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Microcirculatory Resistance After Primary Percutaneous Coronary Intervention Predicts Residual Myocardial Damage and Scar Formation / Candreva, A., Gotschy, A., Stehli, J., Bissig, L., Lodi Rizzini, M., Chiastra, C., Gallo, D., Morbiducci, U., Klingenberg, R., Heg, D., Matter, C.M., Ruschitzka, F., Manka, R., Stähli, B.E.. - In: JOURNAL OF THE AMERICAN HEART ASSOCIATION. CARDIOVASCULAR AND CEREBROVASCULAR DISEASE. - ISSN 2047-9980. - 14:4(2025). [10.1161/jaha.124.036033]

*Availability:*

This version is available at: 11583/2999351 since: 2025-04-18T12:43:02Z

*Publisher:*

American Heart Association

*Published*

DOI:10.1161/jaha.124.036033

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ORIGINAL RESEARCH

# Microcirculatory Resistance After Primary Percutaneous Coronary Intervention Predicts Residual Myocardial Damage and Scar Formation

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**BACKGROUND:** Coronary microvascular dysfunction has been associated with adverse cardiovascular events following acute myocardial infarction. This study evaluates the role of the angiography-derived index of microcirculatory resistance (angio-IMR) in predicting myocardial damage in patients with ST-segment–elevation myocardial infarction undergoing primary percutaneous coronary intervention (PCI).

**METHODS AND RESULTS:** In this post hoc analysis of the CLEVER-ACS (Controlled-Level Everolimus in Acute Coronary Syndromes) trial, the associations between post-PCI angio-IMR of infarct-related coronary arteries (IRAs) and infarct size, microvascular obstruction, and left ventricular ejection fraction at 30 days as assessed by cardiac magnetic resonance were investigated. High post-PCI angio-IMR was defined as  $\geq 40$  mmHg\*s. In non-IRAs, angio-IMR was measured before IRA-PCI. A total of 52 IRAs and 94 non-IRAs of 52 patients were analyzed. Post-PCI angio-IMR was 41.5 (interquartile range [IQR], 28.5–55.7) mmHg\*s in IRAs and pre-PCI angio-IMR was 43.7 (IQR, 31.7–54.0) mmHg\*s in non-IRAs ( $P=0.70$ ). Patients with high post-PCI angio-IMR (52%) exhibited a larger myocardial infarct size (36.0 [IQR, 23.0–52.5] g versus 14.5 [IQR, 6.50–26.5] g,  $P<0.001$ ) and a lower left ventricular ejection fraction (46.5% [IQR, 39.5%–49.5%] versus 55.0% [IQR, 48.0%–61.4%],  $P=0.002$ ) at 30 days as compared with those with low post-PCI angio-IMR values. Post-PCI angio-IMR positively correlated with myocardial infarct size ( $r=0.45$ ,  $P=0.001$ ) and extent of microvascular obstruction ( $r=0.40$ ,  $P=0.004$ ) at 30 days. Post-PCI angio-IMR predicted myocardial infarct size (area under the curve, 0.78 [IQR, 0.65–0.92];  $P=0.001$ ) and extent of microvascular obstruction (area under the curve, 0.74 [IQR, 0.60–0.89];  $P=0.009$ ) at 30 days.

**CONCLUSIONS:** In patients with ST-segment–elevation myocardial infarction, post-PCI angio-IMR was identified as independent predictor of myocardial infarct size and extent of microvascular obstruction.

**REGISTRATION:** URL: <https://clinicaltrials.gov>; Unique Identifier: NCT01529554.

**Key Words:** angiography-derived index of microvascular resistance ■ cardiac magnetic resonance imaging ■ microvascular obstruction

**A**ssessment of coronary microvascular function in acute myocardial infarction (MI) has received increasing attention given its potential to enhance risk stratification of patients with ST-segment–elevation MI (STEMI) undergoing primary percutaneous coronary intervention (PCI).<sup>1,2</sup> The pathophysiology of coronary

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This manuscript was sent to Nadia R. Sutton, MD, MPH, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.124.036033>

For Sources of Funding and Disclosures, see page 9.

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## CLINICAL PERSPECTIVE

### What Is New?

- This study shows that angiography-derived index of microcirculatory resistance, measured immediately after percutaneous coronary intervention, predicts not only acute myocardial and microvascular damage, but also its persistence up to 30 days.
- This establishes angiography-derived index of microcirculatory resistance as a valuable tool for assessing both immediate and sustained clinical impacts of an acute myocardial infarction.

### What Are the Clinical Implications?

- Angiography-derived index of microcirculatory resistance is a practical tool that can be readily integrated into the percutaneous coronary intervention procedure without extending its duration, allowing physicians to stratify patient risk efficiently.
- Clinicians could potentially use angiography-derived index of microcirculatory resistance measurements to stratify risk, tailor post-percutaneous coronary intervention therapeutic strategies, and improve patient outcomes by identifying those who may benefit from closer monitoring, advanced imaging, and targeted therapies to mitigate myocardial injury and facilitate recovery.

