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ORIGINAL RESEARCH

Single-view angiographic microcirculatory resistance index after primary PCI: the EARLY-MYO-AMR study

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ABSTRACT

BACKGROUND: Coronary microvascular dysfunction (CMD) leads to inadequate myocardial perfusion in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI). The index of microcirculatory resistance (IMR) is an intraoperative diagnostic tool for CMD. However, its widespread application is hindered by the requirement for pressure wires and hyperaemic agents. The angiographic microcirculatory resistance (AMR) index is concise, convenient, accurate, and serves as a pressure wire-free alternative to the IMR.

AIMS: This study aimed to demonstrate the ability of AMR to detect CMD in patients with STEMI undergoing PPCI therapy and to assess its predictive value for long-term prognosis.

METHODS: The EARLY-MYO-AMR trial comprised two cohorts. The derivation cohort included 495 patients with STEMI who underwent PPCI within 12 h and cardiac magnetic resonance (CMR) within 14 days of symptom onset. The optimal AMR cutoff value for diagnosing CMD using CMR was determined by analysing the receiver operating characteristic curves. The validation cohort enrolled 2,663 patients with STEMI who underwent PPCI within 12 h of symptom onset from January 2012 to April 2022 across 5 medical centres. All patients were followed up for at least 1 year. The primary endpoint was the occurrence of major adverse cardiovascular events (MACE), including cardiac death, hospitalisation for heart failure, repeat myocardial infarction, and target lesion revascularisation.

RESULTS: The derivation cohort identified an AMR cutoff >26.6 mmHg*s/dm for predicting CMD post-PPCI (area under the curve 0.721, 95% confidence interval [CI]: 0.677-0.763). Multivariable logistic regression analysis indicated that AMR >26.6 mmHg*s/dm was a CMD risk factor (odds ratio 4.10, 95% CI: 2.56-6.56; p<0.001). The MACE incidence was significantly higher among patients in the validation cohort with AMR >26.6 mmHg*s/dm than among those with AMR ≤26.6 mmHg*s/dm (30.9% vs 21.5%, adjusted hazard ratio [HR] 1.47, 95% CI: 1.20-1.80; p<0.001). MACE incidence increased with AMR, with an adjusted HR of 1.30 (95% CI: 1.17-1.46; p<0.001) per 10 mmHg*s/dm increase. The Bland-Altman and Kappa analyses showed good intra- and interobserver agreement for AMR (intraobserver: bias=–0.104, k=0.914; interobserver: bias=–0.032, k=0.958).

CONCLUSIONS: AMR >26.6 mmHg*s/dm predicts CMD during PPCI and increased MACE incidence in patients with STEMI. This convenient tool helps in risk stratification and treatment guidance for STEMI prognosis.

KEYWORDS: angiography microcirculatory resistance; coronary microvascular dysfunction; index of microcirculatory resistance; major adverse cardiovascular events; receiver operating characteristic curve; ST-segment elevation myocardial infarction

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The goal of primary percutaneous coronary intervention (PPCI) is to restore blood flow in the epicardial vessels and achieve effective myocardial perfusion at the tissue level in patients with ST-segment elevation myocardial infarction (STEMI). Coronary microvascular dysfunction (CMD) is an important factor affecting myocardial perfusion in patients with acute STEMI undergoing PPCI[1]. The index of microcirculatory resistance (IMR) is currently the most commonly used method for intraoperative diagnosis of CMD[2]. Numerous studies have demonstrated that a high IMR during PPCI is associated with a poor prognosis[3-5]. However, the measurement of the IMR involves invasive procedures, cumbersome steps, and the need for a pressure wire, which has prevented its widespread adoption as a routine procedure globally and has resulted in many patients with CMD being overlooked. Therefore, a more concise, convenient, and sufficiently accurate method to replace the IMR and improve this situation is needed. In recent years, some microcirculation indices based on angiographic images and calculated using the quantitative flow ratio (QFR) have been explored[6-9], though they all have certain computational limitations, especially regarding vessel bifurcations[10]. Recently, μQFR, based on the single-view Murray's Law, has been developed, and its derived parameter – angiographic microcirculatory resistance (AMR) – has been validated in patients with acute (ACS) and chronic coronary syndromes (CCS)[11]. The AMR is an ideal intraoperative tool for assessing CMD in patients with STEMI. However, no large-sample studies have verified the predictive role of AMR for the prognosis of patients with STEMI. Thus, we designed this study to validate the association between AMR and CMD in STEMI patients after PPCI and to assess the predictive value of AMR for long-term prognosis.

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Impact on daily practice

The EARLY-MYO-AMR study demonstrated that angiographic microcirculatory resistance (AMR) is a reliable, convenient tool for assessing coronary microvascular dysfunction in ST-segment elevation myocardial infarction (STEMI) patients after primary percutaneous coronary intervention (PPCI). An AMR threshold of >26.6 mmHg*s/dm was associated with a higher incidence of major adverse cardiovascular events, primarily driven by cardiac death and hospitalisation for heart failure. These findings suggest that AMR could serve as an alternative tool to the index of microcirculatory resistance for risk stratification in STEMI patients post-PPCI. Incorporating AMR assessment into routine PPCI clinical practice may help identify high-risk patients early and facilitate targeted interventions to improve long-term outcomes.

Methods

STUDY DESIGN AND POPULATION

The EARLY-MYO-AMR study (ClinicalTrials.gov: NCT05653765) conformed with the Declaration of Helsinki and was approved by the ethics committee of each participating hospital. Given the retrospective nature of this study, and with approval from the ethics committees of the respective centres, all patients in the EARLY-MYO-AMR study were exempt from providing written informed consent.

This study included derivation and validation cohorts **(Central illustration)**. Derivation cohort data were obtained from 495 patients enrolled in the EARLY-MYO-CMR study[12] (ClinicalTrials.gov: NCT03768453). The validation cohort, also retrospective, included 2,663 patients who underwent PPCI for STEMI between January 2012 and April 2022 at 5 medical centres: Fuwai Central China Cardiovascular Hospital; Renji Hospital, affiliated with Shanghai Jiao Tong University School of Medicine; First Affiliated Hospital of Xinxiang Medical University; Shangqiu First People's Hospital; and Yongcheng Central Hospital. All patients were followed for at least 12 months, with a median follow-up period of 44 months.

The inclusion criteria were as follows: (1) clinically diagnosed STEMI patients who underwent PPCI within 12 hours of symptom onset; (2) culprit vessel diameter ≥2.5 mm.

Conversely, the exclusion criteria were defined as follows: (1) poor image quality or extreme vessel tortuosity that prevented accurate lesion analysis; (2) inability to identify the culprit vessel; (3) post-PPCI QFR ≤0.80 in the culprit vessel; (4) concomitant dilated cardiomyopathy or severe structural heart disease, such as moderate to severe aortic stenosis/insufficiency, mitral stenosis/insufficiency, congenital ventricular septal defects; (5) absence of dual antiplatelet therapy post-PPCI; (6) post-PPCI Thrombolysis in Myocardial Infarction (TIMI) flow grade 0-1; (7) haemodynamic instability requiring mechanical support after PPCI; (8) history of coronary artery bypass grafting; (9) incomplete clinical data; or (10) loss to follow-up.

CLINICAL FOLLOW-UP

The primary clinical outcome of this study was the occurrence of major adverse cardiovascular events (MACE), defined as a composite of cardiac death, hospitalisation for heart failure, target lesion revascularisation (TLR), and repeat myocardial infarction (MI). The secondary endpoint events included the components of the primary endpoint and all-cause mortality. All deaths were considered cardiac, unless there was a clear alternative cause. Hospitalisation for heart failure was defined

