. There were two endpoints in the rosuvastatin group (emergency PCI due to ACS). There were no end points in the combined group.

Discussion

This study evaluated the effects of ezetimibe combined with rosuvastatin on the incidence of ISR and the LDL-C target achievement rate in patients with T2DM and UAP at a one-year follow-up. The results demonstrated that the combination

TABLE 1 Comparison of clinical characteristics in two groups before PCI.

Characteristics	Rosuvastatin (*n* = 61)	Rosuvastatin + Ezetimibe (*n* = 60)	*P* value
Age (yeat)	67.53 ± 9.88	64.20 ± 11.05	0.597
Male (%)	33 (54%)	39 (65%)	0.222
Hypertension (%)	50 (82%)	48 (80%)	0.783
Severity of myocardial infarction (%)			
Single vessel lesion (%)	18 (29.5%)	12 (20%)	0.226
Double vessel lesion, *n* (%)	11 (18%)	13 (21.7%)	0.616
Three vessel lesion, *n* (%)	32 (52.5%)	35 (58.3%)	0.516
HbA1c (%), mean ± SD	8.15 (6.90–9.43)	8.00 (7.10–8.70)	0.565
FBG (mmol/L), mean ± SD	7.91 (6.10–9.63)	7.07 (5.68–9.07)	0.158
ALT (U/L), mean ± SD	21 (15–32)	20 (15–28)	0.870
CK (U/L), mean ± SD	113.09 ± 70.86	110.65 ± 70.56	0.902
Cr (umol/L), mean ± SD	59.00 (48.00–77.50)	69 (57.25–80.00)	0.268
TC (mmol/L), mean ± SD	4.66 ± 0.93	4.68 ± 1.05	0.896
TG (mmol/L), mean ± SD	1.67 (1.00–2.45)	1.83 (1.26–2.71)	0.247
HDL-C (mmol/L), mean ± SD	1.02 (0.88–1.28)	0.95 (0.81–1.08)	0.054
LDL-C (mmol/L), mean ± SD	2.79 ± 0.92	2.77 ± 0.77	0.920
non-HDL-C (mmol/L), mean ± SD	3.56 ± 0.98	3.65 ± 1.06	0.621
LVEF (%), mean ± SD	65 (58.50–68.00)	65 (58.00–68.00)	0.629
LVDD (mm), mean ± SD	47 (43–50)	48(44–50)	0.805

HbA1c, hemoglobin A1c; FBG, fasting blood glucose; ALT, alanine aminotransferase; Cr, creatinine; TC, total cholesterol; TG, triacylglycerol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein-cholestero; non-HDL-C, none high-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; LVDD, left ventricular end diastolic dimension.

TABLE 2 Comparison of clinical characteristics in two groups one year after operation.

Characteristics	Rosuvastatin (n = 61)	Rosuvastatin + Ezetimibe (n = 60)	P value
HbA1c (%)	7.50 (6.90–8.30)	7.45 (6.63–8.28)	0.405
FBG (mmol/L)	7.23 (5.84–9.19)	6.80 (5.82–7.63)	0.075
ALT (U/L)	20 (12.5–29)	22 (16.25–28.75)	0.195
CK (U/L)	109.28 ± 71.10	112. ± 71.23	0.921
Cr (umol/L)	65 (52.5–78.5)	71 (57.25–83.00)	0.091
TC (mmol/L)	3.84 ± 1.15	3.19 ± 0.75	0.000
TG (mmol/L)	1.3 (0.98–1.66)	1.28 (0.99–1.75)	1.000
HDL-C (mmol/L)	0.98 (0.84–1.16)	0.98 (0.81–1.24)	0.758
LDL-C (mmol/L)	1.92 (1.52–2.61)	1.38 (1.18–1.64)	0.000
non-HDL-C (mmol/L)	2.70 (1.99–3.56)	1.97 (1.72–2.42)	0.000
LVEF (%)	65 (57–70)	65 (60–68.75)	0.840
LVDD (mm)	47 (44–50)	47.5 (44–49.75)	0.500
ISR (%)	10 (16.39%)	2 (3.33%)	0.016
The rate of reaching the standard of LDL-C (%)	19 (31%, 95% CI 0.210–0.446)	39 (65%, 95% CI 0.560–0.809)	0.000

HbA1c, hemoglobin A1c; FBG, fasting blood glucose; ALT, alanine aminotransferase; Cr, creatinine; TC, total cholesterol; TG, triacylglycerol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein-cholestero; non-HDL-C, none high-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; LVDD, left ventricular end diastolic dimension; ISR In stent restenosis.

therapy group exhibited a significantly lower incidence of ISR (at one year post-procedure) than the intermediate-intensity statin monotherapy group. Furthermore, the rosuvastatin-ezetimibe combination achieved lipid-lowering targets more rapidly than rosuvastatin alone, while maintaining an excellent safety profile. The absence of a high-intensity statin arm limits direct comparison of additive vs. dose-escalation strategies. However, our design reflects regional prescribing patterns where combination therapy increasingly supplements moderate statin doses.

ISR is defined as the progressive narrowing of the treated coronary artery segment due to arterial injury and subsequent neointimal hyperplasia after stent implantation. Typically occurring 6–12 months after PCI, ISR most commonly presents as recurrent angina pectoris but may also manifest as a myocardial infarction. As one of the primary factors compromising the long-term efficacy of PCI, ISR currently lacks standardized treatment strategies (9).

Recent advancements in coronary stent technology and antiplatelet therapies have reduced ISR incidence from historical rates of 40%–50% to approximately 10% (2). However, ISR prevention and management remain significant challenges in the field of cardiovascular medicine. The pathogenesis of ISR involves complex pathological mechanisms with multiple contributing factors, including: Current understanding suggests that various risk factors collectively induce endothelial cell injury or dysfunction, triggering local thrombosis and inflammatory responses in the body. This process, mediated by numerous cytokines, leads to smooth muscle cell proliferation, excessive extracellular matrix production, and vascular wall deposition, ultimately resulting in intimal hyperplasia and ISR (10). Notably, in-stent neoatherosclerosis may accelerate coronary plaque formation, promoting ISR progression.

Diabetes mellitus is an independent risk factor for ISR. Endothelial dysfunction mediated by advanced glycation end products plays a crucial role in ISR pathogenesis (11). These glycation products participate in post-PCI vascular remodeling processes, indicating that glycemic control alone cannot reverse the progression of vascular complications (12). Strict post-PCI glucose management combined with targeted AGE therapy may reduce ISR incidence (13, 14).

Lipid metabolism parameters demonstrate strong associations with ISR risk, with LDL-C being the most extensively studied and primary therapeutic target for dyslipidemia management (15). Substantial evidence indicates a positive correlation between serum LDL-C levels and ISR incidence, and LDL-C reduction effectively suppresses neointimal hyperplasia and delays ISR progression (16).

Abnormal lipid metabolism is the main cause of arteriosclerosis and a risk factor for coronary heart disease. Hyperlipidemia in patients leads to a large amount of lipid deposition on the vascular endothelium, resulting in endothelial cell proliferation and calcification, which results in gradual narrowing or even occlusion of the lumen. Abnormal blood lipid levels can be reflected by increased TG, TC, and LDL-C levels and/or decreased HDL-C levels. Therefore, all blood lipid regulation guidelines stipulate that the main purpose of reducing blood lipids is to reduce LDL-C and TC levels. Ezetimibe is a highly selective drug that interferes with cholesterol absorption. It can inhibit the protein transport of cholesterol in the small intestine, thus inhibiting the function of cholesterol uptake in the intestine, regulating the level of free cholesterol in the plasma, and reducing cholesterol storage in the liver. This product can be combined with statins to reduce LDL-C levels. While controlling the high-fat diet, it can be used independently to regulate blood lipids or in combination with HMG-CoA reductase inhibitors (statins) to treat hypercholesterolemia caused by various reasons, and it can significantly reduce the levels of LDL-C, TC, and apolipoprotein B in plasma. Ezetimibe regulates cholesterol by inhibiting its intestinal reabsorption; therefore, it is a new type of anti-lipid drug compared with statins. The pharmacological mechanism of this drug is to

interfere with the transport of cholesterol by the NPC1L1 protein in the brush edge of the small intestine villus, so that the small intestine cannot fully absorb a large amount of cholesterol. It can also prevent the liver from storing and transporting cholesterol, regulate the level of cholesterol in the liver, increase the number of LDL-C receptors, and accelerate the metabolism of cholesterol in the plasma (17). The combination of ezetimibe and statins can play a synergistic role in preventing the generation of blood lipids from endogenous and exogenous sources, significantly reducing the level of cholesterol in plasma, reducing blood lipids, and slowing down the trend of atherosclerosis. These findings are in line with those of the CONNECT trial (18), showing that neoatherosclerosis was lower over a 3-year follow-up in patients undergoing intensive lipid-lowering therapy.

In our study, the sample size was small, and the follow-up period was one year. Therefore, more trials and long-term studies are needed to assess the clinical efficacy of rosuvastatin combined with ezetimibe in the treatment of patients with UAP complicated with T2DM after the first coronary stent implantation. While the observed ISR reduction was statistically significant, its magnitude should be interpreted cautiously given the small absolute event numbers. Confirmatory studies with larger cohorts are warranted.

Conclusions

Compared with rosuvastatin alone, the combined use of ezetimibe can better reduce LDL-C levels, prevent in-stent restenosis, and reduce coronary artery disease and adverse events. Rosuvastatin combined with ezetimibe is safe.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by This study was in accordance with the Declaration of Heksinki and was approved by the medical ethics committee of Wenzhou People's Hospital. Informed consent was obtained from all the study subjects before enrollment. Clinical trial number: 2018196. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

FY: Formal analysis, Data curation, Visualization, Resources, Validation, Project administration, Investigation, Writing – review & editing, Methodology, Software, Supervision, Funding acquisition, Conceptualization, Writing – original draft. HC: Writing – original draft, Data curation. HL: Funding acquisition, Writing – original draft, Writing – review & editing, Data curation.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Siontis GC, Stefanini GG, Mavridis D, Siontis KC, Alfonso F, Perez-Vizcayno MJ, et al. Percutaneous coronary interventional strategies for treatment of in-stent restenosis: a network meta-analysis. *Lancet*. (2015) 386(9994):655–64. doi: 10.1016/S0140-6736(15)60657-2

2. Dangas GD, Claessen B, Caixeta A, Sanidas EA, Mintz GS, Mehran R. In-stent restenosis in the drug-eluting stent era. *J Am Coll Cardiol*. (2010) 56(23):1897–907. doi: 10.1016/j.jacc.2010.07.028

3. Kaul U, Bangalore S, Seth A, Arambam P, Abhaichand RK, Patel TM, et al. Paclitaxel-eluting versus everolimus-eluting coronary stents in diabetes. *N Engl J Med*. (2016) 375(4):398. doi: 10.1056/NEJMx150039

4. Rachner TD, Kasimir-Bauer S, Göbel A, Erdmann K, Hoffmann O, Browne A, et al. Prognostic value of RANKL/ OPG serum levels and disseminated tumor cells in nonmetastatic breast cancer. *Clin Cancer Res*. (2019) 25(4):1369–78. doi: 10.1158/1078-0432.CCR-18-2482

5. Narimani R, Kachuei A, Rezvanian H, Feizi A, Poorpoone M. Effect of sitagliptin on proteinuria in patients with type 2 diabetes – A renoprotective effect of sitagliptin. *J Res Med Sci*. (2021) 26(4):35. doi: 10.4103/jrms.JRMS_78_20

6. Topal D, Mutluer FO, Aydin O, Cakir H, Kanat S, Aslan B, et al. The relationship between hemoglobin A1c levels and thrombus load in patients with type 2 diabetes mellitus and non-ST-segment elevation myocardial infarction. *J Res Med Sci*. (2021) 26(1):118. doi: 10.4103/jrms.JRMS_997_18

7. Deng X, Liu Y, Luo M, Wu J, Ma R, Wan Q, et al. Circulating miRNA-24 and its target YKL-40 as potential biomarkers in patients with coronary heart disease and type 2 diabetes mellitus. *Oncotarget*. (2017) 8(38):63038–46. doi: 10.18632/oncotarget.18593

8. François M, Colin B, Catapano AL, Koskinas KC, Manuela C, Lina B, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. (2020) 41(1):111. doi: 10.1093/eurheartj/ehz455

9. Alfonso F, Byrne RA, Rivero F, Kastrati A. Current treatment of in-stent restenosis. *J Am Coll Cardiol*. (2014) 63(24):2659–73. doi: 10.1016/j.jacc.2014.02.545

10. Byrne RA, Michael J, Adnan K. Stent thrombosis and restenosis: what have we learned and where are we going? The andreas gruntzig lecture ESC 2014. *Eur Heart J*. (2015) 36(47):3320–31. doi: 10.1093/eurheartj/ehv511

11. Wang H, Weihrauch D, Kersten JR, Toth JM, Passerini AG, Rajamani A, et al. Alagebrium inhibits neointimal hyperplasia and restores distributions of wall shear stress by reducing downstream vascular resistance in obese and diabetic rats. *Am J Physiol Heart Circ Physiol*. (2015) 309(7):H1130–1140. doi: 10.1152/ajpheart.00123.2014

12. Nirala BK, Perumal V, Gohil NK. Glycated serum albumin stimulates expression of endothelial cell specific molecule-1 in human umbilical vein endothelial cells: implication in diabetes mediated endothelial dysfunction. *Diab Vasc Dis Res*. (2015) 12(4):290–7. doi: 10.1177/1479164115583192

13. Pino AD, Urbano F, Zagami RM, Filippello A, Mauro SD, Piro S, et al. Low endogenous secretory receptor for advanced glycation end-products levels are associated with inflammation and carotid atherosclerosis in prediabetes. *J Clin Endocrinol Metab*. (2016) 101(4):1701–9. doi: 10.1210/jc.2015-4069

14. Prasad K, Tiwari S. Therapeutic interventions for advanced glycationend products and its receptor-mediated cardiovascular disease. *Curr Pharm Des*. (2017) 23(6):937–43. doi: 10.2174/1381612822666161006143032

15. Jang JY, Kim JS, Shin DH, Kim BK, Ko YG, Choi D, et al. Favorable effect of optimal lipidlowering therapy on neointimal tissue characteristics after drugeluting stent implantation: qualitative optical coherence tomographic analysis. *Atherosclerosis*. (2015) 242(2):553–9. doi: 10.1016/j.atherosclerosis.2015.08.014

16. Qin Z, Zheng F-W, Zeng C, Zhou K, Geng Y, Wang J-L, et al. Elevated levels of very lowdensity lipoprotein cholesterol independently associated with in-stent restenosis in diabetic patients after drug-eluting stent implantation. *Chin Med J (Engl)*. (2017) 130(19):2326–32. doi: 10.4103/0366-6999.213575

17. Friedman HS, Rajagopalan S, Barnes JP, Roseman H. Combination therapy with ezetimibe/simvastatin versus statin monotherapy for low-density lipoprotein cholesterol reduction and goal attainment in a real-world clinical setting. *Clin Ther*. (2011) 33(2):212–24. doi: 10.1016/j.clinthera.2011.02.011

18. Taniwaki M, Häner JD, Kakizaki R, Ohno Y, Yahagi K, Higuchi Y, et al. Long-term effect of biodegradable vs. Durable polymer everolimus-eluting stents on neoatherosclerosis in ST-segment elevation myocardial infarction: the CONNECT trial. *Eur Heart J*. (2024) 46(29):2906–16. doi: 10.1093/eurheartj/ehae589

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Immediate versus staged complete revascularization in patients with acute coronary syndrome and multivessel disease: a meta-analysis of randomized controlled trials

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Background: A series of trials have confirmed that complete revascularization is more beneficial for patients with acute coronary syndrome (ACS) and multivessel disease than culprit-only revascularization. However, the optimal timing of complete revascularization remains controversial. It is unclear whether immediate complete revascularization is safer and more effective than staged complete revascularization.

Method: This meta-analysis of randomized controlled trials aimed to compare the efficacy and safety of immediate vs. staged revascularization in patients with ACS. The primary outcome was major adverse cardiovascular events (MACE), which were defined as a composite endpoint. Risk ratios (RRs) were calculated using the Mantel–Haenszel (M-H) fixed-effect model. Trial sequential analysis was additionally performed to validate the results. This study is registered with PROSPERO (CRD42023461852).

Results: In total, 11 randomized studies involving 5,666 patients met the inclusion criteria. At a mean follow-up of 16 months, immediate complete revascularization significantly decreased the incidence of MACE compared with staged complete revascularization [RR: 0.76, 95% confidence interval (CI): 0.66–0.89, $P = 0.0004$]. Significant decreases were also observed in repeat myocardial infarction (RR: 0.59, 95% CI: 0.43–0.82, $P = 0.002$), repeat revascularization (RR: 0.62, 95% CI: 0.48–0.79, $P = 0.0001$), and the composite outcome of myocardial infarction or death (RR: 0.67, 95% CI: 0.48–0.92, $P = 0.01$). However, no significant differences were found in all-cause mortality (RR: 0.92, 95% CI: 0.64–1.33, $P = 0.66$) or cardiovascular mortality (RR: 0.96, 95% CI: 0.58–1.61, $P = 0.89$).

Conclusion: In patients with ACS and multivessel disease, immediate complete revascularization significantly decreased the risk of MACE, repeat myocardial infarction, and repeat revascularization, without increasing the risk of all-cause death.

KEYWORDS

percutaneous coronary intervention, acute coronary syndrome, immediate complete revascularization, staged complete revascularization, multivessel disease (MVD)

Introduction

Acute coronary syndrome (ACS) is a common cardiovascular disease caused by insufficient blood supply to the coronary arteries. This insufficient blood supply can lead to myocardial infarction (MI) or unstable angina. Multivessel disease (MVD), defined as the presence of significant stenoses or occlusions in multiple coronary arteries, is frequently encountered in ACS, with approximately 50% of patients with ST-segment elevation myocardial infarction (STEMI) found to have MVD on initial coronary angiography (1). Compared to those with single-vessel disease, these patients have higher short- and long-term mortality rates (2–4). Percutaneous coronary intervention (PCI) has emerged as a cornerstone therapy for STEMI, significantly improving prognoses and providing net clinical benefits (2). Numerous studies have now demonstrated that complete revascularization (CR) is superior to infarct-related vessel revascularization alone and can significantly reduce the risk of recurrent myocardial infarction in these patients without cardiogenic shock (5–9). Contemporary developments in coronary intervention have further improved the prognosis of these patients, particularly through the application of extracorporeal membrane oxygenation.

Patients who have undergone immediate complete revascularization (ICR) have achieved good short-term outcomes with higher rates of coronary revascularization, faster postoperative recovery, and a lower complication rate. However, this treatment strategy is technically demanding, requires an experienced medical team, and may increase the risk of operative time and postoperative recovery. Comparatively, patients who undergo staged complete revascularization (SCR) may need to undergo multiple procedures and have a longer treatment course. However, this strategy is less risky and less physically taxing on the patient. Moreover, this treatment approach allows for a gradual recovery through the different surgical phases, reduces the load on the heart, and is safer for elderly or frail patients. The current guidelines recommend CR for patients with ACS and MVD who are free of cardiogenic shock (10–12). However, the optimal timing for treating non-culprit lesions in this population remains undefined. The European Society of Cardiology (ESC) guidelines recommend that patients with ACS combined with multibranch vasculopathy should undergo CR within 45 days (12). However, it is controversial whether patients who undergo ICR gain any additional benefit.

Based on previous research, this study aimed to include relevant randomized controlled trials (RCTs) to explore the efficacy and safety of ICR compared with SCR. In addition, a trial sequential analysis (TSA) was used to assess the outcomes.

Method

Data sources and inclusion and exclusion criteria

We conducted this meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (13). A comprehensive search without language restrictions was performed in PubMed, Embase, and the Cochrane Library from database inception to 1 March 2025. The PubMed search strategy included the following keywords: “ST-elevation myocardial infarction”, “Multivessel disease”, “complete revascularization”, “staged revascularization”, “simultaneous revascularization”, “culprit only revascularization”, “infarct-related artery revascularization”, and “randomized controlled trial”. Detailed search terms are provided in Supplementary Table S1.

In addition to electronic database searches, the reference lists of the included studies were manually screened. Conference proceedings from major cardiology societies (e.g., American Heart Association, American College of Cardiology, Transcatheter Cardiovascular Therapeutics, European Society of Cardiology, and Congress of the European Association of Percutaneous Cardiovascular Interventions) were also reviewed for relevant abstracts. The selection process comprised the following two stages: (1) the initial exclusion of irrelevant studies based on title/abstract review and (2) a detailed assessment of potentially eligible studies.

Two reviewers (LH and BS) independently evaluated each study’s eligibility, with discrepancies resolved by a third investigator (P-YZ). Studies were included if they met all the following criteria: involving patients with ACS, including STEMI, unstable angina, or non-STEMI; comparing ICR and SCR; reporting predefined clinical outcomes (e.g., cardiovascular events); and being an RCT. Studies were excluded if they lacked a valid control group or relevant cardiovascular/cerebrovascular outcome data or were non-original publications (e.g., reviews, editorials, commentaries). Non-English studies were translated using professional translation services or software when necessary.

Data extraction and outcome assessments

Two authors (LH and BS) independently extracted data from eligible studies using piloted data extraction sheets. The extracted data covered aspects including the first author, publication year, study setting, follow-up duration, study design, sample size, and the personal and clinical characteristics of the participants.

The primary outcome was defined as major adverse cardiovascular events (MACE). The definition of MACE was the same as that used in the original study. For RCTs with multiple definitions, we selected the primary MACE outcome that was consistent with those in the other RCTs. For the efficacy evaluation, the outcomes included were repeat myocardial infarction and repeat revascularization. Regarding the safety assessment, the outcomes included all-cause mortality, cardiovascular mortality, and the composite outcome of death or myocardial infarction.

