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ORIGINAL ARTICLE

Comparison of Ticagrelor with Clopidogrel on Coronary Microvascular Dysfunction Following Acute Myocardial Infarction Using Angiography-Derived Index of Microcirculatory Resistance

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Abstract

Purpose This research aimed to assess the impact of ticagrelor and clopidogrel on coronary microvascular dysfunction (CMD) and prognosis following acute myocardial infarction (AMI), using the angiography-derived index of microcirculatory resistance (angio-IMR) as a non-invasive assessment tool.

Methods In this retrospective study, angio-IMR was performed to evaluate CMD before and after dual antiplatelet therapy (DAPT) with either ticagrelor (90 mg twice daily, $n=184$) or clopidogrel (75 mg once daily, $n=72$). The primary endpoint is the improvement of CMD evaluated by angio-IMR (delta angio-IMR) following DAPT. Secondary endpoints included myocardial reinfarction and readmission for heart failure during 2-year follow-up.

Results Compared with clopidogrel, ticagrelor exhibited a significantly higher delta angio-IMR [−3.09 (5.14) versus −1.99 (1.91), $P=0.008$], indicating a superior improvement of CMD with ticagrelor treatment. Multivariate Cox regression indicated that ticagrelor treatment was related to a reduced risk of readmission for heart failure [8 (4.3) versus 9 (12.5), adjusted HR = 0.329; 95% CI = 0.116–0.934; $P=0.018$] and myocardial reinfarction [7 (3.8) versus 8 (11.1), adjusted HR = 0.349; 95% CI = 0.125–0.975; $P=0.026$]. Furthermore, ticagrelor treatment serves as an independent predictor of readmission for heart failure (HR = 0.322; 95% CI = 0.110–0.943; $P=0.039$).

Conclusion The results of this study indicate a potential association between ticagrelor treatment and improved CMD, as well as a reduced risk of cardiovascular events, including myocardial reinfarction and readmission for heart failure in AMI patients. Further randomized controlled trials are necessary to confirm the potential benefits of ticagrelor on CMD and cardiovascular prognosis. This clinical trial was registered in www.clinicaltrials.gov (NCT05978726).

Keywords Coronary microvascular dysfunction · Index of microcirculatory resistance · Acute myocardial infarction · Clopidogrel · Ticagrelor

Abbreviations

AMI	Acute myocardial infarction
MI	Myocardial infarction
PCI	Percutaneous coronary intervention
STEMI	ST-segment-elevation myocardial infarction
NSTEMI	Non-ST-segment elevation myocardial infarction
CMD	Coronary microvascular dysfunction
MACE	Major adverse cardiovascular events
DAPT	Dual antiplatelet therapy
ACS	Acute coronary syndrome
angio-IMR	Angiography-derived index of microcirculatory resistance
LVEF	Left ventricular ejection fraction
TVR	Target vessel revascularization
nTVR	Non-target vessel revascularization
CTO	Chronic total occlusion

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Introduction

Acute myocardial infarction (AMI) is a globally significant cardiovascular condition, causing a tremendous burden on public health worldwide [1]. Percutaneous coronary intervention (PCI) is the preferred therapy for AMI as it effectively revascularizes the culprit vessel, relieves myocardial damage, and enhances prognosis [2]. However, despite successful PCI in promptly reestablishing normal blood flow of epicardial coronary arteries, roughly half of ST-segment-elevation myocardial infarction (STEMI) patients still exhibit impaired function in smaller coronary vessels known as coronary microvascular dysfunction (CMD) [3]. A meta-analysis combining multiple researches indicated that severe CMD following STEMI increased the risk of major adverse cardiovascular events (MACE) (pooled HR = 3.42) [4]. It is gradually recognized that CMD serves as a crucial prognostic indicator of the long-term prognosis in AMI as well as the promising target for therapeutic interventions [5].

Dual antiplatelet therapy (DAPT), consisting of aspirin in combination with either clopidogrel or ticagrelor, has been considered the cornerstone of AMI treatment due to its superior efficacy in reducing ischemic events and improving prognosis [6, 7]. By reversibly binding to platelet ADP $P2Y_{12}$ receptors, ticagrelor exerts more rapid and potent effect on platelets inhibition than other $P2Y_{12}$ inhibitors. The PLATO trial demonstrated the significantly reduced risk of cardiovascular events, including all-cause death, vascular death, or myocardial infarction (MI) among patients with acute coronary syndrome (ACS) treated with ticagrelor [8]. However, the observed clinical benefits may not solely be attributed to antiplatelet effects. Several studies have provided evidence that ticagrelor effectively raises the concentration of plasma adenosine in ACS patients by blocking the absorption of adenosine by red blood cells, which may potentially protect against CMD by reducing necrotic injury and edema formation while enhancing coronary blood flow velocity [9–11].

The angiography-derived index of microcirculatory resistance (angio-IMR) was newly proposed to evaluate coronary microcirculation solely based on coronary angiographic images. Considering its superiority in not requiring pressure–temperature sensor guidewire and hyperemic agents, as well as its ease of use in clinical practice, angio-IMR is promising to replace guidewire-derived IMR for assessing CMD after PCI in AMI patients [12, 13]. Previous study by our team has established a robust correlation coefficient of 0.81 between angio-IMR and guidewire-derived IMR, boasting an overall diagnostic accuracy of 91.1% (95% CI 86.4–94.7%) and a sensitivity of 89.4% (95% CI 80.9–95.0%) [14]. In patients with ACS who underwent PCI, 6-month ticagrelor treatment has demonstrated significant improvement in CMD as measured by guidewire- derived IMR in comparison with clopidogrel [15]. Another study involving non-ST-segment elevation ACS patients also revealed a significant benefit of ticagrelor over clopidogrel on CMD after PCI [16]. However, the role of ticagrelor on coronary microcirculation and long-term prognosis in AMI patients receiving complete DAPT is not well established. Therefore, we performed clinical research to evaluate the impact of complete DAPT with ticagrelor or clopidogrel on CMD and prognosis in AMI patients, using angio-IMR as the assessment index.

Methods

Study Design and Population

This single-center, observational study retrospectively enrolled patients diagnosed with AMI, including STEMI and non-ST-segment elevation myocardial infarction (NSTEMI), who received successful PCI and regular follow-up coronary angiography at the Second Affiliated Hospital of Zhejiang University School of Medicine from June 1, 2017, to May 31, 2020. All enrolled patients were older than 18 years. The diagnosis of AMI was based on established clinical guidelines. Successful PCI was attaining residual diameter stenosis below 20% in the culprit lesion confirmed through visual examination or quantitative coronary angiography with TIMI flow grade 3 present. Exclusion criteria encompassed (1) prior treatment with $P2Y_{12}$ inhibitors; (2) requirement for oral anticoagulation treatment; (3) adjustment of DAPT during follow-up; (4) history of coronary artery bypass grafting; (5) chronic renal dysfunction with estimated glomerular filtration rate < 30 mL/(min·1.73 m^2) or undergoing hemodialysis; (6) liver cirrhosis classified as ≥ Child–Pugh B; (7) malignant tumor diagnosis; (9) hemodynamic instability; and (10) inadequate quality of coronary angiographic images. This research was performed with the approval of the Medical Ethics Committee of the Second Affiliated Hospital of Zhejiang University, waiving the need for written informed consent. Furthermore, this study adhered to STROBE reporting criteria. (NCT05978726).

Angiographic Analysis and Antiplatelet Therapy

Coronary angiography and PCI procedures were conducted by skilled interventional cardiologists using standard techniques. All patients were administered a loading dose of oral aspirin 300 mg with ticagrelor 180 mg or clopidogrel 300 mg before PCI. Subsequently, DAPT was maintained with a daily intake of aspirin (100 mg) in combination with

either ticagrelor (90 mg twice daily) or clopidogrel (75 mg once daily). The duration of DAPT was defined as the period between discharge and coronary follow-up, with a minimum duration of 9 months post-PCI. If no in-stent thrombosis or in-stent restenosis was observed during coronary follow-up, antiplatelet therapy was adjusted to monotherapy with either aspirin (100 mg once daily) or clopidogrel (75 mg once daily). Patients were assigned to two groups based on the antiplatelet agent received: ticagrelor or clopidogrel. The choice of stents and administration of ancillary drugs, including antiplatelet agents and anticoagulants, were at the primary operator's discretion according to current guidelines.

