

## Original article

## Functional angiography-derived index of microcirculatory resistance validated with microvascular obstruction in cardiac magnetic resonance after STEMI



Doosup Shin,<sup>a</sup> Juwon Kim,<sup>b</sup> Ki Hong Choi,<sup>b</sup> Neng Dai,<sup>c</sup> YinLiang Li,<sup>c</sup> Seung Hun Lee,<sup>d</sup> Hyun Sung Joh,<sup>b</sup> Hyun Kuk Kim,<sup>e</sup> Sung-Mok Kim,<sup>f</sup> Sang Jin Ha,<sup>g</sup> Mi Ja Jang,<sup>b</sup> Taek Kyu Park,<sup>b</sup> Jeong Hoon Yang,<sup>b</sup> Young Bin Song,<sup>b</sup> Joo-Yong Hahn,<sup>b</sup> Seung-Hyuk Choi,<sup>b</sup> Yeon Hyeon Choe,<sup>f</sup> Hyeon-Cheol Gwon,<sup>b</sup> and Joo Myung Lee<sup>b,\*</sup>

<sup>a</sup> Division of Cardiovascular Medicine, Department of Internal Medicine, University of Iowa Carver College of Medicine, Iowa City, IA, United States

<sup>b</sup> Division of Cardiology, Department of Internal Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

<sup>c</sup> Department of Cardiology, Zhongshan Hospital, Fudan University, Shanghai Institute of Cardiovascular Diseases, Shanghai, China

<sup>d</sup> Division of Cardiology, Department of Internal Medicine, Chonnam National University Hospital, Gwangju, Korea

<sup>e</sup> Department of Internal Medicine and Cardiovascular Center, Chosun University Hospital, University of Chosun College of Medicine, Gwangju, Korea

<sup>f</sup> Department of Radiology, Cardiovascular Imaging Center, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

<sup>g</sup> Division of Cardiology, Department of Internal Medicine, Gangneung Asan Hospital, University of Ulsan College of Medicine, Gangneung, Korea

## Article history:

Received 17 October 2021

Accepted 21 January 2022

Available online 3 March 2022

## Keywords:

Index of microcirculatory resistance

Microvascular obstruction

Cardiac magnetic resonance imaging

ST-elevation myocardial infarction

Myocardial infarction

## ABSTRACT

**Introduction and objectives:** The index of microcirculatory resistance (IMR) measured after primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI) is associated with microvascular obstruction (MVO) and adverse clinical events. To evaluate MVO after successful primary PCI for STEMI without pressure wires or hyperemic agents, we investigated the feasibility and usefulness of functional angiography-derived IMR (angio-IMR).

**Methods:** The current study included a total of 285 STEMI patients who underwent primary PCI and cardiac magnetic resonance (CMR). Angio-IMR of the culprit vessel after successful primary PCI was calculated using commercial software. MVO, infarct size, and myocardial salvage index were assessed using CMR, which was obtained a median of 3.0 days [interquartile range, 3.0-5.0] after primary PCI.

**Results:** Among the total population, 154 patients (54.0%) showed elevated angio-IMR (> 40 U) in the culprit vessel. MVO was significantly more prevalent in patients with angio-IMR > 40 U than in those with angio-IMR ≤ 40 U (88.3% vs 32.1%,  $P < .001$ ). Infarct size, extent of MVO, and area at risk were significantly larger in patients with angio-IMR > 40 U than in those with angio-IMR ≤ 40 U ( $P < .001$  for all). Angio-IMR showed a significantly higher discriminatory ability for the presence of MVO than thrombolysis in myocardial infarction flow grade or myocardial blush grade (area under the curve: 0.821, 0.504, and 0.496, respectively,  $P < .001$ ).

**Conclusions:** Angio-IMR was significantly associated with CMR-derived infarct size, extent of MVO, and area at risk. An elevated angio-IMR (> 40 U) after primary PCI for STEMI was highly predictive of the presence of MVO in CMR.

This trial was registered at ClinicalTrials.gov (Identifier: NCT04828681).

© 2022 Sociedad Española de Cardiología. Published by Elsevier España, S.L.U. All rights reserved.

## Índice de resistencia microcirculatorio y obstrucción microvascular en la resonancia magnética cardíaca tras un IAMCEST

## RESUMEN

**Introducción y objetivos:** El índice de resistencia microcirculatoria (IRM) medido tras una angioplastia primaria (ICPp) por infarto agudo de miocardio con elevación del segmento ST (IAMCEST) se asocia con la aparición de obstrucción microvascular (OMV) y eventos clínicos adversos. Para evaluar la OMV tras una ICPp exitosa por IAMCEST sin guías de presión ni administración de agentes hiperémicos, variables que parecen limitar la adopción del IRM en el laboratorio de hemodinámica, se investiga la viabilidad y la utilidad de la medición del IRM mediante resonancia magnética cardíaca (RMC) (angio-IRM).

## Palabras clave:

Índice de resistencia microcirculatoria

Obstrucción microvascular

Resonancia magnética cardíaca

Infarto agudo de miocardio con elevación

del segmento ST

Infarto de miocardio

## SEE RELATED CONTENT:

<https://doi.org/10.1016/j.rec.2022.05.011>

\* Corresponding author: Division of Cardiology, Department of Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, 06351 Seoul, Republic of Korea.

E-mail addresses: [drone80@hanmail.net](mailto:drone80@hanmail.net), [joomyung.lee@samsung.com](mailto:joomyung.lee@samsung.com) (J.M. Lee).

<https://doi.org/10.1016/j.rec.2022.01.004>

1885-5857/© 2022 Sociedad Española de Cardiología. Published by Elsevier España, S.L.U. All rights reserved.

**Métodos:** El estudio incluyó a 285 pacientes con IAMCEST sometidos a ICPp y RMC. Con un programa informático comercial, se calculó el angio-IRM del vaso culpable tras la ICPp exitosa. Se evaluaron la OMV, el tamaño del infarto y el índice de rescate miocárdico medidos una mediana de 3 [rango intercuartílico, 3–5] días después de la ICPp.

**Resultados:** De la población total, 154 pacientes (54,0%) mostraron valores de angio-IRM elevados ( $> 40$  U) en el vaso culpable. La OMV fue significativamente más frecuente en los pacientes con angio-IRM  $> 40$  U que en aquellos con angio-IRM  $\leq 40$  U (el 88,3 frente al 32,1%;  $p < 0,001$ ). El tamaño del infarto, la extensión de la OMV y el área en riesgo fueron significativamente mayores en los pacientes con angio-IRM  $> 40$  U que con angio-IRM  $\leq 40$  U ( $p < 0,001$  para todas las comparaciones). El angio-IRM mostró una capacidad de discriminación de OMV significativamente mayor que el grado de flujo TIMI o de *blush* miocárdico (área bajo la curva, 0,821, 0,504 y 0,496 respectivamente;  $p < 0,001$ ).

**Conclusiones:** El angio-IRM se asoció significativamente con el tamaño del infarto, la extensión de la OMV y el área en riesgo. Cifras altas del angio-IRM ( $> 40$  U) tras una ICPp por IAMCEST fueron muy predictivas de OMV en la RMC.

Ensayo clínico registrado en ClinicalTrials.gov (Identifier: NCT04828681).

© 2022 Sociedad Española de Cardiología. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

### Abbreviations

Angio-IMR: angiography-derived index of microcirculatory resistance

CMR: cardiac magnetic resonance imaging

IMR: index of microcirculatory resistance

MVO: microvascular obstruction

PCI: percutaneous coronary intervention

STEMI: ST-segment elevation myocardial infarction

### INTRODUCTION

Despite restoration of epicardial coronary blood flow by primary percutaneous coronary intervention (PCI) in patients with acute ST-segment elevation myocardial infarction (STEMI), failure of myocardial reperfusion can occur in up to two-thirds of STEMI patients, which is attributed to the occurrence of coronary microcirculatory dysfunction and microvascular obstruction (MVO).<sup>1–3</sup> Therefore, assessment of microcirculatory dysfunction and MVO after primary PCI would be important to evaluate the efficacy of the reperfusion therapy and need for potential further treatments. Cardiac magnetic resonance imaging (CMR) is considered the gold standard to assess MVO, which is known as an adverse prognostic indicator after primary PCI in STEMI patients.<sup>4</sup> However, obtaining CMR in STEMI patients is not always possible due to limited availability, medical cost, and logistic issues.<sup>5</sup>

The index of microcirculatory resistance (IMR) is a pressure wire-based physiologic index that allows quantitative assessment of the microcirculatory function in a target vessel territory. Previous studies have demonstrated that an elevated IMR in the culprit vessel of STEMI after primary PCI is significantly associated with the presence of MVO and the risk of subsequent cardiac death or heart failure admission.<sup>1,5–7</sup> However, conventional IMR measurement requires a pressure-temperature sensor wire and induction of hyperemia, which limits the adoption of IMR in daily practice, especially after primary PCI in STEMI patients. Recently, technical advances have enabled derivation of physiologic indexes, such as fractional flow reserve (FFR) or IMR, from angiographic images without the use of pressure-temperature sensor wire or hyperemic agents.<sup>8–10</sup> A recent study showed that angiography-derived IMR (angio-IMR) could be used as an alternative to conventional pressure wire-derived IMR in patients with STEMI for prognostic stratification.<sup>11,12</sup> Given its simplicity and time- and cost-effectiveness without need for additional procedure(s), angio-IMR would be particularly beneficial in patients with STEMI.