Risk of bias and certainty of evidence assessment

Two researchers (LH and BS) independently evaluated the risk of bias of the included studies using the Risk of Bias 2 (RoB 2) tool

(14, 15). Two reviewers (LH and BS) assessed the risk level of each study to be low, moderate, serious, critical, or no information. Detailed descriptions and decision criteria for each ROB 2 domains are provided in Supplementary Appendix S4. Discrepancies were resolved by a senior investigator (J-HZ).

Two investigators (Q-JY and J-LH) independently appraised the evidence certainty for each outcome, with disagreements adjudicated by a third reviewer (P-YZ). The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework was employed to evaluate the evidence certainty, categorizing it into the following levels: very low, low, moderate, and high (16).

Statistical analysis

We conducted the statistical analyses using Review Manager (version 5.4). The effect size was measured as relative risk with 95% confidence intervals (95% CIs).

The judgment of heterogeneity was based on Cochran's Q-test. When $P \geq 0.1$, no significant heterogeneity was considered to exist and the Mantel–Haenszel (M-H) fixed-effects model was used. When $P < 0.1$, significant heterogeneity was deemed to exist and the degree of heterogeneity was then evaluated using I^2. Thus, $I^2 < 25\%$, 25%–50%, and >50% were respectively categorized as low, moderate, and high heterogeneity levels (17), respectively. Subgroup analyses were performed based on myocardial infarction subtype, timing of SCR, and definition of MACE. Publication bias was initially assessed via visual inspections of the funnel plots and Egger's test. To minimize the risk of type I errors caused by repeated significance testing or an insufficient sample size, we conducted a TSA to assess the robustness of the pooled effect. The TSA was performed using TSA software (version 0.9.5.10), employing a two-sided testing model with a type I error (α) of 0.05 and a statistical power ($1 - \beta$) of 80%. The relative risk reduction (RRR) was estimated based on data from recently published large-scale RCTs (BIOVASC, MULTISTARS AMI, and Wood et al.), and the required

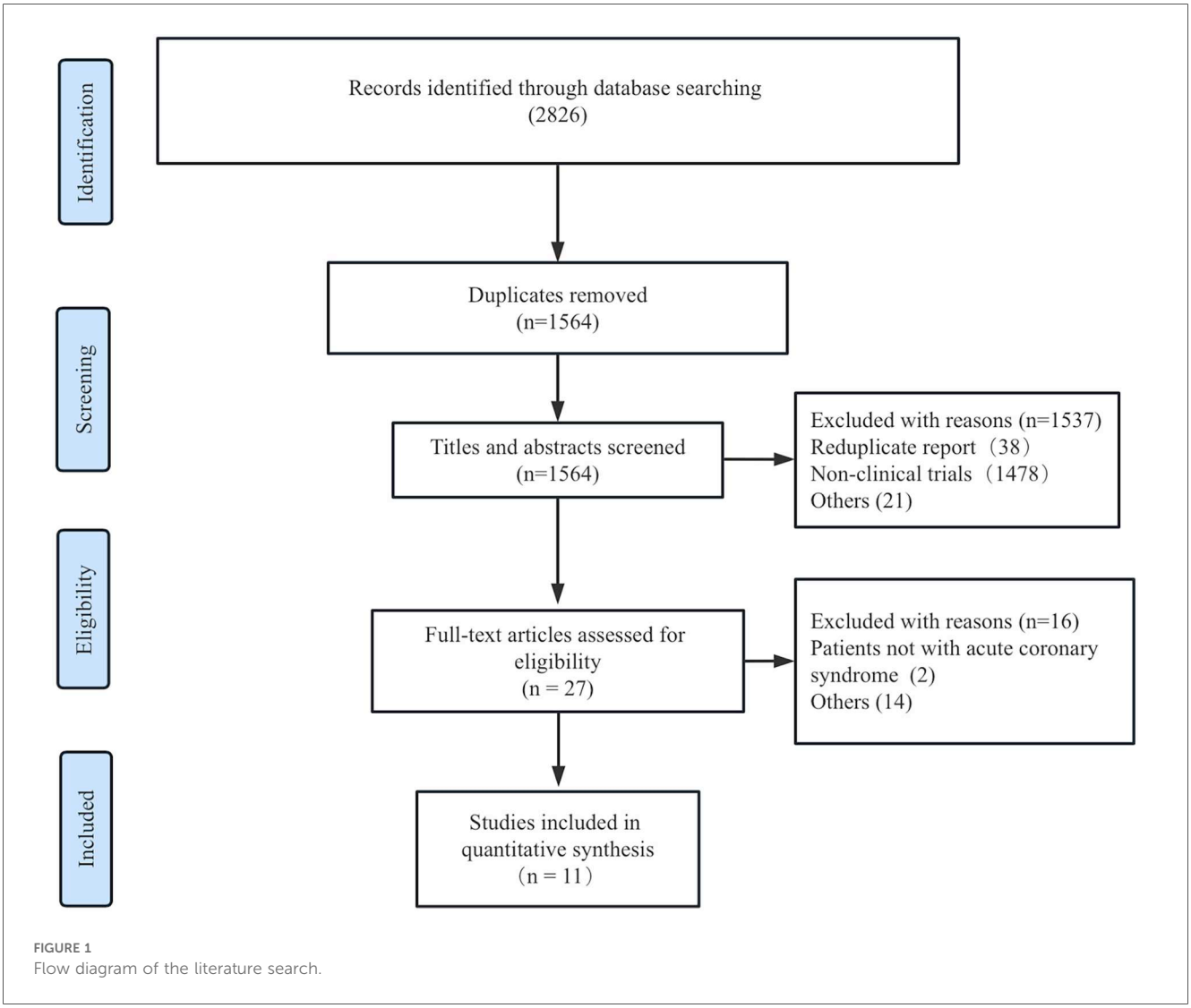

FIGURE 1
Flow diagram of the literature search.

information size (RIS) was calculated accordingly. If the cumulative Z-curve crossed the TSA monitoring boundary or the RIS was reached with the Z-curve exceeding the conventional significance threshold, the evidence was considered sufficient and the result statistically robust.

Results

Search results and baseline characteristics

The literature screening and study selection process is depicted in Figure 1. A total of 2,826 studies were initially retrieved from the PubMed, Embase, and Cochrane Library databases. After reviewing 27 full-text articles, 11 RCTs ultimately met the predefined inclusion criteria (18–27).

Table 1 outlines the characteristics of the included trials. The majority of studies were single-center RCTs involving patients with STEMI without cardiogenic shock. A total of eight RCTs enrolled patients with STEMI, two RCTs only included patients with non-STEMI, and only one RCT (BIOVASC) included patients with unstable angina. The timing of SCR ranged from 2 to 45 days, and the follow-up durations varied from 6 months to 4 years. The baseline patient characteristics are presented in Table 2, with no significant differences in clinical presentations observed between the ICR and SCR groups.

Primary outcome

All the included trials reported the incidence of MACE (Figure 2). The results showed that ICR significantly decreased the incidence of MACE compared to SCR (RR 0.76, 0.66–0.89, $P = 0.0004$, $I^2 = 27\%$, $P_{heterogeneity} = 0.19$). Further subgroup analyses were conducted based on differences in MACE definitions, and the results showed no significant differences in the following subgroups: MACE defined as death, MI, or revascularization (RR 0.90, 95% CI 0.70–1.16, $P = 0.41$; $I^2 = 0\%$, $P_{heterogeneity} = 0.40$); MACE defined as death, MI, revascularization, or cerebrovascular accident (CVA) (RR 0.81, 95% CI 0.58–1.12, $P = 0.20$; $I^2 = 0\%$, $P_{heterogeneity} = 0.78$); MACE defined as death, MI, revascularization, or rehospitalization (RR 1.00, 95% CI 0.56–1.80, $P = 1.00$; $I^2 = 0\%$, $P_{heterogeneity} = 0.39$). In contrast, ICR significantly decreased the risk of MACE (death, MI, revascularization, CVA, or rehospitalization) compared to SCR (RR 0.60, 95% CI 0.46–0.77, $P < 0.0001$, $I^2 = 52\%$, $P_{heterogeneity} = 0.13$).

In the subgroup analysis according to the difference in SCR timing (Supplementary Figure S2), ICR significantly decreased the risk of MACE (RR 0.70, 0.56–0.88, $P = 0.003$) compared to SCR at 14–45 days. However, no difference was found in ICR compared with SCR at <14 days.

The subgroup analysis by myocardial infarction type (Supplementary Figure S3) revealed that in the STEMI subgroup, ICR was associated with a lower incidence of MACE

TABLE 1 Baseline characteristics of the included trials.

Trials	Type of ACS	Single/ multi-center	ICR/ SCR	Timing of SCR (days)	Exclusion criteria	MACE	Follow-up
PRIMA (Ochala et al., 2004)	STEMI	Single	48/44	<7	Cardiogenic shock	AD, MI, TVR	6 months
Politi et al., 2010	STEMI	Single	65/65	20–45	Cardiogenic shock; left main stenosis; previous CABG; severe valvular heart disease	AD, MI, IDR, rehospitalization	30 months
Maamoun et al., 2011	STEMI	Single	42/36	<7	Cardiogenic shock; pulmonary edema; left main stenosis	AD, MI, TVR, CVA, rehospitalization	12 months
Tarasov et al., 2013	STEMI	Single	46/43	8.5 ± 4.2	Acute heart failure Killip III–IV; ≥50% left main stenosis	AD, MI, IDR	6 months
SMILE (Sardella et al., 2016)	Non-STEMI	Single	264/263	4.8 ± 1.2	Cardiogenic shock; chronic total occlusion; previous CABG; severe valvular disease	AD, MI, TVR, stroke, rehospitalization	12 months
BIOVASC (Diletti et al., 2023)	ACS	Multi-center	764/761	30–42	Previous CABG, cardiogenic shock, and CTO	AD, MI, IDR, CVA	12 months
MULTISTARS AMI	STEMI	Multi-center	418/422	19–45	Previous CABG, cardiogenic shock, and CTO	AD, MI, IDR, stroke, rehospitalization	12 months
Park et al., 2023	STEMI	Multi-center	103/106	4.4 (1–11)	History of bleeding diathesis or known coagulopathy; LVEF <25% or presence of cardiogenic shock	AD, MI, IDR	12 months
Elkady et al., 2021 (35)	Non-STEMI	Single	30/30	20–42	Previous CABG, cardiogenic shock, and CTO	AD, MI, IDR, rehospitalization	6 months
Brendea et al., 2021 (36)	STEMI	Single	50/50	2–3	Previous CABG and cardiogenic shock	AD, MI, IDR, stroke	24 months
Wood et al., 2019	STEMI	Multi-center	1,353/ 663	<45	Previous CABG, cardiogenic shock	CD, MI, IDR	4 years

ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; CABG, coronary artery bypass grafting; CD, cardiovascular death; CTO, chronic total occlusion; AD, all-cause death; MI, myocardial infarction; IDR, unplanned ischemia-driven revascularization; CVA, cerebrovascular accident; LVEF, left ventricular ejection fraction; TVR, target vessel revascularization.

TABLE 2 Baseline characteristics of the included patients.

Trials	Age	Male (%)	Diabetes (%)	Hypertension (%)	Smoking (%)	Hyperlipidemia (%)	Anterior myocardial infarction
PRIMA (Ochala et al., 2004)	65/67	73/75	31/34	52/48	36/43	81/91	46/45
Politi et al., 2010	65/64	77/80	14/19	49/65	NR	NR	48/49
Maamoun et al., 2011	55/52	95/89	42/57	38/33	52/57	57/44	62/69
Tarasov et al., 2013	59/59	70/58	26/21	96/86	NR	NR	46/30
SMILE (Sardella et al., 2016)	72/73	78/79	34/35	73/66	45/41	58/54	71/72
BIOVASC (Diletti et al., 2023)	66/65	78/77	21/21	58/52	52/51	51/53	66/63
MULTISTARS AMI	66/64	77/81	16/15	55/50	53/49	27/27	40/41
Park et al., 2023	63/62	80/83	41/35	51/45	52/53	37/39	55/60
Elkady et al., 2021 (35)	NR	NR	NR	NR	NR	NR	NR
Brendea et al., 2021 (36)	NR	37/36	12/11	20/24	25/21	NR	22/18
Wood et al., 2019	62/61	80/82	20/18	50/46	3/4	38/38	NR

The data shown are for the ICR/SCR groups.
NR, Not reported.

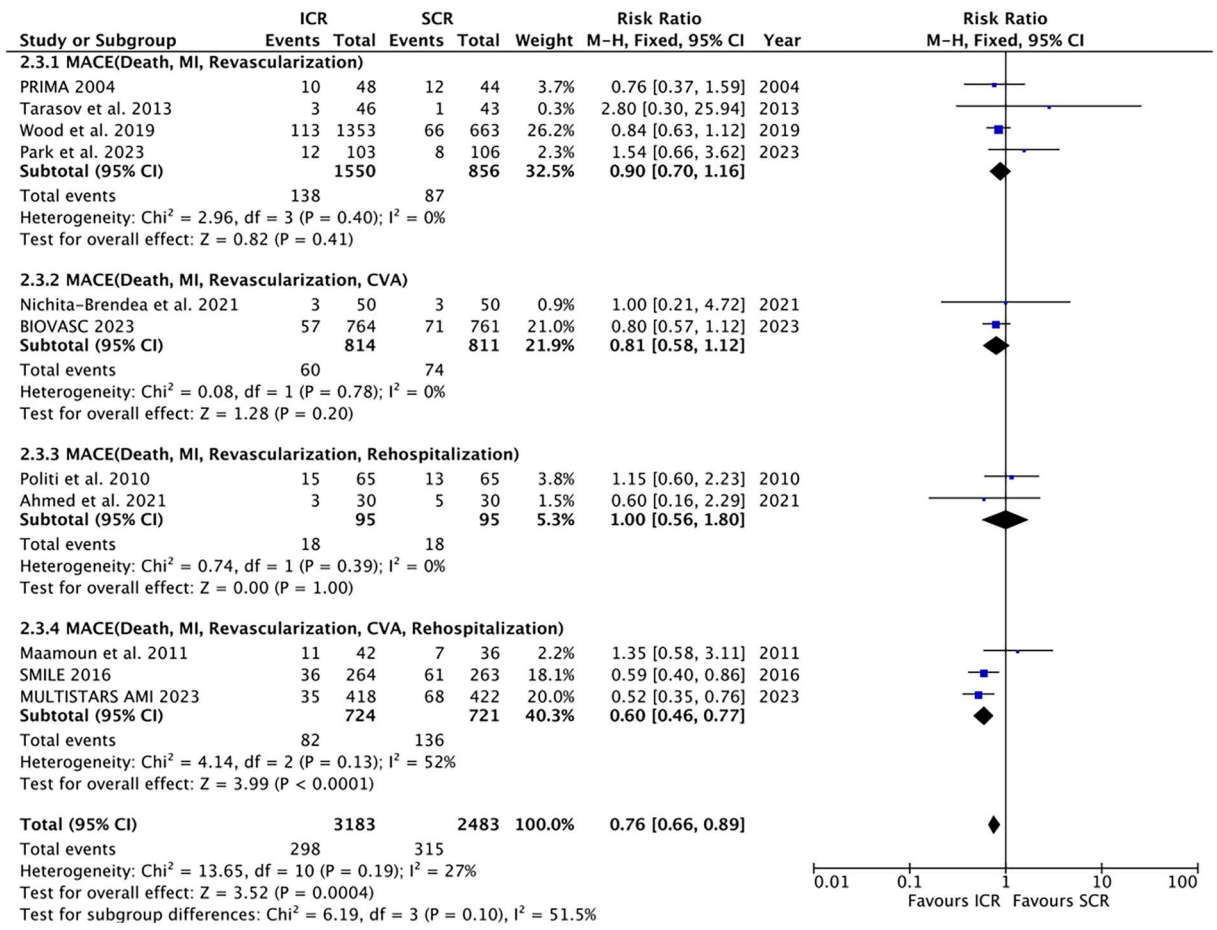

FIGURE 2
Pooled analyses of ICR compared to SCR for the primary outcomes.

compared to SCR (RR 0.81, 95% CI 0.67–0.97, $P = 0.02$). This was consistent with the results observed in the non-STEMI subgroup (RR 0.67, 95% CI 0.51–0.88, $P = 0.004$).

Repeat myocardial infarction and repeat revascularization

Seven trials reported the repeat myocardial infarction and repeat revascularization outcomes (Figure 3). The risk of repeat myocardial infarction decreased by 40% in the ICR group compared with SCR, with low heterogeneity (RR 0.60, 0.44–0.83, $P = 0.002$, $I^2 = 15\%$, $P_{heterogeneity} = 0.32$). Similarly, ICR also decreased the risk of repeat revascularization by 37% compared with the SCR group (RR 0.63, 0.49–0.80, $P = 0.002$, $I^2 = 2\%$, $P_{heterogeneity} = 0.41$).

Further subgroup analysis based on the timing of SCR (Supplementary Figure S2) showed that, when compared with SCR at <14 days, ICR did not decrease the risk of repeat myocardial infarction (RR 0.97, 95% CI 0.59–1.59, $P = 0.91$) and repeat revascularization (RR 0.75, 95% CI 0.52–1.07, $P = 0.12$). However, when compared with SCR at 14–45 days, ICR significantly decreased the risk of repeat revascularization (RR 0.44, 95% CI 0.28–0.68, $P = 0.0002$) and repeat revascularization (RR 0.56, 95% CI 0.40–0.77, $P = 0.0004$). Significant heterogeneity was observed between these subgroups ($P = 0.02$) for the repeat myocardial infarction outcome, but no heterogeneity was observed for the repeat revascularization outcome ($P = 0.24$).

A further subgroup analysis based on myocardial infarction type (Supplementary Figure S3) showed that only one study was included in the non-STEMI subgroup. In the STEMI subgroup, when compared with SCR, ICR did not decrease the risk of repeat myocardial infarction (RR 0.63, 95% CI 0.49–0.80, $P = 0.002$) but significantly decreased the risk of repeat revascularization (RR 0.63, 95% CI 0.49–0.80, $P = 0.002$).

All-cause mortality, death or myocardial infarction, and cardiovascular mortality

The safety outcomes were shown in Figure 4. Six randomized controlled trials included in the all-cause mortality outcome, which showed that ICR did not increase the risk of all-cause mortality compared to SCR (RR: 1.02, 95% CI: 0.78–1.32, $P = 0.89$, $P_{heterogeneity} = 0.41$, $I^2 = 4\%$). Similarly, ICR was not associated with a higher risk of cardiovascular mortality compared to SCR (RR: 1.08, 95% CI: 0.76–1.53, $P = 0.67$, $P_{heterogeneity} = 0.71$, $I^2 = 0\%$). However, ICR decreased the risk of death or myocardial infarction by 24% compared to SCR, without any heterogeneity (RR: 0.76, 95% CI: 0.61–0.95, $P = 0.02$, $P_{heterogeneity} = 0.57$, $I^2 = 0\%$). A further subgroup analysis based on the timing of SCR and myocardial infarction

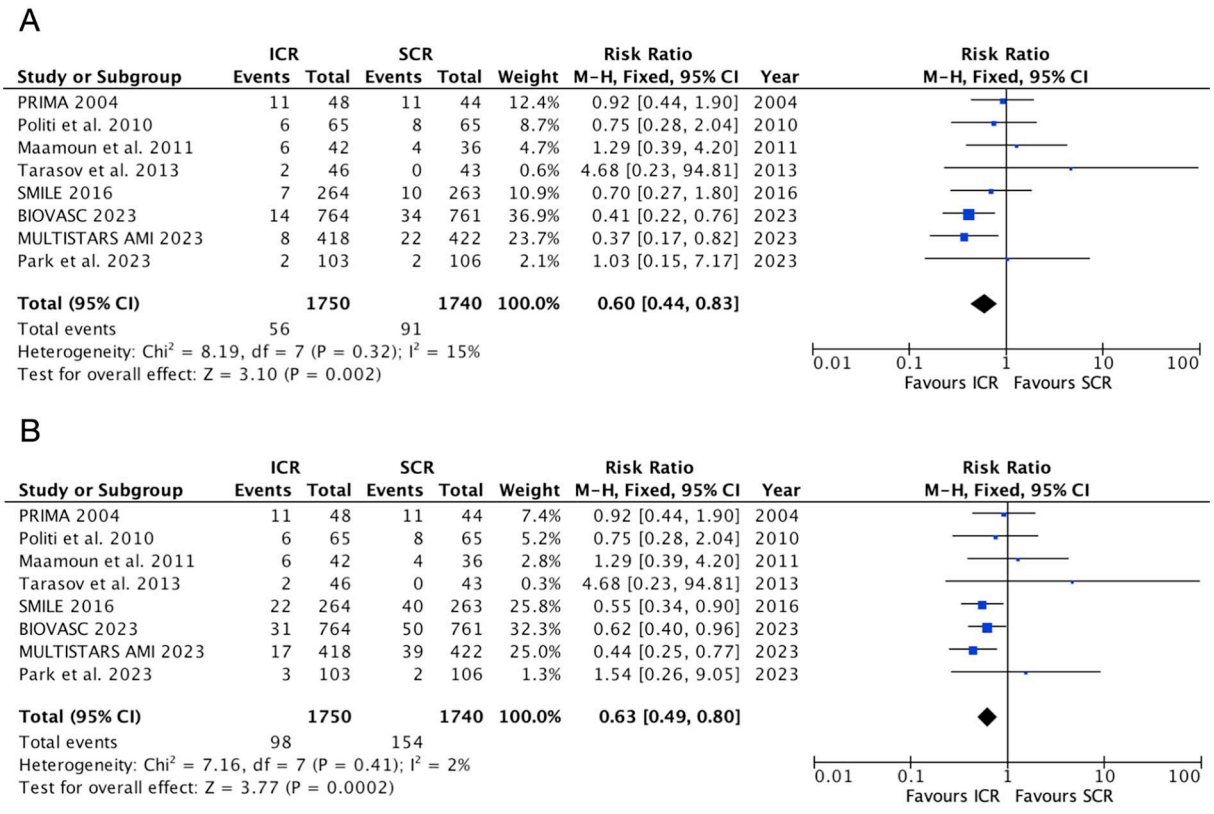

FIGURE 3
Pooled analyses of ICR compared to SCR for the efficacy outcomes. (A) Repeat myocardial infarction and (B) repeat revascularization.