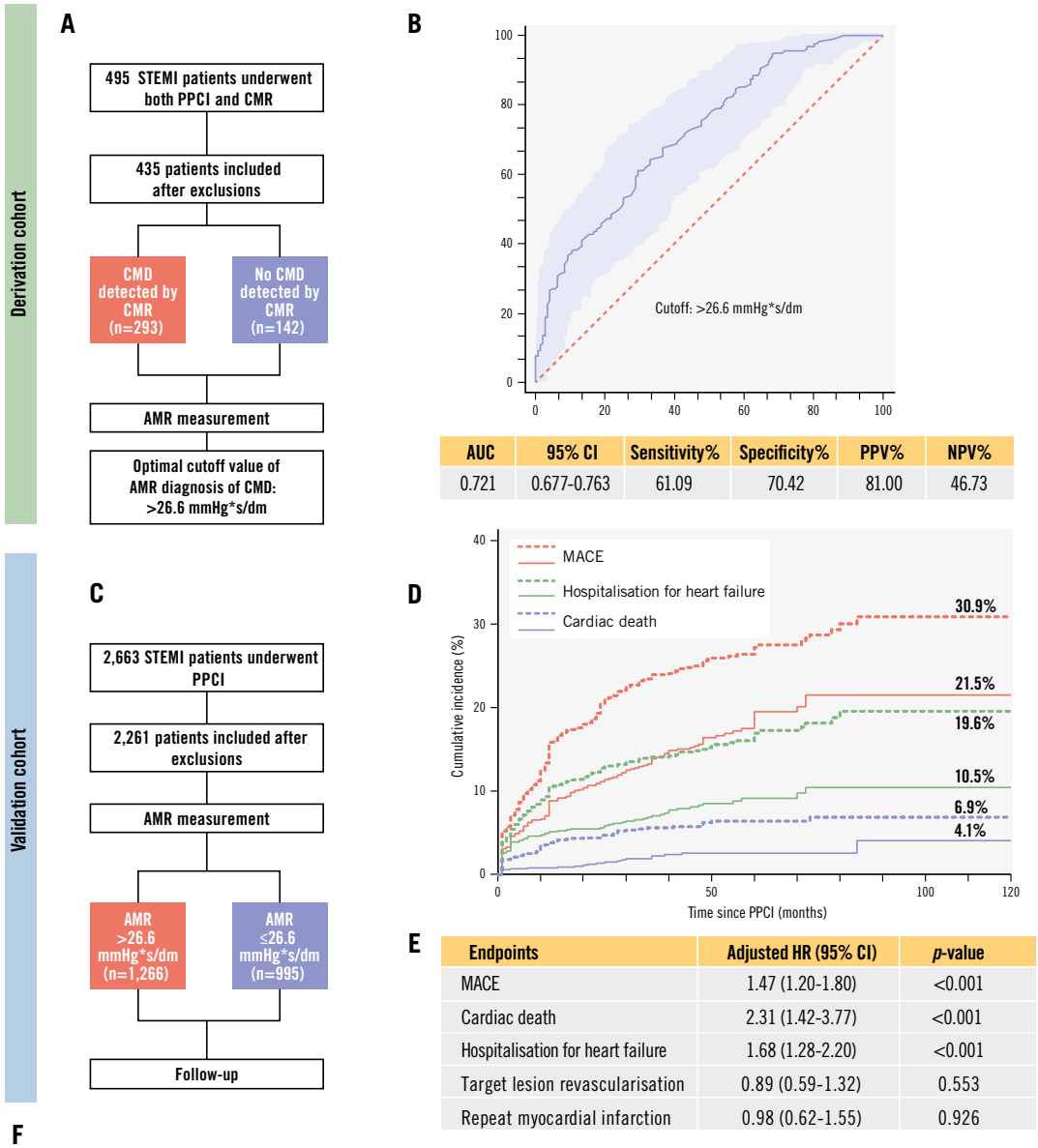
Abbreviations

AMR	angiographic microcirculatory resistance	**MVO**	microvascular obstruction	**SBP**	systolic blood pressure
CMD	coronary microvascular dysfunction	**PPCI**	primary percutaneous coronary intervention	**STEMI**	ST-segment elevation myocardial infarction
CMR	cardiac magnetic resonance	**QFR**	quantitative flow ratio	**TIMI**	Thrombolysis in Myocardial Infarction
IMR	index of microcirculatory resistance	**ROC**	receiver operating characteristic	**TLR**	target lesion revascularisation
MACE	major adverse cardiovascular events				

EuroIntervention — Central Illustration

Study flowchart and key findings of the EARLY-MYO-AMR study.

EARLY-MYO-AMR study



AUC	95% CI	Sensitivity%	Specificity%	PPV%	NPV%
0.721	0.677-0.763	61.09	70.42	81.00	46.73

E

Endpoints	Adjusted HR (95% CI)	*p*-value
MACE	1.47 (1.20-1.80)	<0.001
Cardiac death	2.31 (1.42-3.77)	<0.001
Hospitalisation for heart failure	1.68 (1.28-2.20)	<0.001
Target lesion revascularisation	0.89 (0.59-1.32)	0.553
Repeat myocardial infarction	0.98 (0.62-1.55)	0.926

F

Key findings:

- An AMR threshold of >26.6 mmHg*s/dm effectively identified CMD following PPCI in STEMI patients, with an area under the ROC curve of 0.721 (95% CI: 0.677-0.763).
- STEMI patients with post-PPCI AMR >26.6 mmHg*s/dm had a significantly higher incidence of MACE (30.9% vs 21.5%), with an adjusted 47% increased risk (HR 1.47, 95% CI: 1.20-1.80; $p<0.001$).
- The elevated MACE risk in STEMI patients with high post-PPCI AMR was primarily driven by increased rates of cardiac death and hospitalisation for heart failure.

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*A) Study flowchart of the derivation cohort. B) ROC curve analysis of AMR for the diagnosis of CMD. C) Study flowchart of the validation cohort. D) Kaplan-Meier curves for MACE and its two major contributors. Red represents MACE, green represents hospitalisation for heart failure, and blue represents cardiac death; all solid lines correspond to the AMR ≤26.6 mmHg*s/dm group and dashed lines to the AMR >26.6 mmHg*s/dm group. E) Adjusted hazard ratios for MACE and its individual components. F) Key findings. AMR: angiographic microcirculatory resistance; AUC: area under the curve; CI: confidence interval; CMD: coronary microvascular dysfunction; CMR: cardiac magnetic resonance; HR: hazard ratio; MACE: major adverse cardiovascular events; NPV: negative predictive value; PPCI: primary percutaneous coronary intervention; PPV: positive predictive value; ROC: receiver operating characteristic; STEMI: ST-segment elevation myocardial infarction*

as admission due to new or worsening signs and symptoms of heart failure, together with non-invasive imaging findings or elevated B-type natriuretic peptide (BNP) and/or N-terminal proBNP concentration and a discharge diagnosis of heart failure. Repeat MI was defined according to the Academic Research Consortium-2 Consensus Document[13], which includes elevated markers of myocardial injury along with ischaemic evidence after PPCI. TLR was defined as new stenosis that developed within previously treated coronary segments and within 5 mm of their borders, with corresponding evidence of ischaemia and subsequent treatment by repeat percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). The detailed event definitions are provided in **Supplementary Appendix 1**. Follow-up was conducted through clinic visits, telephone contacts, and medical record reviews. All events were resolved by the Clinical Endpoint Committee, which was blinded to the groups.

CARDIAC MAGNETIC RESONANCE IMAGING

Cardiac magnetic resonance (CMR) imaging was used to assess the myocardium within 14 days of symptom onset, following the protocol outlined in our previous studies[9,12]. The presence of myocardial microvascular obstruction (MVO) or intramyocardial haemorrhage (IMH) detected by CMR indicates coexisting CMD in a patient[14]. See **Supplementary Appendix 1** for detailed CMR protocols.

AMR MEASUREMENT

The final sequence of the eligible angiographic images of the culprit vessel during PPCI was selected, and nitrates were given intracoronarily before angiography to avoid epicardial vasospasm affecting the results of the analysis. Certified analysts with extensive experience performed AMR measurements at a core laboratory using the AngioPlus system (Pulse Medical); they were blinded to the patient grouping, treatment, and clinical outcomes. The detailed measurement methods are described elsewhere[11]. Briefly, images were imported into the software, which automatically outlined vessel contours, including vessel length and branches. The length of the vessel's centreline, divided by the time required for contrast agent filling, provided the contrast flow velocity, which was then converted to hyperaemic flow velocity. The reference vessel diameter was then reconstructed based on the Murray bifurcation fractal law, and the AMR was calculated using the following formula[15], in which Pd is distal coronary artery pressure and Pa is aortic pressure **(Figure 1)**:

$$\mathrm{AMR} = \frac{P_d}{Velocity_{hyp}} = \frac{P_a \times \mu QFR}{Velocity_{hyp}}$$

STATISTICAL ANALYSIS

Continuous variables with a normal distribution are presented as mean±standard deviation (SD). Differences between the two groups were compared using t-tests. Variables without a normal distribution are presented as medians with interquartile ranges (IQR), and group differences were analysed using the Mann-Whitney U test. Receiver operating characteristic (ROC) curves were used to analyse the relationship between AMR and CMD in the derivation cohort and to determine the optimal cutoff value. The cutoff value was calculated using the Youden index. In the derivation cohort, AMR was confirmed as a significant factor in the occurrence of CMD using binary logistic regression, and the variables included in the binary logistic regression were those with a p<0.05 in the univariable analysis. Endpoint event rates during follow-up were compared using log-rank tests. Associations between different variables and clinical events were determined using univariable Cox regression analysis. Significant variables (p<0.05) were included in multivariable Cox regression models to analyse the risk factors influencing prognosis. Intra- and interobserver agreements were assessed using Bland-Altman and kappa analyses. Further, intraobserver variability was analysed by two reviewers who independently assessed the images and were blinded to each other's findings. In contrast, interobserver variability was assessed by the same reviewer by analysing the same image at an interval of at least 3 months. In the validation cohort, AMR was stratified into quartiles due to its non-normal distribution. Univariable analysis was performed to assess the differences in various factors across the quartiles. Factors with a p-value<0.05 in the univariable analysis were included in a multivariable ordinal logistic regression model to explore factors influencing increased AMR. All statistical analyses were performed using R software, version 4.3.2 (R Foundation for Statistical Computing) and SPSS software, version 25.0 (IBM). A p-value<0.05 was considered statistically significant for all analyses.

Results

DERIVATION COHORT

BASELINE CHARACTERISTICS

Patients were excluded from the derivation cohort based on the following criteria: poor AMR image quality (n=8), post-PPCI QFR ≤0.80 (n=11), reperfusion time >12 h (n=4), and CMR >14 days after PPCI (n=37) **(Figure 2)**. Ultimately, data from 435 patients (median age 60 [IQR 54, 65] years, 89.20% male) were analysed. The median time to CMR was 5 (IQR 3, 6) days after PPCI. Among them, 293 and 142 patients were included in the CMD and non-CMD groups. Compared to the non-CMD group, the CMD group exhibited worse Killip classification and lower left ventricular ejection fraction **(Table 1)**.

RELATIONSHIP BETWEEN AMR AND CMD

Among all patients in the derivation cohort, the median AMR was 26.70 (IQR 23.20, 31.05) mmHg*s/dm. The AMR value was significantly higher in the CMD group compared to the non-CMD group (27.80 [IQR 24.40, 32.70] vs 24.15 [IQR 20.60, 27.63] mmHg*s/dm; p<0.001). The ROC curve analysis revealed that an AMR >26.6 mmHg*s/dm was the optimal cutoff for diagnosing CMD (area under the curve=0.721, sensitivity 61.09%, specificity 70.42%) **(Supplementary Figure 1)**. Multivariable logistic regression analysis demonstrated that an AMR >26.6 mmHg*s/dm was an independent risk factor for post-STEMI CMD after adjusting for confounding factors **(Supplementary Table 1)**.