In this regard, the current study aimed to investigate the feasibility of angio-IMR in the evaluation of MVO after successful primary PCI in patients with STEMI.

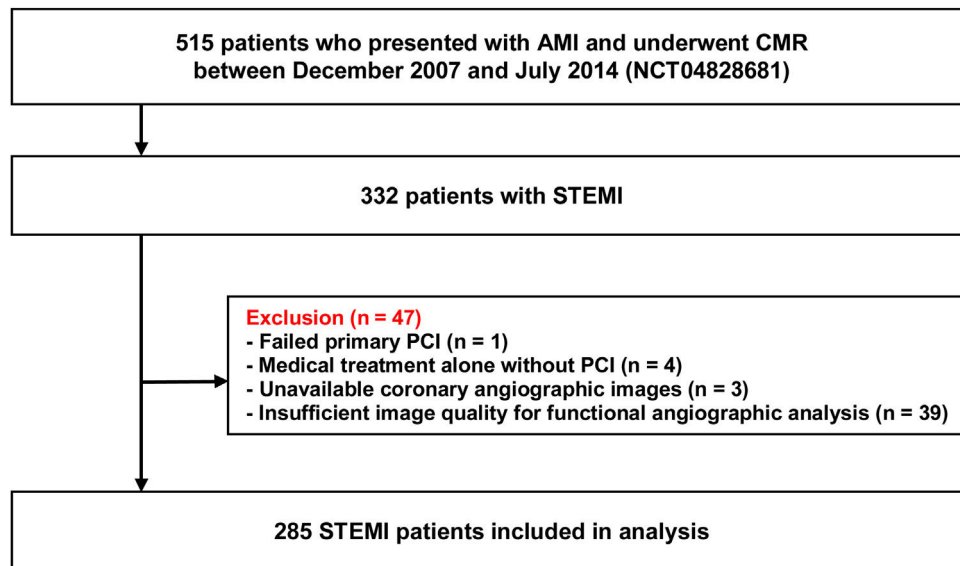
### METHODS

#### Study population

The study population was derived from the prospective acute myocardial infarction (AMI)-CMR registry of an academic tertiary medical center. In this single-center registry, 515 consecutive patients who presented with AMI and underwent CMR were prospectively enrolled between December 2007 and July 2014. The current study was a retrospective post hoc analysis of the prospective registry data. AMI was defined as the presence of clinical, electrocardiographic, or echocardiographic evidence of myocardial ischemia with elevated cardiac troponin levels above the 99th percentile of upper reference limit. Among the total patients, patients with STEMI ( $n = 332$ ) were selected for the current study, in whom electrocardiogram showed a ST-segment elevation more than 1 mm in 2 or more contiguous leads or a presumably new-onset left bundle branch block. Patients with failed primary PCI ( $n = 1$ ), medical treatment alone without PCI ( $n = 4$ ), unavailable coronary angiographic images ( $n = 3$ ), and insufficient image quality for functional angiographic analysis ( $n = 39$ ) were excluded. Following these exclusions, a total of 285 patients were analyzed in the current study (figure 1). The Institutional Review Board of our institute approved this study, and all participants provided written informed consent. Demographic data and cardiovascular risk factors were recorded at the time of the index procedure. The study protocol was registered in clinicaltrials.gov (NCT04828681).

#### Coronary angiography and primary percutaneous coronary intervention

Coronary angiography was performed using standard techniques. Angiographic views were obtained following administration of intracoronary nitrate (100 or 200  $\mu$ g) using a 5-Fr diagnostic catheter and a 6-Fr guiding catheter in pre- and post-PCI, respectively. For contrast injection, contrast media was injected into a coronary artery through the catheter at a rate of 3 and 4 mL/s, respectively, for right and left coronary arteries for approximately 2 seconds using an automated injector (ACIST Medical Systems, Eden Prairie, USA). Primary PCI was performed by standard techniques. All angiograms were analyzed in a blinded fashion by independent core laboratory personnel and quantitative coronary angiography was performed in optimal projections with validated software (CAAS II, Pie Medical Imaging, Netherlands).



**Figure 1.** Flowchart of patient selection. AMI, acute myocardial infarction; CMR, cardiac magnetic resonance; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

### Analysis of angiography-derived index of microcirculatory resistance

For the derivation of angio-IMR, angiographic images were analyzed in a post hoc fashion using commercial software (FlashAngio, Rainmed Ltd, China) at an independent core laboratory (Zhongshan Hospital, Fudan University, Shanghai Institute of Cardiovascular Diseases, Shanghai, China). Prior studies have shown the details of angio-IMR derivation,<sup>10,11</sup> based on the assumption that mean flow velocity in the entire period of diastole is approximately proportional to that in hyperemia. Briefly, Digital Imaging and Communications in Medicine angiography images and aortic pressures were registered in the FlashAngio console.<sup>10</sup> Then, angio-IMR was estimated in 3 steps.<sup>8,10,11</sup> First, a 3-dimensional mesh model of the coronary artery was reconstructed along the vessel from the inlet to the distal segment of the target vessel, using at least 2 angiographic projections separated by at least 30°. Second, angiography-derived FFR (angio-FFR) was estimated by computational pressure-flow dynamics, as described previously.<sup>8</sup> Finally, angio-IMR was calculated using the following equation: angio-IMR = estimated hyperemic aortic pressure (Pa) × angio-FFR × (vessel length / K × V<sub>diastole</sub>).<sup>10,11</sup> Estimated hyperemic Pa was assumed on the basis of mean arterial pressure (MAP) during the index procedure: MAP × 0.2 when MAP ≥ 95 mmHg and MAP × 0.15 when MAP < 95 mmHg.<sup>8,11</sup> Vessel length was determined as the distance between the inlet and the distal segment of the target vessel where angio-FFR and angio-IMR values were acquired.<sup>11</sup> K was the constant to adjust the difference between resting and hyperemic flow velocity. V<sub>diastole</sub> represented resting flow velocity during diastole which was derived from the thrombolysis in myocardial infarction (TIMI) frame count method.<sup>11</sup>

### Cardiac magnetic resonance imaging

CMR was performed a median of 3.0 days (interquartile range [IQR], 3.0–5.0) after primary PCI using a 1.5T scanner (Magnetom Avanto, Syngo MR D13 version; Siemens Medical Solutions, Germany) with a 32-channel phased array receiver coil. Cine images of the left ventricle (LV) were acquired through a steady-state free-precession sequence in the short-axis, 4-chamber,

3-chamber, and 2-chamber views. T<sub>2</sub>-weighted black blood images were acquired using a segmented turbo spin-echo sequence in the same short-axis view as the cine sequences. Late gadolinium enhancement images covering the entire LV were acquired 10 minutes after intravenous injection of 0.15 mmol/kg gadobutrol (Bayer Healthcare, Germany) by using segmented phase-sensitive inversion-recovery turbo fast low-angle shot in a contiguous short-axis LV stack. Inversion times were individually adjusted to optimize nulling of visually normal myocardium (200 to 350 msec). All CMR measurements were independently performed in a blinded fashion by experienced cardiovascular radiologists at the same institute. Left ventricular volume analysis was performed using a commercialized software (CAAS MRV version 1.0, Pie Medical Imaging B.V., The Netherlands).<sup>13</sup> The endocardial and epicardial borders were manually traced, and papillary muscles and LV trabeculae were excluded from the endocardium.<sup>13</sup> The T<sub>2</sub>-weighted image was used to determine the presence of intramyocardial hemorrhage and quantification of area at risk (AAR).<sup>13</sup> Hyperenhanced area was specified as an infarcted area, and hypoenhancement within the hyperenhanced area was considered as evidence of MVO.<sup>13</sup> The volume of delayed hyperenhancement was calculated as the sum of the area of delayed hyperenhancement within each segment multiplied by 10 mm.<sup>13</sup> The proportion of delayed hyperenhancement to LV myocardial volume was defined as infarct size (%). The extent of MVO was calculated in the same manner. The myocardial salvage index was calculated as follows: (AAR–infarct size) × 100/AAR.<sup>13</sup>

### Two-dimensional echocardiography

All patients underwent comprehensive 2-dimensional echocardiography at baseline (median 2.0 days, [1.0–3.0]) and at 6 months of follow-up (median 199.0 days, [179.0–259.0]). LV wall thickness and LV dimensions were measured at the parasternal long-axis view using standard methods based on the current guidelines.<sup>14</sup> LV mass was calculated at the end of diastole by the linear method.<sup>14</sup> LV ejection fraction (LVEF) was assessed by the biplane Simpson technique or visual estimation. Transmittal inflow velocities (E and A) and deceleration time were obtained by pulsed-wave Doppler performed in the apical 4-chamber view.