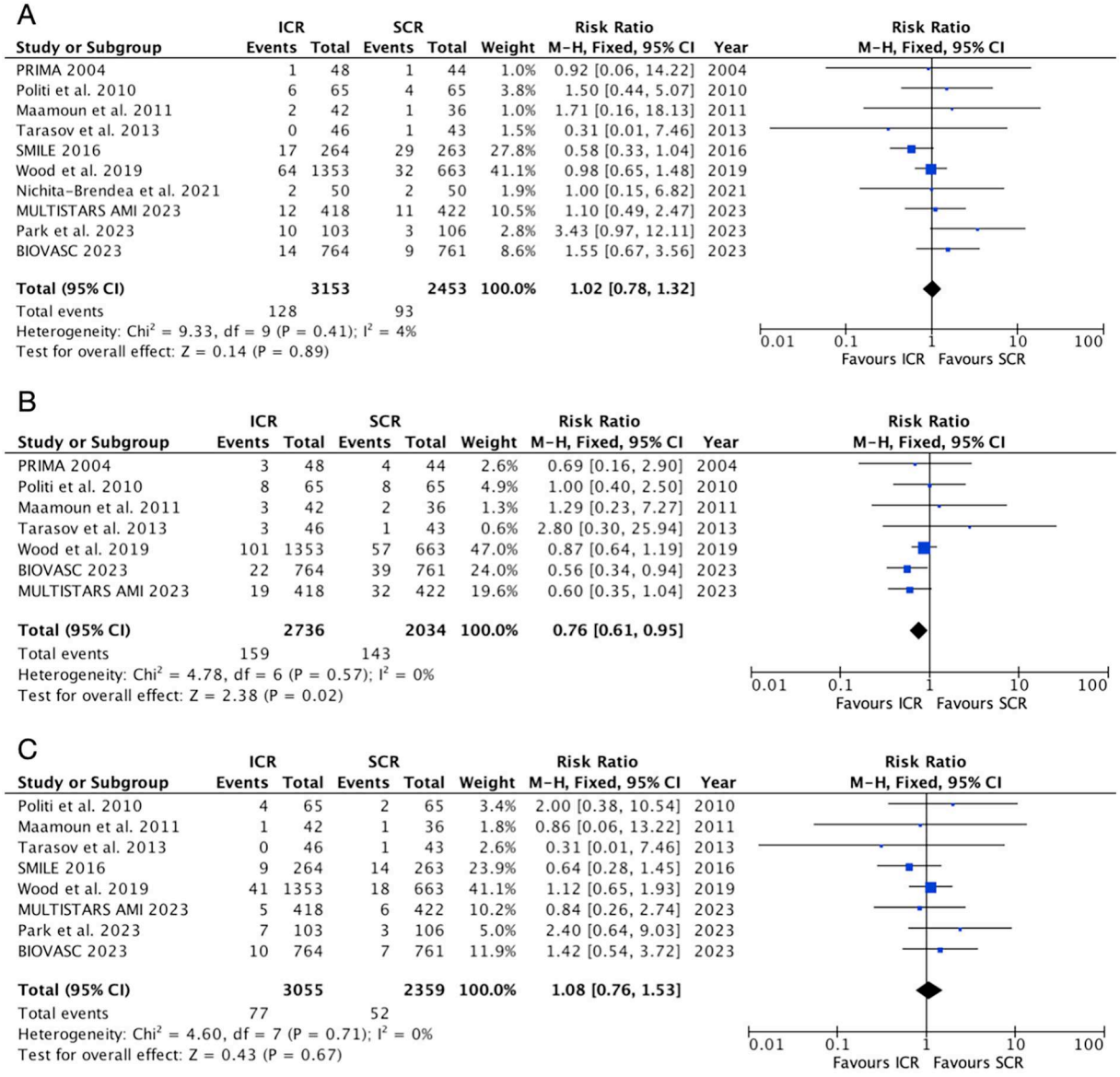

FIGURE 4
Pooled analyses of ICR compared to SCR for the safety outcomes. (A) All-cause mortality, (B) death or myocardial infarction, and (C) cardiovascular mortality.

type (Supplementary Figures S2, S3) showed no difference between the two subgroups for all-cause mortality and cardiovascular mortality. ICR was associated with a lower risk of death or myocardial infarction (RR: 0.62, 95% CI: 0.44–0.88, $P = 0.007$) compared to SCR at 14–45 days. However, no significant difference was observed between ICR and SCR at <14 days (RR: 1.16, 95% CI: 0.45–3.02, $P = 0.76$).

Publication bias and assessment of quality

The publication bias analyses resulted in asymmetrically distributed funnel plots for all the outcomes (Supplementary Figure S4). The Egger's tests, the results of which are presented in Supplementary Table S2, indicated that for each of the outcomes, no significant publication bias was found, as evidenced by all the *P*-values being greater than 0.05. The quality assessment of each trial and the GRADE evidence evaluations are detailed in Supplementary Table S3. All the included trials exhibited a low risk of bias across the selection, detection, performance, and reporting domains. The GRADE assessments confirmed moderate to high certainty for all the evaluated outcomes.

Trial sequential analysis

The TSA results are presented in Figure 5. For MACE, repeat myocardial infarction, and repeat revascularization, the

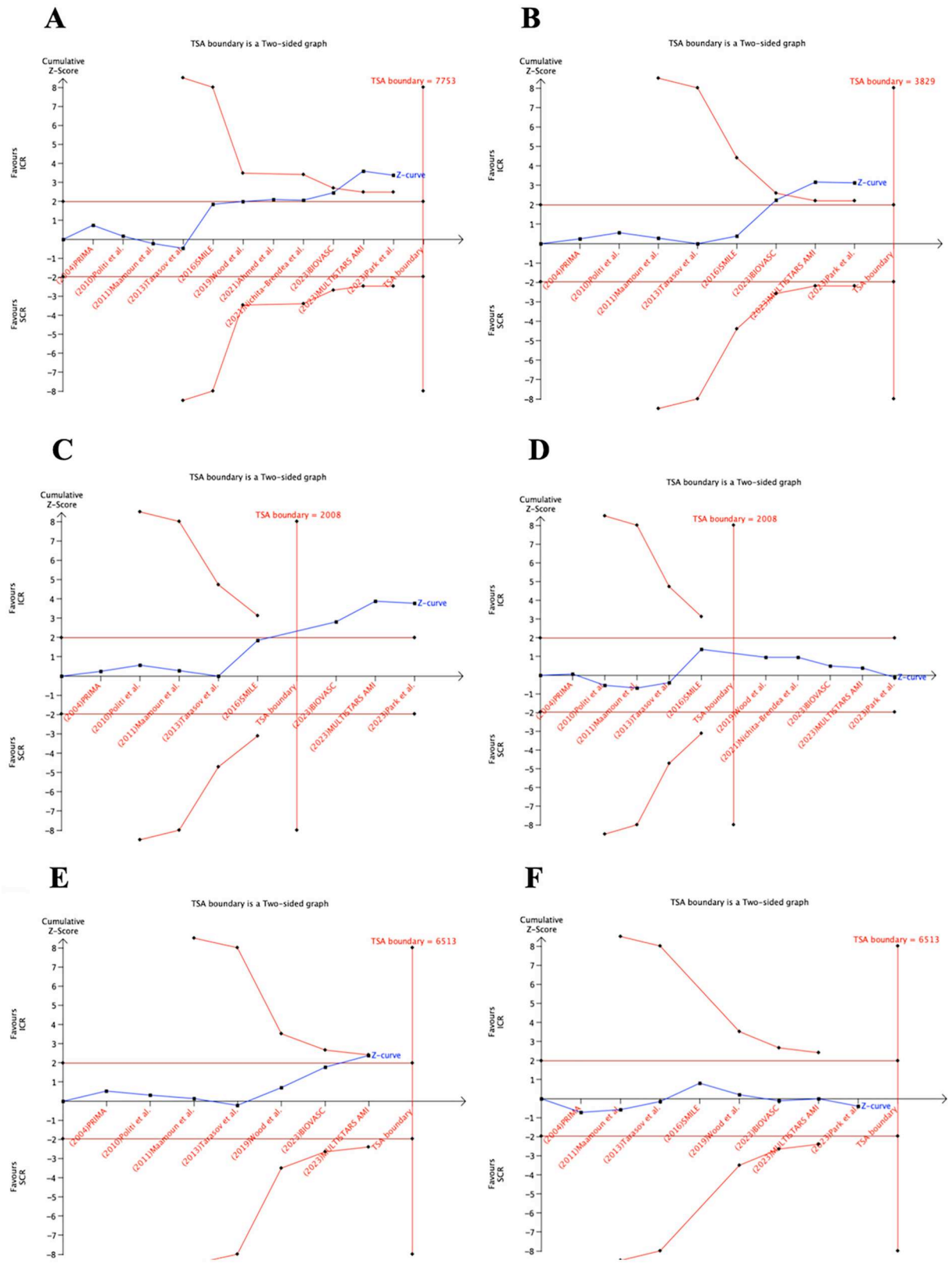

FIGURE 5
TSA of the studies that compared ICR and SCR. RIS, required information size. ICR, immediate complete revascularization; SCR, staged complete revascularization; TSA, trial sequential analysis; I have comfimed RIS, required information size.

cumulative z-curves crossed the conventional statistical significance boundaries and reached the RIS. For all-cause death, the z-curve did not cross the conventional statistical significance boundaries but still achieved the RIS. For the composite outcome of death or myocardial infarction, the z-curve crossed both the conventional and TSA boundaries. However, for cardiovascular death, the z-curve did not cross either the conventional or TSA boundaries, and an RIS of 6,513 would be required to robustly address this outcome.

Discussion

ICR was associated with a lower risk of MACE, repeat myocardial infarction, repeat revascularization, and death or myocardial infarction compared to SCR. Moreover, ICR did not increase the risk of all-cause mortality and cardiovascular mortality.

MVD is highly prevalent in patients with ACS, with these individuals having a higher risk of mortality and poorer clinical outcomes compared to those with single-vessel disease (28). Multiple RCTs have demonstrated that complete revascularization provides greater net clinical benefits for patients with ACS and MVD than culprit vessel revascularization alone (5–9). The efficacy of ICR has been validated in several RCTs. The BIOVASC trial, a multi-center randomized study involving 1,525 patients with ACS across 29 hospitals, compared ICR and SCR (22). The results showed that ICR significantly reduced the incidence of myocardial infarction [hazard ratio (HR) 0.41, 95% CI 0.22–0.76, $P = 0.0045$] and unplanned ischemia-driven revascularizations (HR 0.61, 95% CI 0.39–0.95, $P = 0.030$). However, no significant effect was observed for all-cause mortality (HR 1.56, 95% CI 0.68–3.61, $P = 0.30$). Similarly, the MULTISTARS AMI trial found that immediate multivessel PCI was non-inferior to staged multivessel PCI in reducing the risk of composite outcomes, including all-cause death, fatal/non-fatal myocardial infarction, stroke, and heart failure-related hospitalizations, within 1 year (23).

The net clinical benefit of ICR in hemodynamically stable patients with STEMI and MVD remains unclear. The 2023 ESC guidelines for ACS management recommend culprit vessel revascularization (Class Ia) during primary PCI, followed by SCR (Class IIa) for patients with MVD and cardiogenic shock. In addition, patients with STEMI without cardiogenic shock are advised to undergo complete revascularization either during the initial procedure or within 45 days (12).

ICR can restore the blood supply at an early stage. This can confer multiple benefits, such as reducing the incidence of thrombotic events in the acute phase, improving early cardiac function, and cutting medical costs (29). However, ICR may increase the use of contrast agents and prolong the operating time. Thus, these disadvantages must be weighed against the increased risk of periprocedural myocardial infarction, particularly during complex multivessel PCI (30). However, acute myocardial infarction can cause microangiopathy, which diminishes the vasodilatory response. This situation can affect the assessment of non-culprit vessels, leading to further overestimation of the degree of stenosis and resulting in more stent implantations. Therefore, SCR can reduce the risk associated with primary PCI and allow for a more accurate assessment of non-culprit vessels.

In patients with STEMI, the culprit lesion can be distinctly identified based on an ECG. However, in non-ST-segment elevation acute coronary syndromes, ECG-based identification may be misleading. Misidentification of the culprit lesion could lead to treatment of a non-culprit lesion (31–33). In the context of acute coronary syndromes, non-culprit lesions may also exhibit unstable characteristics. These characteristics make them prone to plaque rupture and the development of acute coronary syndromes within the time interval between immediate and staged surgery (27). Both of these scenarios may support an ICR strategy. Furthermore, they help explain the 41% decrease in the risk of myocardial infarction and the 38% decrease in the risk of unplanned ischemia-driven revascularization observed in our study.

Zhou et al. conducted a meta-analysis that compared ICR and SCR in patients with MDV, which was similar to our study (34). The results showed that ICR decreased the risk of MACE, myocardial infarction, and repeat revascularization by 27%, 47%, and 36%, respectively. All-cause mortality, cardiovascular death incidence, and stroke incidence did not significantly differ between the two groups. The findings of Zhou et al. are consistent with ours. Our study further conducted subgroup analyses based on the timing of SCR and the type of myocardial infarction. Compared with SCR performed within 14 days, ICR did not reduce the risk of MACE, myocardial infarction, or repeat revascularization. This suggests that the effectiveness of ICR may be more evident when compared with SCR performed between 14 and 45 days. Therefore, in clinical practice, both ICR and SCR performed within 14 days may be preferable options. Furthermore, a total of 11 RCTs were included in this article, among which eight RCTs enrolled patients with STEMI, two RCTs included only patients with non-STEMI, and only one RCT (BIOVASC) included patients with unstable angina. Therefore, the included studies focused more on patients with myocardial infarction, and the research conclusions were consistent for the patients with STEMI or non-STEMI. For unstable angina, however, more clinical trial data are needed, and the current conclusions cannot be directly applied to this patient population.

Based on the TSA, ICR can adequately reduce the risk of MACE, repeat myocardial infarction, repeat revascularization, all-cause death, and death or myocardial infarction. Further RCTs are not required to demonstrate this. Furthermore, the all-cause death outcome has met the RIS, and I have comfimed this finding likely reflects a true negative result.

Conclusions

In patients with ACS and MVD, ICR significantly decreases the risk of MACE, repeat myocardial infarction, and repeat revascularization, with no associated increase in all-cause

mortality. This favorable effect is especially pronounced when compared with SCR administered between 14 and 45 days.

Limitations

This meta-analysis of randomized controlled trials had several limitations. First, it was based on study-level data rather than individual patient data, which may have limited the depth of the subgroup analyses and the adjustments for potential confounders. Second, the majority of included trials were open-label, which could have introduced performance bias, particularly in the outcomes that were assessed subjectively. Third, the timing of SCR ranged from a few days to 45 days, which increased the heterogeneity of the studies, making it difficult to determine a uniform optimal treatment regimen. Finally, there were large differences in the prevalence of risk factors for coronary heart disease, namely, diabetes, hypertension, and hyperlipidemia, between the two groups, which may have contributed to the differences in outcomes.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Author contributions

LH: Formal analysis, Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft. Q-JY: Data curation, Investigation, Validation, Writing – original draft. BS: Data curation, Validation, Writing – original draft. CG: Data curation, Validation, Writing – original draft. J-LH: Data curation, Validation, Software, Writing – original draft. H-PL: Data curation, Validation, Writing – original draft. J-HZ: Writing – review & editing. P-YZ: Formal analysis, Funding acquisition, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet*. (2003) 361(9351):13–20. doi: 10.1016/S0140-6736(03)12113-7

2. Ibánez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Rev Esp Cardiol (Engl Ed)*. (2017) 70(12):1082 (in English and Spanish). doi: 10.1016/j.rec.2017.11.010

3. van der Schaaf RJ, Timmer JR, Ottervanger JP, Hoorntje JC, de Boer MJ, Suryapranata H, et al. Long-term impact of multivessel disease on cause-specific mortality after ST elevation myocardial infarction treated with reperfusion therapy. *Heart*. (2006) 92(12):1760–3. doi: 10.1136/hrt.2005.086058

4. Sorajja P, Gersh BJ, Cox DA, McLaughlin MG, Zimetbaum P, Costantini C, et al. Impact of multivessel disease on reperfusion success and clinical outcomes in patients undergoing primary percutaneous coronary intervention for acute myocardial infarction. *Eur Heart J*. (2007) 28(14):1709–16. doi: 10.1093/eurheartj/ehm184

5. Mehta SR, Wood DA, Storey RF, Mehran R, Bainey KR, Nguyen H, et al. Complete revascularization with multivessel PCI for myocardial infarction. *N Engl J Med*. (2019) 381(15):1411–21. doi: 10.1056/NEJMoa1907775

6. Wald DS, Morris JK, Wald NJ, Chase AJ, Edwards RJ, Hughes LO, et al. Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med*. (2013) 369(12):1115–23. doi: 10.1056/NEJMoa1305520

7. Engstrøm T, Kelbæk H, Helqvist S, Høfsten DE, Kløvgaard L, Holmvang L, et al. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3—PRIMULTI): an open-label, randomised controlled trial. *Lancet*. (2015) 386(9994):665–71. doi: 10.1016/s0140-6736(15)60648-1

8. Smits PC, Laforgia PL, Abdel-Wahab M, Neumann FJ, Richardt G, Boxma-de Klerk B, et al. Fractional flow reserve-guided multivessel angioplasty in myocardial infarction: three-year follow-up with cost benefit analysis of the compare-acute trial. *EuroIntervention*. (2020) 16(3):225–32. doi: 10.4244/EIJ-D-20-00012

9. Gershlick AH, Banning AS, Parker E, Wang D, Budgeon CA, Kelly DJ, et al. Long-term follow-up of complete versus lesion-only revascularization in STEMI and multivessel disease: the CvLPRIT trial. *J Am Coll Cardiol*. (2019) 74(25):3083–94. doi: 10.1016/j.jacc.2019.10.033

10. Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. (2022) 145(3):e4–17. doi: 10.1161/CIR.0000000000001039

11. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. (2021) 42(14):1289–367. doi: 10.1093/eurheartj/ehad879

12. Buske M, Feistritzer HJ, Jobs A, Thiele H. Management des akuten koronarsyndroms: ESC-leitlinie 2023 [Management of acute coronary syndrome: ESC guidelines 2023]. *Herz*. (2024) 49(1):5–14. doi: 10.1007/s00059-023-05222-1

13. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Br Med J*. (2021) 372:n71. doi: 10.1136/bmj.n71

14. McIntyre HD, Catalano P, Zhang C, Desoye G, Mathiesen ER, Damm P. Gestational diabetes mellitus. *Nat Rev Dis Primers*. (2019) 5:47. doi: 10.1038/s41572-019-0098-8

15. Reece EA, Leguizamón G, Wiznitzer A. Gestational diabetes: the need for a common ground. *Lancet*. (2009) 373:1789–97. doi: 10.1016/S0140-6736(09)60515-8

16. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *Br Med J*. (2008) 336(7650):924–6. doi: 10.1136/bmj.39489.470347.AD

17. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Br Med J*. (2003) 327(7414):557–60. doi: 10.1136/bmj.327.7414.557

18. Politi L, Sgura F, Rossi R, Monopoli D, Guerri E, Leuzzi C, et al. A randomised trial of target-vessel versus multi-vessel revascularisation in ST-elevation myocardial infarction: major adverse cardiac events during long-term follow-up. *Heart*. (2010) 96(9):662–7. doi: 10.1136/hrt.2009.177162

19. Maamoun W, Elkhaeat N, Elarasy R. Safety and feasibility of complete simultaneous revascularization during primary PCI in patients with STEMI and multi-vessel disease. *Egypt Heart J*. (2011) 63:39–43. doi: 10.1016/j.ehj.2011.08.030

20. Tarasov RS, Ganiukov VI, Popov VA, Shushpannikov PA, Barbarash OL, Barbarash LS. Effect of the terms of complete revascularization on the outcomes of treatment of patients with st segment elevation myocardial infarction and multivessel coronary artery disease. *Angiol Sosud Khir*. (2013) 19:14–20.

21. Sardella G, Lucisano L, Garbo R, Pennacchi M, Cavallo E, Stio RE, et al. Single-staged compared with multi-staged PCI in multivessel NSTEMI patients: the SMILE trial. *J Am Coll Cardiol*. (2016) 67(3):264–72. doi: 10.1016/j.jacc.2015.10.082

22. Diletti R, den Dekker WK, Bennett J, Schotborgh CE, van der Schaaf R, Sabaté M, et al. Immediate versus staged complete revascularisation in patients presenting with acute coronary syndrome and multivessel coronary disease (BIOVASC): a prospective, open-label, non-inferiority, randomised trial. *Lancet*. (2023) 401(10383):1172–82. doi: 10.1016/S0140-6736(23)00351-3

23. Stähli BE, Varbella F, Linke A, Schwarz B, Felix SB, Seiffert M, et al. Timing of complete revascularization with multivessel PCI for myocardial infarction. *N Engl J Med*. (2023) 389(15):1368–79. doi: 10.1056/NEJMoa2307823

24. Ochala A, Smolka GA, Wojakowski W, Dudek D, Dziewierz A, Krolikowski Z, et al. The function of the left ventricle after complete multivessel one-stage percutaneous coronary intervention in patients with acute myocardial infarction. *J Invasive Cardiol*. (2004) 16(12):699–702.