VALIDATION COHORT

BASELINE CHARACTERISTICS

The validation cohort included 2,663 patients from 4 centres. Among them, 130 patients had angiographic images that

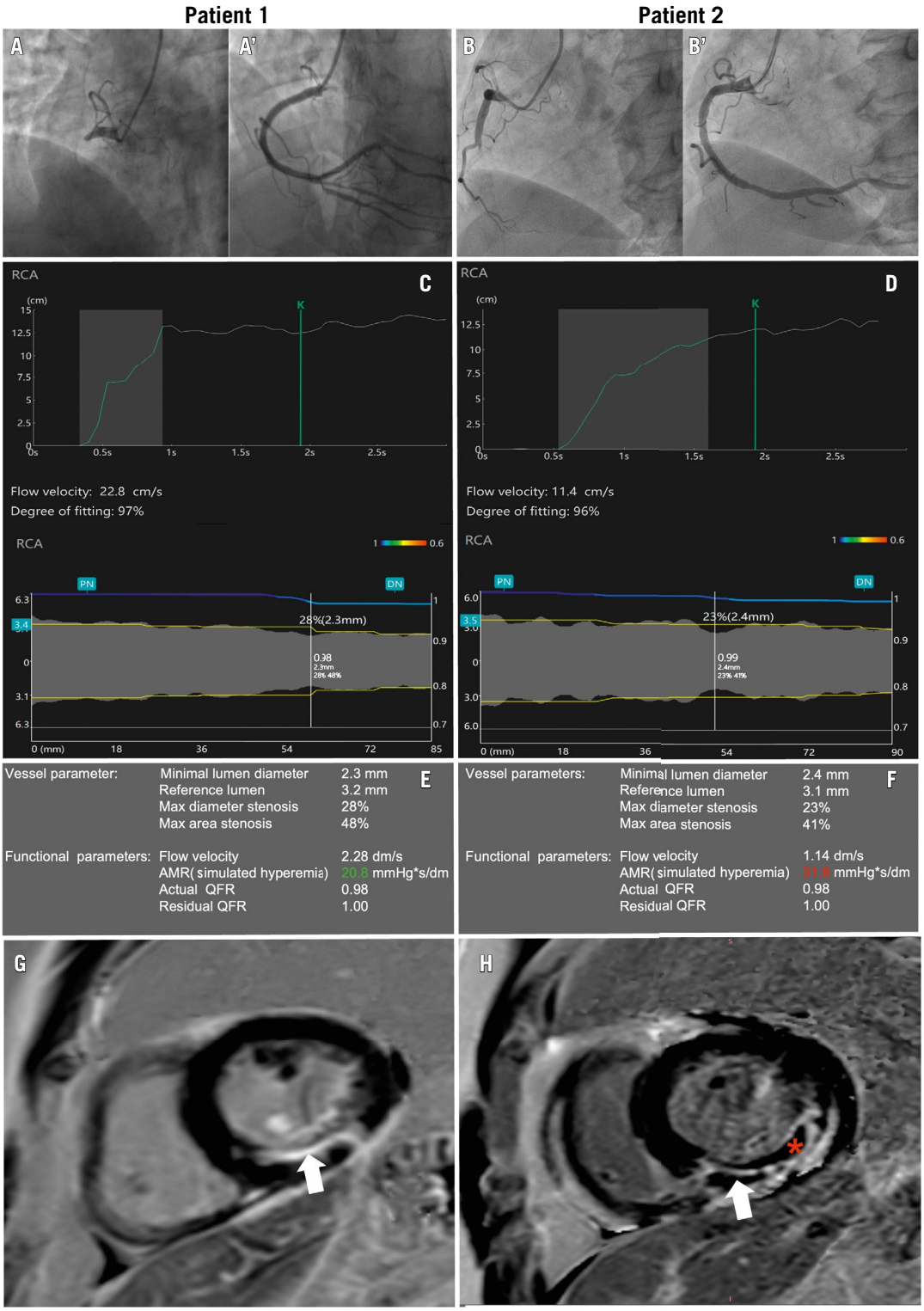

Figure 1. *Measurement of AMR and CMR images. A, B) Pre- and (A', B') post-PPCI angiographic images of two patients with right coronary artery occlusions. C, D) Automated calculation process of flow velocity and vessel diameter. E, F) μQFR and AMR results of the culprit vessels in Patient 1 and Patient 2, respectively. G, H) MVO as identified on CMR using LGE imaging. MVO is defined as a hypointense core (red asterisk) within a region of hyperintense LGE (white arrow), manually delineated on short-axis PSIR slices, obtained 10 minutes after contrast agent injection. G) Patient without MVO. H) Patient with MVO. AMR: angiographic microcirculatory resistance; CMR: cardiac magnetic resonance; LGE: late gadolinium enhancement; MVO: microvascular obstruction; PSIR: phase-sensitive inversion recovery sequence; QFR: quantitative flow ratio; RCA: right coronary artery; μQFR: Murray law-based quantitative flow ratio*

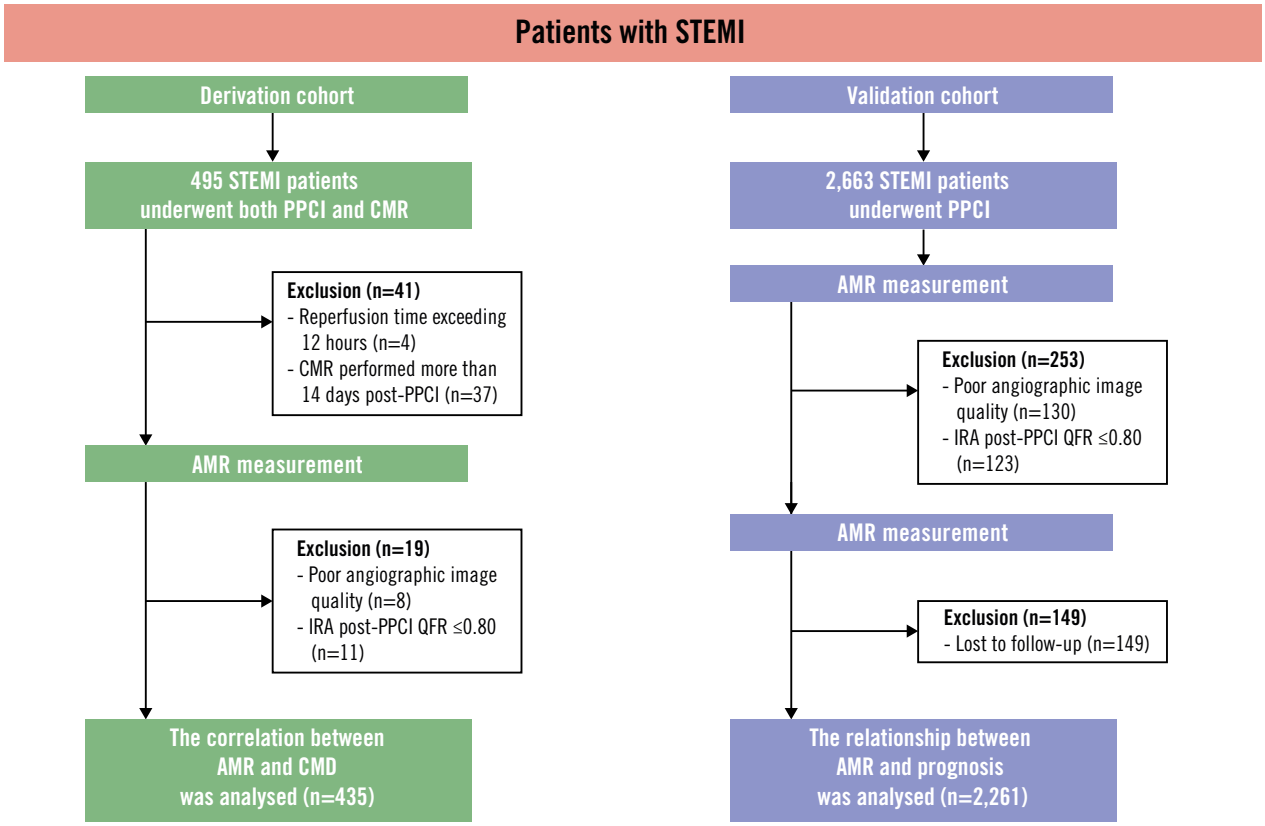

Figure 2. *Study flowchart. The study comprised a derivation cohort and a validation cohort. The derivation cohort was used to determine the optimal cutoff value of AMR for diagnosing CMD. This value was then validated in the validation cohort. AMR: angiographic microcirculatory resistance; CMD: coronary microvascular dysfunction; CMR: cardiac magnetic resonance; IRA: infarct-related artery; PPCI: primary percutaneous coronary intervention; QFR: quantitative flow ratio; STEMI: ST-segment elevation myocardial infarction*

could not be analysed for AMR, 123 had a post-PPCI QFR of ≤0.80, and 149 were lost to follow-up. Ultimately, 2,261 patients were included in the analysis (median age 62 [IQR 52, 69] years, 74.7% male) with a median follow-up time of 44 months **(Table 2, Figure 2)**.

VALIDATION ANALYSES

The CMD group had a significantly higher cumulative incidence of MACE compared to the non-CMD group (30.9% vs 21.5%, adjusted hazard ratio [HR] 1.47, 95% confidence interval [CI]: 1.20-1.80; p<0.001) **(Table 3, Supplementary Table 2, Figure 3)**. In addition, the cumulative incidences of cardiac death (6.9% vs 4.1%, adjusted HR 2.31, 95% CI: 1.42-3.77; p<0.001), hospitalisation for heart failure (19.6% vs 10.5%, adjusted HR 1.68, 95% CI: 1.28-2.20; p<0.001), and all-cause death (9.3% vs 5.8%, adjusted HR 1.82, 95% CI: 1.18-2.80; p=0.007) were higher in patients with an AMR >26.6 mmHg*s/dm than in those with an AMR ≤26.6 mmHg*s/dm. The cumulative incidences of repeat MI and TLR did not differ significantly between the groups **(Table 3, Supplementary Table 3, Figure 3)**. When AMR was used as a continuous variable, MACE incidence increased with AMR (per 10 mmHg*s/dm increase of AMR, adjusted HR 1.30, 95% CI: 1.17-1.46; p<0.001) **(Supplementary Figure 2)**. The results of the subgroup analyses are similar to the full set of analyses, and the specific results are presented in **Supplementary Figure 3**.

REPRODUCIBILITY ANALYSES

We assessed the reproducibility of the AMR measurements in a random sample of 100 patients. The results of the Bland-Altman analyses revealed good consistency of intra- and interobserver AMR measurements (bias: –0.104; p=0.142, and bias: –0.032; p=0.784, respectively). Kappa analysis also showed good intra- and interobserver consistency (k=0.914 and k=0.958, respectively; p<0.001 for both).

ADDITIONAL ANALYSES

To explore the factors contributing to elevated AMR, and considering its non-normal distribution, AMR was categorised into quartiles **(Supplementary Table 4)**. Multivariable logistic regression **(Supplementary Table 5)** revealed several factors significantly associated with increased AMR. Age (odds ratio [OR] 1.01, 95% CI: 1.00-1.02; p=0.013) and prolonged ischaemia time (OR 1.05, 95% CI: 1.02-1.07; p<0.001) were associated with increased AMR, as were hypertension (OR 2.62, 95% CI: 2.14-3.21; p<0.001) and high thrombus burden (OR 2.19, 95% CI: 1.82-2.65; p<0.001). Pre-PPCI TIMI flow grades <3 were strongly associated with higher

Table 1. Baseline characteristics of the derivation cohort.