Angio-IMR Assessment

The initial assessment of angio-IMR was conducted post-revascularization of the culprit vessel, while the second measurement was taken during the routine coronary angiography follow-up. In cases without in-stent thrombosis or restenosis during the follow-up coronary angiography, angio-IMR was measured directly. In contrast, if in-stent thrombosis or restenosis was detected, angio-IMR was assessed prior to the re-stent implantation. The specific assessment process involved the following key steps using dedicated software (AccuIMR, version 1.0, ArteryFlow Technology, Hangzhou, China), which is based on coronary angiographic images [14]. First, the AccuIMR system automatically extracted features of angiographic images and delineated the lumen contour. Subsequently, the culprit vessel's three-dimensional mesh image was reconstructed using anatomical information obtained from two different angiographic views. Next, the TIMI frame count method was utilized to determine hyperemic blood flow velocity (V_{hyp}), while a specific computational fluid dynamics approach was employed to calculate the pressure gradient (ΔP_{hyp}) along the culprit vessel. Finally, angio-IMR assessment was conducted using the subsequent formula:

$$\text{angio} - \text{IMR} = (P_{a,hyp} - \Delta \mathrm{P}_{hyp}) \bullet L/V_{hyp}$$

where $P_{\mathrm{a,hyp}}$ refers to mean aortic pressure during hyperemia, ΔP_{hyp} denotes the pressure gradient along the culprit vessel, L signifies the length of the culprit vessel from its inlet to distal segment, and V_{hyp} indicates the hyperemic mean blood flow velocity.

Angio-IMR can also be calculated as follows:

$$\text{angio} - \text{IMR} = P_{a,hyp} \bullet \mathrm{FFR}_{hyp} \bullet L/V_{hyp}$$

where $\mathrm{FFR}_{\mathrm{hyp}}$ is the hyperemic fractional flow reserve (FFR), which was also assessed based on coronary angiographic images as previously studied.[14] For patients with an $\mathrm{FFR}_{\mathrm{hyp}} < 0.80$, the angio-IMR was adjusted according to Yong's formula [17]. Diagnostic thresholds for coronary microcirculation dysfunction were set at 40 units for STEMI patients and 25 units for NSTEMI patients [18, 19]. Angio-IMR assessment was carried out by an independent core lab with blinding procedures (Fig. 1).

Follow-Up and Endpoints

Follow-up was carried out at 1, 6, 12, and 24 months through outpatient clinic visits, medical record reviews, and telephone interviews. Additionally, patients underwent follow-up coronary angiography at our hospital between the 9th and 15th month after discharge. The primary endpoint was the difference in CMD improvement (defined as a reduction in angio-IMR) between the two groups before and after maintenance treatment with DAPT. Secondary endpoints included cardiovascular events such as readmission for heart failure, myocardial reinfarction, target vessel revascularization (TVR), non-target vessel revascularization (nTVR), cerebral hemorrhage, and other bleeding events during 2-year follow-up. Clinical events were determined based on the standards outlined in the academic research consortium report, and any discrepancies were settled by consensus [20].

Statistical Analysis

The results of categorical variables were presented as counts (percentages) and analyzed with appropriate statistical tests, such as chi-square or Fisher's exact test. For continuous variables, normally distributed variables were described by mean ± standard deviation (SD), while non-normally distributed variables were described by medians (interquartile range). The analysis was performed using the independent samples *t*-test or Wilcoxon rank sum test as appropriate. Normality assessment was conducted using the Kolmogorov–Smirnov test. Multiple imputation methods were applied to impute missing covariates. The adjusted hazard ratios (HR) and 95% confidence intervals (CI) were estimated using Cox proportional hazards models to compare the risks of clinical endpoints based on ticagrelor treatment. Adjusted co-variables included sex, age (> 60 years), diabetes mellitus, and left ventricular ejection fraction (LVEF). Multivariable Cox regression models were employed to identify independent predictors of myocardial reinfarction and readmission for heart failure. Additionally, different covariates were incorporated into several multivariable Cox regression models to validate the robustness of angio-IMR in predicting clinical events. Subgroup analyses were conducted to evaluate the impact of ticagrelor on clinical events across high cardiovascular risk groups. All statistical analyses were carried out using R programming language and SPSS software (version 26.0, Chicago, Illinois).

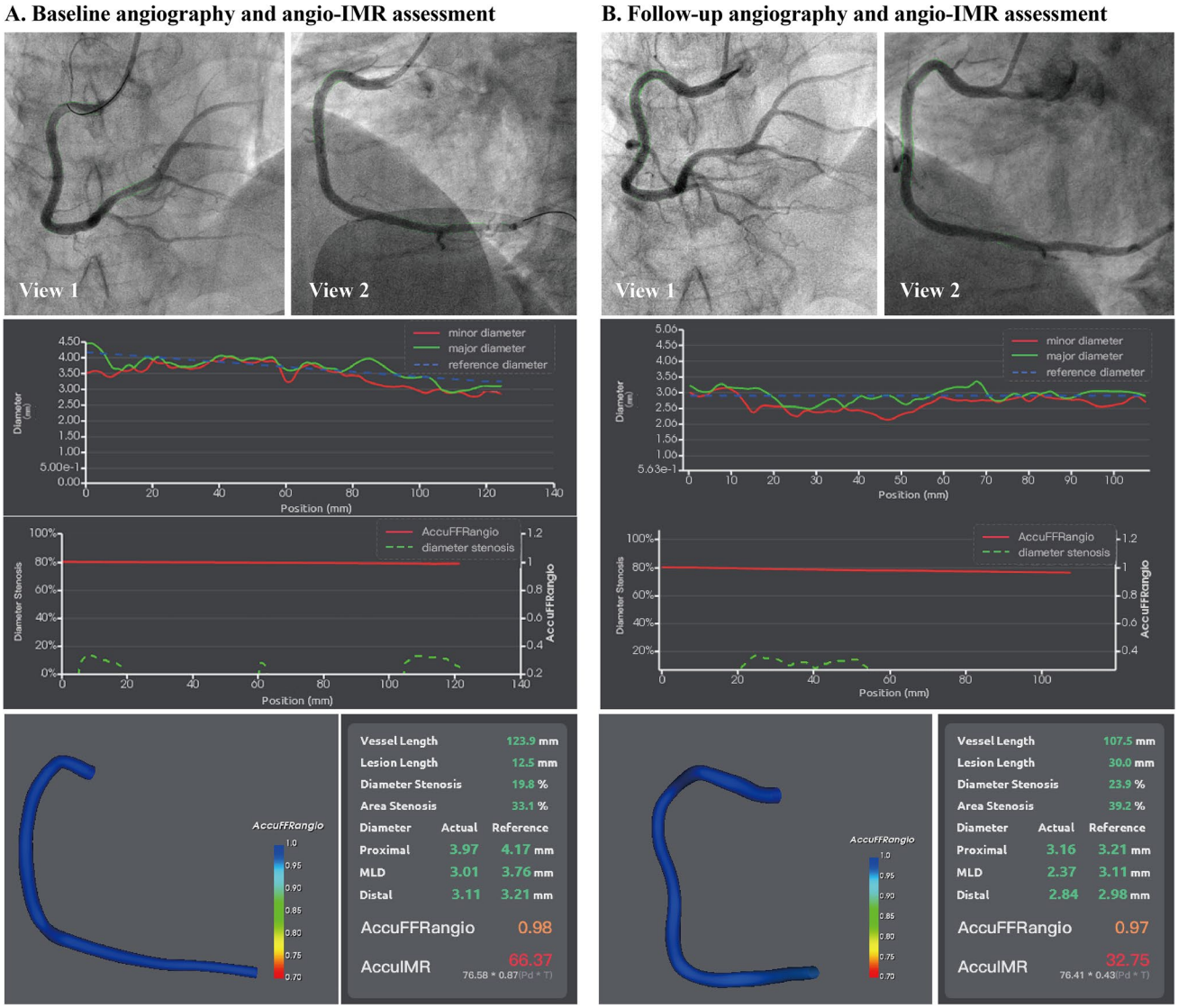

Fig. 1 A case example of baseline and follow-up angio-IMR measurements in a patient with acute myocardial infarction. Representative case of AMI with both baseline and follow-up angio-IMR measurements in the culprit vessel. **A** Patient with impaired coronary microcirculation function, manifested as a higher angio-IMR. **B** Patient with improved coronary microcirculation function, manifested as a lower angio-IMR, angio-IMR angiography-derived index of microcirculatory resistance, angio-FFR angiography-derived fractional flow reserve