Tissue Doppler imaging was used to assess early (e') and late (a') atrial diastolic annular velocities in the apical 4-chamber view, and the lateral and septal mitral annulus velocities were averaged. A semiquantitative wall motion score was visually assessed and assigned to each LV segment to calculate the wall motion score index as the average of the scores of all segments visualized (sum score of all segments assessed/number of segments assessed).<sup>14</sup>

## Statistical analysis

All categorical variables are presented as numbers with relative frequencies, and continuous variables as means with standard deviations or medians with IQR according to their distributions, which were checked by the skewness and kurtosis test and visual inspection of Q-Q plots. The correlations between angio-IMR values and CMR-derived quantitative parameters (extent of MVO, infarct size, and AAR) were assessed by calculating Pearson or Spearman correlation coefficients according to the normality. The CMR-derived parameters and echocardiographic parameters were compared according to angio-IMR values with a cutoff value of 40, based on the previous studies.<sup>1,5–7,11</sup> Multivariable logistic regression analysis was used to calculate odds ratios (OR) with 95%

confidence intervals (95%CI) to find independent predictors for MVO. A multivariable regression model was constructed using all variables with a *P* value < .1 in the univariable analyses. Using a receiver operating characteristic curve and an area under the curve (AUC), the discriminatory ability of angio-IMR values to predict the presence of MVO in CMR was compared with that of conventional angiographic measures of culprit vessel reperfusion, including TIMI flow grade and myocardial blush grade. All probability values were 2-sided, and *P* values < .05 were considered statistically significant.

## RESULTS

### Baseline characteristics of study population

Among the total population, 154 patients (54.0%) had angio-IMR > 40 U and 131 patients (46.0%) had angio-IMR ≤ 40 U. There was no significant difference in demographics or cardiovascular risk factors between the 2 groups (table 1). Patients with angio-IMR > 40 U had higher peak troponin I and creatine kinase-MB levels and tended to have left anterior descending artery as the culprit vessel of STEMI than those with angio-IMR ≤ 40 U. Although there was no significant difference in door-to-balloon

**Table 1**  
Baseline characteristics of the study population

Variables	Total (N=285)	Angio-IMR ≤ 40 U (n=131, 46.0%)	Angio-IMR > 40 U (n=154, 54.0%)	<i>P</i>
<b>Patient characteristics</b>				
<i>Demographics</i>				
Age, y	59.5 ± 12.1	60.4 ± 11.7	58.7 ± 12.5	.236
Male sex	232 (81.4)	104 (79.4)	128 (83.1)	.420
Body mass index, kg/m <sup>2</sup>	24.6 ± 3.4	24.5 ± 3.2	24.7 ± 3.6	.661
<i>Cardiovascular risk factors</i>				
Hypertension	122 (42.8)	61 (46.6)	61 (39.6)	.237
Diabetes mellitus	70 (24.6)	31 (23.7)	39 (25.3)	.746
Hyperlipidemia	47 (16.5)	20 (15.3)	27 (17.5)	.608
Current smoker	138 (48.4)	62 (47.3)	76 (49.4)	.733
Previous percutaneous coronary intervention	14 (4.9)	7 (5.3)	7 (4.6)	.789
Previous myocardial infarction	10 (3.5)	5 (3.8)	5 (3.3)	.999
Multivessel disease	123 (43.2)	57 (43.5)	66 (42.9)	.999
<i>Hemodynamic parameters</i>				
Systolic blood pressure, mmHg	115 [102-127]	112 [99-124]	115 [107-131]	.046
Diastolic blood pressure, mmHg	71 [63-80]	70 [60-78]	73 [65-81]	.017
<i>Laboratory profiles</i>				
Peak troponin I, ng/mL	61.2 [16.3-143.1]	31.9 [7.6-83.8]	86.9 [38.4-173.2]	< .001
Peak CK-MB, ng/mL	171.1 [60.8-276.4]	101.5 [36.7-196.7]	234.8 [133.6-319.7]	< .001
High sensitivity CRP, mg/dL	1.2 [0.3-7.6]	1.3 [0.3-7.9]	1.2 [0.3-7.5]	.964
Low density lipoprotein, mg/dL	127.0 [100.0-150.0]	123.0 [99.0-142.0]	131 [100.0-151.0]	.111
<i>Discharge medication</i>				
Aspirin	281 (98.6)	130 (99.2)	151 (98.1)	.397
P2Y <sub>12</sub> inhibitor	279 (97.9)	129 (98.5)	150 (97.4)	.530
Beta-blocker	262 (91.9)	120 (91.6)	142 (92.2)	.852
RAAS blockade	233 (81.8)	107 (81.7)	126 (81.8)	.976
Statin	272 (95.4)	128 (97.7)	144 (93.5)	.152
<b>Lesion characteristics</b>				
<i>Culprit vessel</i>				.001
Left anterior descending artery	155 (54.4)	63 (48.1)	92 (59.7)	
Left circumflex artery	29 (10.2)	8 (6.1)	21 (13.6)	
Right coronary artery	101 (35.4)	60 (45.8)	41 (26.6)	
<i>Procedural characteristics</i>				
Door-to-balloon time, min	68 [50-81]	68 [48-82]	67 [51-80]	.588

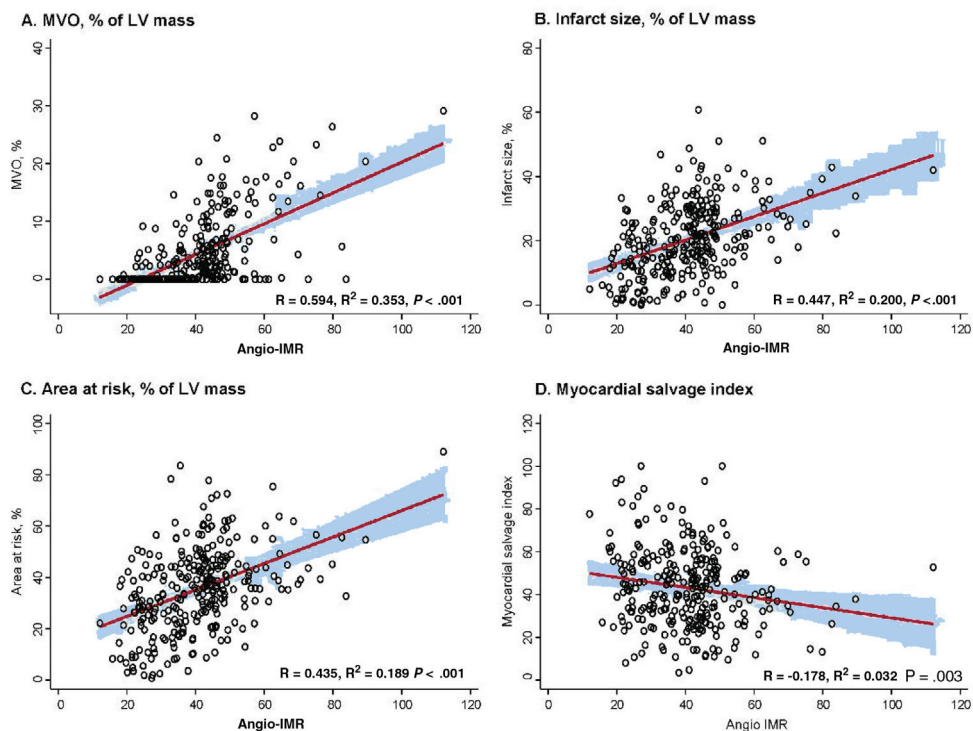
**Table 1** (Continued)