## Nonstandard Abbreviations and Acronyms

<b>angio-IMR</b>	angiography-derived index of microcirculatory resistance
<b>CLEVER-ACS</b>	Controlled-Level Everolimus in Acute Coronary Syndromes
<b>IMR</b>	index of microcirculatory resistance
<b>IRA</b>	infarct-related artery
<b>MVO</b>	microvascular obstruction

microvascular dysfunction in the context of acute coronary syndromes is multifaceted.<sup>3</sup> Mechanisms include distal microembolization, reperfusion injury, and dysregulated inflammatory responses.<sup>4–6</sup> Coronary microvascular resistance reflects the degree of patency of the coronary microcirculation as underlined by the association of coronary microvascular resistance with microvascular obstruction (MVO) and infarct size.<sup>7</sup> Furthermore, microvascular dysfunction has been associated with adverse cardiovascular events following the STEMI index event. Specifically, in patients with STEMI undergoing coronary revascularization, MVO,

as assessed by postinfarction cardiac magnetic resonance (CMR) imaging, has been identified as predictor of all-cause death and decompensated heart failure.<sup>8</sup> Additionally, the index of microcirculatory resistance (IMR) has been associated with increased infarct size and adverse clinical outcomes.<sup>7,9</sup>

Recently, angiography-derived computational algorithms have emerged as novel tools for the quantitative assessment of microcirculatory resistance on the basis of coronary angiography alone (angiography-derived index of microcirculatory resistance [angio-IMR]).<sup>7,10</sup> These modalities bear the advantage over conventional invasive measurements of avoiding the use of a pressure wire and the induction of hyperemia, and several studies have proven the high correlation of angiography-derived measurements with invasive IMR.<sup>10–13</sup> The relation of angio-IMR with myocardial damage in patients with STEMI is incompletely understood.<sup>14</sup>

The aim of this study was to assess the value of angio-IMR in predicting the size of an MI and the extent of MVO as assessed by CMR in patients with STEMI undergoing PCI, using data from the CLEVER-ACS (Controlled-Level Everolimus in Acute Coronary Syndromes) trial.<sup>15</sup>

## METHODS

### Study Design

This study is a post hoc analysis of the CLEVER-ACS trial. The data that support the findings of this study are available from the corresponding author upon reasonable request. The CLEVER-ACS trial evaluated the effects of targeting inflammation by mammalian target of rapamycin inhibition in patients with STEMI undergoing PCI.<sup>15,16</sup> The CLEVER-ACS trial enrolled a total of 150 patients with STEMI undergoing PCI and randomly assigned them to either oral everolimus (days 1–3: 7.5 mg daily; days 4–5: 5.0 mg daily) or placebo for 5 days. To assess the changes in MI size and MVO, patients underwent CMR at both baseline (12 hours to 5 days after PCI) and 30 days. Exclusion criteria included known hypersensitivity to mammalian target of rapamycin inhibitors, contraindications to CMR or its contrast agent, recent use of immunosuppressants within 4 weeks before STEMI, mechanical complications of MI, need for revascularization of nonculprit arteries within the trial period, scheduled PCI within 30 days, major elective surgery during the trial, an estimated glomerular filtration rate <30 mL/min, malignancy unless in remission for >5 years, chronic infections such as HIV or tuberculosis, suspected or known noncompliance to medication, substance abuse, pregnancy or lactation, unwillingness to use contraception, participation in another trial within

30 days, and positive SARS-CoV-2 test or symptoms. The trial showed no significant reduction in MI size in the treated patient cohort.

For the purpose of this study, postprocedural microvascular dysfunction was evaluated using the angiography-derived index of microvascular resistance (angio-IMR). Associations between angio-IMR and myocardial infarct size, MVO, and left ventricular ejection fraction (LVEF) as determined by CMR were examined. Patients enrolled at the University Hospital Zurich were included in the study. The study was approved by the local ethics committee (BASEC 2022-01645). All patients provided written informed consent. The study was conducted following the principles of the Declaration of Helsinki, and in accordance with local law and regulations.

### Quantitative Coronary Angiography and Angiography-Derived Assessment of Microvascular Resistance

Coronary angiographies of infarct-related arteries (IRAs) were analyzed both before and after PCI. In completely occluded IRAs, only post-PCI measurements were performed. Non-IRA vessels were analyzed before PCI of the IRA. Three-dimensional quantitative coronary angiography, contrast-flow quantitative flow reserve, and nonhyperemic angio-IMR were measured offline using QAngio XA 3D software (Medis, Leiden, the Netherlands) from 2 coronary angiography projections taken at least 25° apart, as detailed elsewhere.<sup>17</sup> Invasive aortic blood pressures measured at the time of the coronary angiography were obtained from the coronary angiography protocols and used for the angio-IMR calculation. Thrombolysis in Myocardial Infarction Thrombus Grading Score and Thrombolysis in Myocardial Infarction flow grade before and after PCI were obtained as previously reported.<sup>15</sup> The analysis was performed by 1 operator (A.C.) blinded to clinical and CMR data. Further details on the analysis can be found elsewhere.<sup>10,11</sup>

### CMR Imaging

CMR imaging was performed following PCI both at baseline (or within 5 days from the index PCI) and at 30 days ( $\pm 3$  days). Complete CMR evaluation at 30 days was available in 50 patients (96.1%). Imaging consisted of steady-state free precession cine imaging for the quantification of left ventricular (LV) volumes and ejection fraction, T1- and T2-weighted black-blood images for tissue characterization, and late gadolinium enhancement imaging for the delineation of myocardial scar. All CMR analyses were performed in a dedicated CMR core laboratory by personnel blinded to all clinical data. Left ventricular end-diastolic and end-systolic

volumes were contoured manually in a contiguous short-axis stack of steady-state free precession cine images, covering the entire left ventricle. The extent of edema for the calculation of the area at risk was quantified in T2-weighted images. The late gadolinium enhancement sequences were acquired 15 minutes after the administration of gadolinium-based contrast agents. The extent of scar and MVO was manually segmented in the late gadolinium enhancement images.