25. Wood DA, Cairns JA, Wang J, Mehran R, Storey RF, Nguyen H, et al. Timing of staged nonculprit artery revascularization in patients with ST-segment elevation myocardial infarction: COMPLETE trial. *J Am Coll Cardiol*. (2019) 74(22):2713–23. doi: 10.1016/j.jacc.2019.09.051

26. Park S, Rha SW, Choi BG, Cho JH, Park SH, Lee JB, et al. Immediate versus staged complete revascularization in patients with ST-segment elevation myocardial infarction and multivessel coronary artery disease: results from a prematurely discontinued randomized multicenter trial. *Am Heart J*. (2023) 259:58–67. doi: 10.1016/j.ahj.2023.01.020

27. Park S, Rha SW, Choi BG, Cho JH, Park SH, Lee JB, et al. Total versus staged versus functional revascularization in NSTEACS patients with multivessel disease. *Egypt Heart J*. (2021) 73(1):56. doi: 10.1186/s43044-021-00179-0

28. Park DW, Clare RM, Schulte PJ, Pieper KS, Shaw LK, Califf RM, et al. Extent, location, and clinical significance of non-infarct-related coronary artery disease among patients with ST-elevation myocardial infarction. *JAMA*. (2014) 312(19):2019–27. doi: 10.1001/jama.2014.15095

29. Zhong PY, Sun B, Cao HP, Wang W, Xiong TL. Optional revascularization strategies for patients with ST-segment elevation myocardial infarction and multivessel disease. *Rev Cardiovasc Med*. (2024) 25(6):209. doi: 10.31083/j.rcm2506209

30. Mitsis A, Spirito A, Valgimigli M. Complete revascularisation in STEMI: consider the benefits but do not forget the risks! *Ann Transl Med*. (2019) 7(Suppl 8):S331. doi: 10.21037/atm.2019.09.121

31. Kerensky RA, Wade M, Deedwania P, Boden WE, Pepine CJ. Revisiting the culprit lesion in non-Q-wave myocardial infarction. Results from the VANQWISH trial angiographic core laboratory. *J Am Coll Cardiol*. (2002) 39(9):1456–63. doi: 10.1016/s0735-1097(02)01770-9

32. Balbi MM, Scarparo P, Tovar MN, Masdjedi K, Daemen J, Den Dekker W, et al. Culprit lesion detection in patients presenting with non-ST elevation acute coronary syndrome and multivessel disease. *Cardiovasc Revasc Med*. (2022) 35:110–8. doi: 10.1016/j.carrev.2021.03.019

33. Heitner JF, Senthilkumar A, Harrison JK, Klem I, Sketch MH Jr, Ivanov A, et al. Identifying the infarct-related artery in patients with non-ST-segment-elevation myocardial infarction. *Circ Cardiovasc Interv*. (2019) 12(5):e007305. doi: 10.1161/CIRCINTERVENTIONS.118.007305

34. Zhou YM, Sun B. Immediate versus staged complete revascularization in patients presenting with acute coronary syndrome and multivessel coronary disease without cardiac shock: a study-level meta-analysis of randomized controlled trials. *Cardiovasc Drugs Ther*. (2024). doi: 10.1007/s10557-024-07597-7

35. Elkady AO, Abdelghany M, Diab R, Ezz A, Elagha AA. Total versus staged versus functional revascularization in NSTEACS patients with multivessel disease. *Egypt Heart J*. (2021) 73(1):56. doi: 10.1186/s43044-021-00179-0

36. Brendea MTN, Popescu MI, Popa V, Carmen PCD. A clinical trial comparing complete revascularization at the time of primary percutaneous coronary intervention versus during the index hospital admission in patients with multivessel coronary artery disease and STEMI uncomplicated by cardiogenic shock. *Anatol J Cardiol*. (2021) 25(11):781–8. doi: 10.5152/AnatolJCardiol.2021.71080

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Predictive value of the electrocardiogram exercise stress test for the presence or absence of left main disease

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Background: The ability of the electrocardiogram exercise stress test (ECG-EST) in excluding the presence of left main (LM) coronary artery disease (CAD) has been poorly investigated.
Methods: We retrospectively selected patients who underwent both ECG-EST and elective invasive coronary angiography (ICA) at our Institution between January 2018 and December 2023 due to angina pain suspected of obstructive CAD. Preventively defined individual and combined ECG-EST variables suggesting no/mild myocardial ischemia were assessed as predictors of the absence of LM disease. Some ECG-EST variables suggesting extensive/severe myocardial ischemia were instead assessed as predictors of the presence of LM disease, defined as a stenosis ≥50% of the left main artery.
Results: Overall, 515 patients were included (age 66.2 ± 11 years; 74% men). LM disease at ICA was found in 26 patients (5%). Individual and combined ECG-EST variables showed low positive predictive values for LM-CAD [maximum 15% for a combination of ST-segment depression (STD) in ≥ 5 leads and ECG-EST duration <360 s]. The negative predictive value, however, was very high for some combined ECG-EST variables. Very low risk of LM disease (≤2.5%) was particularly shown in patients with peak heart rate (HR) ≥ 75% of maximal predicted HR for age and STD < 2 mm (prevalence 63.1%; risk 2.2%) and peak HR ≥85% of maximal predicted HR for age and maximal STD < 2 mm (prevalence 46.2%; risk 2.5%).
Conclusions: Among patients with angina chest pain suspected of obstructive CAD, ECG-EST results can reliably identify those at very low risk of LM disease at coronary angiography.

KEYWORDS

coronary artery disease, left main disease, electrocardiogram exercise stress test, invasive coronary angiography, negative predictive value

1 Introduction

Randomized clinical trials in the 1980s showed that, among patients with suspected or ascertained obstructive coronary artery disease (CAD), coronary artery bypass graft surgery consistently improved survival only in patients with left main (LM) CAD or those with three-vessel disease CAD who also had impaired left ventricular function (1, 2).

Importantly, while subsequent randomized clinical trials confirmed the lack of any significant benefit on survival of coronary revascularization interventions, compared to optimal medical therapy, in patients with stable CAD but no evidence of LM disease (3–5), percutaneous coronary intervention (PCI) was found to provide similar survival rates to bypass surgery in several subgroups of patients with LM disease (6–8). According to these results, most patients with suspected or known CAD could be treated by optimal medical therapy only, but exclusion of LM disease and impaired left ventricular function would be mandatory.

Several studies investigated whether LM disease might be identified through electrocardiogram exercise stress test (ECG-EST), showing that some abnormal ECG-EST results, particularly, stress-induced ST-segment elevation (STE) in lead aVR and/or V1, ST-segment depression (STD) in five or more leads, and a greater magnitude of STD, may predict the presence of LM disease (9–11). However, according to the previously mentioned results from clinical trials, ruling out LM disease in individual patients would be just as important as identifying it, since it would suggest that conservative medical treatment might be sufficient for their management.

Thus, in this study, we specifically aimed to investigate, in a population of patients referred to undergo a first ECG-EST for a suspected angina chest pain, whether and how accurately ECG-EST results may reliably exclude the presence of LM disease. To this scope, we preventively chose a series of ECG-EST variables and combinations of variables suggesting either no/mild myocardial ischemia and assessed their relationship with the absence of LM disease at invasive coronary angiography (ICA). At the same time, however, we also assessed the relation with LM disease of preventively defined ECG-EST variables indicating severe/extensive myocardial ischemia.

2 Methods

We retrospectively included in this study consecutive clinically stable patients who underwent both ECG-EST and elective ICA at our Department of Cardiovascular Sciences, Policlinico Universitario A. Gemelli IRCCS, Rome, between 1 January 2018 and 31 December 2023, due to suspected obstructive CAD.

The patients were excluded when any of the following conditions were present: (1) ICA performed after >6 months from the ECG-EST; (2) ECG abnormalities preventing reliable assessment of ST-segment changes during ECG-EST (e.g., atrial fibrillation, intraventricular conduction disorders, pacemaker rhythm, and significant ST-segment abnormalities at baseline); (3) use of an ECG-EST protocol different from standard treadmill Bruce protocol; or (4) any previous history of CAD or coronary angiography. The main clinical data of the patients were obtained from the institutional database of our hospital.

2.1 Exercise stress test

All patients underwent treadmill ECG-EST following a standard symptom- and sign-limited Bruce protocol. Three ECG leads (DII, V2, and V5) were continuously monitored throughout the test, and up-to-date averaged QRS complexes from all ECG leads continuously displayed on the screen. Criteria for stopping the test included physical exhaustion, increasing angina severity (Borg scale >6) (12), relevant clinical events (e.g., dyspnea, severe arrhythmias, hypotension), and STD >4 mm in any ECG lead. Blood pressure (BP) and heart rate (HR) were recorded at baseline and at peak EST. A summary report with full ECG-EST and 10 s 12-lead ECG strips recorded at baseline, at the end of each stage, at the time of significant ST-segment changes, at peak EST, every minute in the recovery phase, and when clinically indicated, was digitally stored in a database and available for analysis.

ECG-ESTs were reviewed, and the following findings were obtained: (1) HR and systolic and diastolic BP at baseline and peak exercise; (2) duration of the test; (3) occurrence of STD ≥1 mm in each lead, except aVR; (4) maximal STD; (5) number of leads showing STD ≥1 mm; (6) occurrence of symptoms (angina, dyspnea, etc.).

Two investigators independently reviewed ECG-ESTs, and discrepancies were solved by consensus and supervision of a third investigator. ECG-EST was considered positive for myocardial ischemia when a horizontal or downsloping STD ≥1 mm at 60–80 ms from the J-point was detected in at least two contiguous leads, but not aVR. Furthermore, EST was considered maximal when peak HR was above 75% of maximal predicted HR for age, calculated according to Fox's formula: maximal HR = 220 − age (in years) (13).

2.2 ECG-EST variables predictive for the presence/absence of LM disease

Based on the results of our previous study (10), we assessed the association with LM disease of the following preventively established individual and combined variables suggesting severe and/or extensive myocardial ischemia: (1) STD involving ≥5 ECG leads; (2) STD ≥2 mm; (3) STD involving ≥5 ECG leads and ECG-EST duration <360 s; and (4) STD >2 mm and ECG-EST duration <360 s. Furthermore, the relationship between LM disease and ST-segment elevation in lead aVR was also assessed (14–16).

The following, preventively established ECG-EST variables, suggesting no/mild myocardial ischemia, were instead tested for the absence of LM disease at ICA: (1) negative ECG-EST; (2) ECG-EST duration ≥12 min; (2) ECG-EST duration ≥9 min; (3) ECG-EST duration ≥9 min with negative ECG-EST; (4) peak HR ≥85% of maximal predicted HR for age with negative EST; (5) peak HR ≥75% of maximal predicted HR for age with negative EST; (6) peak HR ≥85% of maximal predicted HR for age and STD < 2 mm; and (7) HR ≥75% of maximal predicted HR for age and STD < 2 mm.

ECG-EST variables were considered to be associated with a very low risk of LM disease when the latter was found in ≤2.5% of patients.

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2.3 Invasive coronary angiography

ICA was performed within 6 months of EST (usually within 1 month) through radial access, following standard procedures. LM disease was considered to be present when a stenosis of ≥50% of the vessel lumen of the LM coronary artery was detected. Coronary stenoses in the other main epicardial coronary arteries were considered significant if they caused a ≥70% reduction of the vessel lumen or were associated with a fractional flow reserve ≤0.80.

2.4 Statistical analyses

All variables assessed in this study showed a distribution not significantly different from normal according to Kolmogorov–Smirnov testing. Thus, continuous variables were compared by analysis of variance, whereas comparisons of proportions were performed using the chi-square test. Data are reported as means with standard deviations and numbers (percentages). Statistical significance was defined as $p < 0.05$. Data were analyzed with SPSS 28.0 statistical software (SPS Statistics, Florence, Italy).

3 Results

3.1 Characteristics of the population

Overall, among 15,550 ECG-ESTs performed at our exercise stress test laboratory between January 2018 and December 2023, 515 (3.3%) were performed in patients fulfilling the inclusion/exclusion criteria for the study. The main clinical characteristics and angiographic findings of patients eventually included in the study are summarized in Table 1.

The study population included 381 men (74%) and 134 women (26%), with a mean age was 66.2 ± 11 years. The most prevalent cardiovascular risk factor was hypertension (78.1%), and diabetes was present in 26.4% of patients. Approximately half of patients (43.9%) were taking beta-blocker therapy, either bisoprolol ($n = 156$, 69%) or metoprolol ($n = 73$, 31%). A low dose of beta-blockers (i.e., ≤ 5 mg/day of bisoprolol or ≤100 mg/day of metoprolol) was taken by 97% of patients. Furthermore, 23.5% of patients were taking calcium-channel blockers, and 3.9% were taking ranolazine.

Overall, 26 patients (5%) were found to have LM disease at ICA. Intracoronary physiological or imaging assessment to confirm the hemodynamic relevance of left main stenosis was performed in only three (12%) patients: fractional flow reserve, optical coherence tomography, and intravascular ultrasound (IVUS) imaging. Treatment of patients with LM disease included coronary artery bypass grafting in 13 patients (50%) and percutaneous coronary intervention in 10 (38%), whereas 3 patients (12%) were managed with medical therapy alone.

Besides LM disease, ICA documented obstructive CAD in 277 patients (53.8%), and one-, two-, and three-vessel CAD were found in 28.5%, 11.6%, and 13.8% of patients, respectively.

TABLE 1 Main clinical characteristics of patients included in the study.

Number of patients	515
Age (years)	66.2 ± 10.6
Sex (M)	381 (74.0%)
Body mass index (kg/m^2)	26.5 ± 4.6
Cardiovascular risk factors	
Hypertension	402 (78.1%)
Diabetes	136 (26.4%)
Hypercholesterolemia	238 (46.2%)
Smoking	267 (51.8%)
Beta-blocker therapy	226 (43.9%)
Number of diseased vessels at ICA[a]	
0	238 (46.2%)
1	147 (28.5%)
2	59 (11.5%)
3	71 (13.8%)

CAD, coronary artery disease; ICA, invasive coronary angiography; PCI, percutaneous coronary intervention.
[a]Number of diseased coronary vessels other than the left main artery.

3.2 Clinical/ECG-EST findings and LM disease

The main clinical and angiographic findings, as well as the primary results of the ECG-EST, for patients with and without LM disease are summarized in Tables 2 and 3, respectively. As shown, among the clinical characteristics, only male gender ($p = 0.029$) was significantly associated with LM disease.

Compared with patients without, those with LM disease showed only a tendency to a higher rate of positive ECG-EST ($p = 0.07$), but more frequently showed STD in ≥5 ECG leads ($p = 0.036$) and STD ≥2 mm ($p < 0.001$). Furthermore, maximal STD level during ECG-EST was significantly higher in patients

TABLE 2 Main clinical characteristics and angiographic findings of patients with and without left main disease.

	LM disease ($n = 26$)	No LM disease ($n = 489$)	p
Age	69.1 ± 10.8	66.1 ± 10.6	0.15
Sex (M)	24 (92.3%)	357 (73.0%)	0.029
Body mass index (kg/m^2)	26.1 ± 2.3	26.5 ± 4.7	0.64
Cardiovascular risk factors			
Hypertension	21 (80.8%)	381 (77.9%)	0,73
Diabetes	9 (36.6%)	127 (26.0%)	0.33
Hypercholesterolemia	11 (42.3%)	227 (46.4%)	0.68
Smoking	17 (65.4%)	250 (51.1%)	0.16
Beta-blocker therapy	15 (57.7%)	211 (43.1%)	0.14
Number of diseased vessels at ICA[a]			<0.001
0	1 (3.8%)	237 (48.5%)	
1	7 (26.9%)	140 (28.6%)	
2	7 (26.9%)	52 (10.6%)	
3	11 (42.3%)	60 (12.3%)	

CAD, coronary artery disease; ICA, invasive coronary angiography; PCI, percutaneous coronary intervention.
[a]Number of diseased coronary vessels other than the left main artery.

TABLE 3 Main exercise stress test results.

	LM disease (n = 26)	No LM disease (n = 489)	p
Baseline			
Heart rate (bpm)	74 ± 12	76 ± 13	0.41
Systolic BP (mmHg)	131 ± 18	131 ± 17	0.92
Diastolic BP (mmHg)	79 ± 10	79 ± 9	0.99
Peak EST			
Heart rate (bpm)	130 ± 18	139 ± 20	0.02
% heart rate max	86 ± 11	90 ± 12	0.14
Systolic BP (mmHg)	173 ± 25	171 ± 26	0.60
Diastolic BP (mmHg)	92 ± 14	90 ± 12	0.35
EST duration (s)	394 ± 135	417 ± 158	0.46
Ischemic ECG changes			
Positive EST	23 (88.5%)	354 (72.4%)	0.07
No of leads with STD	3.08 ± 2.0	2.42 ± 1.8	0.07
No. of patients with STD in ≥5 leads	6 (23.1%)	49 (10.0%)	0.036
Max STD (mm)[a]	1.64 ± 1.1	1.17 ± 0.9	0.02
STD ≥2 mm	15 (57.7%)	129 (26.4%)	<0.001
STE in aVR	1 (3.8%)	15 (3.1%)	0.82
Other EST findings			
Angina	9 (34.6%)	62 (12.7%)	0.002
Dyspnea	1 (3.8%)	8 (1.6%)	0.40
EST-related VAs	9 (34.6%)	160 (32.8%)	0.59
Recovery VAs	6 (23.1%)	119 (24.5%)	0.70

BP, blood pressure; EST, exercise stress test; STD, ST-segment depression; STE, ST-segment elevation; VAs, ventricular arrhythmias.
[a]In patients with positive ECG-EST.

with vs. those without LM disease ($p = 0.02$). Finally, patients with LM disease reported a higher rate of angina ($p = 0.002$). Of note, all but one of the LM disease patients (96.2%) showed a significant stenosis in at least one other coronary artery vessel.

3.3 ECG-EST variables and presence/absence of LM disease

The ability of ECG-EST variables selected for predicting the presence of LM disease is summarized in Table 4. As shown, the prevalence and the positive predictive value of these variables were very low.

The negative predictive value for LM disease of selected individual and combined ECG-EST variables is summarized in Table 5 and partially shown also in Figure 1.

All considered, the ECG-EST variables were associated with a very low risk of LM disease. A negative ECG-EST (prevalence 26.8%) was associated with only 2.2% of LM disease, whereas the lowest risk (1.3% only) was found in those who had a negative test, achieving 85% or more of the theoretical maximal HR for age (prevalence 15%). A very low risk of LM disease (2.2%) was particularly detected in the subgroup of patients who achieved ≥75% of maximal HR for age and had STD <2 mm, which included 63.1% of patients.

4 Discussion

Our data show that, among patients referred for an initial assessment of angina pain suspected of CAD, several ECG-EST results may identify patients with a very low risk (≤2.5%) of LM disease. ECG-EST results, on the other hand, showed a very low predictive value for the presence of the disease.

The present evidence from clinical trials is that, among clinically stable patients with obstructive CAD, coronary revascularization by surgical intervention (CABG) results in improvement of long-term prognosis only when LM disease or three-vessel CAD (with a reduced left ventricular function) is found at coronary angiography (1, 2). However, PCI has been shown to result in similar long-term outcomes compared with CABG in some subgroups of patients with LM disease, particularly non-diabetic patients and those with isolated LM disease or SYNTAX score <32 (6–8).

On the other hand, large clinical trials have demonstrated that, among patients with normal left ventricular function and no LM disease, coronary revascularization does not result in significant clinical advantages compared with optimal medical therapy (3–5). Thus, patients in whom LM disease can reliably be excluded by non-invasive tests might safely be treated with medical therapy and avoid invasive assessment.

In this study, we show that ECG-EST is valuable for this scope. Some individual and combined ECG-EST variables, indeed, were highly predictive for the lack of LM disease being associated with a very low risk of the disease. The lowest rate of LM disease was found in the subgroup of patients who achieved a peak HR ≥85% and had no STD during ECG-EST (only 1.3%), but this subgroup included only 15% of patients. On the other hand, the combination of peak HR ≥75% of the maximal HR predicted for age and ST-segment depression <2 mm was

TABLE 4 ECG-EST predictors for left main disease.

	No. of patients	Prevalence (%)	Positive predictive value (%)
STD in ≥5 leads	55	10.7	10.9
STD ≥2 mm	144	28.0	10.4
STE ≥1 mm in aVR	16	3.1	6.2
STD in ≥5 leads and ECG-EST duration <360 s	20	2.6	15.0
STD in ≥5 leads and HR <75% of maximal HR for age	19	3.7	7.7
STD ≥2 mm and ECG-EST duration <360 s	59	7.7	13.5
STD ≥2 mm and HR <75% of maximal HR for age	57	11.1	12.3

ECG-EST, exercise stress test; HR, heart rate; STD, ST-segment depression; STE, ST elevation.

TABLE 5 Predictive value for the absence of left main disease of individual and combined ECG-EST variables.

	No. of patients	Prevalence (%)	Negative predictive value (%)	Risk of LM disease (%)
Negative test	138	26.8	97,8	2.2
ECG-EST ≥12 min	16	3.1	96.7	3.3
ECG-EST ≥9 min	143	27.8	95.8	4.2
Peak HR ≥75% of maximal HR for age	462	89.7	95.9	4.1
Peak HR ≥85% of maximal HR for age	346	67.2	95.4	4.6
ECG-EST ≥9 min + negative EST	37	7.2	97.3	2.7
Peak HR ≥75% of maximal HR for age + negative EST	108	21.0	98.1	1.9
Peak HR ≥75% of maximal HR for age + STD < 2 mm	325	63.1	97.8	2.2
Peak HR ≥85% of maximal HR for age + negative EST	77	15.0	98.7	1.3
Peak HR ≥85% of maximal HR for age + STD < 2 mm	238	46.2	97.5	2.5

ECG-EST, exercise stress test; HR, heart rate; STD, ST-segment depression; STE, ST elevation.