Baseline characteristics of the study population

Variables	Total (N=285)	Angio-IMR ≤ 40 U (n=131, 46.0%)	Angio-IMR > 40 U (n=154, 54.0%)	P
Pre-PCI TIMI grade				.440
TIMI 0	215 (75.4)	95 (72.5)	120 (77.9)	
TIMI 1	17 (6.0)	9 (6.9)	8 (5.2)	
TIMI 2	28 (9.8)	12 (9.2)	16 (10.4)	
TIMI 3	25 (8.8)	15 (11.5)	10 (6.5)	
Post-PCI TIMI grade				.014
TIMI ≤ 2	17 (6.0)	2 (1.5)	15 (9.7)	
TIMI 3	268 (94.0)	129 (98.5)	139 (90.3)	
Post-PCI myocardial blush grade				.243
Grade 1	1 (0.4)	1 (0.8)	0 (0.0)	
Grade 2	19 (6.7)	6 (4.6)	13 (8.4)	
Grade 3	265 (93.0)	124 (94.7)	141 (91.6)	
TIMI frame count	9 [7-12]	9 [7-11]	10 [7-13]	.103
No reflow	17 (6.0)	5 (3.8)	12 (7.8)	.158
Thrombus aspiration	181 (63.5)	75 (57.3)	106 (68.8)	.043
Side branch occlusion	6 (2.1)	2 (1.5)	4 (2.6)	.690
Glycoprotein IIb/IIIa inhibitor use	50 (17.5)	18 (13.7)	32 (20.8)	.119
Total number of stents	1.2 ± 0.6	1.2 ± 0.7	1.2 ± 0.6	.954
Mean stent diameter	3.2 ± 0.5	3.2 ± 0.5	3.2 ± 0.6	.628
Total length of stents	31.0 ± 17.2	30.9 ± 17.2	31.1 ± 17.2	.952
<i>Angiography-derived physiologic indices</i>				
Angiography-derived FFR, post-PCI	0.90 ± 0.05	0.88 ± 0.05	0.92 ± 0.05	< .001
Angiography-derived IMR, U	40.6 ± 13.8	29.5 ± 6.4	50.2 ± 10.9	< .001

CK-MB, creatine kinase-MB; CRP, C-reactive protein; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; PCI, percutaneous coronary intervention; RAAS, renin-angiotensin-aldosterone system; TIMI, thrombolysis in myocardial infarction.

Values are expressed as No. (%), mean ± standard deviation, or median [interquartile range].



**Figure 2.** Correlation between angio-IMR and CMR parameters. The correlations between angio-IMR and CMR-derived parameters after primary PCI for STEMI, including (A) MVO (% of LV mass), (B) infarct size (% of LV mass), (C) area at risk (% of LV mass), and (D) myocardial salvage index, are demonstrated. Angio-IMR, functional angiography-derived IMR; CMR, cardiac magnetic resonance; IMR, index of microcirculatory resistance; LV, left ventricular; MVO, microvascular obstruction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

**Table 2**

CMR parameters according to angiography-derived IMR

CMR parameters	Total (N = 285)	Angio-IMR ≤ 40 U (n = 131, 46.0%)	Angio-IMR > 40 U (n = 154, 54.0%)	P
Time from PCI to CMR, d	3.0 [3.0-5.0]	4.0 [3.0-5.0]	3.0 [3.0-4.0]	.516
LVEDV, mL	146.6 ± 34.5	143.3 ± 38.0	149.4 ± 31.1	.135
LVESV, mL	72.2 ± 31.4	66.8 ± 35.9	76.8 ± 26.3	.008
LVEF, %	52.1 ± 10.6	55.1 ± 11.2	49.5 ± 9.3	<.001
Infarct size, mL	21.5 ± 12.8	15.1 ± 9.7	27.0 ± 12.6	<.001
Infarct size, % of LV mass	20.5 ± 11.2	15.3 ± 9.9	24.9 ± 10.4	<.001
Area at risk, % of LV mass	35.5 ± 16.3	28.3 ± 15.8	41.6 ± 14.1	<.001
Myocardial salvage index	43.2 ± 18.3	46.4 ± 19.4	40.5 ± 16.8	.006
MVO	178 (62.5)	42 (32.1)	136 (88.3)	<.001
MVO, % of LV mass	2.0 [0.0-6.3]	0.0 [0.0-1.8]	5.2 [1.5-11.8]	<.001
Intramycardial hemorrhage	136 (48.1)	39 (30.2)	97 (63.0)	<.001

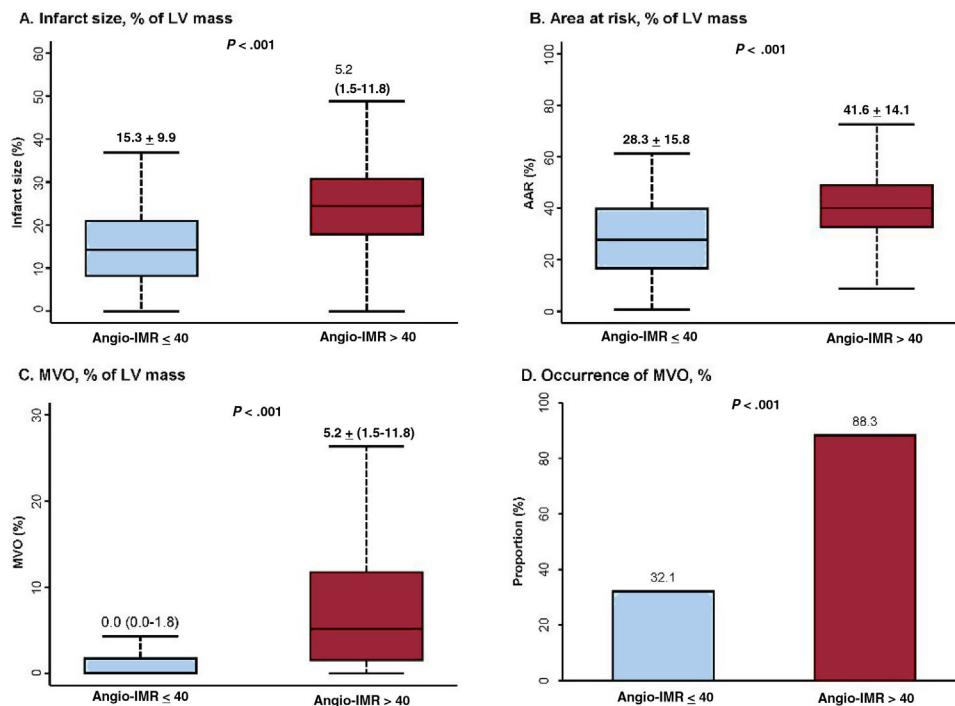
CMR, cardiac magnetic resonance imaging; IMR, index of microcirculatory resistance; LV, left ventricle; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; MVO, microvascular obstruction; PCI, percutaneous coronary intervention. Values are expressed as No. (%), mean ± standard deviation, or median [interquartile range].

time and pre-PCI TIMI flow grade between the 2 groups, TIMI flow grade ≤ 2 after primary PCI was more prevalent among patients with angio-IMR > 40 U. In contrast, post-PCI myocardial brush grade and the incidence of no reflow were similar between the 2 groups. Patients with angio-IMR > 40 U showed a higher mean post-PCI angio-FFR value than those with angio-IMR ≤ 40 U ( $0.88 \pm 0.05$  vs  $0.92 \pm 0.05$ ,  $P < .001$ ) (table 1).

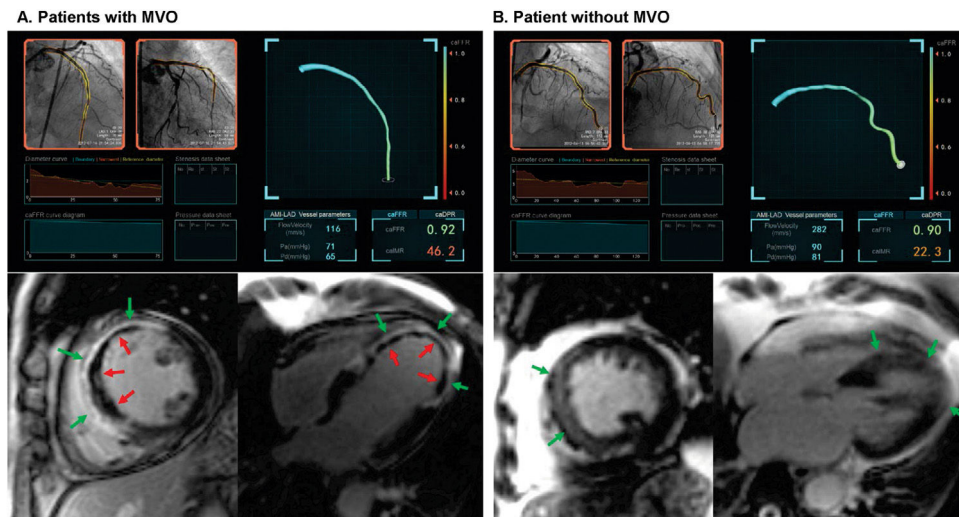
### Cardiac magnetic resonance parameters according to angio-index of microcirculatory resistance

Angio-IMR showed a significant correlation with CMR-derived infarct size, extent of MVO, and AAR ( $P < .001$  for all) (figure 2).