Results

Baseline Characteristics

A total of 325 AMI patients who received successful PCI and regular follow-up coronary angiography in our hospital were identified. Following the application of exclusion criteria, 256 patients were selected for final analysis, and angio-IMR calculation was performed in the culprit vessel after PCI and DAPT treatment (Fig. 2). Among them, 184 patients received ticagrelor twice daily at 90 mg with aspirin once daily at 100 mg, while 72 patients received clopidogrel once daily at 75 mg with aspirin once daily at 100 mg as DAPT. The baseline demographic characteristics of both groups are presented in Table 1. Both groups did not differ significantly in any characteristic except for age, with the ticagrelor group younger than the clopidogrel group (59.40 ± 12.31 versus 65.83 ± 12.13, $P < 0.001$). The laboratory findings revealed significant differences in fasting plasma glucose (5.61 ± 1.13 versus 6.18 ± 1.62, $P = 0.007$) and triglycerides (1.73 ± 0.89 versus 1.35 ± 0.48, $P < 0.001$). Importantly, the duration of DAPT maintenance treatment was similar between the two groups (12.56 ± 1.44 versus 12.27 ± 0.89, $P = 0.07$). All patients enrolled had no history of prior treatment with

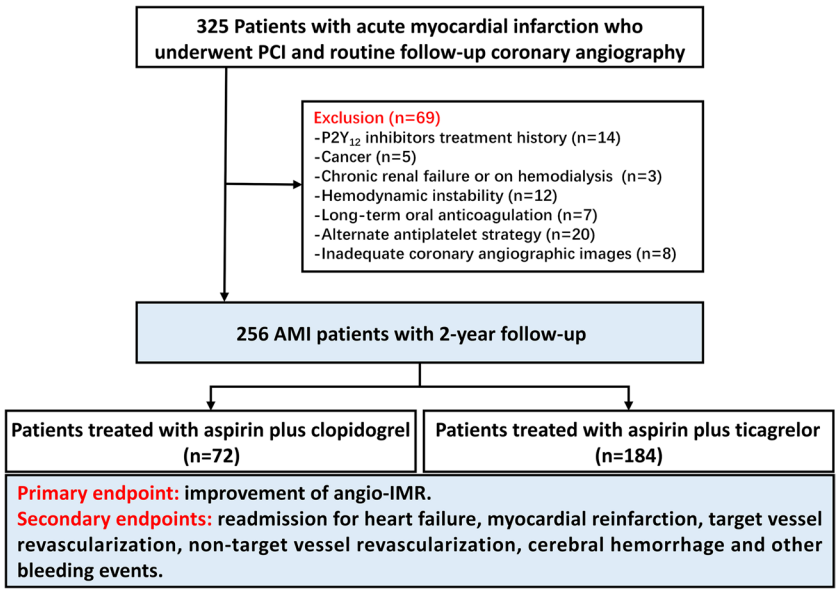

Fig. 2 Study flow

$P2Y_{12}$ inhibitors as those who had received such treatment were excluded. Patients who switched from ticagrelor to clopidogrel due to bleeding and dyspnea were also excluded.

Table 2 summarizes the baseline angiographic and procedural features observed in the 256 enrolled patients, revealing no notable differences between both groups. The stenosis severity in the culprit vessel before revascularization and the number of diseased vessels exhibited no differences between both groups. In addition, the presence of multivessel disease, left main disease, and chronic total occlusion (CTO) were also comparable between the two groups. All patients received stent implantation for culprit lesions, with no significant differences in stent characteristics including number, diameter, and length. Of concern, perioperative utilization of glycoprotein (GP) IIb/IIIa inhibitors was observed to be higher in the ticagrelor group [143 (77.7) versus 39 (54.2), $P < 0.001$], while the use of other perioperative adjunctive medications was similar between both groups, including low molecular weight heparin and bivalirudin.

Comparison of Coronary Physiological Characteristics and Primary Endpoints

The baseline and follow-up coronary physiological characteristics were assessed in the culprit vessels of all 256 enrolled patients (Table 3), with no missing data. The median baseline angio-IMR and angio-FFR of the culprit vessel were comparable between the two groups. After DAPT maintenance treatment, the ticagrelor group exhibited a lower median follow-up angio-IMR compared with the clopidogrel group [16.94 (6.43) versus 19.34 (10.78), $P = 0.01$], while the median follow-up angio-FFR showed no difference. Figure 3 illustrates individual changes from baseline to follow-up in angio-IMR and angio-FFR for each patient. The primary outcome, namely the change of angio-IMR from baseline to follow-up, was significantly higher with ticagrelor [− 3.09 (5.14) versus − 1.99 (1.91), $P = 0.008$], indicating superior preservation of coronary microvascular function with ticagrelor treatment (Fig. 4). Other intracoronary physiological indices, including lesion length, diameter stenosis percentage, area stenosis percentage, and minimal lumen diameter, were similar between the groups.

Clinical Endpoints and Prognostic Implication

All patients underwent successful revascularization and were followed up for 24 months. The clinical outcomes of both groups are summarized in Table 4. Patients administered ticagrelor demonstrated a lower risk of readmission for heart failure [8 (4.3) versus 9 (12.5), adjusted HR = 0.329; 95% CI = 0.116–0.934; $P = 0.018$] and myocardial reinfarction [7 (3.8) versus 8 (11.1), adjusted HR = 0.349; 95% CI = 0.125–0.975; $P = 0.026$] compared with those administered clopidogrel. The cumulative event curves of both outcomes are shown in Fig. 5 and Fig. 6, respectively. Additionally, the risks of TVR, nTVR, cerebral hemorrhage, and other bleeding events were similar between both groups.

The independent predictors for readmission for heart failure and myocardial reinfarction during the 2-year follow-up in AMI patients are shown in Table 5 and Table 6, respectively. In multivariable Cox regression models, ticagrelor emerged as a significant predictor for readmission for heart failure (adjusted HR = 0.322; 95% CI = 0.110–0.943; $P = 0.039$), but not for myocardial reinfarction (adjusted HR = 0.592; 95% CI = 0.178–1.968;