	Total (n=435)	No CMD (n=142)	CMD (n=293)	*p*-value
Age, years	60.00 [54.00, 65.00]	61.00 [56.00, 66.00]	59.00 [54.00, 65.00]	0.046
Male	388 (89.20)	122 (85.92)	266 (90.78)	0.125
BMI, kg/m²	24.58 [22.86, 26.45]	25.02 [23.23, 26.57]	24.51 [22.72, 26.30]	0.245
HR, bpm	76.00 [67.00, 87.00]	73.50 [65.00, 82.00]	78.00 [67.00, 88.00]	0.022
SBP, mmHg	134.62 (20.75)	134.86 (20.91)	134.50 (20.71)	0.867
DBP, mmHg	80.00 [72.00, 93.00]	79.00 [73.00, 88.00]	83.00 [72.00, 94.00]	0.036
Hypertension	220 (50.57)	64 (45.07)	156 (53.24)	0.110
Diabetes mellitus	130 (29.89)	40 (28.17)	90 (30.72)	0.586
Smoking	291 (66.90)	89 (62.68)	202 (68.94)	0.193
Hyperlipidaemia	202 (46.44)	57 (40.14)	145 (49.49)	0.067
CKD	10 (2.30)	3 (2.11)	7 (2.39)	0.999
LVEF, %	53.03 [46.22, 61.23]	59.05 [51.66, 64.79]	50.84 [43.12, 58.04]	<0.001
STB time, hours	4.60 [3.40, 6.25]	4.78 [3.40, 6.81]	4.58 [3.37, 6.00]	0.479
Culprit vessel				0.181
LAD	276 (63.45)	94 (66.20)	182 (62.12)	
LCx	33 (7.59)	6 (4.22)	27 (9.21)	
RCA	126 (28.96)	42 (29.58)	84 (28.67)	
Killip heart function classification				<0.001
I	324 (74.48)	122 (85.92)	202 (68.94)	
II-IV	111 (25.52)	18 (14.08)	70 (31.06)	
Number of stents				0.303
0	15 (3.45)	6 (4.23)	9 (3.07)	
1	322 (74.02)	103 (72.54)	219 (74.74)	
2	92 (21.15)	29 (20.42)	63 (21.50)	
3	6 (1.38)	4 (2.82)	2 (0.68)	
Occlusion position				0.831
Proximal	224 (51.49)	76 (53.52)	148 (50.51)	
Middle	199 (45.75)	62 (43.66)	137 (46.76)	
Distal	12 (2.76)	4 (2.82)	8 (2.73)	
Multivessel disease	242 (55.63)	81 (57.04)	161 (54.95)	0.680
TIMI flow pre-PCI				0.367
0	286 (65.75)	86 (60.56)	200 (68.26)	
1	44 (10.11)	18 (12.68)	26 (8.87)	
2	34 (7.82)	11 (7.75)	23 (7.85)	
3	71 (16.32)	27 (19.01)	44 (15.02)	
High thrombus burden	309 (71.03)	97 (68.31)	212 (72.35)	0.383
Thrombus aspiration	102 (23.45)	26 (18.31)	76 (25.94)	0.078
AMR, mmHg*s/dm	26.70 [23.20, 31.10]	24.15 [20.60, 27.73]	27.80 [24.40, 32.75]	<0.001
μQFR	0.96 [0.93, 0.98]	0.95 [0.92, 0.97]	0.96 [0.93, 0.98]	0.075
Blood flow velocity, dm/s	1.46 [1.14, 1.78]	1.67 [1.38, 2.08]	1.30 [1.04, 1.70]	<0.001

Values are n (%) or mean [interquartile range]. AMR: angiographic microcirculatory resistance; BMI: body mass index; CKD: chronic kidney disease; CMD: coronary microvascular dysfunction; DBP: diastolic blood pressure; HR: heart rate; LAD: left anterior descending artery; LCx: left circumflex artery; LVEF: left ventricular ejection fraction; RCA: right coronary artery; SBP: systolic blood pressure; STB: symptom-to-balloon; TIMI: Thrombolysis in Myocardial Infarction; μQFR: Murray law-based quantitative flow ratio

AMR: TIMI 0 (OR 1.52, 95% CI: 1.25-1.84; p<0.001), TIMI 1 (OR 2.21, 95% CI: 1.51-3.23; p<0.001), and TIMI 2 (OR 2.04, 95% CI: 1.51-2.76; p<0.001). Thrombus aspiration (OR 0.70, 95% CI: 0.56-0.87; p=0.001), higher systolic blood pressure (SBP; OR 0.99, 95% CI: 0.98-0.99; p<0.001) and ticagrelor use (OR 0.58, 95% CI: 0.40-0.85; p=0.006) were associated with lower AMR.

Discussion

This study investigated the predictive value of AMR as a novel non-invasive microcirculatory resistance measurement tool for assessing CMD and long-term prognosis in patients with STEMI treated with PPCI. Our findings were as follows: (1) AMR >26.6 mmHg*s/dm was identified as the optimal cutoff value for diagnosing

Table 2. Baseline characteristics of the validation cohort.

	Total (n=2,261)	AMR ≤26.6 mmHg*s/dm	AMR >26.6 mmHg*s/dm	*p*-value
Age, years	62.00 [52.00, 69.00]	61.00 [51.00, 69.00]	63.00 [54.00, 70.00]	<0.001
Male	1,689 (74.70)	765 (76.88)	924 (72.99)	0.034
BMI, kg/m²	25.52 [23.63, 27.65]	25.65 [23.66, 27.76]	25.46 [23.60, 27.57]	0.256
HR, bpm	76.00 [66.00, 88.00]	77.00 [67.00, 88.00]	76.00 [65.00, 88.00]	0.467
SBP, mmHg	126.00 [110.00, 143.00]	128.00 [112.00, 144.00]	124.50 [110.00, 141.00]	0.001
DBP, mmHg	78.00 [68.00, 90.00]	79.00 [70.00, 91.00]	77.00 [67.00, 89.00]	0.002
Hypertension	1,132 (50.07)	415 (41.71)	717 (56.64)	<0.001
Diabetes mellitus	590 (26.09)	266 (26.73)	324 (25.59)	0.540
Smoking	1,122 (49.62)	514 (51.66)	608 (48.03)	0.086
CKD	65 (2.87)	28 (2.81)	37 (2.92)	0.878
MI history	50 (2.21)	24 (2.41)	26 (2.05)	0.666
STB time, hours	5.00 [3.00, 7.00]	4.60 [2.92, 6.00]	5.00 [3.00, 8.00]	<0.001
Killip heart function classification				0.004
I	1,344 (59.44)	625 (62.81)	719 (56.79)	
II-IV	917 (40.56)	370 (37.19)	547 (43.21)	
Culprit vessel				0.123
LAD	1,112 (49.18)	487 (48.94)	625 (49.37)	
LCx	268 (11.85)	104 (10.45)	164 (12.95)	
RCA	881 (38.97)	404 (40.60)	477 (37.68)	
Number of stents				0.846
0	185 (8.18)	86 (8.64)	99 (7.82)	
1	1,776 (78.55)	782 (78.59)	994 (78.52)	
2	283 (12.52)	120 (12.06)	163 (12.88)	
3	17 (0.75)	7 (0.70)	10 (0.79)	
Occlusion position				0.244
Proximal	1,096 (48.47)	464 (46.63)	632 (49.92)	
Middle	853 (37.73)	384 (38.59)	469 (37.05)	
Distal	312 (13.80)	147 (14.77)	165 (13.03)	
Multivessel disease	506 (22.38)	237 (23.82)	269 (21.25)	0.160
TIMI flow pre-PPCI				<0.001
0	1,506 (66.61)	657 (66.03)	849 (67.06)	
1	112 (4.95)	37 (3.72)	75 (5.92)	
2	203 (8.98)	63 (6.33)	140 (11.06)	
3	440 (19.46)	238 (23.92)	202 (15.96)	
High thrombus burden	1,759 (77.80)	687 (69.05)	1,072 (84.68)	<0.001
Thrombus aspiration	325 (14.40)	174 (17.49)	151 (11.93)	<0.001
AMR, mmHg*s/dm	27.80 [23.00, 33.40]	22.50 [19.90, 24.40]	32.70 [29.50, 37.38]	<0.001
μQFR	0.96 [0.92, 0.98]	0.93 [0.88, 0.96]	0.97 [0.94, 0.98]	<0.001
Blood flow velocity, dm/s	1.34 [1.00, 1.79]	1.84 [1.61, 2.15]	1.05 [0.82, 1.25]	<0.001
Medication use				
GPIIb/IIIa inhibitor	1,787 (79.04)	786 (78.99)	1,001 (79.07)	0.966
Statin	2,229 (98.58)	980 (98.49)	1,249 (98.66)	0.742
Aspirin	2,250 (99.51)	995 (100.00)	1,255 (99.13)	0.003
Ticagrelor	2,143 (94.78)	963 (96.78)	1,180 (93.21)	<0.001
Clopidogrel	118 (5.22)	32 (3.22)	86 (6.79)	<0.001
ACEi/ARB/ARNI	2,200 (97.30)	971 (97.59)	1,229 (97.08)	0.457
β-blocker	2,220 (98.19)	976 (98.09)	1,244 (98.26)	0.761

Values are n (%) or mean [interquartile range]. ACEi: angiotensin-converting enzyme inhibitor; AMR: angiographic microcirculatory resistance; ARB: angiotensin II receptor blockers; ARNI: angiotensin receptor-neprilysin inhibitors; BMI: body mass index; CKD: chronic kidney disease; DBP: diastolic blood pressure; GP: glycoprotein; HR: heart rate; LAD: left anterior descending artery; LCx: left circumflex artery; PPCI: primary percutaneous coronary intervention; RCA: right coronary artery; SBP: systolic blood pressure; STB: symptom-to-balloon; TIMI: Thrombolysis in Myocardial Infarction; μQFR: Murray law-based quantitative flow ratio

Table 3. Cox regression analysis of clinical events in the validation cohort.