Compared with patients with angio-IMR ≤ 40 U, those with angio-IMR > 40 U had a significantly larger infarct size ( $15.3 \pm 9.9$  vs  $24.9 \pm 10.4$ ,  $P < .001$ ), AAR ( $28.3 \pm 15.8$  vs  $41.6 \pm 14.1$ ,  $P < .001$ ), and extent of MVO ( $0.0$  [0.0-1.8] vs  $5.2$  [1.5-11.8],  $P < .001$ ). Conversely, the angio-IMR ≤ 40 U group showed a significantly higher myocardial salvage index than the angio-IMR > 40 U group. In the current study, 62.5% ( $n = 178$ ) of STEMI patients who underwent primary PCI and CMR were found to have MVO (table 2). Most patients with angio-IMR > 40 U (88.3%) were found to have MVO in CMR, whereas less than one-third of patients with angio-IMR ≤ 40 U (32.1%) showed MVO in CMR (table 2 and figure 3). The extent of MVO among those patients with angio-IMR ≤ 40 U and MVO was significantly less than that of patients with angio-IMR > 40 U and MVO ( $3.0$  [2.1-5.1]



**Figure 3.** Comparison of CMR parameters according to angio-IMR. CMR-derived parameters including (A) infarct size, (B) area at risk, (C) extent of MVO, and (D) proportion of MVO are compared according to the angio-IMR after primary PCI for ST-segment elevation myocardial infarction. Values are expressed as means ± standard deviations or proportions (%). In box-and-whisker plots, the horizontal line indicates median value, box indicates the interquartile range, and whiskers indicate the minimum and maximum values excluding outliers. AAR, area at risk; angio-IMR, functional angiography-derived IMR; CMR, cardiac magnetic resonance; IMR, index of microcirculatory resistance; LV, left ventricular; MVO, microvascular obstruction.



**Figure 4.** Representative case examples. Two representative case examples of ST-segment elevation myocardial infarction patients who underwent successful revascularization of the epicardial culprit vessel (LAD) during primary percutaneous coronary intervention are shown. A: the patient had an elevated angio-IMR value of 46.2, which was calculated from postpercutaneous coronary intervention angiographic images. Cardiac magnetic resonance imaging demonstrated an infarcted area (in green arrows) and evidence of MVO (in red arrows). B: the patient had an angio-IMR value of 22.3, which suggested relatively preserved microcirculatory function after ST-segment elevation myocardial infarction. Cardiac magnetic resonance imaging demonstrated an infarcted area (in green arrows) but there was no evidence of MVO. IMR, index of microcirculatory resistance; MVO, microvascular obstruction.

vs 6.0% [2.5-13.2], respectively,  $P < .001$ ) (figure 1 of the supplementary data). Figure 4 shows representative case examples of patients with and without MVO and their angio-IMR values.

### Echocardiographic parameters according to angio-index of microcirculatory resistance

Table 3 and figure 5 show baseline and follow-up echocardiographic parameters according to angio-IMR. Compared with patients with angio-IMR  $\leq 40$  U, those with angio-IMR  $> 40$  U had a lower LVEF ( $55.6 \pm 10.4\%$  vs  $49.7 \pm 9.8\%$ ,  $P < .001$ ) and a higher

wall motion score index ( $1.2$  [1.1-1.5] vs  $1.5$  [1.3-1.8],  $P < .001$ ) on baseline echocardiography. This difference persisted at the 6-month follow-up echocardiogram (LVEF:  $59.6 \pm 9.8$  vs  $52.8 \pm 10.8$ ; wall motion score index  $1.1$  [1.0-1.3] vs  $1.4$  [1.2-1.7],  $P < .001$  for all). At baseline, there was no statistically significant difference in LV mass index or LV internal dimension in end diastole between the 2 groups. At the 6-month follow-up echocardiography, however, patients with angio-IMR  $> 40$  U showed a larger LV internal dimension in end diastole and higher LV mass index than those with angio-IMR  $\leq 40$  U (table 3 and figure 5). Figure 2 of the supplementary data shows changes in LVEF, E/e', and wall motion score index during follow-up according to angio-IMR.

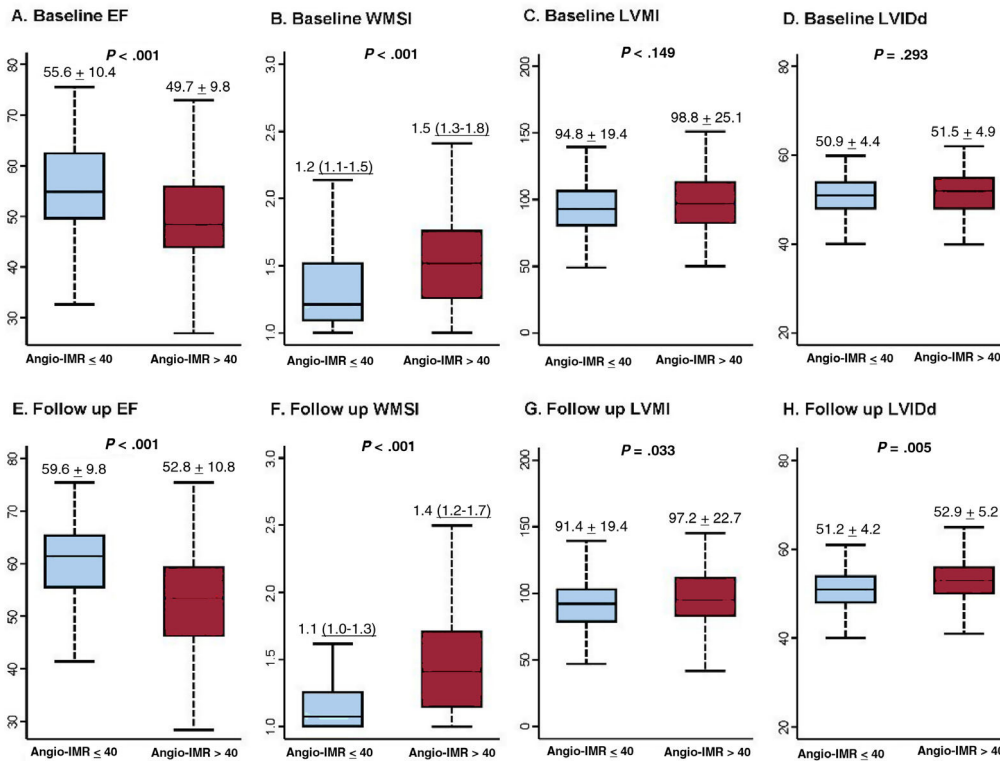
**Table 3**

Echocardiographic parameters according to angiography-derived IMR

Echocardiographic parameters	Total (N=285)	Angio-IMR $\leq 40$ U (n=131, 46.0%)	Angio-IMR $> 40$ U (n=154, 54.0%)	P
<i>Baseline echocardiogram</i>				
Time to echocardiogram, d	2.0 [1.0-3.0]	3.0 [1.0-4.0]	2.0 [1.0-3.0]	.342
LVEF, %	$52.4 \pm 10.5$	$55.6 \pm 10.4$	$49.7 \pm 9.8$	$< .001$
Wall motion score index	1.4 [1.2-1.7]	1.2 [1.1-1.5]	1.5 [1.3-1.8]	$< .001$
LVIDd, mm	$51.2 \pm 4.7$	$50.9 \pm 4.4$	$51.5 \pm 4.9$	.293
LVIDs, mm	$33.8 \pm 6.2$	$32.5 \pm 6.0$	$34.8 \pm 6.1$	.002
LV mass index	$96.9 \pm 22.7$	$94.8 \pm 19.4$	$98.8 \pm 25.1$	.149
Mitral E/e'	$10.8 \pm 4.4$	$10.7 \pm 5.0$	$10.9 \pm 3.8$	.722
<i>Follow-up echocardiogram</i>				
Time to echocardiogram, d	199.0 [179.0-259.0]	199.0 [179.0-239.0]	201.0 [178.0-282.0]	.470
LVEF, %	$55.9 \pm 10.9$	$59.6 \pm 9.8$	$52.8 \pm 10.8$	$< .001$
Wall motion score index	1.2 [1.1-1.6]	1.1 [1.0-1.3]	1.4 [1.2-1.7]	$< .001$
LVIDd, mm	$52.1 \pm 4.8$	$51.2 \pm 4.2$	$52.9 \pm 5.2$	.005
LVIDs, mm	$33.6 \pm 6.2$	$32.0 \pm 5.5$	$34.8 \pm 6.4$	$< .001$
LV mass index	$94.6 \pm 21.4$	$91.4 \pm 19.4$	$97.2 \pm 22.7$	.033
Mitral E/e'	$9.6 \pm 3.5$	$9.3 \pm 3.7$	$9.8 \pm 3.4$	.308