### Statistical Analysis

Analyses were performed at the per-vessel and per-patient levels. Patients were stratified according to post-PCI angio-IMR values ( $<40$  or  $\geq 40$  mmHg\*s).<sup>9,10</sup> Continuous variables are presented as mean $\pm$ SD or medians and interquartile range as appropriate. Categorical variables are presented as numbers and percentages. Normality was assessed with the Shapiro–Wilk test. The  $\chi^2$  test was used for the comparison of categorical variables. Student's *t* test or the Mann–Whitney *U* test was used for the comparison of continuous variables as appropriate. Correlations between variables were assessed using the Pearson correlation coefficient. Receiver operating characteristic curve analysis was performed to assess the role of post-PCI angio-IMR in predicting infarct size, extent of MVO, and LVEF at the CMR before discharge as well as at 30 days. Myocardial infarct size above the 66th percentile value was defined as large MI, MVO values above the 66th percentile as large extent of MVO, and LVEF values below the 33rd percentile as reduced LVEF, respectively. Univariate and multivariate generalized linear models were used to assess independent association between post-PCI angio-IMR, patient's age and cardiovascular risk factors (type 2 diabetes, arterial hypertension, and dyslipidemia) with myocardial infarct size, MVO, and LVEF at baseline as well as at 30 days. Odd ratios per unit increase in the independent variable and their 95% CIs were obtained from the exponential of the standardized correlation coefficients. A *P* value  $\leq 0.05$  was considered statistically significant. Analyses were performed using SPSS Statistics 29 software (IBM Corp., Armonk, NY).

## RESULTS

### Baseline Characteristics

A total of 52 patients (46 men [88.5%]) with 52 IRAs and 94 non-IRAs were included in the analysis. The mean age was  $58 \pm 11$  years in patients with a post-PCI angio-IMR  $<40$  mmHg\*s and  $61 \pm 11$  years in those with a post-PCI angio-IMR  $\geq 40$  mmHg\*s ( $P=0.39$ ). Baseline characteristics and medications are provided in [Table 1](#).

**Table 1. Baseline Characteristics According to Post-PCI Angio-IMR of the IRA**

	Post-PCI angio-IMR <40 mmHg*s (n=25)	Post-PCI angio-IMR ≥40 mmHg*s (n=27)	P value
Clinical characteristics			
Age, y	58.0±10.57	60.59±11.01	0.39
Women	3 (12.0)	3 (11.11)	0.92
Body mass index, kg/m <sup>2</sup>	27.37±3.12	27.13±3.68	0.80
Type 2 diabetes	0 (0.0)	3 (11.11)	0.43
Hypertension	11 (44.0)	12 (44.44)	0.97
Dyslipidemia	15 (60.0)	17 (62.96)	0.09
Smoking	18 (72.0)	19 (70.37)	0.90
History of CAD	8 (32.0)	6 (22.22)	0.43
Previous MI	0 (0.0)	0 (0.0)	...
Previous PCI	1 (4.0)	0 (0.0)	0.29
Previous stroke/TIA	0 (0.0)	0 (0.0)	...
Baseline medication			
Aspirin	22 (88.0)	24 (88.89)	0.22
Clopidogrel	2 (8.0)	2 (7.41)	0.63
Prasugrel	17 (68.0)	20 (74.07)	0.37
Ticagrelor	4 (16.0)	2 (7.41)	0.43
Oral anticoagulation	1 (4.0)	2 (7.41)	0.53
ACE inhibitor	17 (68.0)	16 (59.26)	0.60
Angiotensin II antagonists	3 (12.0)	3 (11.11)	0.63
β blocker	15 (60.0)	13 (48.15)	0.53
Calcium channel blocker	3 (12.0)	2 (7.41)	0.56
Nitroglycerin	1 (4.0)	3 (11.11)	0.37
Diuretics	6 (24.0)	6 (22.22)	0.63
Oral antidiabetics	0 (0.0)	3 (11.11)	0.13
Insulin	0 (0.0)	1 (3.70)	0.38
Statin	20 (80.0)	24 (88.89)	0.07

Values are given as mean±SD or n (%). ACE indicates angiotensin-converting enzyme; angio-IMR, angiography-derived index of microcirculatory resistance (in mmHg\*s); IRA, infarct-related artery; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; and TIA, transient ischemic attack.

In patients with high post-PCI angio-IMR values, the culprit lesion was more frequently located in the left anterior descending coronary artery (77.8% versus 44.0%,  $P=0.04$ ). Procedural characteristics are given in [Table 2](#).