Table 1 Patient demographics and baseline characteristics

	Total ($n=256$)	Ticagrelor ($n=184$)	Clopidogrel ($n=72$)	P value
Clinical characteristics				
Age, y	61.21 ± 12.58	59.40 ± 12.31	65.83 ± 12.13	< 0.001
Male	224 (87.5)	164 (89.1)	60 (83.3)	0.21
HR, bpm	77.08 ± 12.51	77.56 ± 12.86	75.84 ± 11.56	0.32
SBP, mmHg	124.40 ± 16.84	124.97 ± 16.85	122.95 ± 16.84	0.39
LVEF, %	59.17 ± 8.74	59.66 ± 8.71	57.92 ± 8.73	0.16
LVEF, follow-up, %	61.93 ± 8.37	62.15 ± 7.87	61.37 ± 9.56	0.53
Smoke	175 (68.4)	132 (71.7)	43 (59.7)	0.06
Diabetes mellitus	75 (29.3)	52 (28.3)	23 (31.9)	0.56
Hypertension	155 (60.5)	108 (58.7)	47 (65.3)	0.33
Hyperlipidemia	108 (42.2)	80 (43.5)	28 (38.9)	0.50
Prior stroke	21 (8.2)	13 (7.1)	8 (11.1)	0.29
Prior MI	14 (5.5)	10 (5.4)	4 (5.6)	1.00
Prior PCI	14 (5.5)	11 (6.0)	3 (4.2)	0.76
Biochemistry values				
Hemoglobin, g/L	144.57 ± 17.68	145.29 ± 17.54	142.72 ± 18.01	0.30
Platelet, *10^9/L	204.87 ± 49.49	206.08 ± 49.95	201.76 ± 48.50	0.53
Creatinine clearance, mL/min	74.67 ± 15.72	73.60 ± 14.38	77.40 ± 18.56	0.12
FPG, mmol/L	5.77 ± 1.31	5.61 ± 1.13	6.18 ± 1.62	0.007
HbA1c, %	6.21 ± 0.80	6.18 ± 0.73	6.30 ± 0.97	0.34
Lipid profile, mmol/L				
Total cholesterol	4.51 ± 1.06	4.51 ± 1.06	4.50 ± 1.08	0.93
LDL cholesterol	2.46 ± 0.73	2.47 ± 0.74	2.42 ± 0.69	0.61
HDL cholesterol	1.06 ± 0.24	1.04 ± 0.23	1.11 ± 0.26	0.052
Triglycerides	1.62 ± 0.81	1.73 ± 0.89	1.35 ± 0.48	< 0.001
Peak CK, U/L	811.80 (1637.00)	958.00 (2217.00)	522.50 (1265.00)	0.02
Peak CK-MB, U/L	68.00 (149.00)	90.00 (168.00)	48.00 (125.00)	0.04
Discharge medication				
Aspirin	256 (100)	184 (100)	72 (100)	NA
Clopidogrel	72 (28.1)	0 (0)	72 (100)	< 0.001
Ticagrelor	184 (71.9)	184 (100)	0 (0)	< 0.001
Statins	256 (100)	184 (100)	72 (100)	NA
Beta-blockers	213 (83.2)	159 (86.4)	54 (75.0)	0.03
RAAS blockers	218 (85.2)	163 (88.6)	55 (76.4)	0.01
Duration of DAPT	12.49 ± 1.32	12.56 ± 1.44	12.27 ± 0.89	0.07

All data presented as mean ± SD or medians (IQR) for continuous variables and counts (percentages) for categorical variables. *HR* heart rate, *SBP* systolic blood pressure, *LVEF* left ventricular ejection fraction, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *FPG* fast plasma glucose, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *CK* creatine kinase, *CK-MB* creatine kinase isoenzyme MB, *RAAS* renin angiotensin aldosterone system, *DAPT* dual antiplatelet therapy

$P = 0.393$). Besides, baseline angio-IMR emerged as a significant predictor for both outcomes, exhibiting an HR of 1.097 (per unit increased, 95% CI = 1.042–1.154; $P < 0.001$) for readmission for heart failure and an HR of 1.083 (per unit increased, 95% CI = 1.027–1.142; $P = 0.003$) for myocardial reinfarction, indicating the significant association between CMD and cardiovascular outcomes.

Sensitivity Analyses and Subgroup Analyses

The sensitivity analyses were performed to evaluate the prognostic value of baseline angio-IMR in predicting readmission for heart failure and myocardial reinfarction, as illustrated in Fig. 7. We included different covariates in each model to adjust for potential confounding factors. Model 1 included baseline angio-IMR as a predictor. Model

Table 2 Baseline angiographic and procedural characteristics

	Total ($n=256$)	Ticagrelor ($n=184$)	Clopidogrel ($n=72$)	P value
Radial access	252 (98.4)	181 (98.4)	71 (98.6)	0.69
Right dominant	162 (63.3)	120 (65.2)	42 (58.3)	0.30
Culprit vessel				
LAD	110 (43.0)	79 (42.9)	31 (43.1)	0.99
LCX	70 (27.3)	51 (27.7)	19 (26.4)	0.83
RCA	77 (30.1)	55 (29.9)	22 (30.6)	0.92
Initial TIMI flow grade				
TIMI 0/1	116 (45.3)	88 (47.8)	28 (38.9)	0.20
TIMI 2	19 (7.4)	14 (7.7)	5 (6.9)	0.85
TIMI 3	120 (46.9)	81 (44.3)	39 (54.2)	0.15
Pre-PCI diameter stenosis, %	99.00 (10.00)	99.00 (5.00)	99.00 (10.00)	0.11
Number of diseased vessels	2.19 ± 0.81	2.18 ± 0.82	2.19 ± 0.80	0.93
Left main disease	27 (10.5)	20 (10.9)	7 (9.7)	0.79
Proximal lesion	93 (36.3)	61 (33.2)	32 (44.4)	0.09
Multivessel disease	191 (74.6)	136 (73.9)	55 (76.4)	0.68
Chronic total occlusion	28 (10.9)	22 (12.0)	6 (8.3)	0.40
Procedural characteristics				
Stent number	1.24 ± 0.60	1.22 ± 0.59	1.28 ± 0.61	0.51
Stent length, mm	27.22 ± 6.97	27.16 ± 7.19	27.34 ± 6.48	0.85
Stent diameter, mm	2.99 ± 0.45	2.98 ± 0.44	3.00 ± 0.47	0.71
Aspiration thrombectomy	101 (39.5)	75 (40.8)	26 (36.1)	0.49
Low molecular weight heparin	64 (25.0)	40 (21.7)	24 (33.3)	0.05
GP IIb/IIIa inhibitors	182 (71.1)	143 (77.7)	39 (54.2)	< 0.001
Bivalirudin	13 (5.1)	10 (5.4)	3 (4.2)	0.48

All data presented as mean ± SD or medians (IQR) for continuous variables and counts (percentages) for categorical variables. *LAD* left anterior descending artery, *LCX* left circumflex artery, *RCA* right coronary artery, *TIMI* thrombolysis in myocardial infarction, *PCI* percutaneous coronary intervention, *GP* glycoprotein

2 added sex, age, and LVEF based on Model 1. Model 3 added hypertension and diabetes mellitus based on model 2. Model 4 added CTO and multivessel disease based on model 3. Model 5 added ticagrelor and GP IIb/IIIa inhibitors based on model 4. The inclusion of these covariates in model 5 ensures a robust adjustment for potential confounders, rendering baseline angio-IMR as a reliable predictor for both outcomes. The subgroup analyses depicted in Fig. 8 and Fig. 9 explore the differential impacts of ticagrelor versus clopidogrel across various patient subgroups. Preliminary findings revealed that ticagrelor may be associated with a lower risk of readmission for heart failure, particularly in several high cardiovascular risk subgroups, including patients with diabetes mellitus (HR = 0.20, 95% CI 0.05–0.80), hyperlipidemia (HR = 0.08, 95% CI 0.01–0.74), LVEF < 50% (HR = 0.25, 95% CI 0.07–0.88), and multivessel disease (HR = 0.34, 95% CI 0.12–0.93). Additionally, a significantly reduced risk of myocardial reinfarction was also observed in patients with hypertension (HR = 0.21, 95% CI 0.05–0.84) and CTO (HR = 0.16, 95% CI 0.03–0.94).