IMR, index of microcirculatory resistance; LV, left ventricle; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal dimension in end diastole; LVIDs, left ventricular internal dimension in end-systole.

Values are expressed as medians [interquartile ranges] or means  $\pm$  standard deviations.



**Figure 5.** Baseline and follow-up echocardiographic parameters according to angio-IMR. Baseline (A-D) and follow-up echocardiographic parameters (E-H) according to angio-IMR are compared. Values are expressed as means ± standard deviations or proportions (%). In box-and-whisker plots, the horizontal line indicates median value, box indicates the interquartile range, and whiskers indicate the minimum and maximum values excluding outliers. EF, ejection fraction; IMR, index of microcirculatory resistance; LVIDd, left ventricular internal dimension in end diastole; LVMI, left ventricular mass index; WMSI, wall motion score index.

**Independent predictors and discriminatory ability for microvascular obstruction determined by cardiac magnetic resonance**

In the multivariable logistic regression analysis, elevated angio-IMR > 40 U was a strong independent predictor for the presence of MVO in CMR after primary PCI for STEMI (OR, 12.24; 95%CI, 6.310-23.75, *P* < .001) (table 4). Furthermore, angio-IMR in a continuous

variable was independently associated with the presence of MVO (per 1 U increase of angio-IMR: OR, 1.102; 95%CI, 1.068-1.137, *P* < .001) (table 1 of the supplementary data). When comparing the discriminatory ability of angio-IMR with that of conventional angiographic measures of myocardial reperfusion, angio-IMR showed a significantly higher discriminatory ability for the presence of MVO than TIMI flow grade or myocardial blush grade after primary PCI (AUC 0.821, 0.504, and 0.496, respectively,

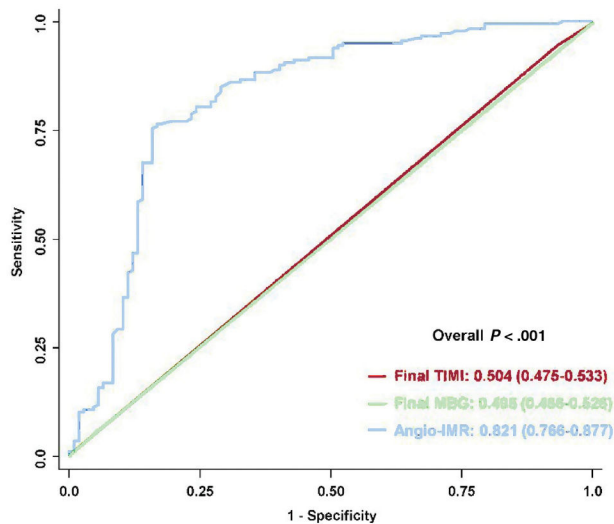
**Table 4**  
Independent predictors for MVO determined by CMR

Variable	Univariable analysis		Multivariable analysis*	
	OR (95%CI)	<i>P</i>	OR (95%CI)	<i>P</i>
Angio-IMR > 40 U	16.01 (8.670-29.57)	<.001	12.24 (6.310-23.75)	<.001
Age	0.991 (0.971-1.011)	.362		
Female sex	1.795 (0.983-3.279)	.057	2.137 (0.958-4.765)	.064
Diabetes mellitus	1.556 (0.871-2.777)	.135		
Current smoker	1.419 (0.876-2.299)	.156		
Door-to-balloon time, per 1 min increase	0.998 (0.996-1.000)	.083	0.998 (0.995-1.001)	.236
Peak CK-MB, per 1 ng/mL increase	1.008 (1.005-1.010)	<.001	1.003 (1.000-1.006)	.030
Peak troponin I, per 1 ng/mL increase	1.011 (1.007-1.015)	<.001	1.006 (1.001-1.010)	.011
Initial TIMI flow of 0	1.837 (1.063-3.175)	.029	1.318 (0.622-2.792)	.471
Post TIMI flow ≤ 2	0.850 (0.314-2.305)	.750		
Post MBG ≤ 2	1.126 (0.434-2.916)	.808		
No reflow	1.475 (0.505-4.308)	.478		
TIMI frame count	1.004 (0.951-1.059)	.896		
Use of glycoprotein IIb/IIIa inhibitor	0.882 (0.472-1.647)	.693		

95%CI, 95% confidence interval; CK-MB, creatine kinase-MB; CMR, cardiac magnetic resonance imaging; IMR, index of microcirculatory resistance; MBG, myocardial blush grade; MVO, microvascular obstruction; OR, odds ratios; TIMI, thrombolysis in myocardial infarction.

\* C-statistics of the model: 0.881 (95%CI, 0.840-0.921).





**Figure 6.** Comparison of discriminatory ability to predict CMR-defined MVO. The receiver operating characteristic curves of post-PCI angio-IMR (in blue), final TIMI flow grade (in red), and final MBG (in green) to predict CMR-defined MVO are compared. Values are area under the curves and 95% confidence intervals. IMR, index of microcirculatory resistance; MBG, myocardial blush grade; MVO, microvascular obstruction; TIMI, Thrombolysis in Myocardial Infarction.

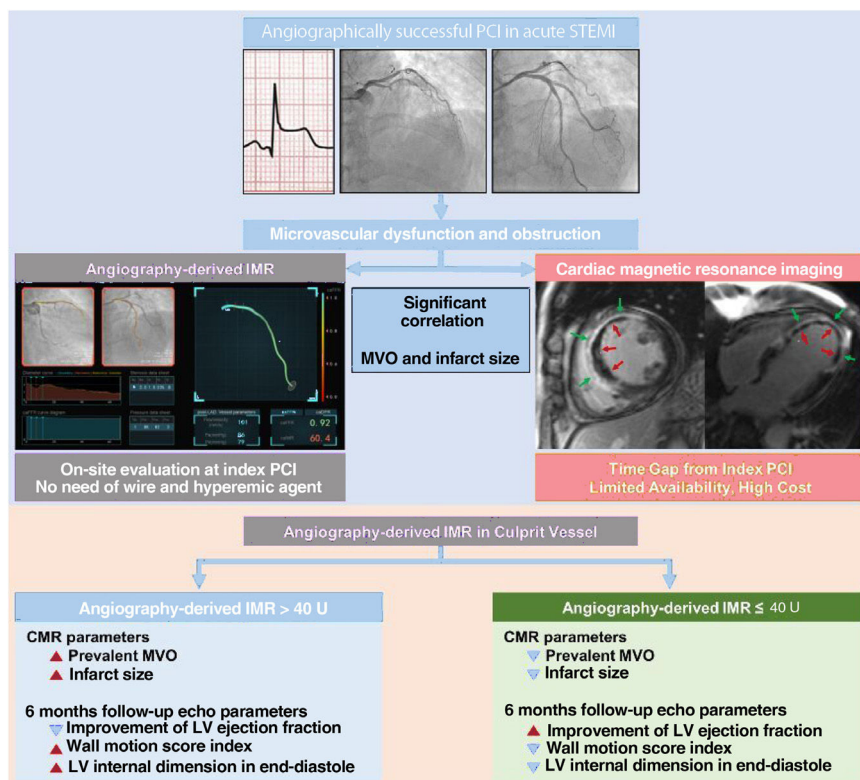
$P < .001$ ) (figure 6). This result persisted irrespective of the culprit vessel location (figure 3 of the supplementary data). Furthermore, angio-IMR also showed a significantly higher discriminatory ability for the presence of MVO than TIMI frame count (AUC 0.821 vs 0.502, respectively,  $P < .001$ ) (figure 4 of the supplementary data).