### Coronary Angiography–Derived Analyses

Coronary angiography–derived analyses are presented in [Table 3](#). Pre-PCI angio-IMR measurements were performed in IRAs (n=16 [30.7%]) with partial occlusion. In these vessels, high angio-IMR values were

**Table 2. Procedural Characteristics According to Post-PCI Angio-IMR of the IRA**

	Post-PCI angio-IMR <40 mmHg*sm (n=25)	Post-PCI angio-IMR ≥40 mmHg*s (n=27)	P value
Culprit coronary artery			
LAD	11 (44.0)	21 (77.8)	
LCX	3 (12.0)	1 (3.7)	
RCA	11 (44.0)	5 (18.5)	
Symptom-to-balloon time, min	181 (130–307)	219 (154–515)	0.19
First medical contact-to-balloon time, min	80 (69–95)	86 (69–96)	0.69
Transfer to PCI center	8 (32.0)	12 (44.4)	0.36
Intracoronary imaging	5 (20.0)	3 (11.1)	0.38
Number of implanted stents			
1	11 (44.0)	13 (48.2)	
≥2	14 (56.0)	14 (51.9)	
Thrombus aspiration	7 (28.0)	11 (40.7)	0.34
Glycoprotein IIb/IIIa inhibitor	7 (28.0)	17 (63.0)	0.01

Values are given as medians (interquartile range) or n (%). Angio-IMR indicates angiography-derived index of microcirculatory resistance (in mmHg\*s); IRA, infarct-related artery; LAD, left anterior descending artery; LCX, left circumflex artery; PCI, percutaneous coronary intervention; and RCA, right coronary artery.

noted, showing a trend toward decreased values after PCI (pre-PCI angio-IMR, 61.8 [30.7–68.6] mmHg\*s versus post-PCI angio-IMR, 41.5 [28.5–55.7] mmHg\*s;  $P=0.08$ ; [Figure 1](#)). Post-PCI angio-IMR values were higher in culprit left anterior descending coronary vessels as compared with non-left anterior descending artery culprit vessels (50.6 [33.6–65.6] mmHg\*s versus 40.2 [28.6–53.2] mmHg\*s,  $P=0.010$ ). Post-PCI angio-IMR values were similar between the 2 treatment groups of the CLEVER-ACS trial ([Table S1](#)).

### Predictive Role of the Angio-IMR

Baseline CMR imaging was performed at 2.0 (1.0–3.0) days and follow-up CMR imaging at 31.0 (29.0–35.0) days after the index STEMI event. A total of 26 (52.0%) patients displayed high post-PCI angio-IMR values. Myocardial infarct size both at baseline (53.5 [39.0–69.0] g versus 24.3 [12.0–48.0] g,  $P<0.001$ ) and at 30 days (36.0 [23.0–52.50] g versus 14.5 [6.50–26.5] g,  $P<0.001$ ) was larger in patients with high post-PCI angio-IMR values as compared with those with low values ([Table 4](#)). The extent of MVO both at baseline (9.0 [2.0–19.0] g versus 2.0 [0.0–10.0] g,  $P=0.02$ ) and at 30 days (0.0 [0.0–1.4] g versus 0.0 [0.0–0.0] g,  $P=0.04$ ) was larger in patients with high post-PCI

**Table 3. Coronary Angiography–Based Analyses**

	Non-IRA (n=94)	IRA (n=52)		P value		
	Pre-PCI (n=94)	Pre-PCI (n=16/52)	Post-PCI (n=52)	Non-IRA vs pre-PCI IRA	Non-IRA vs post-PCI IRA	Pre-PCI IRA vs post-PCI IRA
AS, %	34.45 (24.70–49.70)	89.30 (84.45–92.90)	38.00 (25.90–47.40)	<0.001	0.71	<0.001
MLD, mm	2.00 (1.60–2.30)	0.80 (0.65–1.00)	2.00 (1.60–2.35)	<0.001	0.47	<0.001
Vessel reference diameter, mm	2.90 (2.40–3.40)	2.95 (2.65–3.45)	...	0.34	...	...
Plaque volume, mm <sup>3</sup>	13.25 (5.70–34.10)	52.85 (36.25–87.60)	...	<0.001	...	...
QFR	0.99 (0.95–1.00)	0.68 (0.61–0.75)	0.98 (0.96–0.99)	<0.001	0.24	<0.001
Δ-QFR	0.01 (0.00–0.03)	0.27 (0.21–0.33)	0.01 (0.00–0.02)	<0.001	0.13	<0.001
QFR-PPG index	0.88 (0.77–0.95)	0.79 (0.64–0.85)	0.84 (0.77–0.90)	0.001	0.42	0.002
Angio-IMR, mmHg/s	43.72 (31.66–54.02)	61.81 (30.73–68.62)	41.52 (28.50–55.74)	0.01	0.70	0.08
Flow velocity, cm/s	16.25 (12.10–19.80)	6.40 (4.55–12.75)	16.00 (12.75–21.55)	<0.001	0.27	<0.001
Resistance, mmHg/s per m	3.54 (0.66–12.71)	132.17 (90.27–153.0)	5.49 (1.57–11.02)	<0.001	0.23	<0.001

Pre-PCI angio-IMR was obtained in 16 of 52 cases. Each *P* value column reports the *P* value for the distribution analysis among the 2 groups taken into account. Continuous values are presented as medians (interquartile range). Angio-IMR indicates angiography-derived index of microcirculatory resistance (in mmHg\*s); AS, area stenosis; IRA, infarct-related artery; MLD, minimal lumen diameter; PCI, percutaneous coronary intervention; QFR, quantitative flow ratio; QFR-PPG, quantitative flow ratio–derived pullback pressure gradient; and Δ-QFR, translesional drop in quantitative flow ratio.

angio-IMR values as compared with those with low values (Table 4). At baseline, LVEF was similar between the 2 post-PCI angio-IMR groups. In patients with high post-PCI angio-IMR values, LVEF was lower at 30 days as compared with baseline (55.0% [48.0%–61.4%] versus 46.5% [39.5%–49.5%], *P*=0.002; Table 4).