Discussion

In this single-center, retrospective, observational study, we evaluated the impacts of DAPT with ticagrelor or clopidogrel on CMD and clinical prognosis over 2-year follow-up in AMI patients. We are the first to evaluate changes in coronary microvascular function using angio-IMR, a novel wire-free measurement for CMD, before and after different DAPT regimens. The main findings were as follows: (1) Following an average duration of approximately 12 months of DAPT maintenance treatment, ticagrelor demonstrated a significant reduction in angio-IMR, indicating its superior efficacy in preserving coronary microvascular function compared with clopidogrel in AMI patients. (2) Ticagrelor treatment was related to a lower risk of readmission for heart failure and myocardial reinfarction during 2-year follow-up when compared with clopidogrel treatment, which may be partially attributed to the greater improvements in CMD with ticagrelor. (3) Ticagrelor treatment independently predicted readmission

Table 3 Baseline and follow-up coronary physiological measurements

	Total ($n=256$)	Ticagrelor ($n=184$)	Clopidogrel ($n=72$)	*P* value
Baseline coronary physiological measurements				
Lesion length, mm	17.55 (16.35)	17.95 (17.33)	17.45 (13.15)	0.53
Diameter stenosis, %	30.49 ± 10.01	29.75 ± 9.70	32.29 ± 10.58	0.07
Area stenosis, %	42.20 ± 13.98	42.04 ± 14.49	42.62 ± 12.65	0.77
Minimal lumen diameter, mm	1.81 ± 0.52	1.81 ± 0.53	1.80 ± 0.49	0.94
Angio-FFR	0.95 (0.06)	0.95 (0.06)	0.95 (0.05)	0.86
Angio-IMR	21.41 (9.79)	20.96 (8.81)	22.98 (14.97)	0.21
Diagnostic CMD	59 (23.0)	44 (23.9)	15 (20.8)	0.60
Follow-up coronary physiological measurements				
Lesion length, mm	16.50 (16.20)	17.30 (18.48)	15.80 (10.34)	0.07
Diameter stenosis, %	33.39 ± 13.96	34.35 ± 14.14	30.96 ± 13.26	0.08
Area stenosis, %	45.20 ± 16.90	46.74 ± 17.79	41.15 ± 13.57	0.01
Minimal lumen diameter, mm	1.80 ± 0.55	1.73 ± 0.56	1.96 ± 0.50	0.002
Angio-FFR	0.95 (0.06)	0.95 (0.06)	0.96 (0.06)	0.08
Angio-IMR	17.55 (7.59)	16.94 (6.43)	19.34 (10.78)	0.01
Diagnostic CMD	21 (8.2)	16 (8.7)	5 (6.9)	0.65
Delta angio-FFR	0.01 (0.05)	0.00(0.05)	0.01 (0.04)	0.25
Delta angio-IMR	− 2.51 (4.29)	− 3.09 (5.14)	− 1.99 (1.91)	0.008

All data presented as mean ± SD or medians (IQR) for continuous variables and counts (percentages) for categorical variables. Diagnostic thresholds for CMD were set at 40 units for STEMI patients and 25 units for NSTEMI patients. *Angio-FFR* angiography-derived fractional flow reserve, *Angio-IMR* angiography-derived index of microcirculatory resistance, *CMD* coronary microvascular dysfunction, *STEMI* ST-segment-elevation myocardial infarction, *NSTEMI* non-ST-segment elevation myocardial infarction

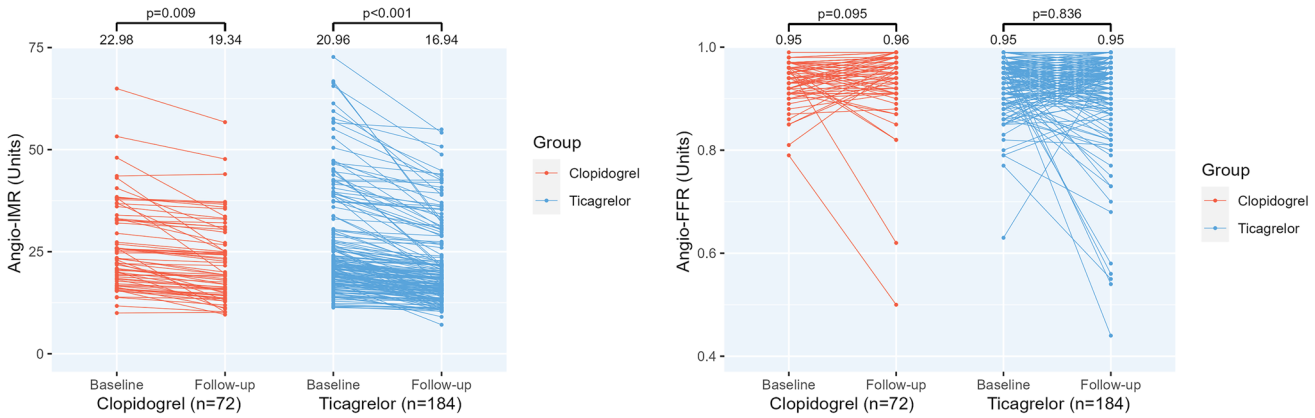

Fig. 3 Change in angio-IMR and angio-FFR from baseline to follow-up according to dual antiplatelet therapy (DAPT) regimens. Plot illustrates the individual angio-IMR and angio-FFR at baseline and after complete DAPT maintenance treatment. Abbreviations as in Fig. 1

for heart failure. (4) Angio-IMR emerged as a significant predictor for readmission for heart failure and myocardial reinfarction, highlighting the predictive value of CMD for cardiovascular outcomes in AMI patients.

CMD is frequently observed in patients with AMI, particularly following successful revascularization of the culprit vessel. A comprehensive understanding of CMD considered that microembolization, platelet aggregation, endothelial dysfunction, and vasomotion jointly contribute to its development in AMI [21]. Furthermore, CMD has been strongly associated with MACE, including heart failure, myocardial infarction, arrhythmia, and mortality [22]. Recent studies indicated that ticagrelor may exert protective effects on CMD beyond its antiplatelet effect. For instance, ticagrelor has been reported to elevate plasma adenosine concentration by inhibiting its absorption by red blood cells, as well as enhance adenosine-induced coronary vasodilation [9, 11]. Additionally, ticagrelor appears to exert a positive influence on inflammation and oxidative stress, potentially mitigating endothelial dysfunction and related prothrombotic effects

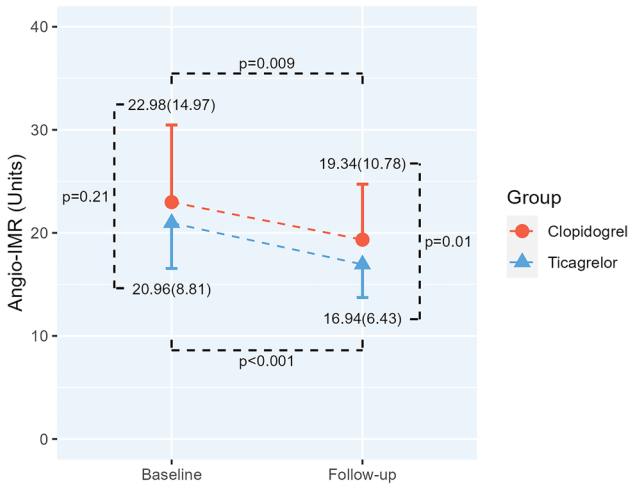

Fig. 4 Median angio-IMR at baseline and follow-up in different groups according to dual antiplatelet therapy (DAPT) regimens. Comparison of median angio-IMR at baseline and after complete DAPT maintenance treatment, as well as comparison of change in angio-IMR between ticagrelor and clopidogrel group. Abbreviations as in Fig. 1

[23]. In comparison with other $P2Y_{12}$ inhibitors, ticagrelor may also inhibit vasoconstriction by preventing ADP-induced contraction of vascular smooth muscle cells [24]. Collectively, these mechanisms potentially contribute to the observed reduction in microvascular resistance. Nonetheless, it is important to acknowledge that the precise mechanisms by which ticagrelor influences CMD remain incompletely understood. Further mechanistic studies still needed to elucidate the pathway of effect of ticagrelor.

However, clinical evidence regarding the impact of ticagrelor on CMD in AMI patients is limited and inconsistent. Xu et al. and Choi et al. indicated that ticagrelor significantly enhanced guidewire-derived IMR following PCI among ACS patients, as compared with clopidogrel [16, 25]. Similarly, another study reported a greater reduction in guidewire-derived IMR following 6-month maintenance therapy with ticagrelor than clopidogrel among ACS patients [15]. However, a recent study found no benefit when comparing ticagrelor to clopidogrel using myocardial contrast echocardiography-derived global myocardial perfusion score index to evaluate CMD in STEMI patients [26]. Our study demonstrated a significant reduction in angio-IMR among AMI patients who received PCI when treated with ticagrelor maintenance therapy, suggesting superior efficacy of ticagrelor in attenuating CMD. The underlying mechanisms for this effect are likely attributed to the aforementioned properties of ticagrelor. However, further research is necessary to clarify the precise underlying mechanisms.