	Univariable		Multivariable	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
MACE	1.66 (1.37-2.02)	<0.001	1.47 (1.20-1.80)	<0.001
Cardiac death	2.63 (1.63-4.24)	<0.001	2.31 (1.42-3.77)	<0.001
Hospitalisation for heart failure	1.97 (1.51-2.57)	<0.001	1.68 (1.28-2.20)	<0.001
Target lesion revascularisation	1.07 (0.73-1.57)	0.739	0.89 (0.59-1.32)	0.553
Repeat myocardial infarction	1.15 (0.75-1.76)	0.514	0.98 (0.62-1.55)	0.926
All-cause death	2.10 (1.39-3.17)	<0.001	1.82 (1.18-2.80)	0.007

CI: confidence interval; HR: hazard ratio; MACE: major adverse cardiovascular events

CMD in patients with STEMI treated with PPCI. 2) The incidence of MACE was significantly higher among patients with STEMI and an AMR >26.6 mmHg*s/dm compared to those with an AMR ≤26.6 mmHg*s/dm after PPCI. 3) AMR demonstrated good reproducibility and served as a convenient intraoperative diagnostic tool for CMD. 4) Age, prolonged ischaemia time, hypertension, and lower pre-PPCI TIMI flow grades were independently associated with elevated AMR, while thrombus aspiration, higher SBP, and ticagrelor use correlated with lower AMR.

Although PPCI successfully restores the epicardial blood flow in patients with STEMI, myocardial perfusion at the microcirculatory level is crucial. During CMD, microvascular spasm, oedema, blockage, or endothelial cell death in the myocardium leads to inadequate restoration of blood supply[1]. This can result in increased infarct size, decreased cardiac function, and increased rates of adverse events[16]. Therefore, it is crucial to identify CMD during PPCI and perform appropriate, timely interventions to improve a patient's prognosis.

Traditional angiographic methods such as TIMI flow, corrected TIMI frame count, and myocardial blush grade are subjective, have relatively poor repeatability, and are inappropriate for directly assessing microvascular dysfunction[1,17,18]. Although non-invasive examinations such as CMR and positron emission tomography-computed tomography can accurately detect microvascular dysfunction, their application in catheterisation laboratories is impractical due to time, cost, and spatial limitations[19,20]. The IMR is more accurate, repeatable, and provides real-time results. An elevated IMR after PPCI in patients with STEMI affects prognosis[3-5]. Although using the IMR as a risk assessment tool for patients after STEMI appears beneficial, the need for intraoperative equipment changes and vasodilators increases the risk of prolonging the operating duration, hypotension, and arrhythmia[21]. Furthermore, the IMR can only be measured intraoperatively and cannot be repeated postoperatively. These limitations hinder widespread application of the IMR.

Previous studies explored alternative pressure wire-free tools derived from angiography to assess microcirculatory resistance as a replacement for the IMR. These methods calculate QFR based on angiography and estimate microcirculatory resistance using blood flow velocity and aortic pressure. While they avoid the need for dedicated wires for IMR measurement and intraoperative detection, at least two angiographic views (>25°) per vessel should be acquired, resulting in increased contrast agent usage and procedural complexity[6-9]. These methods also assume that the reference lumen of the coronary artery narrows linearly from the proximal to the distal end, which can lead to inaccurate QFR results in vessels with multiple branches and miscalculated microcirculatory resistance[11]. These limitations restrict the widespread adoption of these techniques. In contrast, the AMR applied herein uses a μQFR calculation based on Murray's law and only requires a single view[22]. The maximum hyperaemic flow velocity was then algorithmically determined at rest[15]. These features eliminate the need for vasodilators, leading to faster (<1 min/vessel) and more accurate measurement, and the learning curve is short. The consistency between AMR and the IMR has been demonstrated[11].

In the derivation cohort, a cutoff value of >26.6 mmHg*s/dm was found to be the most appropriate for predicting CMD, which was subsequently validated in the validation cohort. Notably, spline-based Cox regression analysis determined that an optimal AMR threshold of >27.6 mmHg*s/dm was the most appropriate for predicting MACE **(Supplementary Figure 2)**, closely aligning with the derivation cohort findings. In the present study, the cutoff value for AMR was lower than that employed in previous studies using the IMR as an indicator. Most of these studies used a cutoff value of 40[2,23,24]. Given the good agreement between AMR and the IMR, the lower values were not due to inaccuracies in assessing microcirculatory resistance using AMR[11]. Meanwhile, our study demonstrated a significant increase in the incidence of MACE in patients in the derivation cohort with an AMR >26.6 mmHg*s/dm, which is numerically similar to the results of a recently published study in a smaller sample of patients. In that study, AMR was associated with prognosis in patients with STEMI using a cutoff of 25 mmHg*s/dm[25]. A lower threshold value helps reduce the likelihood of missing a diagnosis of CMD after PPCI and allows for early intervention during the procedure.

In the additional analysis, we explored the factors associated with elevated AMR in the validation cohort. These factors are generally consistent with previous studies. Advanced age is a known risk factor for coronary microvascular dysfunction[24]. In this study, we identified hypertension as a risk factor for elevated AMR. However, higher SBP during PPCI was associated with lower AMR values. These findings are not contradictory. Extensive

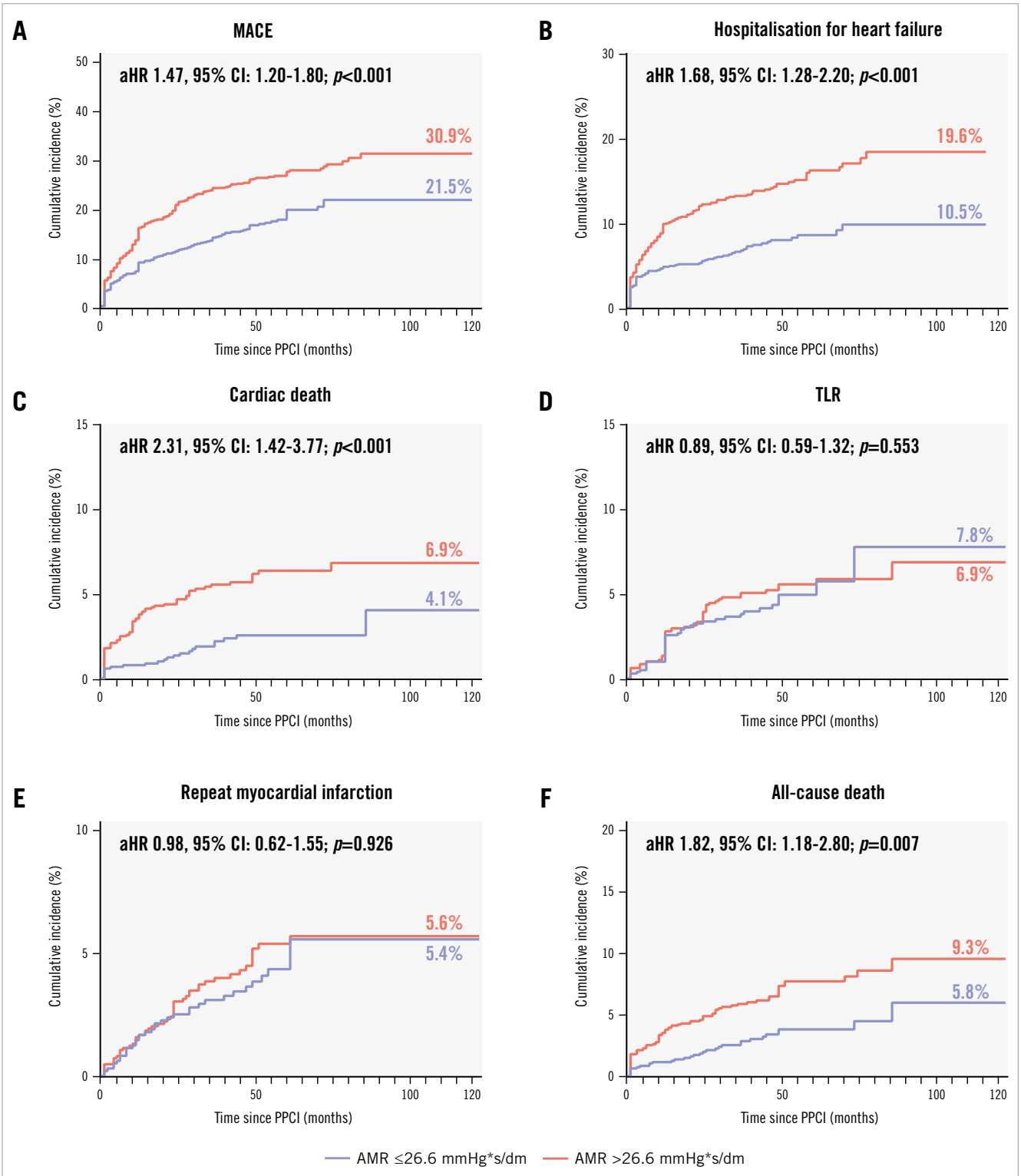

Figure 3. *Kaplan-Meier survival curves for the endpoint events. A) MACE; (B) hospitalisation for heart failure; (C) cardiac death; (D) TLR; (E) repeat myocardial infarction; (F) all-cause death. aHR: adjusted hazard ratio; AMR: angiographic microcirculatory resistance; CI: confidence interval; MACE: major adverse cardiovascular events; PPCI: primary percutaneous coronary intervention; TLR: target lesion revascularisation*

research has shown that hypertension contributes to endothelial injury[26], which in turn increases microcirculatory resistance and raises AMR. However, in STEMI patients, maintaining higher blood pressure is a critical strategy to sustain myocardial perfusion. Adequate myocardial perfusion helps mitigate microvascular damage, reduce

microcirculatory resistance, and consequently lower AMR. Previous studies have also confirmed that higher SBP levels at admission in STEMI patients are associated with a better prognosis[27,28]. Patients with low pre-PPCI TIMI flow grades and prolonged symptom-to-balloon times experience longer periods of myocardial ischaemia or hypoperfusion, leading to more severe injury and necrosis of endothelial and smooth muscle cells in the infarcted area, thereby exacerbating microvascular dysfunction[29]. Patients with high thrombus burden are more likely to experience distal embolisation during PPCI[30]. Thrombus aspiration, although not routinely recommended by current guidelines, can effectively reduce AMR by preventing distal embolism in patients with a high thrombus load[31]. Regarding perioperative antiplatelet therapy, both ticagrelor and clopidogrel are adenosine diphosphate (ADP) inhibitors; however, ticagrelor was associated with lower AMR. This may be due to ticagrelor's ability to more rapidly inhibit platelet aggregation, increase plasma adenosine concentration to enhance coronary blood flow, and inhibit ADP-induced vascular smooth muscle contraction, thereby reducing vascular spasm[32].