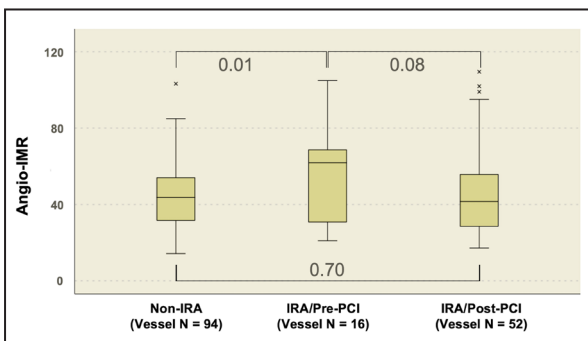
Significant correlations were observed between post-PCI angio-IMR values and myocardial infarct size (*r*=0.45 [95% CI, 0.20–0.65], *P*=0.001) and extent of MVO (*r*=0.40 [95% CI, 0.14–0.61], *P*=0.004; Figure 2), but not with LVEF (*r*=−0.26 [95% CI, −0.51 to 0.02], *P*=0.06).

Post-PCI angio-IMR showed a prediction from low to fair for larger myocardial infarct size (area under the curve [AUC] at baseline, 0.80 [95% CI, 0.68–0.92]; *P*=0.001; AUC at 30 days, 0.78 [0.65–0.92]; *P*=0.001),

larger extent of MVO (AUC at baseline, 0.68 [0.52–0.83]; *P*=0.045; AUC at 30 days, 0.74 [0.60–0.89]; *P*=0.009), and reduced LVEF (AUC at baseline, 0.62 [0.44–0.80]; *P*=0.17; AUC at 30 days, 0.70 [0.54–0.86]; *P*=0.02; Figure 3).

In multivariate analysis, post-PCI angio-IMR independently predicted myocardial infarct size, MVO extent, and LVEF after correction for age and cardiovascular risk factors at both time points (Table 5). No adjustment for the study arm was necessary for any of the variables considered, as they were independent of the randomization arm (Table S1). Results of the univariable analysis are presented in Table S2.

High-sensitivity troponin T and creatine kinase reached higher post-PCI peak levels in case of elevated microvascular resistance after primary PCI (high-sensitivity troponin T, 5.07 [3.09–11.7] mg/L versus 26.5 [13.5–4'998] mg/L, *P*<0.001; creatine kinase: 1'926 [1'020–3'288] U/L versus 4'706 (2'375–5'865) U/L, *P*=0.001; Table S3). Post-PCI angio-IMR values correlated with both post-PCI high-sensitivity troponin T (*r*=0.41 [95% CI 0.15–0.62], *P*=0.002) and post-PCI creatine kinase (*r*=0.49 [95% CI 0.25–0.68], *P*<0.001) peak levels.



**Figure 1. Angiography-derived index of microcirculatory resistance in IRA and non-IRA coronary arteries.**

Data analysis at vessel level. Angio-IMR indicates angiography-derived index of microcirculatory resistance (in mmHg\*s); IRA, infarct-related coronary artery; and PCI, percutaneous coronary intervention.

## DISCUSSION

The present subanalysis of the CLEVER-ACS study demonstrated that, in patients with acute STEMI undergoing PCI, elevated coronary microvascular resistance as assessed by angio-IMR was related to size of MI, extent of MVO, and persistence of LV systolic dysfunction at 30 days, independently from patient's age and

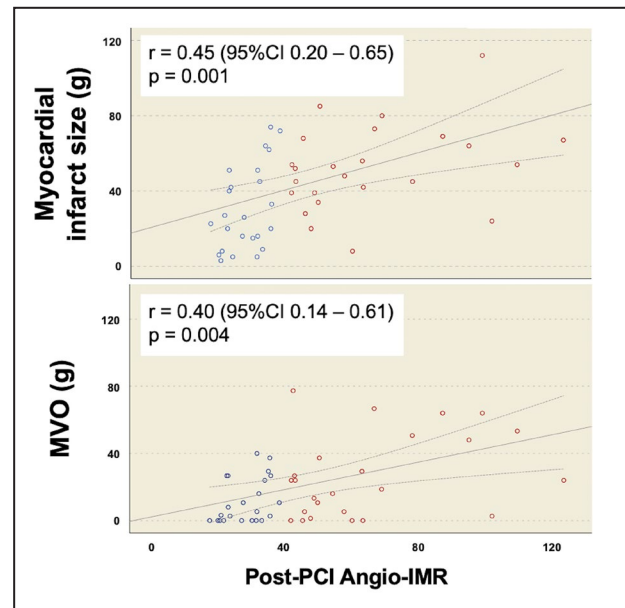
**Table 4. Cardiac Magnetic Resonance Findings at Baseline and at 30Days According to Post-PCI Angio-IMR of the IRA**