In our retrospective research, we observed that maintenance therapy with ticagrelor was associated with a lower risk of readmission for heart failure and myocardial reinfarction compared with clopidogrel during the 2-year follow-up in AMI patients. These observations align with the results of the PLATO trial, which demonstrated the ticagrelor's superior efficacy over clopidogrel in improving clinical prognosis including myocardial reinfarction in patients with ACS [8]. Additionally, ticagrelor remained an independent predictor for readmission for heart failure according to multivariable analysis, though it did not show the same predictive value for myocardial reinfarction. This may indicate that ticagrelor has a more pronounced effect on heart failure than myocardial reinfarction in AMI patients. The potential mechanisms underlying these benefits may be partially attributed to improvements in CMD with ticagrelor, as evidenced by the independent predictive value of angio-IMR for both readmission for heart failure and myocardial reinfarction. This aligns with previous research indicating that angio-IMR independently predicts cardiac death or readmission for heart failure among STEMI patients [13]. Furthermore, it has been demonstrated that CMD is prevalent in patients diagnosed with heart failure with preserved ejection fraction (HFpEF), which may explain why either group exhibited significant improvement in LVEF after DAPT, whereas the risk of readmission for heart failure was significantly reduced

Table 4 Clinical outcomes over 2-year follow-up in patients with acute myocardial infarction according to dual antiplatelet therapy

	Total ($n=256$)	Ticagrelor ($n=184$)	Clopidogrel ($n=72$)	Univariable HR (95% CI)	Multivariable HR (95% CI)	*P* value
Readmission for heart failure	17 (6.6)	8 (4.3)	9 (12.5)	0.336 (0.130–0.871)	0.329 (0.116–0.934)	0.018
Myocardial reinfarction	15 (5.9)	7 (3.8)	8 (11.1)	0.334 (0.121–0.920)	0.349 (0.125–0.975)	0.026
Target vessel revascularization	45 (17.6)	36 (19.6)	9 (12.5)	1.584 (0.763–3.288)	1.634 (0.776–3.440)	0.207
Non-target vessel revascularization	54 (21.1)	37 (20.1)	17 (23.6)	0.820 (0.462–1.457)	0.863 (0.481–1.550)	0.489
Stroke	0	0	0	NA	NA	NA
Cerebral hemorrhage	1 (0.4)	1 (0.5)	0 (0)	NA	NA	NA
Bleeding events	19 (7.4)	15 (8.2)	4 (5.6)	1.475 (0.489–4.444)	1.586 (0.521–4.829)	0.484

The cumulative incidence of clinical outcomes presented as event number (percentages). *P* values are log-rank *P* values in survival analysis. Covariables included in the multivariable Cox regression model were sex, age ≥ 60 years, diabetes mellitus, and left ventricular ejection fraction. *CI* confidence interval, *HR* hazard ratio

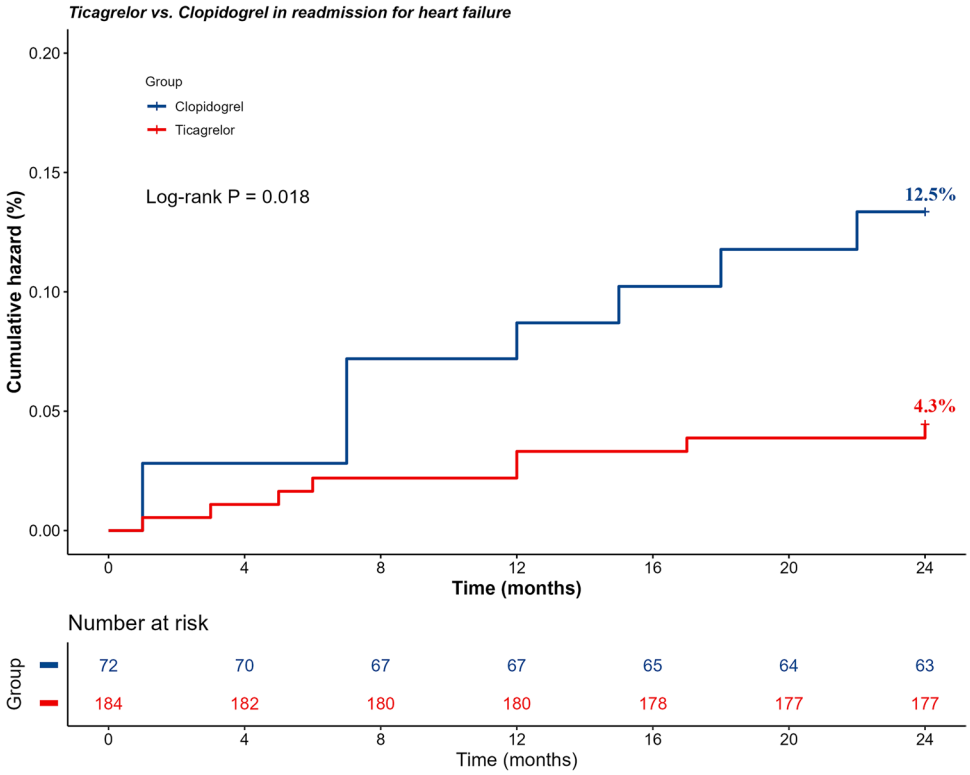

Fig. 5 Readmission for heart failure over 2-year follow-up. Cumulative incidence of readmission for heart failure over 2-year follow-up is presented according to dual antiplatelet therapy (DAPT) regimens. *P* value is log-rank *P* values in survival analysis

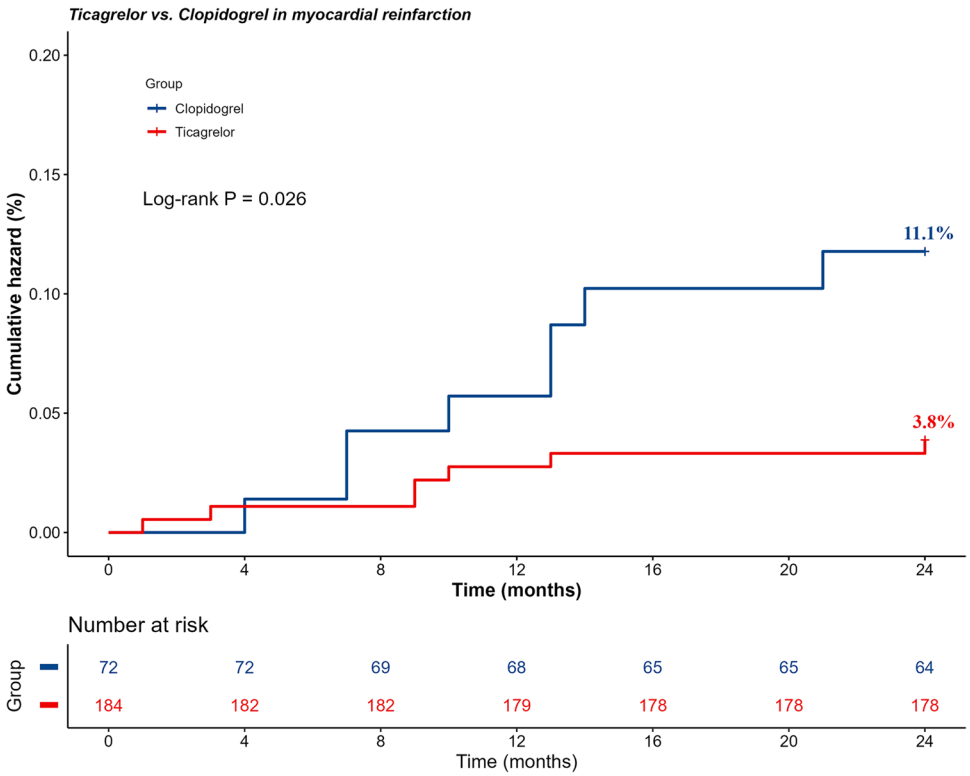

Fig. 6 Myocardial reinfarction over 2-year follow-up. Cumulative incidence of readmission for myocardial infarction over 2-year follow-up is presented according to dual antiplatelet therapy (DAPT) regimens. *P* value is log-rank *P* values in survival analysis

Table 5 Independent predictors for readmission for heart failure over 2-year follow-up in patients with acute myocardial infarction