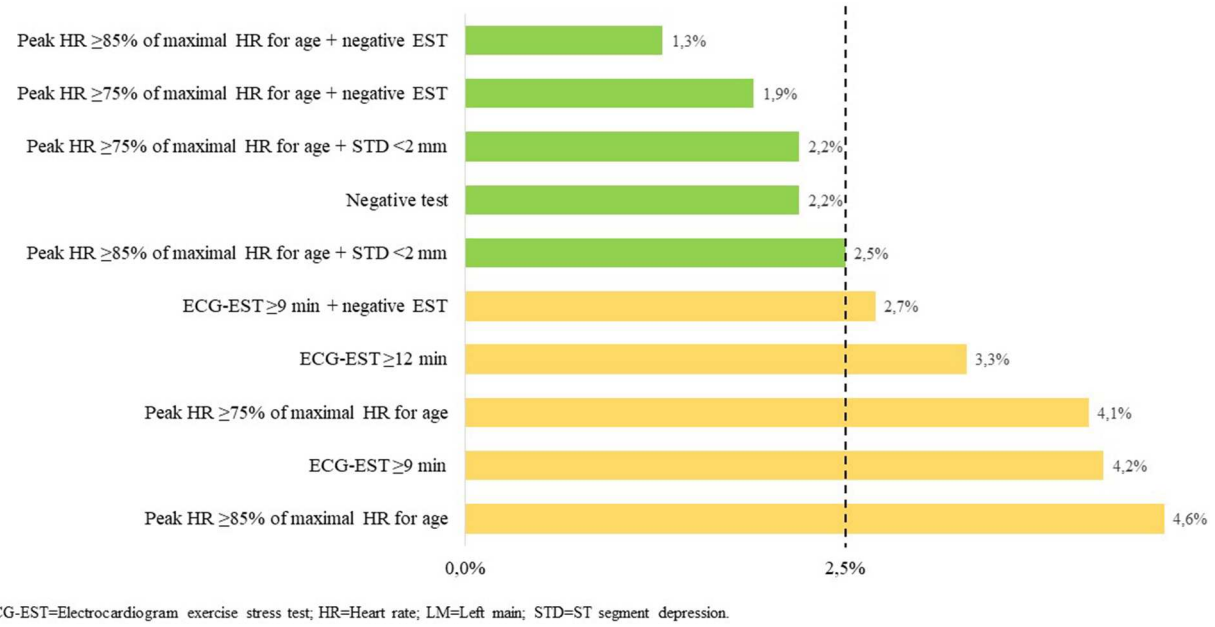

FIGURE 1
Risk of LM disease of individual and combined ECG-EST variables. Very low risk of LM disease is set at ≤2.5%.

detected in a sizeable proportion of 63.1% of patients and was associated with a 2.2% risk for LM disease. Similarly, the combination of peak HR ≥85% of the maximal HR predicted for age and ST-segment depression <2 mm was detected in 46.2% of patients and was associated with a 2.5% only of the risk of LM disease. In these patients, further tests might, therefore, be safely avoided, even considering that it remains unclear whether prognosis is actually improved by coronary revascularization in the small subgroup of patients with LM disease who do not develop significant signs of myocardial ischemia and show good exercise tolerance during ECG-EST (17).

Our data confirm, on the other hand, that ECG-EST results do not allow for reliable prediction of the presence of LM disease (9–11). In agreement with our previous study (10), extensive (in ≥5 leads) or severe (≥2 mm) ST-segment depression were indeed associated with an increased risk of LM disease, but their positive predictive value for LM disease of ECG-EST remained very low (<20%), thus making these variables of limited utility in the individual patient in clinical practice. Of note, while some data previously reported a high predictive value for LM disease of ST elevation in lead aVR (14–16, 18, 19), the results of the present study confirm our previous observation of the lack of any significant impact on the detection of LM disease of STE in aVR (10), which also showed a very low rate of occurrence in our population.

4.1 Limitations of the study

Some limitations of our study should be acknowledged. First, the number of patients with LM disease was rather low, and, therefore, larger studies are desirable to validate the results of

this investigation. Second, the indication for coronary angiography was clearly influenced by the ECG-EST results and, for those with a negative test, was probably driven by a high clinical probability of CAD, which suggests that the negative predictive value for LM disease of low-risk ECG-EST is even higher among a less selected population of patients undergoing the test to assess exercise-induced ischemia. Finally, anti-ischemic therapy was not systematically withdrawn before the test, and therefore might have influenced the results of ECG-EST and its relation with the presence/absence of LM disease.

4.2 Conclusions

Our data show that, among patients with a history of angina chest pain suspected of obstructive CAD, the results of ECG-EST can identify subgroups of patients at very low risk for LM disease. These patients may be safely managed with medical therapy.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Università Cattolica del Sacro Cuore, Rome, Italy. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin because the study was retrospective and, therefore, patients were not directly involved.

Author contributions

ST: Investigation, Methodology, Data curation, Writing – original draft. NC: Investigation, Methodology, Data curation, Writing – review & editing. AGM: Investigation, Methodology, Data curation, Writing – review & editing. FDB: Investigation, Methodology, Data curation, Writing – review & editing. LL: Investigation, Methodology, Data curation, Writing – review & editing. CA: Resources, Supervision, Validation, Writing – review & editing. CT: Resources, Supervision, Validation, Writing – review & editing. FB: Resources, Supervision, Validation, Writing – review & editing. GAL: Project administration, Resources, Software, Formal analysis, Supervision, Validation, Writing – review & editing.

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Conflict of interest

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References

1. Yusuf S, Zucker D, Peduzzi P, Fisher LD, Takaro T, Kennedy JW, et al. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet*. (1994) 344:563–70. doi: 10.1016/S0140-6736(94)91963-1

2. CASS Principal Investigators and Their Associates. Coronary artery surgery study (CASS): a randomized trial of coronary artery bypass surgery. Survival data. *Circulation*. (1983) 68:939–50. doi: 10.1161/01.CIR.68.5.939

3. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al. Optimal medical therapy with or without PCI for stable coronary disease. *New Engl J Med*. (2007) 356:1503–16. doi: 10.1056/NEJMoa070829

4. The Bari 2D Study Group, Frye RL, August P, Brooks MM, Hardison RM, Kelsey SF. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *New Engl J Med*. (2009) 360:2503–15. doi: 10.1056/NEJMoa0805796

5. Maron DJ, Hochman JS, Reynolds HR, Bangalore S, O'Brien SM, Boden WE, et al. Initial invasive or conservative strategy for stable coronary disease. *New Engl J Med*. (2020) 382:1395–407. doi: 10.1056/NEJMoa1915922

6. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. (2020) 360:961–72. doi: 10.1056/NEJMoa1915922

7. Stone GW, Kappetein AP, Sabik JF, Pocock SJ, Morice MC, Puskas J, et al. Five-year outcomes after PCI or CABG for left main coronary disease. *N Engl J Med*. (2019) 381:1820–30. doi: 10.1056/NEJMoa1909406

8. Mäkikallio T, Holm NR, Lindsay M, Spence MS, Erglis A, Menown IB, et al. Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial. *Lancet*. (2016) 388:2743–52. doi: 10.1016/S0140-6736(16)32052-9

9. D'Ascenzo F, Presutti DG, Picardi E, Moretti C, Omedè P, Sciuto F, et al. Prevalence and non-invasive predictors of left main or three-vessel coronary disease: evidence from a collaborative international meta-analysis including 22 740 patients. *Heart*. (2012) 98:914–9. doi: 10.1136/heartjnl-2011-301596

10. Russo G, Ravenna SE, De Vita A, Aurigemma C, Lamendola P, Lanza GA, et al. Exercise test predictors of severe coronary artery disease: role of ST-segment elevation in lead aVR. *ClinCardiol*. (2017) 40:102–8. doi: 10.1002/clc.22637

11. Senior R, Reynolds HR, Min JK, Berman DS, Picard MH, Chaitman BR, et al. Predictors of left main coronary artery disease in the ISCHEMIA trial. *J Am Coll Cardiol*. (2022) 79:651–61. doi: .org/10.1016/j.jacc.2021.11.052

12. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc*. (1982) 14(5):377–81. doi: 10.1249/00005768-198205000-00012

13. Fox SM 3rd, Naughton JP, Haskell WL. Physical activity and the prevention of coronary heart disease. *Ann Clin Res*. (1971) 3(6):404–32.

14. Uthamalingam S, Zheng H, Leavitt M, Pomerantsev E, Ahmado I, Gurm GS, et al. Exercise-induced ST-segment elevation in ECG lead aVR is a useful indicator of significant left main or ostial LAD coronary artery stenosis. *JACC Cardiovasc Imaging*. (2011) 4:176–86. doi: 10.1016/j.jcmg.2010.11.014

15. Ozmen N, Yiginer O, Uz O, Kardesoglu E, Aparci M, Isilak Z, et al. ST elevation in the lead AVR during exercise treadmill testing may indicate left main coronary artery disease. *Kardiol Pol*. (2010) 68:1107–11.

16. Tuna Katircibaşi M, Tolga Koçum H, Tekin A, Erol T, Tekin G, Baltali M, et al. Exercise-induced ST-segment elevation in leads aVR and V1 for the prediction of left main disease. *Int J Cardiol*. (2008) 128:240–3. doi: 10.1016/j.ijcard.2007.05.022

17. Gyenes GT, Ghali WA. Should all patients with asymptomatic but significant (>50%) left main coronary artery stenosis undergo surgical revascularization? *Circulation*. (2008) 118:422–5. doi: 10.1161/circulationaha.107.743914

18. Rostoff P, Wnuk M, Piwowarska W. Clinical significance of exercise-induced ST-segment elevation in lead aVR and V1 in patients with chronic stable angina pectoris and strongly positive exercise test results. *Pol Arch Med Wewn*. (2005) 114:1180–9.

19. Neill J, Shannon HJ, Morton A, Muir AR, Harbinson M, Adgey JA. ST segment elevation in lead aVR during exercise testing is associated with LAD stenosis. *Eur J Nucl Med Mol Imaging*. (2007) 34:338–45. doi: 10.1007/s00259-006-0188-1

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The intracoronary wires hand-in-hand technique for uncrossable bilateral microcatheters in CTO lesions: a single-center case series

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Background: The tip-in and rendezvous techniques are alternative strategies for antegrade conversion when the retrograde microcatheter (MC) cannot cross the chronic total occlusion (CTO) lesion. However, subsequent antegrade MC failure to cross the CTO lesion may increase the failure rate of the CTO procedure.
Objectives: We sought to evaluate the efficacy of the intracoronary wires hand-in-hand (WHIH) technique in this scenario for achieving complete antegrade CTO recanalization.
Method: From September 2023 to December 2024, 14 CTO patients were applied the WHIH technique. The main process of the WHIH technique involves keeping the antegrade and retrograde MCs in close proximity along the retrograde wire, then advancing both wires forward and backward in a hand-in-hand manner along the path created by the retrograde wire until the antegrade wire crosses the CTO lesion. Device success was defined as the achievement of antegrade wire crossing the CTO into the distal vessel after the WHIH technique.
Results: The WHIH success was achieved in all cases. The mean age of the patients was 61.2 ± 12.4 years, and 85.7% of patients were male. The median CTO lesion length was 27.6 mm (range: 7.1–87.3 mm), and the mean J-CTO score was 2.5 ± 0.9. The retrograde approach was predetermined as the first choice in six cases (42.9%), and in eight cases (57.1%) was promptly adopted after the initial antegrade approach failed. Eight cases (57.1%) were accessed through septal collaterals, whereas the remaining six cases (42.9%) via epicardial channels and four of them used ipsilateral epicardial channels. All patients were treated with the tip-in technique, and the median length between two MCs was 4.5 mm (range: 2–20 mm). The WHIH success was achieved in all cases. In-hospital major adverse cardiovascular (MACE) events were not observed.
Conclusion: This intracoronary wires hand-in-hand technique safely and effectively enables antegrade conversion from a retrograde approach, which may serve as a last-resort technique for antegrade access.

KEYWORDS

chronic total occlusion (CTO), percutaneous coronary intervention (PCI), tip-in, rendezvous, major adverse cardiovascular (MACE)

Introduction

The introduction of retrograde techniques in percutaneous coronary intervention (PCI) for chronic total occlusion (CTO) has substantially enhanced the success rates (1). After the retrograde wire crosses the CTO lesion into the antegrade guiding catheter (GC), a microcatheter (MC) is advanced to facilitate the subsequent 300 cm retrograde wire externalization (RWE), such as RG3 (2). The tip-in and rendezvous techniques in antegrade GC are the two main options for achieving antegrade conversion (3–5). The two techniques not only avoid RWE use, thereby reducing potential damage to collateral channels and the ostium of the donor artery, but also potentially lead to a reduction in procedure time and contrast consumption. However, encountering an uncrossable dilemma in bilateral MCs was not uncommon during retrograde CTO-PCI due to complex anatomical features, such as proximal calcification or severe tortuosity. Some related variant strategies have been developed, and all of these collectively form a well-defined category known as "portal techniques" (6).

In this study, we detailed the intracoronary antegrade and retrograde wires hand-in-hand (WHIH) technique, which was successfully used to achieve CTO recanalization in cases where bilateral MCs were uncrossable. This study primarily focused on assessing the efficacy of this technique and aimed to further enrich the "portal techniques".

Materials and methods

Patient populations

From September 2023 to December 2024, at the Xijing Hospital of Air Force Military Medical University, we enrolled 14 patients and performed the WHIH technique due to the failure of both retrograde and antegrade MCs crossing of the CTO lesion after the retrograde wire entered the antegrade GC. The indication for CTO-PCI was the presence of symptomatic angina or extensive silent myocardial ischemia with evidence of viable myocardium in the territory of the occluded vessel, as estimated by echocardiography, SPECT, or cardiac magnetic resonance imaging (MRI). The Ethics Committee of Xijing Hospital approved this study, which was conducted in accordance with the principles of the Declaration of Helsinki, and written informed consents were obtained from all patients. The medical records and coronary angiograms of these patients were reviewed to elucidate the application, effectiveness, and complications of the WHIH technique.

Intracoronary wires hand-in-hand technique (WHIH) description

The indication of WHIH technique: When the retrograde MC fails to cross the CTO lesion following the retrograde guidewire into the antegrade GC, and the antegrade MC also fails to cross the CTO lesion along the retrograde guidewire.

Technical Description (Figure 1): When the retrograde MC fails to cross the CTO lesion following the retrograde guidewire into the antegrade GC, then performing the tip-in technique for retrograde wire into antegrade MC and pushing the retrograde wire as deeply as possible into the antegrade MC to provide strong support (Figure 1A). Subsequently, to maximize the extent of bilateral MCs' penetration into the CTO body, thereby making both MCs as close as possible (Figure 1B). Furthermore, the next most important step is to slowly pull the retrograde guidewire while simultaneously pushing the antegrade guidewire, allowing the two wires to move in a hand-in-hand manner as two operators manipulate them (Figure 1C). When the antegrade wire reaches the retrograde MC tip, manipulate the wire into the retrograde MC as in the Rendezvous technique until reaching the distal vessel (Figure 1D). For this WHIH technique, the same devices as for classic rendezvous or tip-in is required.

Definitions

A CTO lesion was defined as a complete obstruction of a native coronary artery with Thrombolysis in Myocardial Infarction (TIMI) flow grade 0 and an estimated duration of at least 3 months. The duration of the occlusion was determined by the interval from the last episode of an acute coronary syndrome that was consistent with the location of the occlusion or proved by previous coronary angiography. Heavy calcification was defined as radiopacity noted at the site of the target lesion before contrast injection generally compromising both sides of the arterial lumen. Severe angulation was defined as the vessel body being bent with greater than 45° or exhibiting marked tortuosity. Device success was defined as the antegrade wire crossing the CTO lesion after performing the WHIH technique. Technical success was defined as a visual assessment of recovery antegrade TIMI flow grade III in the target vessel and residual stenosis < 30%. In-hospital MACEs included cardiac death, PCI-related MI, ischemia-driven revascularization PCI, or emergency cardiac surgery.

Statistical analyses

Continuous parameters were presented as mean ± SD or median (Q1–Q3). Categorical variables were presented as percentages. The Student's *t*-test was used to estimate the differences in continuous variables. A P value < 0.05 was chosen to indicate a significant difference. All analyses were performed using SPSS for Windows 13.0.

Results

Baseline demographics and angiographic characteristics

A total of 14 patients underwent successful PCI for CTO lesions using this WHIH method. Baseline clinical

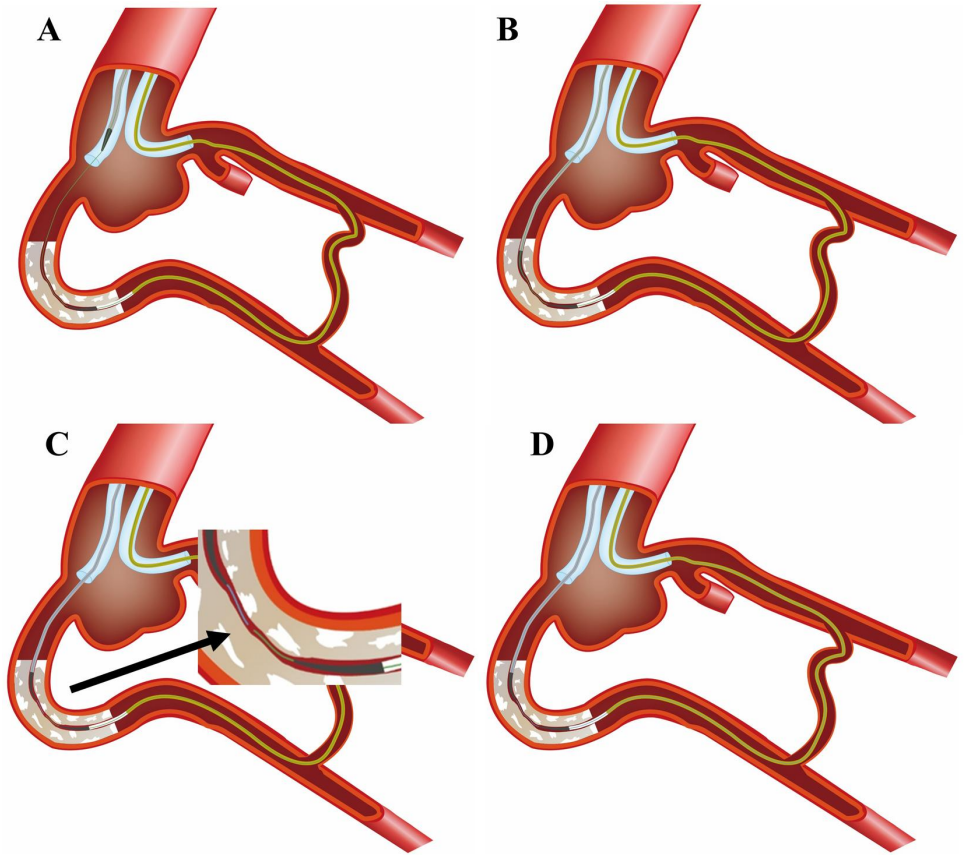

FIGURE 1
The schematic diagram of the WHIH technique. **(A)** Retrograde wire (green) entered into antegrade GC, but retrograde MC failed to cross the CTO lesion. The tip-in technique used for retrograde wire into antegrade MC. **(B)** Antegrade MC advancement along retrograde wire, but fail to cross the CTO lesion. **(C)** Antegrade workhorse wire (blue) tracks along the path left by the retrograde guidewire during retrieval. **(D)** Prompting the antegrade guidewire (blue) to successfully enter the retrograde MC.

characteristics are shown in Table 1. The mean age of the patients was 61.2 ± 12.4 years, and 85.7% were male. Almost half of the patients had multiple risk factors, and 71.4% had a history of previous PCI. 92.9% had unstable angina with CTO lesions, and 78.6% had multivessel disease. The rate of occlusion sites was similar in the RCA (42.9%) and the LAD (42.9%). 95.0% of the lesions had moderate to severe calcification, and 71.4% had an occlusion length of ≥20 mm and with a blunt stump or abrupt proximal cap. The median CTO lesion length was 27.6 mm (range: 7.1–87.3 mm). The CTO complexity calculated using J-CTO score, the mean J-CTO score was 2.5 ± 0.9.

Procedure characteristics and outcomes

The procedural characteristics were listed in Table 2. All procedures were finished with 7 F GC. 71.4% of the patients were with bilateral GC usage. The retrograde approach was pre-determined as the first choice in six cases, and promptly adopted after the first antegrade approach failed in eight cases. Eight cases (57.1%) were accessed through septal collaterals, whereas the remaining six cases (42.9%) via epicardial channels, four of which were ipsilateral epicardial channels. 57.1% of cases with the reverse controlled antegrade and retrograde subintimal tracking (r-CART) technique and all patients achieved retrograde wire across CTO lesion into antegrade GC with stiffer wires. The tip-in technique was successfully performed to advance the retrograde wire into the antegrade MC in all patients. The median distance between antegrade and retrograde MCs was 4.5 (rang: 2–20) mm. Meanwhile, in all cases, the WHIH technique for antegrade workhorse wires such as the Sion (Asahi Intecc) or Sion Black (Asahi Intecc) was attempted, and the device success rate was 100%. There was one case where, after successfully completing the WHIH technique, the antegrade system could not cross the CTO lesion despite trying multiple methods. Eventually, the retrograde wire was repeated to enter another subintimal path, achieving antegrade conversion. There were 3 cases of rotational atherectomy (ROTA) usage due to severely calcified lesions. The technical success rate was 100.0%. No in-hospital MACEs or procedural complications occurred.

The outcomes, such as success rates and complication rates, between WHIH and "portal techniques" (References 4 and 5) showed no significant difference. However, procedural

TABLE 1 Baseline clinical data and angiographic information.