	Post-PCI angio-IMR <40 mmHg*s (n=24)	Post-PCI angio-IMR ≥40 mmHg*s (n=26)	P value
Time after PCI, d			
Baseline	2.0 (1.50 to 3.0)	1.0 (1.0 to 3.0)	0.18
30 d	32.0 (30.0 to 35.0)	31.0 (29.0 to 35.0)	0.30
MI size, g			
Baseline	24.30 (12.0 to 48.0)	53.50 (39.0 to 69.0)	<0.001
30 d	14.50 (6.50 to 26.50)	36.0 (23.0 to 52.50)	<0.001
Change	-11.0 (-19.0 to -3.0)	-18.50 (-26.0 to -10.0)	0.06
MVO, g			
Baseline	2.0 (0.0 to 10.0)	9.0 (2.0 to 19.0)	0.02
30 d	0.0 (0.0 to 0.0)	0.0 (0.0 to 1.40)	0.04
Change	-1.6 (-7.5 to 0.0)	-8.5 (-18.0 to -1.0)	0.03
Area at risk, g			
Baseline	31.50 (20.50 to 54.0)	54.0 (40.0 to 73.0)	0.03
30 d	7.50 (0.00 to 19.00)	18.00 (5.0 to 37.0)	0.10
Change	-21.00 (-40.0 to -14.50)	-30.50 (-60.00 to -9.0)	0.35
LVEF, %			
Baseline	49.75 (42.50 to 54.0)	43.50 (39.0 to 48.0)	0.11
30 d	55.0 (48.0 to 61.4)	46.50 (39.50 to 49.5)	0.002
Change	4.0 (-0.50 to 9.0)	1.0 (-7.0 to 5.0)	0.07
LVEDVI, mL/m <sup>2</sup>			
Baseline	83.5 (73.0 to 90.5)	83.0 (71.0 to 94.0)	0.71
30 d	87.0 (71.0 to 99.0)	93.0 (82.50 to 110.8)	0.16
Change	2.0 (-2.0 to 12.3)	8.50 (1.0 to 18.0)	0.17
LV mass, g			
Baseline	123.5 (114.0 to 146.5)	143.0 (124.0 to 153.0)	0.11
30 d	115.0 (98.0 to 131.0)	120.5 (114.0 to 138.5)	0.26
Change	-14.5 (-23.50 to -6.0)	-23.5 (-36.00 to -4.0)	0.28

Continuous values are presented as medians (interquartile range). The change was obtained as 30-day CMR value—baseline CMR value. Angio-IMR indicates angiography-derived index of microcirculatory resistance (in mmHg\*s); CMR, cardiac magnetic resonance; IRA, infarct-related artery; LV, left ventricular; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MVO, microvascular obstruction; and PCI, percutaneous coronary intervention.

presence of cardiovascular risk factors. These findings provide important insights into the association of coronary microvascular dysfunction with LV scar formation after acute STEMI. Angiography-derived measures of coronary microvascular resistance represent accurate and readily available tools for the evaluation of coronary microvascular function in these patients.

In about half of patients with STEMI, despite successful primary PCI and complete reopening of the culprit epicardial coronary artery, perfusion to the coronary microvasculature is not fully restored.<sup>18</sup> Pathophysiological mechanisms of coronary microvascular dysfunction in patients with STEMI are complex.<sup>3</sup> Several studies have shown that the amount of

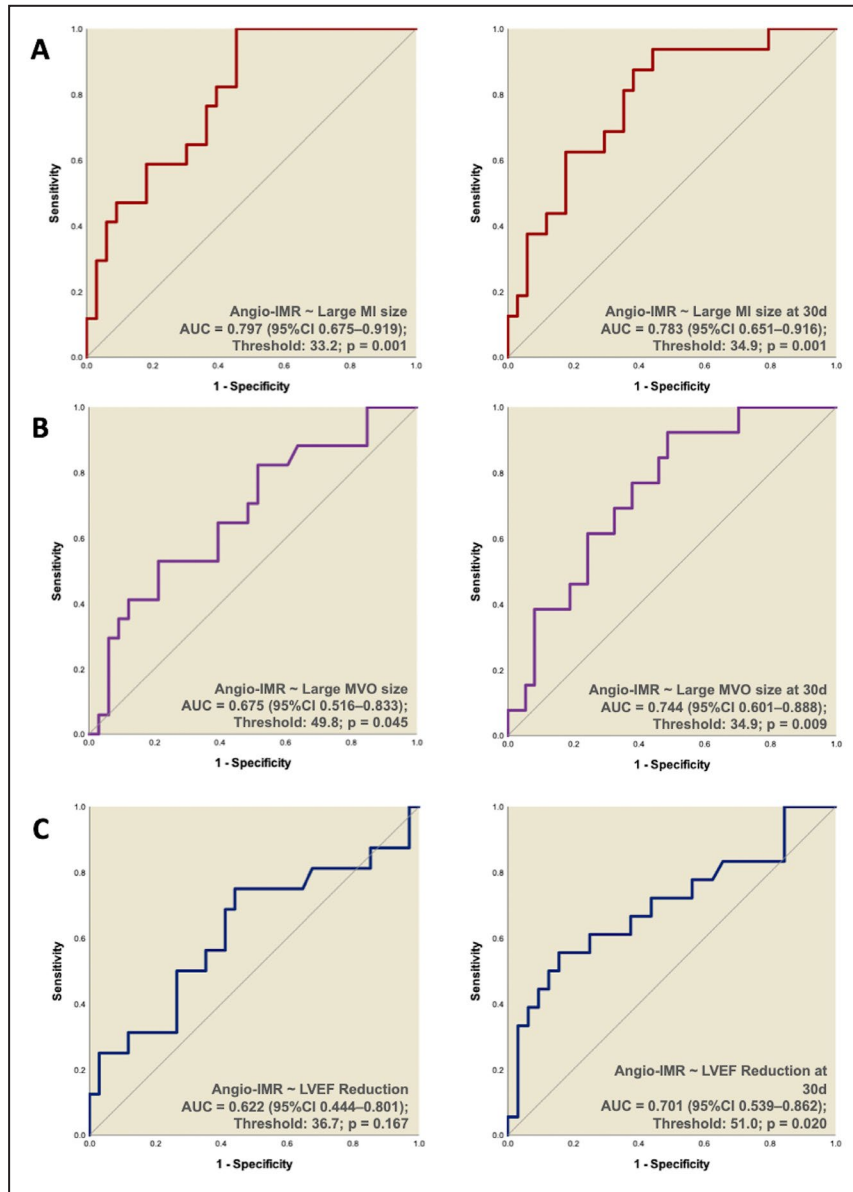
**Figure 2. Relation between post-PCI angio-IMR and myocardial infarction size at baseline.**