Diabetes, a traditional risk factor[33], was not found to be associated with increased AMR or CMD detected by CMR in the derivation cohort. Possible reasons for this include the following: (1) the relationship between CMD and diabetes is complex. Diabetes predisposes patients to CMD during STEMI, but CMD is also influenced by various factors such as age, blood pressure, thrombus burden, ischaemic duration, and procedural interventions, making diabetes not the sole determinant. 2) Cardiovascular damage in diabetes is multifaceted. In addition to its detrimental effects on microvascular function, diabetes also promotes the narrowing of epicardial vessels and the instability of plaques[34]. 3) Due to the retrospective nature of the study, accurate data on patients' blood glucose levels and use of antidiabetic medications prior to STEMI admission were difficult to obtain.

Limitations

The study had the following limitations. First, this was a retrospective study subject to recall bias and lacking a standardised PPCI protocol, particularly in the pharmacological or mechanical management of slow flow/no-reflow phenomena, which may have introduced operator-dependent confounding. A prospective, multicentre, randomised controlled trial with standardised PPCI protocols and AMR-guided interventions is required to further validate the findings of this study. Second, although AMR requires only one projection view, accurate AMR cannot be obtained in approximately 5% of patients due to excessive vessel tortuosity or poor angiographic quality. Third, while CMR remains the most accurate non-invasive method for detecting structural microvascular injury such as MVO and IMH after STEMI, they do not directly measure dynamic microvascular function. Future studies should compare AMR with a functional index, such as myocardial flow reserve assessed by positron emission tomography. Fourth, we excluded patients with a μQFR ≤0.80 after PPCI, and these patients require further investigation.

Conclusions

In conclusion, AMR can be utilised to predict the occurrence of CMD in STEMI patients undergoing PPCI. Furthermore, an increased incidence of MACE has been observed in patients with an AMR >26.6 mmHg*s/dm. This convenient CMD assessment tool has the potential to assist in risk stratification and provide therapeutic guidance, thereby improving the prognosis of STEMI patients.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Supplementary methods.
Supplementary Table 1. Logistic regression analysis of risk factors for CMD.
Supplementary Table 2. Independent predictors for MACE in the validation cohort.
Supplementary Table 3. Log-rank analysis of clinical events over 10 years of follow-up in the validation cohort.
Supplementary Table 4. Baseline data of each group after categorising AMR into quartiles.
Supplementary Table 5. Ordinal logistic regression of increased AMR.
Supplementary Figure 1. ROC curve for AMR diagnosis of CMD.
Supplementary Figure 2. Spline-based Cox regression analysis according to AMR for MACE.
Supplementary Figure 3. Forest plot for subgroup analysis.
Data availability statement.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-00952

Supplementary data

Supplementary Appendix 1. Supplementary methods.

1.1 Definition of endpoint events：

Cardiac death:
All cause deaths will be considered cardiac unless a definite noncardiac cause can be established.

Hospitalization for heart failure:
Hospitalization for heart failure was defined as admission because of new or deteriorating signs and symptoms of heart failure combined with the findings of noninvasive imaging or elevated B-type natriuretic peptide(BNP) and/or N-terminal pro-BNP concentration, and a discharge diagnosis of congestive heart failure.
1) Symptoms of heart failure
·Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea, nocturnal cough in supine position, tachypnea);
·Decreased exercise tolerance (reduced ability to perform activities that involve dynamic movement of large skeletal muscles because of symptoms of dyspnea or fatigue);
·Fatigue (usually described as feeling a lack of energy and motivation in both mental and physical activities, easily tiring and not being able to complete usual activities, and sometimes accompanied by dizziness, lightheadedness);
·Worsened end-organ perfusion (worsening cerebral, renal, liver, abdominal or gastrointestinal, peripheral circulatory function manifested by symptoms such as dizziness, lightheadedness, syncope, confusion, altered mental status, restlessness, decline in cognitive state, nausea, vomiting, abdominal pain, abdominal fullness, abdominal discomfort or abdominal tenderness, cold clammy extremities, discoloration of extremities or lips, jaundice, pain in extremities, reduced urine output, darkening of urine color, chest pain, and/or palpitations);
2) Signs of heart failure:
·Peripheral edema (swelling or pitting indentation when pressed in feet, ankles, legs, thighs, upper extremities, scrotum, presacral area, or abdominal wall);
·Increasing abdominal distention or ascites (in the absence of primary hepatic disease)
·Pulmonary rales/crackles/crepitations;
·Increased jugular venous pressure and/or hepatojugular reflux;
·S3 gallop
·Clinically significant or rapid weight gain thought to be related to fluid retention.
3) Non-invasive imaging
·Echocardiography: Progressive decline in left ventricular ejection fraction (LVEF); Left atrial and/or left ventricular dilation; Increased left ventricular end-diastolic volume (LVEDV) and diameter (LVEDD); Elevated E/e' ratio, indicating increased left ventricular filling pressure

·Chest X-ray or Lung Ultrasound: Worsening pulmonary congestion and interstitial edema; Increased B-lines on lung ultrasound, suggesting pulmonary congestion

Target lesion revascularization(TLR):
The following 3 conditions need to be met at the same time:
1) The new stenosis that developed within previously treated coronary segments and within 5 mm of their borders;
2) The new stenosis resulted in the vessel μQFR ≤ 0.80;
3) The patient subsequently underwent repeat PCI or coronary artery bypass grafting (CABG).

Repeated myocardial infarction:
1) Myocardial infarction within 48 hours post-PPCI:
Absolute rise in cardiac troponin (from baseline) ≥35 times the upper reference limit(in cases where cardiac troponin is unavailable, a CK-MB level exceeding 10 times the upper reference limit is considered abnormal).
Plus at least one of the following criteria:
• New significant Q waves or equivalent (Q-wave criteria requires the development of new Q waves ≥40 ms in duration and ≥1 mm deep in voltage in ≥2 contiguous leads.);
·Flow-limiting angiographic complications, such as coronary dissection, occlusion of a major epicardial artery or a side branch occlusion/thrombus, disruption of collateral flow, or distal embolization.
·New "substantial" loss of myocardium on imaging, such as echocardiography, left ventricular contrast angiography, nuclear perfusion imaging, cardiovascular magnetic resonance and cardiac computed tomography.
2) Myocardial infarction after 48 hours post-PPCI:
Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and with atl east one of the following:
·Symptoms of acute myocardial ischaemia;
·New ischaemic ECG change
·Development of pathological Q waves;
·Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;
·Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy.

1.2 Clinical Endpoint Committee

1) Composition and Qualifications:
Member list:
Feng Cao, PhD, Department of Cardiovascular Medicine, Second Medical Centre, General Hospital of the People's Liberation Army, China;

Weixian Yang, PhD, Department of Cardiovascular Medicine, FuWai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences, China;
Dongmei Shi, PhD, Department of Cardiovascular Medicine, Beijing Anzhen Hospital of Capital Medical University, China.

All three experts have extensive clinical practice and clinical research experience, and they have previously served as members of CEC in other studies.

2) Adjudication Process
The independent CEC received de-identified medical records and was blinded to the AMR values of the culprit vessel to ensure the objectivity of the assessment. Each event was initially reviewed independently by each member. Where there were differences of opinion, consensus was reached through discussion.

1.3 The definition of high thrombosis burden:
Thrombus load was categorized according to the TIMI thrombus grade(TTG) before the wire crossed the lesion, and TTG grades 3-5 were considered high thrombus load.
TIMI thrombus grading (TTG):
Grade 0, no thrombus shadow under contrast;
Grade 1, suspected thrombus, manifested by blurred luminal visualization under contrast, cloudy shadow, irregular contour of the lesion or smooth crescent-shaped image of the completely occluded site protruding from the lumen suggestive of but unable to confirm the diagnosis of thrombus;
Grade 2, clear presence of thrombus, linear dimension $\leqslant$ 1/2 vessel diameter;
Grade 3, definite presence of thrombus with a linear dimension of 1/2 to 2 times the vessel diameter;
Grade 4, definite presence of thrombus, linear dimension $\geqslant$ 2 times the vessel diameter;
Grade 5, thrombus formation leading to complete occlusion.

1.4 CMR Examination Protocol
Contrast-enhanced CMR was performed on a 3.0-T scanner (Achieva TX, Philips Healthcare, Best, The Netherlands) within a median of 5 days after reperfusion. All sequences were acquired in breath-hold with a field of view at 350 × 350 mm2 . Two experienced readers blinded to the clinical data inspected the CMR results with validated software (QMass MR 7.5, Medis, Leiden, The Netherlands). Acquired images were used to determine the ventricular parameters and to calculate the left ventricular ejection fraction (LVEF). Ten minutes after a bolus intravenous administration of contrast agent (0.2 mmol/kg, Magnevist, Bayer HealthCare Pharmaceuticals, Inc. Germany), late gadolinium enhancement was detected using a 3D inversion recovery segmented gradient echo sequence covering the whole left ventricle (TR/TE 3.5/1.7 ms, temporal resolution 190 ms,voxel size 1.5×1.7×10 mm3 interpolated into 0.74×0.74×5 mm3). Infarction was determined as a hyper-enhanced myocardium (a signal

intensity >5 SDs of normal myocardium) and the size of infarction then was normalized to the left ventricular mass (%LV). Microvascular Obstruction (MVO) was determined as hypo-enhanced areas within the infarcted zone. The presence of Intramyocardial Hemorrhage (IMH) was characterized by hypointense areas within the brighter edematous zone on T2-STIR images. The presence of MVO or IMH recognised manifestations of persistent microvascular dysfunction, was defined as the reference diagnosis of MVD.

Supplementary Table 1. Logistic regression analysis of risk factors for CMD.