Variables	WHIH (*n* = 14)
Age, yrs	61.2 ± 12.4
Gender, male *n* (%)	12 (85.7)
Hypertension *n* (%)	11 (78.6)
Diabetes *n* (%)	5 (35.7)
Hyperlipemia *n* (%)	7 (50.0)
Smoker *n* (%)	9 (64.3)
Prior MI *n* (%)	6 (42.9)
Prior PCI *n* (%)	10 (71.4)
Prior CABG *n* (%)	0 (0.0)
Clinical diagnosis	
Stable angina, *n* (%)	1 (7.1)
Unstable angina, *n* (%)	13 (92.9)
LVEF %	50 ± 10
≤35%	3 (21.4)
≥35%	11 (78.6)
Multivessel coronary disease *n* (%)	11 (78.6)
Target CTO vessel *n* (%)	
Proximal LAD	3 (21.4)
Middle LAD	3 (21.4)
Proximal LCx	2 (14.3)
Middle LCx	0 (0.0)
Proximal RCA	3 (21.4)
Middle RCA	3 (21.4)
CTO assessment *n* (%)	
Length > 20 mm	10 (71.4)
Bending > 45°	3 (21.4)
Calcification	7 (50.0)
Blunt stump/abrupt in proximal cap	10 (71.4)
Re-try lesion	4 (28.6)
Diffuse lesion in distal vessel	4 (28.6)
Side branch at landing zone	6 (42.9)
J-CTO score	
Mean J-score	2.5 ± 0.9
≥3 *n* (%)	8 (57.1)

Results are expressed as the mean ± SD.
WHIH, wires hand-in hand; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; CTO, chronic total occlusion; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; MI, myocardial infarction, PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction.

TABLE 2 Procedural characteristics of the study population.

Variables	WHIH (*n* = 14)
GC usage *n* (%)	
Bilateral GC	10 (71.4)
Unilateral GC	4 (28.6)
Ping-pang GC	3 (21.4)
Single GC	1 (7.1)
Retrograde approach *n* (%)	
Primary	6 (42.9)
Promptly after failed antegrade	8 (57.1)
Retrograde collaterals used *n* (%)	
Septal channel	8 (57.1)
Epicardial channel	6 (42.9)
Isplateral epicardial channel	4 (66.7)
Retrograde wires into antegrade GC *n* (%)	
Pilot wires	8 (57.1)
Gaia wires	2 (14.3)
UB3 wire	4 (28.6)
Retrograde MCs uncross the CTO lesion *n* (%)	14 (100.0)
Types of retrograde MCs *n* (%)	
Finecross MCs	2 (14.3)
Corsair MCs	9 (64.3)
RAD-pass MCs	3 (21.4)
Tip-in method usage	14 (85.7)
Antegrade Corsair MCs uncross CTO lesion	14 (100)
Antegrade Wires used for hand-in hand	
Workhorse wire (sion/sion black)	14 (100%)
Success of Wire hand-in hand Technique (WHHT)	14 (100.0)
Distance between antegrade and retrograde MCs (mm)	
Median distance (mm)	4.5 (rang 2–20)
<5 mm *n* (%)	6 (42.9)
≥5 mm *n* (%)	8 (57.1)
ROTA Usage *n* (%)	3 (21.4)
Fluoroscopy time, min	141.5 ± 66.3
Procedure time, min	243.5 ± 69.4
Contrast volume, ml	296.8 ± 73.7

WHIH, wires hand-in hand; CART, controlled antegrade retrograde subintimal tracking; TIMI, thrombolysis in myocardial infarction; MC, microcatheter; ROTA, rotational atherectomy; NA, not applicable.

parameters revealed a statistically significant difference in procedure time ($p = 0.022$) (see Supplementary Table S1).

Two representative cases of WHIH practice

1) An example of the WHTH between two MCs over a long distance in Figure 2.

A 69-year-old male was readmitted for secondary PCI for LAD-CTO with significant anterior wall ischemia on SPECT tests. Diagnostic CAG showed the mid-LAD CTO after giving off the big first diagonal (D1) vessel, and with ambiguous entry, and distal LAD flow filled by apical epicardial collateral channels (CCs) from the proximal diagonal branch vessels (Figure 2A, Supplementary Video S1). IVUS indicated diffuse calcification with aneurysmal dilation in the proximal segment of LAD, and the CTO entrance was unclear. Therefore, retrograde approach was first attempted; Suoh 03 (Asahi Intecc) wire was advanced over 150 mm Finecross MC (Terumo Corporation) MC through the ipsilateral CC into the distal LAD (Figure 2B). Then the UB3 wire was manipulated into the CTO lesion up to the proximal CTO cap. Due to the angulation, the wire could not enter the antegrade GC (Figure 2C), and the retrograde MC was also unable to cross the CTO lesion. Subsequently, the antegrade Gaia 3 wire within the Corsair catheter (Asahi Intecc) was inserted into the supposed proximal cap but deviated from the retrograde wire. After performing the reverse CART technique, the retrograde UB3 wire was manipulated into the antegrade extension catheter (Figure 2D). However, the retrograde MC was still unable to cross the CTO segment even with conventional balloon anchoring in the antegrade GC. Then, the tip-in technique was performed successfully. Unexpectedly, the

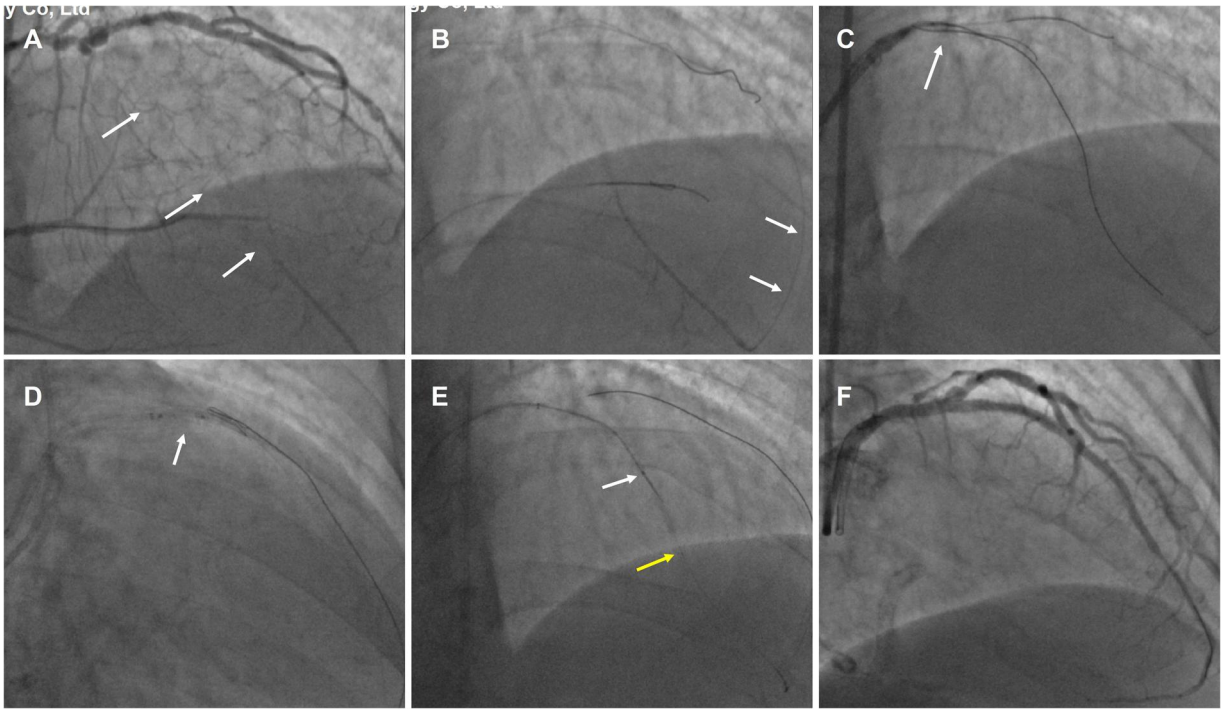

FIGURE 2
An example of the WHTH between two MCs over a long distance. **(A)** mid-LAD CTO (white arrow) after the big first diagonal (D1) vessel and with ambiguous entry. **(B)** Retrograde Suoh 03 wire was advanced through the ipsilateral CC (white arrow) into the distal LAD. **(C)** the retrograde UB3 wire (white arrow) crossed the CTO segment but could not enter the antegrade GC. **(D)** After performing the reverse CART technique (white arrow), the retrograde UB3 wire into the antegrade extension catheter. **(E)** WHIH technique preformed when antegrade MC (white arrow) and retrograde MC (yellow arrow) uncrossable CTO lesion. **(F)** Excellent angiographic results were achieved after the DESs implantation.

antegrade MC advancement over the retrograde wire failed to cross the CTO lesion, and there was still approximately a 15 mm gap between the two MCs even when they were positioned as closely as possible. Subsequently, the antegrade guidewire was pushed smoothly while the retrograde guidewire was pulled simultaneously in a hand in hand manner until the antegrade wire entered the retrograde MC (Figure 2E, Supplementary Video S2). The IVUS confirmed that the wire was located in the subintimal space beyond the D1 vessel and revealed evidence of severe localized calcification in the LAD CTO. Excellent angiographic results were achieved after the drug eluting stens (DESs) implantation (Figure 2F).

2) An example of the WHIH technique in a high-resistance in-stent occlusion lesion in Figure 3

A 65-year-old man with a 10-year history of hemodialysis for chronic kidney failure has severe angina symptoms. Five months ago, DESs were implanted in the LAD for severe stenosis, and the in-stent CTO in the RCA was also treated. However, during the RCA CTO-PCI, the wires were positioned outside the stents in the middle segment, and the stents were dilated using 3.0/3.5 mm non-compliant balloons, achieving TIMI 3 flow in the posterior descending (PD) and posterolateral (PL) vessels. For the second PCI this time, dual CAG showed RCA in-stent re-occlusion from the proximal to just before the distal bifurcation, which was filled by contralateral vessels and featured deformed stents that had collapsed to one side (Figures 3A,B, Supplementary Video S3). Antegrade approach was first attempted, but the wires only extended into the mid-segment of the RCA and were located outside the deformed stents. Next, the retrograde Suoh3 wire crossed the septal vessel into PD vessels with Corsair MC 150. After several attempts with stiffer wires to penetrate the CTO failed, a knuckled Fielder XT-A (Asahi Intecc) wire was successfully advanced into the RCA middle segment. However, the retrograde Corsair MC was hindered at the end of the distal stent. Antegrade Fielder XT-A knuckled wire was pushed into the RCA middle segment, and after 1.5/2.0 mm balloon dilation, IVUS showed that the retrograde wire was located within the in-stent structure (Figure 3C). Subsequently, the retrograde Corsair MC was replaced by TURNPIKE150 MC, which was advanced to the RCA middle segment. After the reverse-CART technique, a new Pilot 200 wire was retrogradely manipulated into the antegrade GC (Supplementary Video S4). However, the TURNPIKE150 MC only reached the RCA 2 segment. The tip-in technique was performed to facilitate antegrade MC advancement over the retrograde wire (Figure 3D, Supplementary Video S5). Due to stent higher resistance, the antegrade MC only extended to the RCA distal stent segment, and in this dilemma, the WHIH technique was performed, and the antegrade wire was smoothly

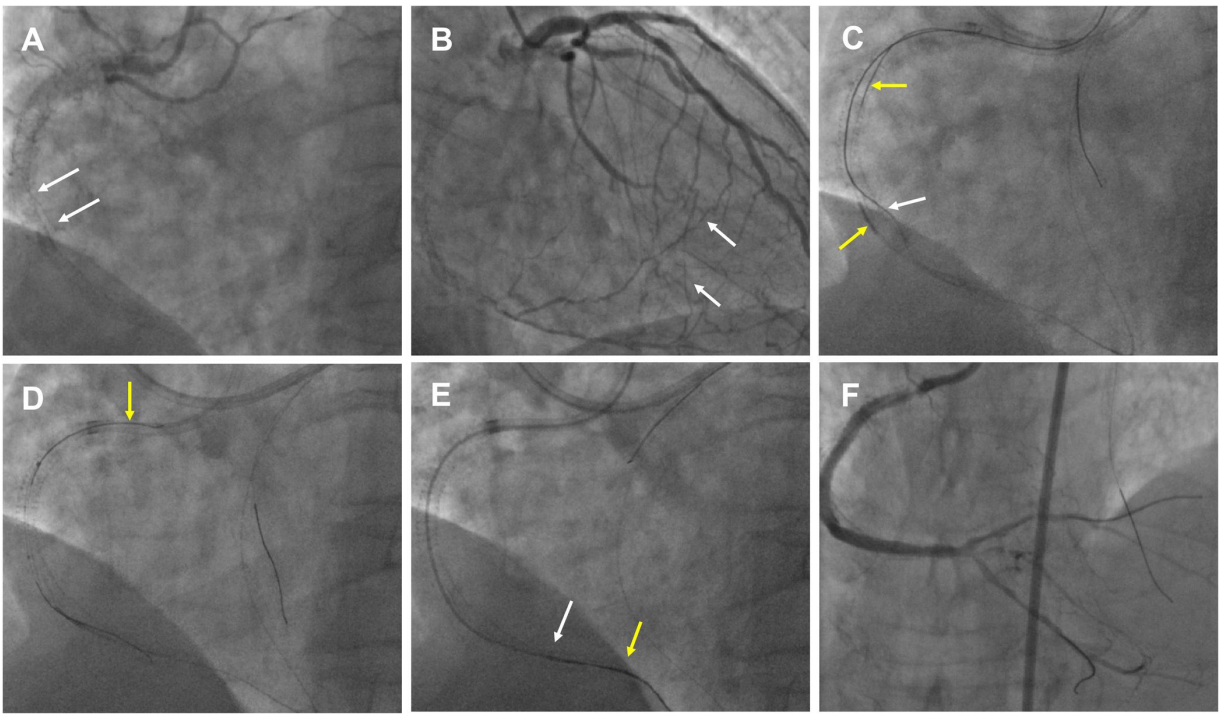

FIGURE 3
An example of the WHIH in an in-stent high-resistance occlusion lesion. **(A)** RCA in-stent re-occlusion (white arrow) with deformed middle stents that had collapsed to one side. **(B)** RCA distal bifurcation vessels filled by contralateral septal vessels (white arrow). **(C)** Antegrade wire (white arrow) and retrograde wire (yellow arrow) were entered the RCA middle segment. **(D)** The tip-in technique performed for antegrade MC advancement over a retrograde wire (yellow arrow). **(E)** WHIH technique preformed when antegrade MC (white arrow) and retrograde MC (yellow arrow) uncrossable CTO lesion. **(F)** Excellent angiographic results were achieved after the DESs and DCB.

advanced into the ostium of the PD vessel while tracing along with the retrograde wire (Figure 3E, Supplementary Video S6). The final angiography showed good results with DESs and DCB (Figure 3F).

Discussion

To our knowledge, the present study is the first report to demonstrate a series of successful cases using the intracoronary WHIH technique to achieve antegrade conversion during retrograde CTO recanalization. This technique serves as a practical and promising alternative in scenarios where both antegrade and retrograde MCs fail to cross the CTO lesion.

Allana SS et al. (7) reported that the tip-in and rendezvous techniques were utilized in 3.0% of procedures, and the most common reasons for the use of these techniques were inability of the retrograde MC to reach the antegrade GC (35.4%), operator preference (18.8%), and use of epicardial collaterals (16.7%) in the PROGRESS-CTO study. CTO-PCI with ipsilateral collateral channels is challenging during retrograde CTO PCI. Azzalini L et al. (2) reported the use of the tip-in technique in 9% of ipsilateral retrograde procedures and the Rendezvous technique in 7% of ipsilateral cases. During the retrograde approach, the tip-in and rendezvous techniques, which were mostly performed in antegrade GC, were used at a high rate based on operator preference and clinical scenarios in our center. In this study, all the retrograde MC uncross the CTO and 28.6% cases with the use of ipsilateral collateral channels; therefore, the tip-in technique was applied in all cases. At the subsequent pivotal step, where the antegrade MC crossing of the CTO lesion along the retrograde wire was unfeasible due to high calcification, severe angulation, or high resistance in the stent struts, we performed the WHIH technique to achieve antegrade conversion. Due to the complex CTO, thereby increasing the procedural attempt time with the WHIH technique.

When facing the challenge of bilateral MCs' inability to pass through the CTO lesion during the retrograde CTO procedure, several variants and solutions (8–11) are introduced to solve this issue, which is called the "portal technique" (6). This WHIH technique shares the same concept as the "Wire Rendezvous and Chasing Wire Technique" reported by Nakabayashi K et al. (10). He pointed out that a very long CTO or a CTO requiring the CART technique might pose risks when using this chasing wire technique. In a similar setting, Wu EB (11) also suggested advancing an antegrade rotablator wire into the retrograde MC if there was a short remaining distance between the bilateral MCs. But in our series of cases, the CTO length, CART/reverse-CART usage, and the remaining distance between the two MCs were not pivotal factors. The underlying mechanism of this technological success was that the channel created by the retrograde wire formed a "stable tunnel", even though the

dissection spaces inside it. The existence of calcified plaque allowed the antegrade workhorse wires to cross the CTO lesion more effectively and alleviated concerns about acute re-occlusion when the retrograde wire retrieved.

The WHIH technique offers potential advantages, including simplifying the retrograde approach without extra device usage. Thus, based on our single-center experience, the WHIH technique could serve as a last-resort solution in scenarios where both antegrade and retrograde microcatheters fail to successfully cross the CTO lesion.

Limitations

This study has several limitations. First, the sample size in this single center is small, which may result in sampling bias. Second, while the implementation of the WHIH procedure in the complex CTO cohort shows a higher success rate, it is imperative to consider that the observed success may be attributable to the considerable expertise, discerning case selection, and strategies adopted by highly experienced operators. Therefore, caution should be exercised regarding the generalizability of the WHIH technique to other centers. Third, due to the retrospective design, some causal inferences cannot be made. These limitations highlight the necessity and importance of launching a prospective study with more cases and a randomized controlled design in the future.

Conclusions

This intracoronary wires hand-in-hand technique safely and more effectively accomplishes the antegrade conversion without adding extra devices, which could serves as a last-resort solution in cases where both antegrade and retrograde microcatheters fail to successfully cross the CTO lesion.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Xijing Hospital Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

HW: Formal analysis, Writing – original draft. GC: Writing – original draft, Data curation, Methodology. YC: Formal analysis, Resources, Software, Writing – review & editing. XL: Data curation, Resources, Writing – review & editing. PH: Data curation, Resources, Writing – review & editing. Yz: Data curation, Resources, Writing – review & editing. LY: Data curation, Resources, Writing – review & editing. KL: Resources, Validation, Writing – review & editing. HG: Funding acquisition, Supervision, Writing – review & editing. cL: Project administration, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Megaly M, Ali A, Saad M, Omer M, Xenogiannis I, Werner GS, et al. Outcomes with retrograde versus antegrade chronic total occlusion revascularization. *Catheter Cardiovasc Interv*. (2020) 96(5):1037–43. doi: 10.1002/ccd.28616

2. Azzalini L, Agostoni P, Benincasa S, Knaapen P, Schumacher SP, Dens J, et al. Retrograde chronic total occlusion percutaneous coronary intervention through ipsilateral collateral channels: a multicenter registry. *JACC Cardiovasc Interv*. (2017) 10(15):1489–97. doi: 10.1016/j.jcin.2017.06.002

3. Vo MN, Ravandi A, Brilakis ES. Tip-in" technique for retrograde chronic total occlusion revascularization. *J Invasive Cardiol*. (2015) 27:E62–4.

4. Kim MH, Yu LH, Tanaka H, Mitsudo K. Experience with a novel retrograde wiring technique for coronary chronic total occlusion. *J Interv Cardiol*. (2013) 26(3):254–8. doi: 10.1111/joic.12031

5. Nihei T, Yamamoto Y, Kudo S, Hanawa K, Hasebe Y, Takagi Y, et al. Impact of the intracoronary rendezvous technique on coronary angioplasty for chronic total occlusion. *Cardiovasc Interv Ther*. (2017) 32(4):365–73. doi: 10.1007/s12928-016-0421-1

6. Ungureanu C, Avran A, Brilakis ES, Mashayekhi K, Alaswad K, Agostoni P, et al. Comprehensive overview of retrograde-antegrade connection techniques without externalization in chronic total occlusion PCI: the portal techniques. *Catheter Cardiovasc Interv*. (2025) 105(1):11–22. doi: 10.1002/ccd.31346

7. Allana SS, Rempakos A, Kostantinis S, Alexandrou M, Mutlu D, Alaswad K, et al. The tip-in and rendezvous techniques in retrograde chronic total occlusion percutaneous coronary interventions. *EuroIntervention*. (2023) 19(10):e856–9. doi: 10.4244/ EIJ-D-23-00474

8. Venuti G, D'Agosta G, Tamburino C, La Manna A. When antegrade microcatheter does not follow: the "facilitated tip-in technique. *Catheter Cardiovasc Interv*. (202) 96(4):E458–61. doi: 10.1002/ccd.28803

9. Ungureanu C, Brilakis ES, Cocoi M, Colletti G, Leibundgut G. iCTT (introverted catch-it, tip-in microcatheter, tip-in balloon): combining techniques for chronic total occlusion coronary intervention. *JACC Cardiovasc Interv*. (2024) 17(19):2304–6. doi: 10.1016/j.jcin.2024.07.045

10. Nakabayashi K, Sunaga D, Kaneko N, Matsui A, Tanaka K, Ando H, et al. The wire rendezvous and chasing wire technique in the bidirectional approach for the percutaneous coronary intervention for chronic total occlusion with a single guiding catheter. *Case Rep Cardiol*. (2018) 2018:7162949. doi: 10.1155/ 2018/ 7162949

11. Wu EB, Kao HL, Lo S, Lim ST, Ge L, Chen JY, et al. From reverse CART to antegrade wire access: a guide to externalisation, tip-in, rendezvous, and snaring from the APCTO club: reverse CART to antegrade access. *AsiaIntervention*. (2020) 6(1):6–14. doi: 10.4244/AIJ-D-19-00031

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A nomogram model in elderly patients with coronary heart disease for predicting prognosis: research based on a real-world registry in China

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Purpose: Coronary heart disease (CHD) is closely associated with aging and has become the leading cause of death in the elderly (≥65 years). This study aimed to identify independent risk factors for 2-year major adverse cardiovascular and cerebrovascular events (MACCE) in elderly patients with CHD, construct a nomogram model for predicting MACCE risk, and validate its performance to assist in identifying high-risk patients and optimizing secondary prevention strategies.