## DISCUSSION

The current study evaluated the feasibility of pressure wire-free, functional angiography-derived IMR (angio-IMR) in the assessment of MVO after primary PCI in patients with STEMI. The study showed that angio-IMR was significantly associated with the extent of MVO in CMR, and an elevated angio-IMR  $> 40$  U was an independent predictor for the presence of MVO with a significantly higher discriminatory ability than conventional angiographic measures of myocardial reperfusion (figure 7).

### Evaluation of microvascular obstruction after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction

Despite successful restoration of epicardial coronary blood flow, failure of myocardial reperfusion has been reported in up to two-thirds of STEMI patients with the occurrence of MVO.<sup>1–3</sup> In line with previous studies, the current study also showed that 62.5% of STEMI patients had evidence of MVO in CMR. CMR is the most sensitive and specific technique that enables direct visualization and quantification of MVO.<sup>15</sup> However, obtaining CMR in STEMI patients is limited in daily practice, and the time gap between primary PCI and CMR may limit the usefulness of CMR in the detection of MVO to guide adjunctive therapies early after revascularization. In contrast, coronary angiographic findings such as reduced antegrade blood flow (TIMI flow grade  $\leq 2$ ) or impaired penetration of contrast into the myocardium (myocardial blush grade  $< 2$ ) enable assessment of MVO at the time of primary PCI. However, these measures have limited reproducibility and accuracy.<sup>1,2</sup> In fact, MVO was found in more than half of STEMI patients in whom TIMI flow grade 3 was achieved after primary PCI,<sup>1,2</sup> and the incidence of MVO assessed by CMR was significantly



**Figure 7.** Central illustration. Functional coronary angiography-derived IMR and CMR for microvascular dysfunction after successful PCI in acute STEMI. CMR, cardiac magnetic resonance; IMR, index of microcirculatory resistance; LV, left ventricle; MVO, microvascular obstruction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

higher than that assessed by conventional angiographic measures.<sup>3</sup> The current study also demonstrated that the presence of MVO was not associated with no reflow, TIMI flow grade  $\leq 2$  or myocardial blush grade  $< 2$  after primary PCI. Furthermore, final TIMI flow grade or myocardial blush grade did not have discriminatory ability to predict the presence of MVO, with an AUC of 0.504 (95%CI, 0.475–0.533) and 0.496 (95%CI, 0.466–0.526), respectively. These results suggested a limited clinical role of an angiographic surrogate marker of MVO or myocardial reperfusion.

### Microcirculatory index and evaluation of microvascular obstruction in ST-segment elevation myocardial infarction

In this context, physiologic evaluation with IMR would be beneficial, which allows objective and more accurate assessment of coronary microcirculatory function at the time of primary PCI. Studies have demonstrated that an elevated IMR  $> 40$  U after primary PCI is significantly associated with the presence of MVO in CMR and the development of adverse clinical events in STEMI patients.<sup>1,5–7</sup> However, measuring IMR requires additional use of a pressure-temperature sensor wire, which prolongs procedure time and induction of hyperemia and which usually causes a hypotensive response. These requirements limit the adoption of IMR in daily practice, especially when dealing with acutely ill patients with STEMI. However, recent technical advances have enabled derivation of IMR from angiographic images (angio-IMR) without the need for pressure wire and hyperemic agent.<sup>8–10</sup> Therefore, the introduction of angio-IMR could significantly expand the use of IMR in daily practice.

We recently published a validation study using the same software and methodology that were used in the current study to calculate angio-IMR, which showed a significant correlation between conventional IMR and angio-IMR in STEMI patients ( $R = 0.782$ ;  $P < .001$ ).<sup>11</sup> It also showed an excellent diagnostic accuracy of angio-IMR to predict conventional IMR  $> 40$  U (sensitivity 75.0%, specificity 84.2%, accuracy 80.6%, and AUC 0.899 [95%CI, 0.786–0.949]), and patients with elevated angio-IMR  $> 40$  U after primary PCI showed a significantly higher risk of adverse cardiovascular events.<sup>11</sup> The current study first demonstrated the use of angio-IMR in the evaluation of MVO after primary PCI for STEMI. Importantly, an elevated angio-IMR  $> 40$  U after primary PCI for STEMI was highly predictive of the presence of MVO with a significantly higher discriminatory ability than conventional angiographic measures of myocardial reperfusion.

### Clinical implications and future directions

Since MVO could be a potential therapeutic target in patients with STEMI, timely on-site evaluation of MVO would be beneficial. Although the exact time required for the derivation of angio-IMR was not assessed in the current study, it can be calculated immediately after the derivation of angio-FFR, which only took a median of 5 minutes [IQR 3.5–6.1] in the recent study.<sup>16</sup> This further supports the applicability of angio-IMR in daily practice. In the current study, 88.3% of patients with an elevated angio-IMR  $> 40$  U after primary PCI showed evidence of MVO in CMR with significantly higher extent of MVO, infarct size, and AAR compared with those with angio-IMR  $\leq 40$ U. Nevertheless, it should be noted that 32.1% of patients with angio-IMR  $\leq 40$  U also showed MVO in CMR. However, the extent of MVO in those patients with angio-IMR  $\leq 40$  U and MVO was significantly less than that of the patients with angio-IMR  $> 40$  U and MVO (3.0% [2.1–5.1] vs 6.0% [2.5–13.2]), respectively,  $P < .001$ . In addition, a prior study showed that patients with MVO but relatively preserved microcirculatory function manifested by IMR  $\leq 40$  U experienced significant

regression in infarct size over time without prespecified adjunctive treatments after primary PCI.<sup>7</sup> Furthermore, angio-IMR showed a significant prognostic value after primary PCI in STEMI patients with a 3-fold increased risk of cardiac death and heart failure readmission among the patients with an elevated angio-IMR  $> 40$ U.<sup>11</sup> Therefore, angio-IMR could play a role in identification of patients who would most benefit from potential adjunctive therapies to reduce MVO following primary PCI. Nevertheless, the results of the current study support an association between angio-IMR and MVO in CMR, but not the equivalence between the two.

There have been efforts to find effective adjunctive treatments, such as intracoronary administration of thrombolytic or vasodilatory agents, to reduce microcirculatory dysfunction or MVO and improve outcomes after primary PCI.<sup>17–19</sup> Yet use of glycoprotein IIb/IIIa inhibitors is only proposed in the current guidelines if there is evidence of no reflow or a thrombotic complication. One important missing factor relates to the identification of patients at higher risk of developing MVO who would benefit from adjunctive treatments. Given the importance of coronary microcirculatory function and the common discrepancy between angiographic and physiologic parameters in evaluation of MVO, angio-IMR may allow better selection of patients benefitting from potential adjunctive therapies following primary PCI. In fact, a recent observational study showed the potential benefits of IMR-guided pressure-controlled intermittent coronary sinus occlusion during primary PCI in patients with STEMI.<sup>20</sup> Therefore, further studies are needed to evaluate the feasibility and efficacy of angio-IMR-guided individualized treatment strategies following primary PCI to reduce MVO in patients with STEMI.

### Limitations

Several limitations should be noted. First, since the current study did not collect clinical outcome data, the prognostic implications of angio-IMR and CMR parameters could not be assessed. Second, follow-up CMR was not performed, which limited detailed investigation on the dynamic changes of microvascular dysfunction after STEMI. Third, since angio-IMR is an angiography-based index, its accuracy depends on the quality of images and optimal projections. Fourth, the current study focused on microcirculatory dysfunction limited to the culprit vessel territory. Therefore, comparative prognosis according to the presence of underlying microcirculatory dysfunction in the non-culprit vessel territory was not evaluated. Fifth, the timing of CMR varied among patients, which could have affected the findings of CMR. However, most of the patients underwent CMR within 3 to 5 days of the primary PCI. Sixth, the accuracy of angio-IMR could not be examined in the current study since conventional pressure wire-based IMR was not available. However, angio-IMR after primary PCI has been validated in the recent studies by the current authors<sup>11</sup> and others.<sup>9</sup>

### CONCLUSIONS

Angio-IMR was significantly associated with CMR-derived infarct size, extent of MVO, and AAR. An elevated angio-IMR  $> 40$  U after primary PCI for STEMI was highly predictive of the presence of MVO in CMR. Therefore, angio-IMR, which does not require use of a pressure-temperature sensor wire or induction of hyperemia, may be a practical alternative to the conventional pressure wire-based physiologic index, which enables assessment of microvascular dysfunction and failed myocardial reperfusion after primary PCI for STEMI.