	OR (95% CI)	P
AMR>26.6 mmHg*s/dm	4.10(2.56-6.56)	<0.001
Age (per 1 year increase)	0.97(0.95-1.01)	0.058
HR (per 1 bpm increase)	1.00(0.99-1.02)	0.562
DBP (per 1 mmHg increase)	1.02(1.01-1.04)	0.009
LVEF (per 1% increase)	0.94(0.92-0.96)	<0.001
Killip heart function classification II-IV	1.88(1.03-3.42)	0.039

CMD: coronary microvascular dysfunction; AMR: angiographic microcirculatory resistance; HR: heart ratio; OR: odds ratio; CI: confidence interval; DBP: diastolic blood pressure; LVEF: left ventricular ejection fraction.

Supplementary Table 2. Independent predictors for MACE in the validation cohort.

	Univariable		Multivariable	
	HR (95% CI)	P	HR (95% CI)	P
AMR>26.6 mmHg*s/dm	1.66(1.37–2.02)	<0.001	1.47(1.20–1.80)	<0.001
Woman	1.53(1.26–1.87)	<0.001	1.34(1.05–1.71)	0.020
Age (per 1 year)	1.02(1.01–1.03)	<0.001	1.02(1.01–1.03)	0.001
BMI	0.99(0.96-1.02)	0.340		
Killip heart function classification II-IV	1.40(1.16-1.68)	<0.001	1.20(0.99-1.46)	0.054
Culprit vessel-LCX (reference LAD)	0.71(0.52–0.98)	0.035	0.77(0.54–1.06)	0.107
Culprit vessel-RCA (reference LAD)	0.78(0.64–0.95)	0.015	0.83(0.67–1.03)	0.083
Occlusion position-middle (reference proximal)	0.78(0.64–0.95)	0.013	0.86(0.70–1.06)	0.161
Occlusion position-distal (reference proximal)	0.67(0.49–0.91)	0.011	0.83(0.60–1.16)	0.280
Multivessel disease	1.20(0.97–1.49)	0.100		
Number of stents (per 1stent)	1.03(0.85–1.26)	0.736		
μQFR	2.42(0.36–16.16)	0.355		
HR, (per 1 bpm)	1.01(1.00–1.02)	<0.001	1.01(1.00–1.02)	<0.001
SBP, (per 1 mmHg)	1.00(0.99–1.00)	0.017	0.99(0.99–1.00)	0.056
DBP, (per 1 mmHg)	0.99(0.99–1.00)	0.040	1.00(0.99-1.01)	0.674
Hypertension	1.08(0.90–1.30)	0.414		
Diabetes mellitus	1.28(1.05–1.56)	0.015	1.19(0.98–1.47)	0.086
MI history	1.56(0.93–2.61)	0.090		
Smoking	0.78(0.65–0.94)	0.009	1.02(0.82–1.28)	0.859
CKD	1.66(1.06–2.60)	0.026	1.36(0.83–2.10)	0.244
STB time, (per 1 hour)	1.04(1.02–1.07)	0.001	1.03(1.01-1.06)	0.019
TIMI flow 0 pre-PPCI (reference TIMI flow3)	1.36(1.05–1.76)	0.020	0.95(0.68–1.33)	0.754
TIMI flow 1 pre-PPCI (reference TIMI flow3)	1.91(1.26–2.90)	0.002	1.33(0.86–2.05)	0.201

TIMI flow 2 pre-PPCI (reference TIMI flow3)	1.24(0.82–1.84)	0.275	1.01(0.69–1.51)	0.949
High thrombus burden	1.62(1.25–2.08)	<0.001	1.72(1.21–2.44)	0.002
Thrombus aspiration	1.04(0.78–1.35)	0.798		
GpIIb/IIIa inhibitor	0.94(0.75-1.71)	0.564		
Stain	1.07(0.48-2.39)	0.870		
Aspirin	0.71(0.23-2.21)	0.555		
Ticagrelor	0.56(0.40-0.79)	0.001	1.08(0.73-1.62)	0.695
ACEI/ARB/ARNI	0.78(0.46-1.30)	0.331		
β blocker	1.00(0.50-2.01)	0.998		

AMR: angiographic microvascular resistance; BMI: Body Mass Index; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; CKD: chronic kidney disease; LVEF: left ventricular ejection fraction; STB: symptom to balloon; LAD: left anterior descending coronary artery; LCX: left circumflex artery; RCA: right coronary artery; QFR: quantitative flow ratio; HR: hazard ratio; CI: confidence interval

Supplementary Table 3. Log-rank analysis of clinical events over 10 years of follow-up in the validation cohort.

	Total (n=2261)	AMR≤26.6 mmHg*s/dm (n=995)	AMR>26.6 mmHg*s/dm (n=1266)	P
MACE	457(26.8)	152(21.5)	305(30.9)	<0.001
Cardiac death	94(5.6)	22(4.1)	72(6.9)	<0.001
Hospitalization for heart failure	262(15.6)	77(10.5)	185(19.6)	<0.001
Target lesion revascularization	107(7.3)	46(7.8)	61(6.9)	0.738
Repeat myocardial infarction	87(5.5)	36(5.4)	51(5.6)	0.513
All cause death	112(7.7)	31(5.8)	81(9.3)	<0.001

The data in parentheses represent the 10-year cumulative event rate estimated by the Kaplan-Meier method.

MACE: major adverse cardiovascular event; AMR: angiographic microcirculatory resistance

Supplementary Table 4. Baseline data of each group after categorising AMR into quartiles.

	Total (n=2261)	AMR=(14.0~23.0)mm Hg*s/dm (n=574)	AMR=(23.1~27.8)mm Hg*s/dm (n=564)	AMR=(27.9~33.4)mm Hg*s/dm (n=559)	AMR=(33.5~72.5)mm Hg*s/dm (n=564)	P
Man(%)	1,689 (74.70)	445 (77.53)	432 (76.60)	400 (71.56)	412 (73.05)	0.065
Age(years)	62.00 [52.00,	60.00 [51.00, 68.00]	62.00 [53.00, 69.00]	62.00 [53.00, 69.00]	63.00 [54.00, 71.00]	<0.001
BMI	25.69 (2.99)	25.79 (3.19)	25.72 (2.90)	25.72 (3.03)	25.53 (2.82)	0.645
Hypertension, n(%)	1,132 (50.07)	245 (42.68)	257 (45.57)	324 (57.96)	306 (54.26)	<0.001
Diabetes mellitus, n (%)	590 (26.09)	153 (26.66)	158 (28.01)	132 (23.61)	147 (26.06)	0.399
MI history, n(%)	50 (2.21)	18 (3.14)	7 (1.24)	16 (2.86)	9 (1.60)	0.078
Smoking, n(%)	1,122 (49.62)	295 (51.39)	295 (52.30)	270 (48.30)	262 (46.45)	0.172
CKD, n (%)	65 (2.87)	20 (3.48)	9 (1.60)	10 (1.79)	26 (4.61)	0.006
Killip heart function classification , n (%)						0.014
I	1,344 (59.44)	357 (62.20)	350 (62.06)	333 (59.57)	304 (53.90)	
II-IV	917 (40.56)	217 (37.80)	214 (37.94)	226 (40.43)	260 (46.10)	
Culprit vessel, n (%)						0.062
LAD	1,112 (49.18)	285 (49.65)	263 (46.63)	260 (46.51)	304 (53.90)	
LCX	268 (11.85)	58 (10.10)	66 (11.70)	76 (13.60)	68 (12.06)	
RCA	881 (38.97)	231 (40.24)	235 (41.67)	223 (39.89)	192 (34.04)	
Occlusion position, n(%)						0.592
proximal	1,096 (48.47)	269 (46.86)	260 (46.10)	277 (49.55)	290 (51.42)	
middle	853 (37.73)	219 (38.15)	225 (39.89)	209 (37.39)	200 (35.46)	
distal	312 (13.80)	86 (14.98)	79 (14.01)	73 (13.06)	74 (13.12)	
μQFR	0.96 [0.92, 0.98]	0.92 [0.86, 0.96]	0.95 [0.91, 0.97]	0.96 [0.94, 0.98]	0.97 [0.95, 0.99]	<0.001
Blood flow velocity(dm/s)	1.34 [1.00, 1.79]	2.09 [1.90, 2.38]	1.55 [1.42, 1.68]	1.18 [1.08, 1.29]	0.80 [0.67, 0.91]	<0.001
Multivessel disease, n (%)	507 (22.42)	139 (24.22)	127 (22.52)	126 (22.54)	115 (20.39)	0.492

HR, bpm	76.00 [66.00,	78.00 [67.00, 88.00]	76.00 [66.00, 87.00]	77.00 [65.00, 88.00]	76.00 [66.00, 88.00]	0.341
SBP, mmHg	126.00 [110.00,	129.00 [113.00,	127.00 [110.00,	124.00 [109.50,	125.00 [110.00,	0.021
DBP, mmHg	78.00 [68.00,	80.00 [70.00, 90.75]	77.00 [68.00, 91.00]	77.00 [67.00, 89.00]	77.00 [68.00, 89.25]	0.010
TIMI flow pre-PPCI, n (%)						<0.001
0	1,506 (66.61)	375 (65.33)	377 (66.84)	365 (65.30)	389 (68.97)	
1	112 (4.95)	23 (4.01)	19 (3.37)	28 (5.01)	42 (7.45)	
2	203 (8.98)	38 (6.62)	39 (6.91)	63 (11.27)	63 (11.17)	
3	440 (19.46)	138 (24.04)	129 (22.87)	103 (18.43)	70 (12.41)	
High thrombus burden, n(%)	1,759 (77.80)	398 (69.34)	407 (72.16)	466 (83.36)	488 (86.52)	<0.001
STB time, hours	5.00 [3.00, 7.00]	4.50 [2.59, 6.00]	5.00 [3.00, 7.00]	5.00 [3.00, 7.48]	5.00 [3.00, 8.00]	<0.001
Thrombus aspiration, n (%)	325 (14.37)	110 (19.16)	78 (13.83)	59 (10.55)	78 (13.83)	<0.001
Number of stents, n (%)						0.670
0	185 (8.18)	48 (8.36)	45 (7.98)	43 (7.69)	49 (8.69)	
1	1,776 (78.55)	456 (79.44)	445 (78.90)	438 (78.35)	437 (77.48)	
2	283 (12.52)	66 (11.50)	67 (11.88)	73 (13.06)	77 (13.65)	
3	17 (0.75)	4 (0.70)	7 (1.24)	5 (0.89)	1 (0.18)	
Medications use						
GpIIb/IIIa inhibitor	1,787 (79.04)	456 (79.44)	447 (79.26)	445 (79.61)	439 (77.84)	0.880
Stain	2,229 (98.58)	565 (98.43)	557 (98.76)	548 (98.03)	559 (99.11)	0.462
Aspirin	2,250 (99.51)	574 (100.00)	564 (100.00)	553 (98.93)	559 (99.11)	0.002
Ticagrelor	2,143 (94.78)	556 (96.86)	545 (96.63)	526 (94.10)	516 (91.49)	<0.001
Clopidogrel	118(5.22)	18 (3.14)	19 (3.37)	33 (5.90)	48 (8.51)	<0.001
ACEI/ARB/ARNI	2,200 (97.30)	561 (97.74)	552 (97.87)	545 (97.50)	542 (96.10)	0.231
β blocker	2,220 (98.19)	563 (98.08)	552 (97.87)	555 (99.28)	550 (97.52)	0.136