Methods: Patients aged ≥65 years diagnosed with CHD were included. The primary outcome of the study was MACCE. The secondary outcomes included cardiovascular death and cardiovascular readmission. A nomogram model was constructed. Patients were divided into low-risk, medium-risk, and high-risk groups according to the tertiles of the nomogram model scores, and the primary and secondary outcomes of patients with different risks were compared.

Results: This study finally included 8,340 elderly patients with CHD. MACCE occurred in 523 patients during the follow-up period, with an incidence rate of 6.3%. The Least Absolute Shrinkage and Selection Operator (LASSO) regression method was used to screen 11 independent factors associated with MACCE within 2 years. The model had a good predictive value for MACCE, with a C-statistic of 0.765 (95% CI: 0.743–0.788). The MACCE rates ranged from low risk 1.6%, medium risk 4.2% to high risk 12.6%, indicating that the nomogram model can effectively distinguish high risk patients (Log-rank $P < 0.001$).

Conclusion: The established MACCE risk nomogram prediction model for elderly patients with CHD could effectively identify high-risk elderly patients with CHD.

KEYWORDS

elderly patients, coronary heart disease, major adverse cardiovascular or cerebrovascular events, nomogram model, risk prediction

Introduction

With the improvement of the world economy and health levels, the proportion of the elderly population has been increasing annually. The World Health Organization predicts that by 2,050, the global population aged > 60 years will exceed 2 billion, with over 700 million people aged >75 years (over 120 million in China) (1). The growing elderly population and the remarkable rise in age-related cardiovascular diseases have resulted in a substantial surge in the prevalence of coronary heart disease (CHD) among elderly patients. Although epidemiological studies have found that dyslipidemia, diabetes, and a sedentary lifestyle are high-risk factors for cardiovascular diseases such as CHD, advanced age is undoubtedly an important risk factor (2). CHD is closely associated with aging and has become the leading cause of death among the elderly (≥65 years) (3). This study aimed to explore the risk factors associated with adverse outcomes in elderly patients with CHD, identify high-risk patients, and maximize the benefits of secondary prevention and drug therapy management.

Risk factor identification and risk stratification are prerequisites for the effective treatment and management of CHD. Clinicians and researchers are increasingly recognizing that patients classified as "extreme risk" may require special attention and intensified treatment, benefiting the most from enhanced risk factor reduction (4). Currently, risk stratification tools have been validated in clinical practice to identify high-risk patients and manage them accordingly. For example, the SYNTAX score is a scoring tool based on coronary angiography parameters that is used to guide the selection of revascularization methods for patients with coronary artery disease, such as coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). The Global Registry of Acute Coronary Events (GRACE) score (5) is widely used to assess the risk of death during hospitalization and within 6 months after discharge in patients with acute coronary syndrome (ACS) and is recommended for risk stratification management in patients with non-ST-segment elevation myocardial infarction (NSTEMI) (6). Thrombolysis in Myocardial Infarction (TIMI) risk score (7) and Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) risk score (8) are also commonly used to evaluate the risk of death in patients with STEMI.

Due to the presence of more risk factors and worse prognosis in elderly patients, and the fact that certain cardiovascular risk factors may have different effects in compared with younger patients, scoring models developed for the general population may not be applicable to elderly patients. For instance, high total cholesterol levels are considered a cardiovascular risk factor; however, in elderly patients (≥85 years), high total cholesterol levels are negatively correlated with the risk of death. For every 1 mmol/L increase in total cholesterol, the mortality rate decreases by 15% (9). Studies by DeFilippis et al. (10) showed that age is an important factor contributing to the overestimation of the AHA-ACC-ASCVD risk score. For each additional decade in age, the average overestimated absolute risk increases by 3.7%. Therefore, risk assessment for elderly patients requires more individualized scoring tools. The primary objective of this study is to develop and validate a user-friendly nomogram model for predicting 2-year MACCE in elderly CHD patients based on real-world registry data, addressing the lack of individualized risk assessment tools for this population.

Methods

Data source

This study was a retrospective analysis of data from the PHARM-Aging registry (NCT05246722). In the PHARM-Aging registry, patients were consecutively recruited from January 2019 to December 2021 if they were diagnosed with CHD at Beijing Anzhen Hospital. Medical data, including baseline and follow-up data, were recorded in an electronic data capture system (EDCs) and regularly monitored for data quality by specialized staff. The study protocol was approved by the ethics committee of Beijing Anzhen Hospital, and patient privacy was protected with the approval of corresponding regulatory agencies throughout the study.

Study population and study design

The inclusion criteria for the study were as follows: (1) patients who provided informed consent; (2) age ≥ 65 years old; (3) patients diagnosed with CHD, CHD was diagnosed based on clinical manifestations (such as typical chest pain) combined with imaging evidence, including coronary artery CT angiography showing ≥50% stenosis in at least one major coronary artery or coronary angiography confirming coronary artery stenosis; and (4) admission for CHD, including stable angina, unstable angina, and acute myocardial infarction.

The exclusion criteria were as follows: (1) severe lack of important information such as medication history, medical history, and surgical history; (2) diagnosis of severe liver dysfunction (Child-Pugh class C); (3) severe renal dysfunction (creatinine clearance rate < 30 mL/min); (4) autoimmune diseases (systemic autoimmune diseases, organ-specific autoimmune diseases); (5) malignant tumors, multi-organ failure; (6) mental abnormalities, inability to communicate with the researchers, or inability to comply with the study protocol; and (7) in-hospital death.

Sample size estimation

The sample size was estimated based on clinical outcomes, supplemented by estimation using the number of variables. This study intends to collect approximately 60 variables. The sample size was estimated to be 30 times the total number of risk factors, requiring at least 1,800 cases for model development. The PHARM-Aging database contains approximately 8,000 patients, which is sufficient for model establishment. Furthermore, the 2-year anticipated incidence rate of the

TABLE 1 Baseline clinical characteristics and demographic information of the enrolled patients with CHD.

Variables	All patients	Without MACCE	With MACCE	*P*
	N = 8,340	*N* = 7,817	*N* = 523	
Demographics				
Age (year)	70.8 ± 4.9	70.5 ± 4.7	74.5 ± 6.9	<0.001
Male, *n* (%)	5137 (61.6)	4805 (61.5)	332 (63.5)	0.360
BMI (kg/m^2)[a]	25.3 (23.2, 27.4)	25.3 (23.2, 27.4)	24.7 (22.5, 27.1)	0.006
Systolic blood pressure (mm Hg)[a]	130 (121, 142)	130 (121, 142)	130 (119, 140)	0.001
Diastolic blood pressure (mm Hg)[a]	75 (68, 80)	75 (68, 80)	72 (65, 80)	<0.001
Heart rate (bpm)	72.6 ± 11.6	72.5 ± 11.5	74.5 ± 12.3	<0.001
Smoking, *n* (%)	1,529 (18.3)	1,446 (18.5)	83 (15.9)	0.125
Complication, *n* (%)				
Hypertension	5,760 (69.1)	5,393 (69.0)	361 (69.0)	0.571
Hyperlipidemia	5,925 (71.0)	5,593 (71.5)	332 (63.5)	<0.001
Diabetes	3,011 (36.1)	2,786 (35.6)	225 (43.0)	0.001
Heart Failure	196 (2.3)	145 (1.8)	51 (9.7)	<0.001
Prior CI	1,019 (12.2)	910 (11.6)	109 (20.8)	<0.001
Prior PCI	2,961 (35.5)	2,850 (36.5)	111 (21.2)	<0.001
Prior CABG	1,171 (14.0)	1,093 (14.0)	78 (14.9)	0.508
CHD type, *n* (%)				
SA	1,332 (16.0)	1,207 (15.4)	125 (23.9)	<0.001
UA	6,355 (76.2)	6,039 (77.3)	316 (60.4)	
Non-STEMI	375 (4.5)	324 (4.1)	51 (9.8)	
STEMI	278 (3.3)	247 (3.2)	31 (5.9)	
Intervention				
PCI	2,668 (32.0)	2,575 (32.9)	93 (17.8)	<0.001
Balloon dilation	350 (4.2)	330 (4.2)	20 (3.8)	0.661
CABG	1,161 (13.9)	1,084 (13.9)	77 (14.7)	0.584
Conservative treatment	4,161 (49.9)	3,828 (49.0)	333 (63.7)	<0.001
Examination				
LVEF (%)	60.4 (60.0, 65.0)	60.4 (60.0, 65.0)	60.0 (51.0, 64.0)	<0.001
LVDD (mm)	32.0 ± 6.3	31.7 ± 6.0	35.4 ± 9.0	<0.001
Uric acid (μmol/L)[a]	329.9 (275.6, 392.9)	328.2 (274.5, 390.3)	366.5 (295.8, 445.7)	<0.001
ALT (U/L)[a]	20 (14, 26)	20 (15, 26)	19 (13, 26)	0.006
AST (U/L)[a]	22 (18, 27)	22 (18, 27)	22 (18, 28)	0.121
BNP (pg/mL)[a]	65 (31, 165)	61 (30, 150)	199 (70, 490)	<0.001
LDL-C (mmol/L)	2.30 ± 0.81	2.29 ± 0.81	2.36 ± 0.84	0.092
HDL-C (mmol/L)	1.12 ± 0.28	1.12 ± 0.28	1.05 ± 0.29	<0.001
TC (mmol/L)	3.99 ± 0.99	3.99 ± 0.99	3.99 ± 1.02	0.998
TG (mmol/L)	1.52 ± 1.01	1.52 ± 1.02	1.43 ± 0.79	0.077
HCY (μmol/L)[a]	13.9 (11.3, 15.8)	13.1 (10.8,16.5)	15.1 (12.2,19.9)	<0.001
hsCRP (mg/L)[a]	1.23 (0.57, 3.14)	1.2 (0.56, 3.04)	2.0 (0.9, 5.1)	<0.001
FBG (g/L)	3.3 ± 0.7	3.27 ± 0.73	3.49 ± 0.90	<0.001
D-Dimer (ng/mL)[a]	145 (92, 253)	141 (90, 254)	229 (140, 353)	<0.001
Urea (mmol/L)	6.40 ± 1.90	6.27 ± 2.69	8.32 ± 4.90	<0.001
eGFR < 60 mL/min/1.73 m^2	2,023 (24.3)	1,816 (23.2)	207 (39.6)	<0.001
Concomitant medication, *n* (%)				
Aspirin	6,742 (80.8)	6,390 (81.7)	352 (67.3)	<0.001
P2Y12 inhibitor	4,634 (55.6)	4,405 (56.4)	229 (43.8)	<0.001
ACE inhibitor/ARB	2,929 (35.1)	2,737 (35.0)	192 (36.7)	0.435
Beta blocker	5,140 (61.6)	4,804 (61.5)	336 (64.2)	0.208
Statin therapy	6,772 (81.2)	6,413 (82.0)	359 (68.6)	<0.001
PPI	5,630 (67.5)	5,284 (67.6)	346 (66.2)	0.488

CHD, coronary heart disease; BMI, body mass index; ACS, acute coronary syndrome; SA, stable angina; UA, unstable angina; STEMI, ST-segment elevation myocardial infarction; CI, cerebral infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; LVDD, left ventricular end diastolic dimension; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, B-type natriuretic peptide; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; HCY, homocysteine; hsCRP, hypersensitive C-reactive protein; FBG, fibrinogen quantification; eGFR, estimate glomerular filtration rate; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; PPI, proton pump inhibitor.
[a]Variables do not conform to normal distribution, expressed as median (quartile), and non-parametric test is used for comparison between groups.

endpoint event is approximately 7∼8%, with an estimated 600 patients experiencing the event. Consequently, the final number of independent variables in the model will not exceed 60.

Study endpoints

The primary endpoint was defined as major adverse cardiovascular and cerebrovascular events (MACCE) within 2 years, which included all-cause death, acute ischemic stroke, and non-fatal acute myocardial infarction (MI) (11). The secondary endpoints included cardiovascular disease mortality within 2 years and cardiovascular disease readmission within 2 years.

Follow-up

The following information was collected: clinical outcomes, changes in antiplatelet drugs, medication compliance, and adverse drug reactions. This information was collected from electronic medical records, telephone interviews, WeChat, or clinic visits, and uploaded to the EDCs.

Statistical analysis

Statistical analyses were performed using SPSS (version 26.0) and R software (version 4.3.2). Continuous variables that followed a normal distribution were presented as mean ± standard deviation, and group comparisons were conducted using *t*-test or one-way analysis of variance (ANOVA). If the continuous variables did not follow a normal distribution, they were presented as median (with interquartile range), and group comparisons were performed using non-parametric tests. Categorical variables are presented as frequencies (percentages), and group comparisons were conducted using the chi-square test.

Variable selection was performed using the least absolute shrinkage and selection operator (LASSO) regression method, implemented through the "glmnet" package in R. The occurrence of MACCE served as the dependent variable, where patients who experienced MACCE were coded as 1 and those who did not were coded as 0. Ten-fold cross-validation was used to select the optimal penalty parameter Lambda (λ), and Lambda + 1se was chosen to avoid model overfitting. To evaluate the model's performance, decision curve analysis (DCA) curve and receiver operating characteristic (ROC) curve were employed. Model calibration was performed using calibration curves based on 1,000 bootstrap samples. Survival analysis was performed using the Cox proportional hazards regression model. Statistical significance was set at P-value <0.05.

Results

A total of 8,340 elderly patients with CHD were included in this study. The average age of the patients was 70.8 ± 4.9 years (range: 65–100 years) (Table 1). Among them, 5,137 (61.6%) were male, and 3,203 (38.4%) were female. The highest proportion of patients with CHD was diagnosed with unstable angina (UA), with 6,355 cases, accounting for 76.2% of the total. A total of 375 cases (4.5%) were diagnosed with NSTEMI, and 278 cases (3.3%) diagnosed with STEMI. Stable CHD was present in 1,332 cases (16.0%). There were 5,760 cases (69.1%) of hypertension, and 5,925 cases (71.0%) of hyperlipidemia. PCI was performed in 2,668 cases (32.0%), with a significantly lower proportion in patients with MACCE (17.8%) than in those without (32.9%, $P < 0.001$).

The average follow-up time for all enrolled patients was 903.5 ± 147.9 days. During the follow-up, 523 patients experienced major adverse cardiovascular and cerebrovascular events (MACCE), with an incidence rate of 6.3%. Among them, 429 patients (5.1%) died, 13 patients (0.2%) had MI, and 84 patients (1.0%) had stroke.

Variable selection was performed using LASSO regression method. Figure 1A displays the variables selected by LASSO regression, while Figure 1B indicates the optimal lambda + 1se position and the 11 variables identified. The results revealed that the risk factors associated with MACCE included age, prior PCI, prior cerebral infarction (CI), heart failure, PCI, uric acid, aspartate aminotransferase (AST), hypersensitive C-reactive protein (hsCRP), D-Dimer, left ventricular ejection fraction (LVEF), and urea. These factors are detailed in Table 2. The 11 significant variables from the LASSO regression model, including age, prior PCI, prior CI, heart failure, PCI, uric acid, AST, hsCRP, D-Dimer, LVEF, and urea were incorporated into the nomogram model. Figure 2 shows the nomogram model, which represents the contribution of each variable to the outcome of the scoring system. The length of each segment corresponded to the score assigned to each factor. The sum of the scores for the 11 variables represents the patient's risk score, with the corresponding 1 or 2-year MACCE risk shown at the bottom of the nomogram model.

The ROC curve of the established nomogram model for MACCE risk in elderly CHD patients is shown in Figure 3. The C-statistic of the model was 0.765 [95% confidence interval (CI):

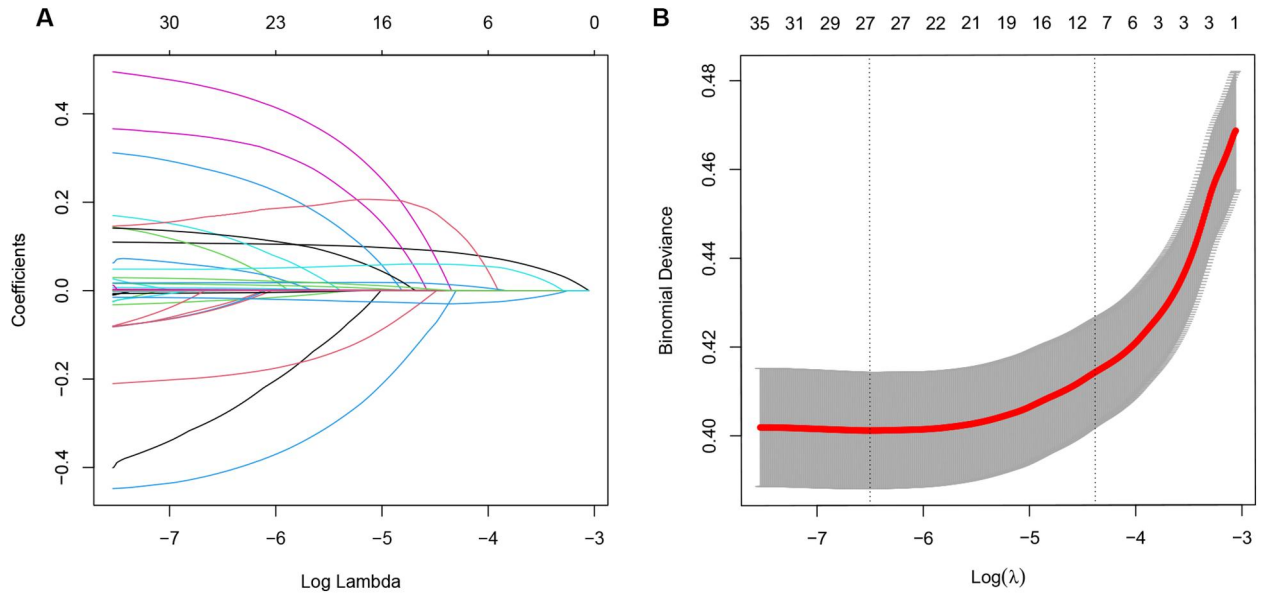

FIGURE 1
The least absolute shrinkage and selection operator (LASSO) regression was used to extract features. **(A)** The results showed that 27 variables were retained at the point where the error was the smallest, which is represented by the position of the dotted line on the left **(B)** To avoid overfitting and simplicity of the model, only variables within one standard error (1se) of the minimum error were selected, and 11 variables were retained, which corresponded to the place on the dotted line on the right **(B)**.

TABLE 2 Multivariable analysis of risk factors associated with MACCE by LASSO regression.

Variables	Risk factors	Coefficient
X1	Age (year)	0.006122
X2	Prior PCI	0.001770
X3	Prior CI	0.039466
X4	Heart Failure	−0.002121
X5	PCI	0.000049
X6	Uric acid (μmol/L)	0.001025
X7	hsCRP (mg/L)	0.000029
X8	AST (U/L)	0.000002
X9	D-Dimer (mg/L)	−0.002221
X10	LVEF (%)	0.005630
X11	Urea (mmol/L)	0.006122
Intercept	–	−0.295268

LASSO, the least absolute shrinkage and selection operator; PCI, percutaneous coronary intervention; CI, cerebral infarction; hsCRP, hypersensitive C-reactive protein; AST, aspartate aminotransferase; LVEF, left ventricular ejection fraction;.

0.743–0.788]. DCA analysis was performed to assess the clinical utility of the model, as depicted in Figure 4A, and calibration curves were plotted to evaluate the consistency between the predicted and observed outcomes, which indicated good calibration of the model (Figure 4B).

Based on the third quartile score of the nomogram model, patients were classified as low-risk (0–59 points) with 2,698 cases, medium-risk (60–77 points) with 2,815 cases, and high-risk (≥78 points) with 2,827 cases. The 2-year MACCE rates in the low, medium, and high-risk groups were 1.6%, 4.2%, and 12.6%, respectively. There was a significant difference in event rates among the groups (Log-rank $P < 0.001$). Further investigation revealed that the nomogram model effectively differentiated the risk of cardiovascular disease mortality and cardiovascular disease readmission. The comparison of cardiovascular disease mortality and cardiovascular disease readmission rates among the low-risk, medium-risk, and high-

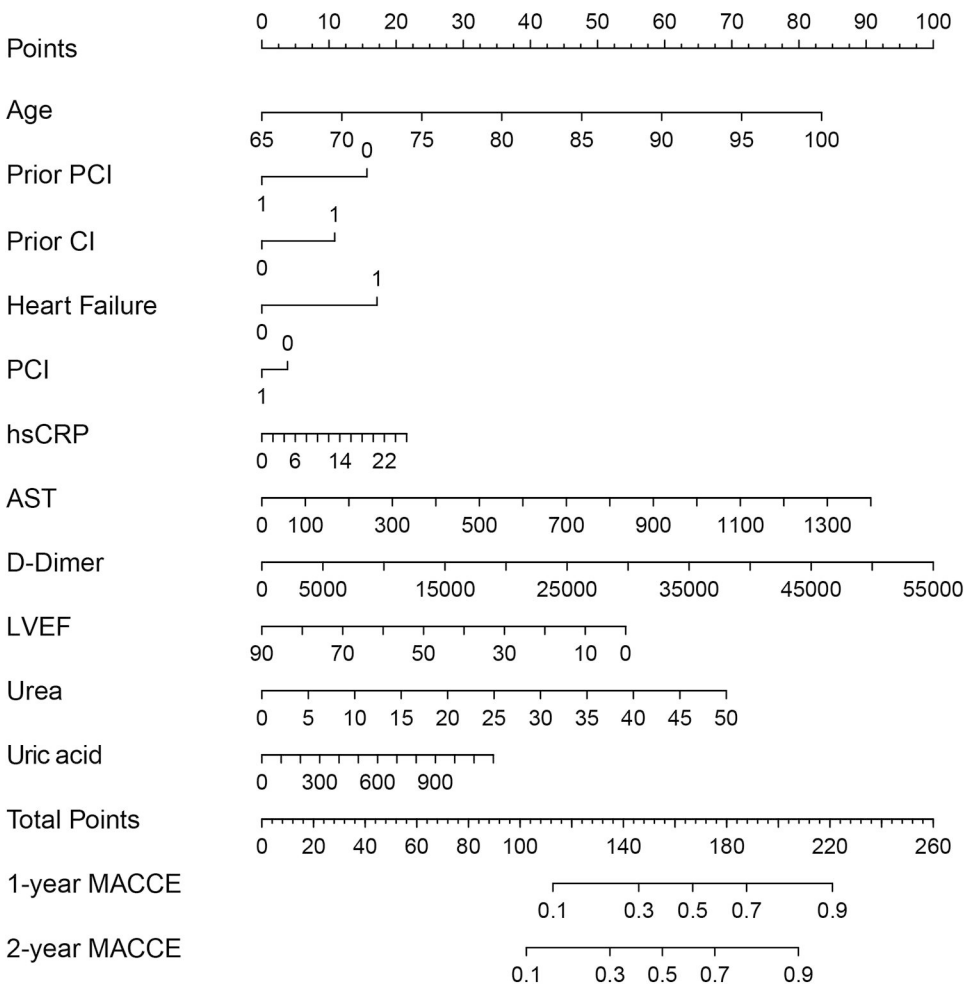

FIGURE 2
MACCE risk nomogram model in elderly patients with CHD. The model showing a scoring system for predicting cardiovascular risks. It includes variables like age, prior PCI, prior CI, heart failure, PCI, hsCRP, AST, D-Dimer, LVEF, urea, and uric acid. Points are calculated and total points relate to the probability of 1-year and 2-year MACCE. MACCE, major adverse cardiac and cerebrovascular events; CHD, coronary heart disease; PCI, percutaneous coronary intervention; CI, cerebral infarction; hsCRP, hypersensitive C-reactive protein; AST, aspartate aminotransferase; LVEF, left ventricular ejection fraction.

risk groups all showed statistically significant differences (Log-rank $P < 0.001$), and the detailed results are shown in Figure 5.