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Baseline angio-IMR	1.093 (1.047–1.142)	< 0.001	1.097 (1.042–1.154)	< 0.001
Ticagrelor	0.336 (0.130–0.871)	0.025	0.322 (0.110–0.943)	0.039
Male	0.646 (0.186–2.248)	0.492	0.761 (0.199–2.904)	0.689
Age (≥ 60 years)	5.312 (1.215–23.228)	0.027	6.969 (0.880–55.182)	0.066
Diabetes mellitus	2.821 (1.088–7.311)	0.033	2.982 (1.000–8.891)	0.050
Hypertension	1.603 (0.565–4.551)	0.375	1.274 (0.411–3.948)	0.675
LVEF (per 10% increase)	0.458 (0.250–0.837)	0.011	0.610 (0.328–1.134)	0.118
Chronic total occlusion	1.780 (0.512–6.194)	0.365	3.285 (0.743–14.530)	0.117
Multivessel disease	2.625 (0.600–11.477)	0.200	1.461 (0.316–6.749)	0.627
GP IIb/IIIa inhibitors	1.330 (0.434–4.080)	0.618	1.445 (0.412–5.075)	0.565

LVEF left ventricular ejection fraction, *GP* glycoprotein, *CI* confidence interval, *HR* hazard ratio

Table 6 Independent predictors for myocardial reinfarction over 2-year follow-up in patients with acute myocardial infarction

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Baseline angio-IMR	1.058 (1.010–1.108)	0.018	1.083 (1.027–1.142)	0.003
Ticagrelor	0.334 (0.121–0.920)	0.034	0.592 (0.178–1.968)	0.393
Male	0.927 (0.209–4.108)	0.921	1.316 (0.265–6.531)	0.737
Age (≥ 60 years)	1.918 (0.611–6.024)	0.265	1.535 (0.424–5.555)	0.514
Diabetes mellitus	0.866 (0.276–2.721)	0.806	0.968 (0.285–3.292)	0.959
Hypertension	0.958 (0.341–2.692)	0.935	0.653 (0.201–2.119)	0.478
LVEF (per 10% increase)	0.894 (0.499–1.603)	0.707	1.146 (0.609–2.158)	0.672
Chronic total occlusion	4.466 (1.526–13.069)	0.006	6.506 (2.023–20.917)	0.002
Multivessel disease	0.939 (0.299–2.948)	0.914	1.375 (0.362–5.213)	0.640
GP IIb/IIIa inhibitors	0.262 (0.093–0.735)	0.011	0.238 (0.071–0.799)	0.020

LVEF left ventricular ejection fraction, *GP* glycoprotein, *CI* confidence interval, *HR* hazard ratio

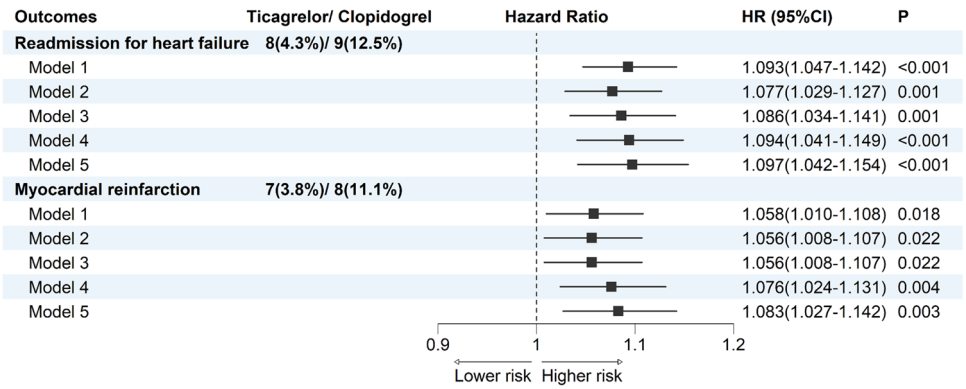

Fig. 7 Sensitivity analysis of baseline angio-IMR for readmission for heart failure and myocardial reinfarction. Different covariates are included in each multivariable Cox regression model. Model 1 includes baseline angio-IMR. Model 2 added sex, age, and left ventricular ejection fraction o based on model 1. Model 3 added hypertension and diabetes mellitus based on model 2. Model 4 added chronic total occlusion and multivessel disease based on model 3. Model 5 added ticagrelor and GP IIb/IIIa inhibitors based on model 4. *P* values are log-rank *P* values in survival analysis. *CI* confidence interval, *HR* hazard ratio

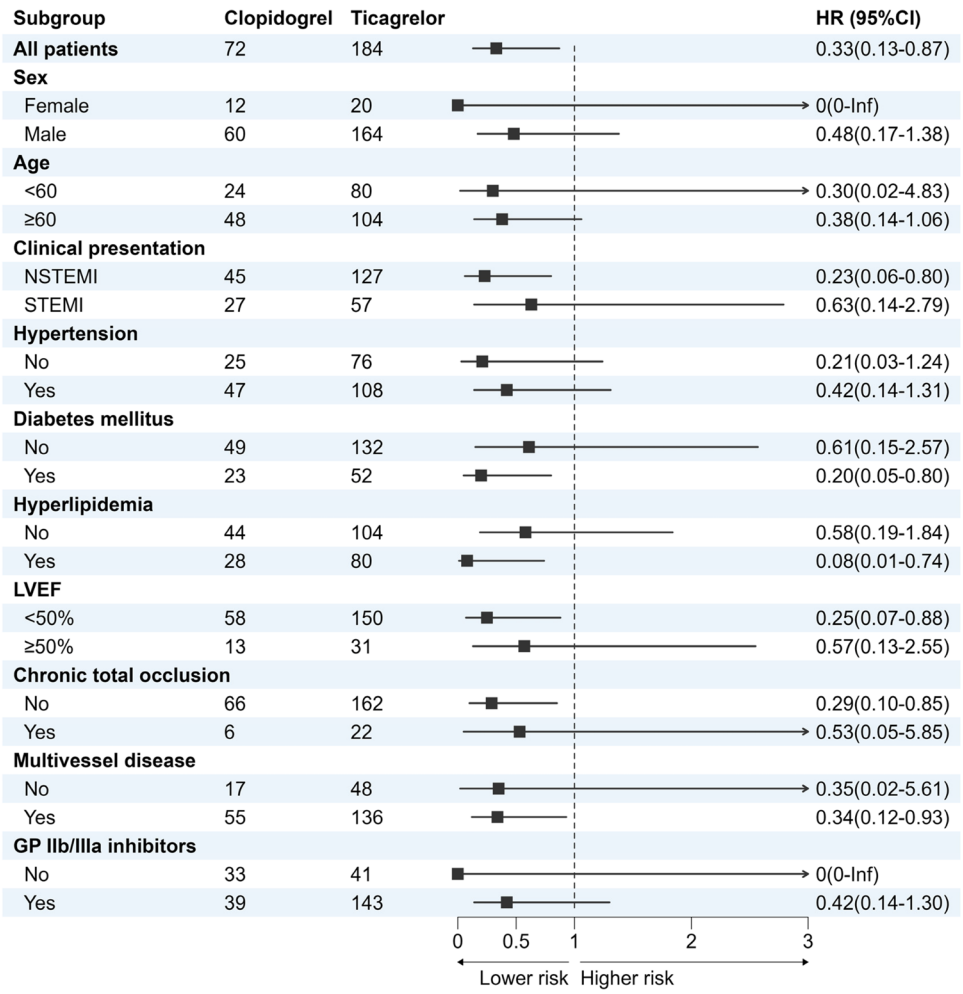

Fig. 8 Subgroup analysis of the effect of ticagrelor and clopidogrel on readmission for heart failure. *P* values are log-rank *P* values in survival analysis. *CI* confidence interval, *HR* hazard ratio, *NSTEMI* non-ST-segment elevation myocardial infarction, *STEMI* ST-segment elevation myocardial infarction, *LVEF* left ventricular ejection fraction; GP glycoprotein

with ticagrelor [27, 28]. Ticagrelor exhibits the potential to enhance cardiac function and inhibit cardiac remodeling by improving coronary microvascular function and myocardial perfusion, which are critical for the development of heart failure. However, it is imperative to approach these findings with caution. The retrospective nature of our study introduces the possibility of selection bias and confounding factors, which may limit the direct attribution of clinical outcomes to the improvement of CMD by ticagrelor. While our data suggest a correlation, they do not establish causation. Therefore, prospective studies are necessary to confirm these results and to further elucidate the role of ticagrelor in the management of CMD and its impact on clinical prognosis in AMI patients. Additionally, the ticagrelor group exhibited a higher perioperative use of GP IIb/IIIa inhibitors, potentially attributed to the presence of more complex coronary lesions and an increased risk of stent thrombosis. However, considering the lack of a significant difference in baseline angio-IMR between the groups and the negligible impact of GP IIb/IIIa inhibitors in the multivariate analyses, it is plausible that the influence of GP IIb/IIIa inhibitors on coronary microcirculation function and clinical outcomes may be limited.