AMR: angiographic microvascular resistance; BMI: Body Mass Index; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; CKD: chronic

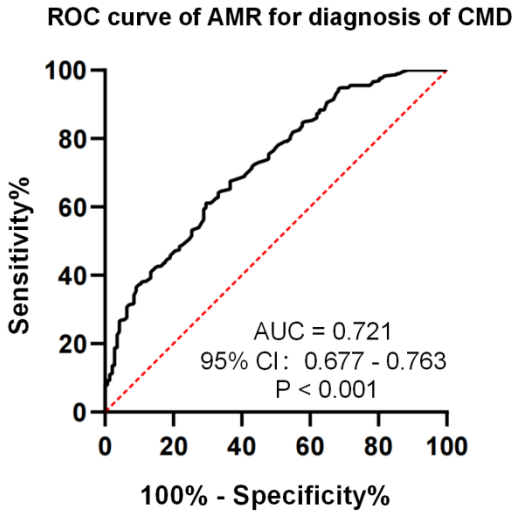
kidney disease; STB: symptom to balloon; LAD: left anterior descending coronary artery; LCX: left circumflex artery; RCA: right coronary artery; QFR: quantitative flow ratio;

Supplementary Table 5. Ordinal logistic regression of increased AMR.

Modle1			Modle2		
	OR (95% CI)	P		OR (95% CI)	P
Age(per 1 year)	1.01(1.00-1.02)	0.013	Age(per 1 year)	1.01(1.00-1.02)	0.009
SBP(per 1 mmHg)	0.99(0.98-0.99)	<0.001	SBP(per 1 mmHg)	0.99(0.98-0.99)	<0.001
DBP(per 1 mmHg)	0.99(0.98-1.00)	0.051	DBP(per 1 mmHg)	0.99(0.98-1.00)	0.052
STB time(per 1h)	1.05(1.02-1.07)	<0.001	STB time(per 1h)	1.06(1.03-1.08)	<0.001
CKD	1.26(0.80-1.26)	0.319	CKD	1.21(0.99-1.90)	0.416
Hypertension	2.62(2.14-3.21)	<0.001	Hypertension	2.52(2.06-3.09)	<0.001
Thrombus aspiration	0.70(0.56-0.87)	0.001	Thrombus aspiration	0.59(0.48-0.74)	<0.001
Aspirin	0.39(0.12-1.25)	0.115	Aspirin	0.36(0.11-1.14)	0.083
Ticagrelor(Comparison with Clopidogrel)	0.58(0.40-0.85)	0.006	Ticagrelor(Comparison with Clopidogrel)	0.60(0.41-0.88)	0.010
TIMI flow grade pre-PPCI (Comparison with TIMI flow 3)			High thrombus burden	2.19(1.82-2.65)	<0.001
0	1.52(1.25-1.84)	<0.001			
1	2.21(1.51-3.23)	<0.001			
2	2.04(1.51-2.76)	<0.001			

Given the strong correlation between “TIMI flow pre-PCI” analysis and “High thrombus burden”, and considering the potential impact of collinearity on the results, these two variables were included in two separate models. “μQFR” and “Blood flow velocity” were not included as independent variables because they are already incorporated in the calculation of AMR, which is the dependent variable. Including them separately would lead to multicollinearity and redundancy, as their effects are indirectly accounted for through AMR

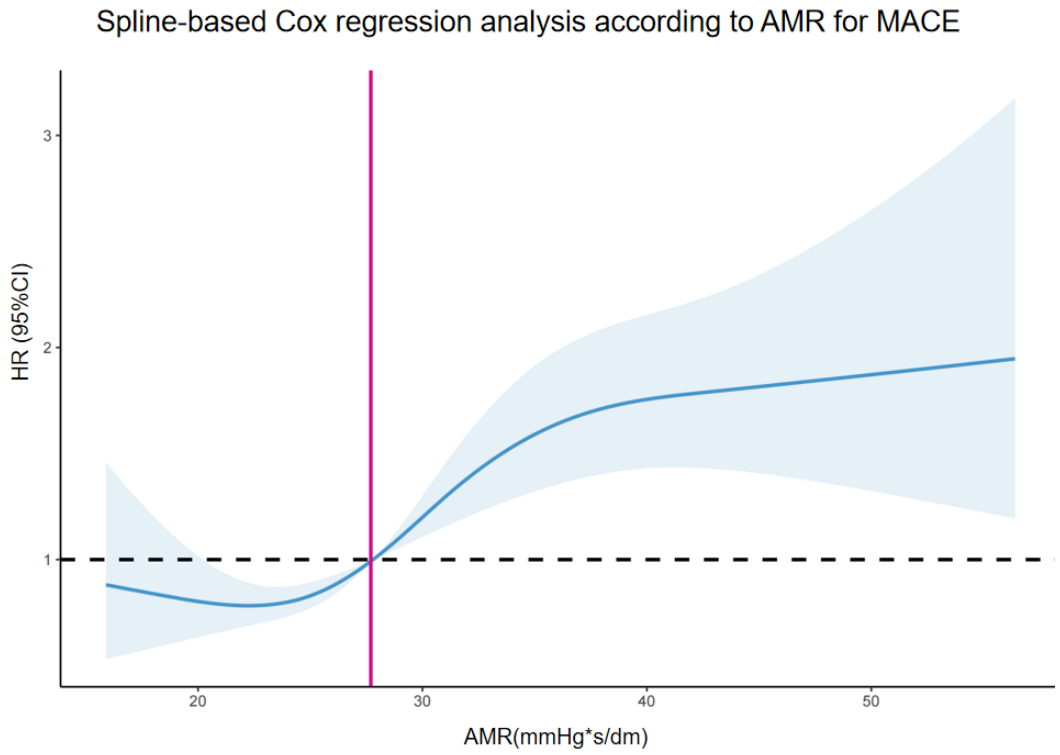
SBP: systolic blood pressure; DBP: diastolic blood pressure; STB: symptom to balloon; LAD: left anterior descending coronary artery; LCX: left circumflex artery; RCA: right coronary artery;



AUC	95% CI	Sensitivity%	Specificity%	Cut-off	PPV%	NPV%
0.721	0.677 - 0.763	61.09	70.42	>26.6 mmHg*s/dm	81.00	46.73

Supplementary Figure 1. ROC curve for AMR diagnosis of CMD.

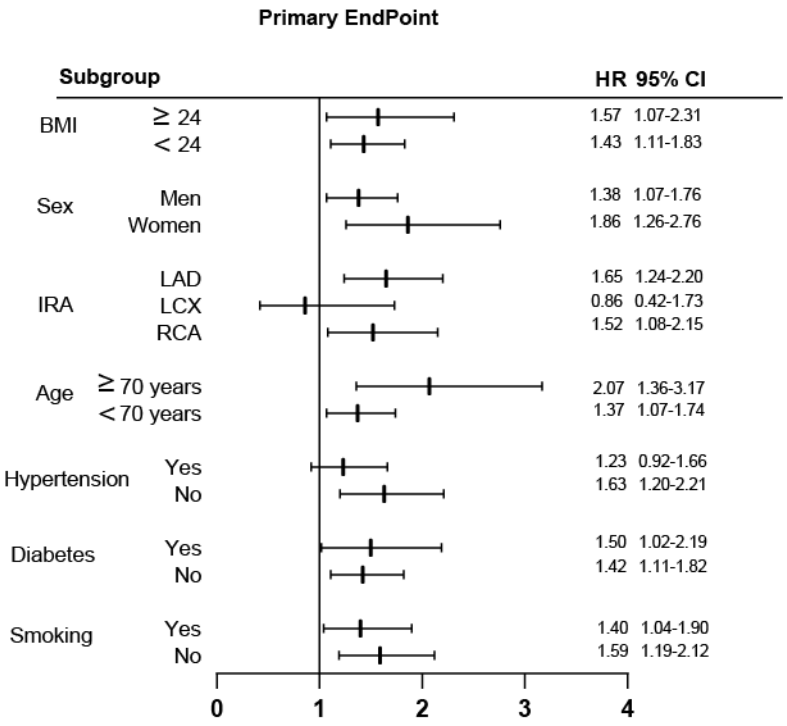
AMR: angiographic microcirculatory resistance; AUC: area under the curve; CMD: coronary microcirculatory dysfunction; ROC: receiver operating characteristic



Supplementary Figure 2. Spline-based Cox regression analysis according to AMR for MACE.

Spline-based Cox regression analysis showed a linear relationship between angiographic microcirculatory resistance (AMR) and major adverse cardiovascular event (MACE). A hazard ratio (HR) of 1 corresponds to an AMR of 27.6 mmHg*s/dm. Per 10 increase of AMR, adjusted HR: 1.30; 95% CI 1.17-1.46, P <0.001.

CI: confidence interval; AMR: angiographic microcirculatory resistance; MACE: major adverse cardiovascular event; HR:hazard ratio



Supplementary Figure 3. Forest plot for subgroup analysis.

BMI: Body Mass Index; IRA:infarction related artery; LAD: left anterior descending coronary artery; LCX: left circumflex artery; RCA: right coronary artery; HR: hazard ratio; CI: confidence interval

Data availability statement

The datasets generated and analysed during the current study are not publicly available because of patient privacy but are available from the corresponding author upon reasonable request.