Discussion

This study was based on real-world cohort data of 8,340 elderly patients with CHD. The LASSO regression method was applied to select 11 independent factors associated with MACCE within 2 years, including age, prior PCI, prior CI, heart failure, PCI, uric acid, AST, hsCRP, D-Dimer, LVEF, and urea. These 11 variables were included in the nomogram model, showing a good predictive value with a C-statistic of 0.765 (95% CI: 0.743–0.788). Patients were divided into high, medium, and low-risk categories based on the tertiles of the nomogram score, and MACCE rates varied from 1.6% in the low-risk group to 4.2% in the medium-risk group and 12.6% in the high-risk group. The results indicated that the nomogram model could effectively identify high-risk elderly CHD patients.

Although the implementation of various strategies for the prevention and treatment of CHD has significantly reduced cardiovascular mortality in recent decades, it remains one of the diseases with the highest incidence and mortality worldwide. Risk factor identification and stratification are prerequisites for the treatment and management of cardiovascular diseases. High-risk patients may benefit more from early and aggressive treatment interventions, improving their clinical prognosis. Previous studies have developed CHD risk prediction models, such as SYNTAX score (12), EuroHeart score (13), TIMI risk score (7), GRACE risk score (5), CADILLAC risk score, and TRS2P score (14). However, due to limitations in the study population and treatment modalities of the model development cohorts, the established models may not be fully applicable to contemporary clinical practice, resulting in limitations in their use and potential errors in risk estimation (10). These limitations include: (1) most scores are based on European and American populations, which may not be fully applicable to Chinese patients due to population differences; (2) except for the GRACE score, most scores are based on data from large randomized controlled trials, and the predictive value of derived

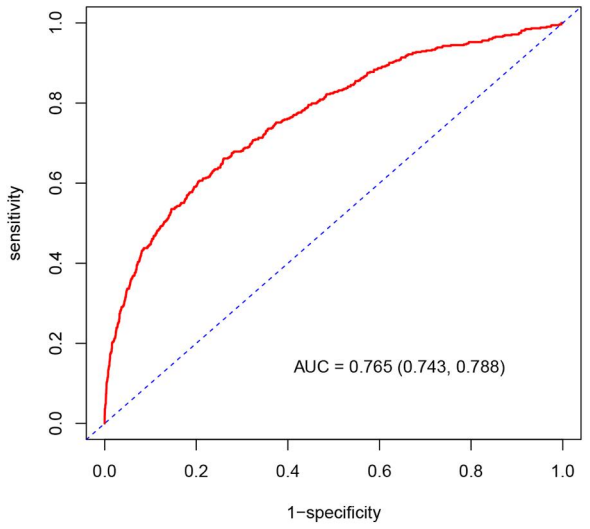

FIGURE 3
ROC curve of MACCE risk nomogram model in elderly patients with CHD. ROC curve, receiver operating characteristic curve; AUC, area under the curve; MACCE, major adverse cardiovascular or cerebrovascular events; CHD, coronary heart disease.

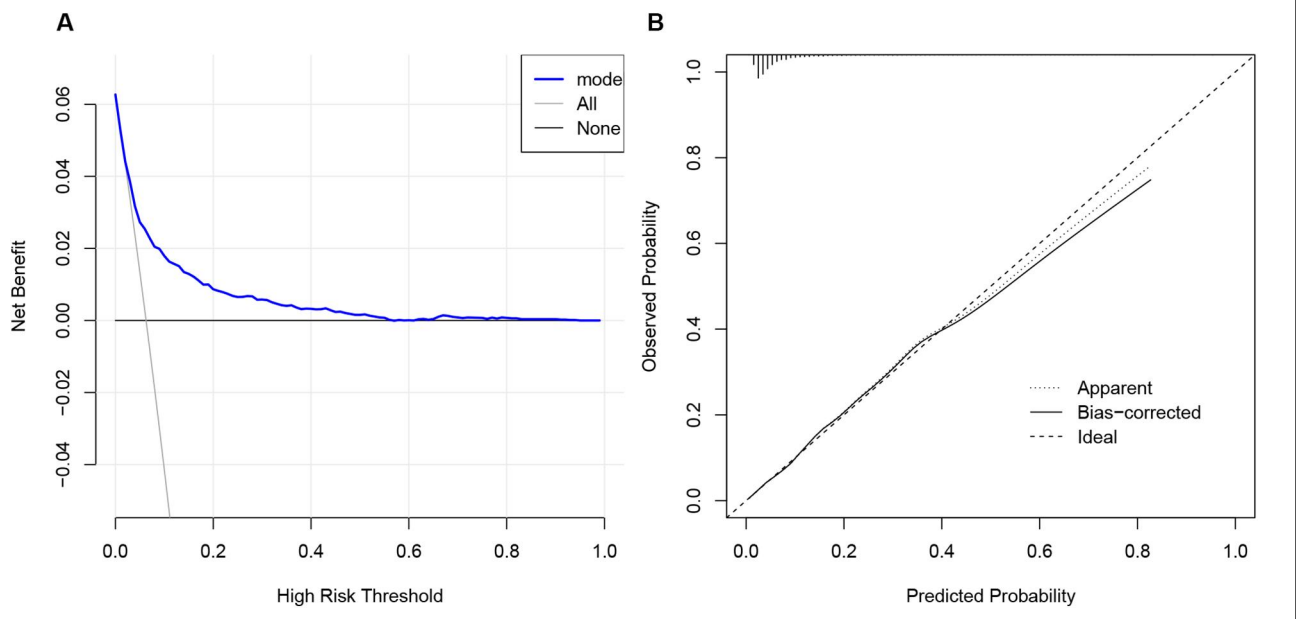

FIGURE 4
Decision curve analysis (A) and calibration curve of nomogram model for MACCE risk in elderly patients with CHD (B). MACCE, major adverse cardiovascular or cerebrovascular events; CHD, coronary heart disease.

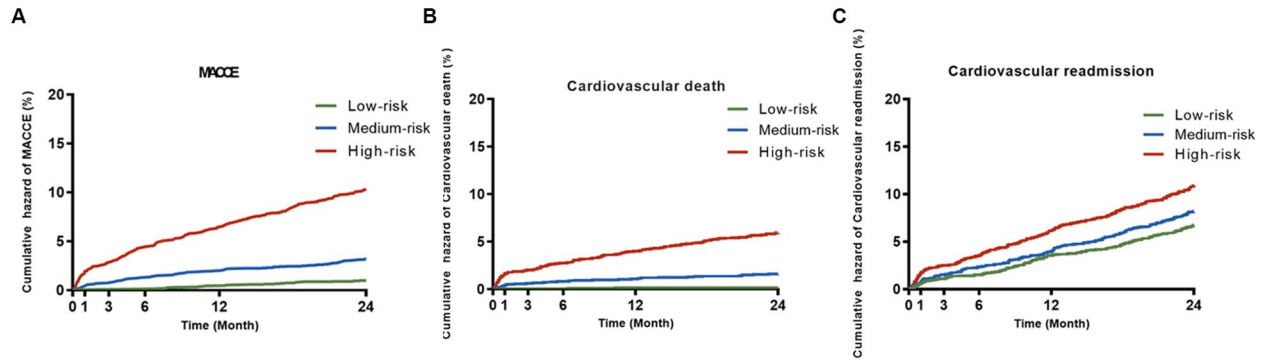

FIGURE 5
Kaplan–meier (K–M) survival curves of patients with different risks. **(A)** MACCE; **(B)** cardiovascular death; **(C)** cerebrovascular readmission. MACCE, major adverse cardiovascular or cerebrovascular events.

models in routine clinical practice needs to be validated; (3) the development cohort of the GRACE model had only 26.6% of ACS patients receiving PCI, and the CADILLAC risk score model's development cohort used bare-metal stents. Additionally, in the era of reperfusion therapy, statins, and antiplatelet drugs are widely used. These differences in treatment modalities may render the previously developed models less applicable to contemporary clinical practice; (4) most previous models were used for short-term treatment decisions and prognosis risk assessment, and there are fewer models that evaluate the long-term prognosis risk of CHD patients; (5) due to the completely different roles of some risk factors in elderly patients compared with younger patients, risk assessment for elderly CHD patients requires more individualized scoring tools.

Several existing nomograms have been developed for cardiovascular outcome prediction in elderly or ischemic heart disease (IHD) patients. Chen et al. (15) developed a PCI-specific nomogram for elderly patients to predict 2-year and 5-year target vessel revascularization, with diabetes, post-PCI quantitative flow ratio (QFR), prior MI, and prior PCI as predictive variables [area under the curve (AUC): 0.742–0.789]. In contrast, our model targets all elderly CHD patients (not just PCI recipients) and predicts MACCE with a C-statistic of 0.765 (95% CI: 0.743–0.788), expanding applicability. Notably, our real-world data showed that PCI was performed in 2,668 (32.0%) cases, with a significantly lower proportion in patients with MACCE (17.8%) than in those without (32.9%, $P < 0.001$), suggesting that performing PCI may be a protective factor for elderly CHD patients. Yang et al. (16) constructed an IHD mortality nomogram (1/3/5-year C-index: 0.658–0.739) using age, uric acid, and liver/cardiac function biomarkers. While sharing age/uric acid as predictors, our model includes more diverse variables and focuses on MACCE (not just mortality), enabling comprehensive risk stratification. Our model also effectively differentiates 2-year MACCE rates across risk groups and cardiovascular death/readmission risks, supporting holistic secondary prevention in elderly CHD patients.

Several prospective cohort studies have indicated that hyperuricemia is an independent risk factor for hypertension, diabetes, coronary artery disease, and stroke (17–19). Luca et al. (20) evaluated the impact of uric acid levels on major adverse cardiovascular events in patients with chronic coronary artery syndrome and found that patients with high uric acid levels had a higher risk of major adverse cardiovascular events (including cardiovascular mortality, hospitalization for MI, heart failure, angina or revascularization) than those with low uric acid levels. Han et al. (21) reported that CRP is risk factor for coronary artery stenosis in elderly patients with CHD, and CRP level is positively correlated with the severity of coronary artery lesions. D-Dimer, as a degradation product of fibrin, indicates the presence of a hypercoagulable state and secondary fibrinolysis. Kikkert et al. (22) investigated the predictive value of D-Dimer for major adverse cardiovascular events (including all-cause death, recurrent MI, stroke, or target vessel revascularization for ischemia) in patients with acute myocardial infarction (AMI) and found that D-Dimer levels ≥0.71 μg/mL upon admission were risk factors.

Although hyperlipidemia was not identified as an independent risk factor for MACCE in the multivariate regression analysis, we found a significantly higher proportion of hyperlipidemia in patients without MACCE than those with MACCE when comparing the baseline data. This finding may be inconsistent with those observed in younger patients. A previous study showed that, although high total cholesterol levels are considered cardiovascular risk factors, in elderly patients (≥85 years old), higher total cholesterol levels were negatively correlated with the risk of death. Each 1 mmol/L increase in total cholesterol was associated with a 15% decrease in mortality. One possible explanation is that higher cholesterol levels are associated with lower cancer levels and are negatively correlated with nosocomial infections, which are the main causes of death in elderly patients (9).

The main limitations of this study are as follows: (1) It was a single-center study with internal validation only, which may affect the generalizability of the model. Future improvements and

validation of the model would require multi-center cohorts. (2) Due to the limitations of observational research, additional variables that may be related to outcomes, such as genotypes and other serum biomarkers, were not obtained. (3) Considering the convenience and usability of the model, the evaluation of CHD severity using coronary artery calcification scores was not included.

Conclusions

The established nomogram model for elderly patients with CHD can effectively predict the risk of MACCE and identify high-risk elderly patients with CHD.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the ethics committee of Beijing Anzhen Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because This retrospective study involves de-identified data from medical records, posing minimal risk to participants. No personal identifiers are included, and there is no direct interaction or intervention with individuals. Obtaining informed consent is impracticable due to the retrospective nature and lack of contact with participants, while the research holds significant scientific value. All data handling complies with ethical standards, ensuring confidentiality and security. A waiver of informed consent is requested to facilitate the study without compromising participants' rights or welfare, in alignment with ethical guidelines and regulations.

Author contributions

WP: Writing – original draft, Writing – review & editing. YZ: Writing – original draft, Writing – review & editing. XS: Writing – review & editing. YL: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics–2012 update: a report from the American Heart Association. *Circulation*. (2012) 125:e2–220. doi: 10.1161/CIR.0b013e31823ac046

2. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part I: aging arteries: a "set up" for vascular disease. *Circulation*. (2003) 107:139–46. doi: 10.1161/01.CIR.0000048892.83521.58

3. Kumar S, de Lusignan S, McGovern A, Correa A, Hriskova M, Gatenby P, et al. Ischaemic stroke, haemorrhage, and mortality in older patients with chronic kidney disease newly started on anticoagulation for atrial fibrillation: a population based study from UK primary care. *Br Med J*. (2018) 360:k342. doi: 10.1136/bmj.k342

4. Dyrbuś K, Gąsior M, Desperak P, Trzeciak P, Nowak J, Penson PE, et al. Risk-factors associated with extremely high cardiovascular risk of mid- and long-term mortality following myocardial infarction: analysis of the hyperlipidaemia therapy in tERtiary cardiological cEnTer (TERCET) registry. *Atherosclerosis*. (2021) 333:16–23. doi: 10.1016/j.atherosclerosis.2021.08.024

5. Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, et al. A validated prediction model for all forms of acute coronary syndrome: estimating the

risk of 6-month postdischarge death in an international registry. *JAMA*. (2004) 291:2727–33. doi: 10.1001/jama.291.22.2727

6. Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European society of cardiology (ESC). *Eur Heart J*. (2016) 37:267–315. doi: 10.1093/eurheartj/ehv320

7. Morrow DA, Antman EM, Charlesworth A, Cairns R, Murphy SA, de Lemos JA, et al. TIMI Risk score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation: an intravenous nPA for treatment of infarcting myocardium early II trial substudy. *Circulation*. (2000) 102:2031–7. doi: 10.1161/01.CIR.102.17.2031

8. Califf RM, Pieper KS, Lee KL, Van de Werf F, Simes RJ, Armstrong PW, et al. Prediction of 1-year survival after thrombolysis for acute myocardial infarction in the global utilization of streptokinase and TPA for occluded coronary arteries trial. *Circulation*. (2000) 101:2231–8. doi: 10.1161/01.CIR.101.19.2231

9. Weverling-Rijnsburger AW, Blauw GJ, Lagaay AM, Knock DL, Meinders AE, Westendorp RG. Total cholesterol and risk of mortality in the oldest old. *Lancet*. (1997) 350:1119–23. doi: 10.1016/S0140-6736(97)04430-9

10. DeFilippis AP, Young R, McEvoy JW, Michos ED, Sandfort V, Kronmal RA, et al. Risk score overestimation: the impact of individual cardiovascular risk factors and preventive therapies on the performance of the American heart association-American college of cardiology-atherosclerotic cardiovascular disease risk score in a modern multi-ethnic cohort. *Eur Heart J*. (2017) 38:598–608. doi: 10.1093/eurheartj/ehw301

11. Smilowitz NR, Gupta N, Ramakrishna H, Guo Y, Berger JS, Bangalore S. Perioperative major adverse cardiovascular and cerebrovascular events associated with noncardiac surgery. *JAMA Cardiol*. (2017) 2(2):181–7. doi: 10.1001/jamacardio.2016.4792

12. Mohr FW, Morice M-C, Kappetein AP, Feldman TE, Ståhle E, Colombo A, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet*. (2013) 381:629–38. doi: 10.1016/S0140-6736(13)60141-5

13. de Mulder M, Gitt A, van Domburg R, Hochadel M, Seabra-Gomes R, Serruys PW, et al. Euroheart score for the evaluation of in-hospital mortality in patients undergoing percutaneous coronary intervention. *Eur Heart J*. (2011) 32:1398–408. doi: 10.1093/eurheartj/ehr034

14. Bohula EA, Morrow DA, Giugliano RP, Blazing MA, He P, Park J-G, et al. Atherothrombotic risk stratification and ezetimibe for secondary prevention. *J Am Coll Cardiol*. (2017) 69:911–21. doi: 10.1016/j.jacc.2016.11.070

15. Chen Q, Chen Y, Hong R, Zhong J, Chen L, Yan Y, et al. A visualized nomogram for predicting prognosis in elderly patients after percutaneous coronary intervention. *Rev Cardiovasc Med*. (2024) 25(5):155. doi: 10.31083/j.rcm2505155

16. Yang L, Dong X, Abuduaini B, Jiamali N, Seyiti Z, Shan X-F, et al. Development and validation of a nomogram to predict mortality risk in patients with ischemic heart disease. *Front Cardiovasc Med*. (2023) 10:1115463. doi: 10.3389/fcvm.2023.1115463

17. Baker JF, Krishnan E, Chen L, Schumacher HR. Serum uric acid and cardiovascular disease: recent developments, and where do they leave us? *Am J Med*. (2005) 118:816–26. doi: 10.1016/j.amjmed.2005.03.043

18. Verdecchia P, Schillaci G, Reboldi G, Santeusanio F, Porcellati C, Brunetti P. Relation between serum uric acid and risk of cardiovascular disease in essential hypertension. The PIUMA study. *Hypertension*. (2000) 36:1072–8. doi: 10.1161/01.HYP.36.6.1072

19. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971–1992. National health and nutrition examination survey. *JAMA*. (2000) 283:2404–10. doi: 10.1001/jama.283.18.2404

20. De Luca L, Gulizia MM, Gabrielli D, Meessen J, Mattei L, D'Urbano M, et al. Impact of serum uric acid levels on cardiovascular events and quality of life in patients with chronic coronary syndromes: insights from a contemporary, prospective, nationwide registry. *Nutr Metab Cardiovasc Dis*. (2022) 32:393–401. doi: 10.1016/j.numecd.2021.09.034

21. Han K, Lu Q, Zhu WJ, Wang TZ, Du Y, Bai L. Correlations of degree of coronary artery stenosis with blood lipid, CRP, Hcy, GGT, SCD36 and fibrinogen levels in elderly patients with coronary heart disease. *Eur Rev Med Pharmacol Sci*. (2019) 23:9582–9. doi: 10.26355/eurrev_201911_19453

22. Kikkert WJ, Claessen BE, Stone GW, Mehran R, Witzenbichler B, Brodie BR, et al. D-dimer levels predict ischemic and hemorrhagic outcomes after acute myocardial infarction: a HORIZONS-AMI biomarker substudy. *J Thromb Thrombolysis*. (2014) 37(2):155–64. doi: 10.1007/s11239-013-0953-5

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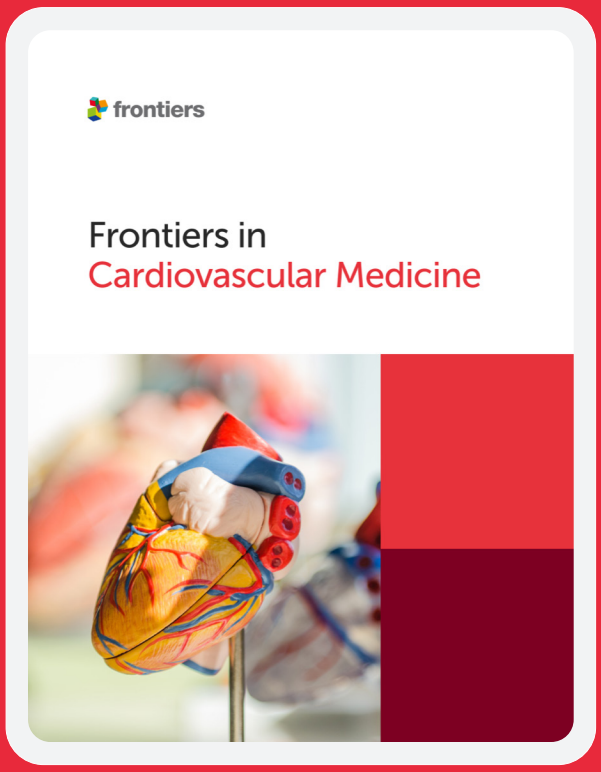

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