Data analysis at patient level (N=50). Angio-IMR indicates angiography-derived index of microcirculatory resistance (in mmHg\*s); MVO, microvascular obstruction; and PCI, percutaneous coronary intervention.

ischemic injury, distal atherothrombotic embolization, microvascular damage due to reperfusion injury, excessive inflammatory responses, and an increased susceptibility of the coronary microvasculature to injury contribute to coronary microvascular dysfunction and subsequent inadequate tissue perfusion.<sup>4-6</sup> Different invasive and noninvasive modalities assess coronary microvascular dysfunction, and good correlations of angiography-derived measures with invasive measurements have been shown.<sup>10-12</sup>

The degree of coronary microvascular dysfunction in patients with STEMI has been linked to worse clinical outcomes.<sup>18</sup> Coronary angiography studies have demonstrated that a delayed contrast agent propagation along the treated coronary artery, as measured by Thrombolysis in Myocardial Infarction frame counting and reflecting an increased microvascular dysfunction, was associated with adverse cardiovascular events both after fibrinolysis as well as after primary PCI.<sup>19,20</sup> Similar findings were observed in reopened culprit arteries that exhibited an impaired coronary microvascular relaxation, as assessed by intracoronary bolus thermodilution following a pharmacological hyperemic stimulus.<sup>9,21</sup> In a most recent study and consistent with our findings, an IMR value >31 mmHg\*s was identified as a strong predictor of MVO after STEMI.<sup>22</sup>

In patients with chronic coronary syndromes undergoing PCI, increased angiography-derived IMR values were associated with rates of cardiac death



**Figure 3.** Receiver operating characteristic curves for myocardial infarction size, MVO), and LVEF.

Data analysis at patient level (N=50). The AUCs demonstrate the predictive potential of the angio-IMR assessed after the primary percutaneous coronary intervention for large MI size (upper panels, **A**), large MVO (middle panels, **B**), and significant reduction in LVEF as assessed by cardiac magnetic resonance (lower panels, **C**) both before hospital discharge (left column) and at 30d (right column). Values above the 66th percentile identified patients with large extent of MI or of MVO, and values below the 33rd percentile identified patients with relevant reduction of the LVEF after STEMI. Angio-IMR indicates angiography-derived index of microcirculatory resistance (in mmHg\*s); AUC, area under the curve; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MVO, microvascular obstruction; and STEMI, ST-segment-elevation myocardial infarction.

and rehospitalization for heart failure.<sup>1</sup> Noninvasive assessment of myocardial viability and microvascular function after an acute MI revealed that larger infarct size, increased extent of MVO, and reduced LVEF were associated with adverse long-term outcomes.<sup>2,8,23</sup> The

assessment of the coronary microvascular function at the time of primary PCI may therefore allow for a timely risk prediction of patients with STEMI and identification of those in need for aggressive medical therapy and close follow-up.

**Table 5. Multivariate Generalized Linear Models**

	MI size, g				MVO, g				LVEF, %			
	Baseline		30d		Baseline		30d		Baseline		30d	
	Odds ratio [95% CI]	P value	Odds ratio [95% CI]	P value	Odds ratio [95% CI]	P value	Odds ratio [95% CI]	P value	Odds ratio [95% CI]	P value	Odds ratio [95% CI]	P value
Post-PCI angio-IMR	1.01 [1.00–1.01]	<0.01	1.01 [1.00–1.01]	<0.01	1.01 [1.00–1.01]	0.04	1.01 [1.00–1.01]	0.02	1.01 [1.00–1.01]	0.02	1.01 [1.00–1.01]	0.01
Age	0.99 [0.98–1.00]	0.11	0.99 [0.98–1.00]	0.56	1.00 [0.99–1.01]	0.90	1.00 [1.00–1.01]	0.05	0.99 [0.98–1.00]	0.04	0.99 [0.98–1.01]	0.41
Type 2 diabetes	1.25 [0.77–2.03]	0.36	1.60 [0.98–2.62]	0.06	1.08 [0.62–1.88]	0.78	1.31 [0.82–2.01]	0.26	1.25 [0.74–2.10]	0.41	1.17 [0.70–1.96]	0.55
Hypertension	0.92 [0.72–1.16]	0.47	1.00 [0.78–1.27]	0.99	0.99 [0.76–1.31]	0.98	0.96 [0.76–1.20]	0.70	0.81 [0.63–1.05]	0.11	1.05 [0.81–1.35]	0.70
Dyslipidemia	0.87 [0.69–1.11]	0.27	0.95 [0.75–1.22]	0.71	0.97 [0.74–1.28]	0.83	0.79 [0.62–0.99]	0.04	0.96 [0.74–1.24]	0.76	0.84 [0.65–1.08]	0.18

Results of the multivariate generalized linear model analysis for myocardial infarction size, MVO, and LVEF at baseline and at 30d. Angio-IMR indicates angiography-derived index of microcirculatory resistance (in mmHg\*s); LVEF, left ventricular ejection fraction; MI, myocardial infarction; MVO, microvascular obstruction; and PCI, percutaneous coronary intervention.