Moreover, the sensitivity analyses underscore the consistent and robust predictive value of angio-IMR for both outcomes. However, model 5 stands out as the most informative due to its comprehensive adjustment for covariates. The results obtained from this model not only affirm the independent predictive capability of angio-IMR but also highlight its clinical relevance in forecasting adverse cardiac events. The consistency observed across all models reinforces the conclusion drawn from model 5, solidifying angio-IMR's role as a reliable prognostic tool. Additionally, we observed that ticagrelor treatment may be related to a reduced risk of readmission for heart failure and myocardial reinfarction in several high cardiovascular risk subgroups. While the data indicate potential benefits in specific comorbidities and lesion characteristics, these findings are preliminary and derived from a non-randomized, retrospective analysis. Consequently, the results should not be construed as definitive evidence but rather as hypotheses generating insights that require validation in prospective, randomized studies.

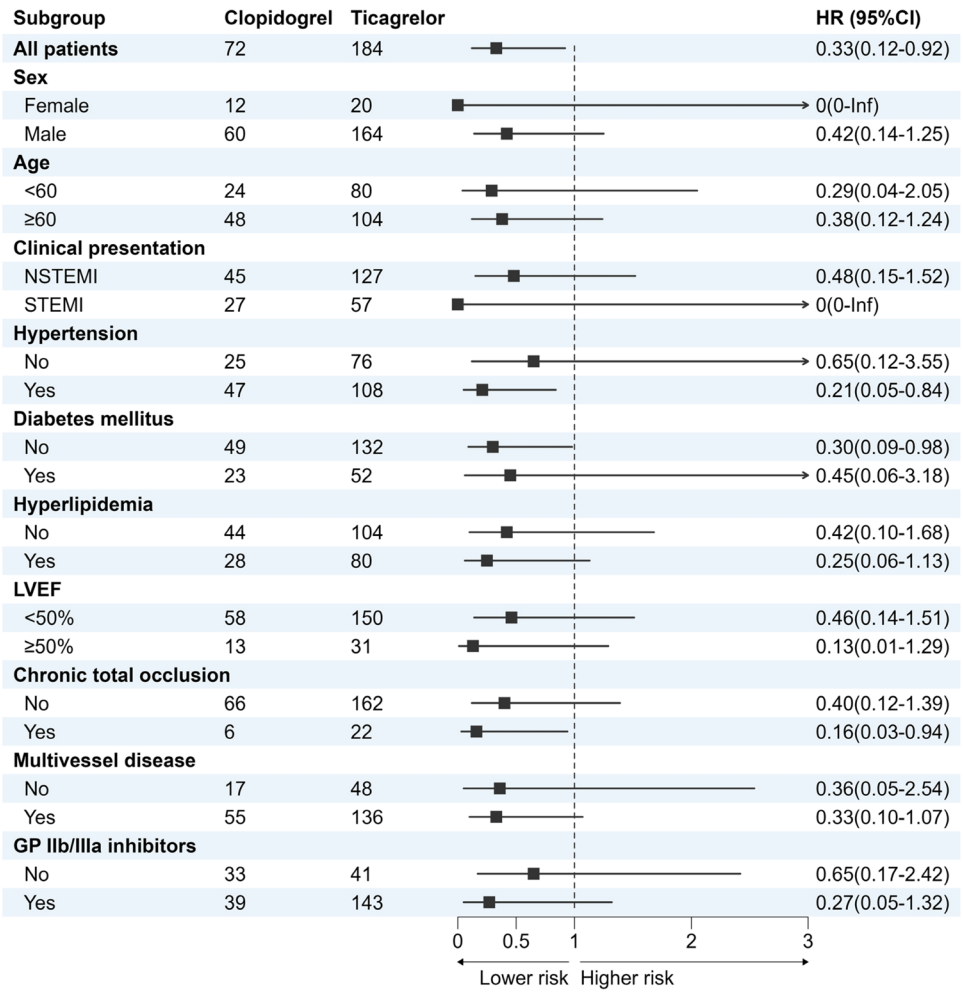

Fig. 9 Subgroup analysis of the effect of ticagrelor and clopidogrel on myocardial reinfarction. *P* values are log-rank *P* values in survival analysis. *CI* confidence interval, *HR* hazard ratio, *NSTEMI* non-ST-segment elevation myocardial infarction, *STEMI* ST-segment elevation myocardial infarction, *LVEF* left ventricular ejection fraction, *GP* glycoprotein

This study leverages a novel, non-invasive approach to measure CMD, characterized by its simplicity in calculation and minimal susceptibility to hemodynamic factors [29]. Additionally, this study excels in its inclusion of a sizable population of AMI patients who received successful PCI, the prospective collection of prognostic data, and long-term follow-up of clinical outcomes. However, certain limitations remained in this study. Firstly, the limited sample size was a result of the exclusion of patients without routine follow-up coronary angiography. Secondly, this was a retrospective observational study and may be susceptible to selection bias, confounding factors, and residual confounding. While our study suggests a correlation between ticagrelor-induced improvement in coronary microvascular function and enhanced clinical outcomes, it does not establish a definitive causal relationship. Therefore, the findings should be interpreted cautiously and validated through prospective randomized trials. Thirdly, our focus was solely on CMD within the culprit vessel territory; thus, the impact of ticagrelor on CMD in the non-culprit vessel territories and its prognostic value remained unclear. Considering the integral role of non-culprit vessel territories in the overall coronary microcirculation, subsequent research is necessary to ascertain their contribution.

Conclusion

In patients with AMI who underwent PCI, ticagrelor maintenance therapy significantly enhanced coronary microvascular function, as evaluated by angio-IMR, and improved cardiovascular prognosis including readmission for heart failure and myocardial infarction during 2-year follow-up compared with clopidogrel. Moreover, ticagrelor emerged as a significant factor in predicting readmission for heart failure. These results indicate that ticagrelor may be a promising therapeutic agent for CMD for improving cardiovascular prognosis in patients with AMI, although further confirmation through prospective clinical studies is warranted.

Author Contribution The authors have all made significant contributions to this study and have given their approval for the final version of the manuscript. Conception and design: Jun Jiang, Yuxuan Zhang, Jiacheng Fang, Xinyi Zhang. Data acquisition: Jiacheng Fang, Yiyue Zheng, Jianping Xiang. Statistical analysis: Jiacheng Fang, Delong Chen, Abuduwufuer Yidilisi, Rui Ji. Data interpretation: Jiacheng Fang, Yuxuan Zhang, Jianping Xiang. Authorship of the final draft: Jiacheng Fang, Jun Jiang. Review and editing: Jiacheng Fang, Yuxuan Zhang, Jun Jiang, Xinyi Zhang.

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Data Availability The data supporting the findings of this research can be obtained from the corresponding author [Jun Jiang], upon reasonable request.

Code Availability Not applicable.

Declarations

Ethics Approval This research was performed with the approval of the Medical Ethics Committee of the Second Affiliated Hospital of Zhejiang University, waiving the need for written informed consent.

Consent to Participate Consent for participation in the study was duly obtained from all the individual participants involved.

Consent for Publication The authors declare that informed consent for the publication of the images depicted in Fig. 1 was obtained from all the individual participants involved.

Competing Interests The authors declare no competing interests.

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