## FUNDING

This work was supported by Rainmed Ltd, Suzhou, China, which provided the software and console of angiography-derived FFR and IMR. The company played no role in the study design, conduct, data analysis or manuscript preparation.

## AUTHORS' CONTRIBUTIONS

D. Shin and J. Kim contributed equally to this work. The authors confirm their contributions to the paper as follows: study conception and design: D. Shin, J. Kim, J.M. Lee; data collection: J. Kim, K.H. Choi, N. Dai, Y. Li, S.H. Lee, H.S. Joh, H.K. Kim, S-M. Kim, S.J. Ha, M.J. Jang, T.K. Park, J.H. Yang, Y.B. Song, J-Y. Hahn, S-H. Choi, Y.H. Choe, H-C. Gwon, J.M. Lee; analysis and interpretation of the results: D. Shin, J. Kim, J.M. Lee; draft manuscript preparation: D. Shin, J. Kim, J.M. Lee; critically revising it for important intellectual contents: D. Shin, J. Kim, K.H. Choi, N. Dai, Y. Li, S.H. Lee, S.J. Ha, H.K. Kim, S-M. Kim, S.J. Ha, M.J. Jang, T.K. Park, J.H. Yang, Y.B. Song, J-Y. Hahn, S-H. Choi, Y.H. Choe, H-C. Gwon, J.M. Lee. All authors reviewed the results and approved the final version of the manuscript.

## CONFLICTS OF INTEREST

Dr J.M. Lee received an Institutional Research Grant from St Jude Medical (Abbott Vascular) and Philips Volcano. Dr J.-Y. Hahn received an Institutional Research Grant from St Jude Medical (Abbott Vascular) and Medtronic Inc. All other authors declare that there is no conflict of interest relevant to the submitted work.

### WHAT IS KNOWN ABOUT THE TOPIC?

- MVO in CMR is an adverse prognostic indicator in STEMI patients after successful primary PCI.
- The IMR is a pressure wire-based physiologic index that allows quantitative assessment of the microcirculatory function in a target vessel territory.
- IMR measured after primary PCI for STEMI is associated with the occurrence of MVO and adverse clinical events.

### WHAT DOES THIS STUDY ADD?

- The current study evaluated the feasibility of pressure wire-free, functional angio-IMR in the evaluation of MVO after primary PCI in patients with STEMI.
- Patients with angio-IMR > 40 U had a significantly larger CMR-derived infarct size and extent of MVO ( $P < .001$  for all) compared with patients with angio-IMR  $\leq$  40 U.
- Elevated angio-IMR > 40 U was a strong independent predictor for the presence of CMR-derived MVO after primary PCI for STEMI (odds ratio 12.24,  $P < .001$ ).
- Angio-IMR is a practical alternative to the conventional pressure wire-based physiologic index, which enables assessment of microvascular dysfunction and failed myocardial reperfusion after primary PCI for STEMI.

## APPENDIX. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at <https://doi.org/10.1016/j.rec.2022.01.004>

## REFERENCES

1. Carrick D, Haig C, Ahmed N, et al. Comparative Prognostic Utility of Indexes of Microvascular Function Alone or in Combination in Patients With an Acute ST-Segment-Elevation Myocardial Infarction. *Circulation*. 2016;134:1833–1847.
2. Niccoli G, Scalone G, Lerman A, et al. Coronary microvascular obstruction in acute myocardial infarction. *Eur Heart J*. 2016;37:1024–1033.
3. Durante A, Laricchia A, Benedetti G, et al. Identification of High-Risk Patients After ST-Segment-Elevation Myocardial Infarction: Comparison Between Angiographic and Magnetic Resonance Parameters. *Circ Cardiovasc Imaging*. 2017;10:e005841.
4. de Waha S, Patel MR, Granger CB, et al. Relationship between microvascular obstruction and adverse events following primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: an individual patient data pooled analysis from seven randomized trials. *Eur Heart J*. 2017;38:3502–3510.
5. Ahn SG, Hung OY, Lee JW, et al. Combination of the Thermodilution-Derived Index of Microcirculatory Resistance and Coronary Flow Reserve Is Highly Predictive of Microvascular Obstruction on Cardiac Magnetic Resonance Imaging After ST-Segment Elevation Myocardial Infarction. *JACC Cardiovasc Interv*. 2016;9:793–801.
6. Cuculi F, De Maria GL, Meier P, et al. Impact of microvascular obstruction on the assessment of coronary flow reserve, index of microcirculatory resistance, and fractional flow reserve after ST-segment elevation myocardial infarction. *J Am Coll Cardiol*. 2014;64:1894–1904.
7. De Maria GL, Alkhalil M, Wolfrum M, et al. Index of Microcirculatory Resistance as a Tool to Characterize Microvascular Obstruction and to Predict Infarct Size Regression in Patients With STEMI Undergoing Primary PCI. *JACC Cardiovasc Imaging*. 2019;12:837–848.
8. Li J, Gong Y, Wang W, et al. Accuracy of computational pressure-fluid dynamics applied to coronary angiography to derive fractional flow reserve: FLASH FFR. *Cardiovasc Res*. 2020;116:1349–1356.
9. De Maria GL, Scarsini R, Shanmuganathan M, et al. Angiography-derived index of microcirculatory resistance as a novel, pressure-wire-free tool to assess coronary microcirculation in ST elevation myocardial infarction. *Int J Cardiovasc Imaging*. 2020;36:1395–1406.
10. Ai H, Feng Y, Gong Y, et al. Coronary Angiography-Derived Index of Microvascular Resistance. *Front Physiol*. 2020;11:605356.
11. Choi KH, Dai N, Li Y, et al. Functional Coronary Angiography-Derived Index of Microcirculatory Resistance in Patients With ST-Segment Elevation Myocardial Infarction. *JACC Cardiovasc Interv*. 2021;14:1670–1684.
12. Kotronias RA, Terentes-Printzios D, Shanmuganathan M, et al. Long-Term Clinical Outcomes in Patients With an Acute ST-Segment-Elevation Myocardial Infarction Stratified by Angiography-Derived Index of Microcirculatory Resistance. *Front Cardiovasc Med*. 2021;8:717114.
13. Gwag HB, Park TK, Song YB, et al. Morphine Does Not Affect Myocardial Salvage in ST-Segment Elevation Myocardial Infarction. *PLoS One*. 2017;12:e0170115.
14. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1–39e14.
15. Stiermaier T, Thiele H, Eitel I. Coronary Microvascular Obstruction: Key Factor in the Prognosis of ST-Segment-Elevation Myocardial Infarction. *Circ Cardiovasc Imaging*. 2017;10:e006568.
16. Westra J, Andersen BK, Campo G, et al. Diagnostic Performance of In-Procedure Angiography-Derived Quantitative Flow Reserve Compared to Pressure-Derived Fractional Flow Reserve: The FAVOR II Europe-Japan Study. *J Am Heart Assoc*. 2018;7:e009603.
17. Fu Y, Gu XS, Hao GZ, et al. Comparison of myocardial microcirculatory perfusion after catheter-administered intracoronary thrombolysis with anisodamine versus standard thrombus aspiration in patients with ST-elevation myocardial infarction. *Catheter Cardiovasc Interv*. 2019;93:839–845.
18. Stone GW, Maehara A, Witzenbichler B, et al. Intracoronary abciximab and aspiration thrombectomy in patients with large anterior myocardial infarction: the INFUSE-AMI randomized trial. *Jama*. 2012;307:1817–1826.
19. Niccoli G, Rigattieri S, De Vita MR, et al. Open-label, randomized, placebo-controlled evaluation of intracoronary adenosine or nitroprusside after thrombus aspiration during primary percutaneous coronary intervention for the prevention of microvascular obstruction in acute myocardial infarction: the REOPEN-AMI study (Intracoronary Nitroprusside Versus Adenosine in Acute Myocardial Infarction). *JACC Cardiovasc Interv*. 2013;6:580–589.
20. De Maria GL, Alkhalil M, Borlotti A, et al. Index of microcirculatory resistance-guided therapy with pressure-controlled intermittent coronary sinus occlusion improves coronary microvascular function and reduces infarct size in patients with ST-elevation myocardial infarction: the Oxford Acute Myocardial Infarction - Pressure-controlled Intermittent Coronary Sinus Occlusion study (OxAMI-PICOS study). *EuroIntervention*. 2018;14:e352–e359.