This study provides first evidence for the link between angiography-derived measures of microvascular dysfunction and LV remodeling in European patients with large STEMI undergoing PCI. Increased post-PCI angio-IMR values as derived from the initial coronary angiogram were linked with size of MI, extent of MVO, and LV systolic function at 30-day follow-up. These findings extend the results recently obtained from an unselected Chinese STEMI population undergoing PCI to European patients with large STEMI and underline the role of angiography-derived measures of microvascular dysfunction in the setting of acute STEMI.<sup>14</sup> These data obtained with angiography-derived parameters are in line with previous studies on patients with STEMI showing an association between invasively measured parameters of microcirculatory function and MVO,<sup>7,11</sup> with angio-IMR values differing only slightly from the initially proposed IMR cutoff value of 40 mmHg\*s. The present investigation further validates and expands findings from previous studies.<sup>10–12</sup> In particular, our study focused on patients with large STEMI and did not include patients with non-STEMI or chronic coronary syndromes. Thereby our study includes a clearly defined patient population. Further, myocardial and microvascular damage were assessed at 2 time points, not only within 5 days from the primary PCI but also at 30 days. In addition, angio-IMR was obtained without the use of a pressure wire or the induction of a hyperemic state, thereby validating previous results using a simplified methodology, and was performed in culprit and non-culprit vessels. Finally, patients suffering from a larger area of myocardial damage, as reflected either by CMR or cardiac biomarker elevations, could be identified using angio-IMR. Indeed, angiography-derived

modalities represent reliable, readily available, and cost-effective tools for a real-time assessment of coronary microvascular dysfunction without the need for pressure wire advancement and hyperemia induction, which may be of particular value in the acute setting. Postprocedural assessment of coronary microvascular function in patients with STEMI may provide a rationale for more personalized treatment strategies.

The present study presents several limitations. The study represents a post hoc analysis of the CLEVER-ACS trial, and therefore results need to be interpreted in the context of the inclusion and exclusion criteria of the main study,<sup>15</sup> and patients may not represent a broader all-comer STEMI population. Furthermore, as follow-up CMR was performed at 30 days, no conclusions can be drawn about the association between angiography-derived measures of coronary microvascular resistance and long-term outcomes after a STEMI event. Despite the threshold adopted to define large MI size, large extent of MVO and reduced LVEF are arbitrary, and the presented findings are insensitive to the choice of the threshold value (Table S4).

## CONCLUSIONS

In patients with acute STEMI undergoing PCI, angiography-derived measures of coronary microcirculatory dysfunction were associated with myocardial infarct size, extent of MVO, and LV systolic dysfunction at 30 days. These findings support the use of pressure wire-free modalities for evaluating microvascular function in patients with STEMI. Further investigations are warranted to explore the potential benefits of microvascular dysfunction-based management strategies for STEMI.

## ARTICLE INFORMATION

Received April 12, 2024; accepted November 7, 2024.

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### Acknowledgments

For the first draft of the manuscript, the authors used Chat-GPT 4.0 to improve readability of the manuscript. After using this tool/service, the authors reviewed, rewrote, and edited the content as needed and take full responsibility for the content of the publication.

### Sources of Funding

This study was executed without any external financial support. The CLEVER-ACS trial was supported by the Swiss National Science Foundation (33IC30\_166872; Swiss Clinical Trials Program).

### Disclosures

Dr Candrea has consultancy agreements with Medyria AG and Nanoflex AG. Dr Heg is employed by the Department of Clinical Research, University of Bern, which has a staff policy of not accepting honoraria or consultancy fees. However, the Department of Clinical Research is involved in design, conduct, or analysis of clinical studies funded by not-for-profit and for-profit organizations. In particular, pharmaceutical and medical device companies provide direct funding to some of these studies. For an up-to-date list of DCR conflicts of interest, see [https://www.ctu.unibe.ch/research\\_projects/declaration\\_of\\_interest/index\\_eng.html](https://www.ctu.unibe.ch/research_projects/declaration_of_interest/index_eng.html). Dr Matter has received research grants to the institution from Eli Lilly, AstraZeneca, Roche, Amgen, Novartis, Novo Nordisk, Lindenberg Family Office, Swiss National Science Foundation, Swiss Heart Foundation, and MSD, including speaker or consultant fees. Dr Stähli received research grants to the institution from the OPO Foundation, the Iten-Kohaut Foundation, the German Center for Cardiovascular Research, Boston Scientific, and Edwards Lifesciences and has received consulting and speaker fees from Boston Scientific and Abbott Vascular. Dr Stähli has been supported by the H. H. Sheikh Khalifa bin Hamad Al-Thani Research Program. The remaining authors have no disclosures to report.

### Supplemental Material

Tables S1–S4

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