

Predictors of Intramyocardial Hemorrhage After Reperfused ST-Segment Elevation Myocardial Infarction

Raquel P. Amier, MD;* Ruben Y. G. Tijssen, MD;* Paul F. A. Teunissen, MD, PhD; Rodrigo Fernández-Jiménez, MD; Gonzalo Pizarro, MD, PhD; Inés García-Lunar, MD; Teresa Bastante, MD; Peter M. van de Ven, PhD; Aernout M. Beek, MD, PhD; Martijn W. Smulders, MD; Sebastiaan C. A. M. Bekkers, MD, PhD; Niels van Royen, MD, PhD; Borja Ibanez, MD, PhD; Robin Nijveldt, MD, PhD

Background—Findings from recent studies show that microvascular injury consists of microvascular destruction and intramyocardial hemorrhage (IMH). Patients with ST-segment elevation myocardial infarction (STEMI) with IMH show poorer prognoses than patients without IMH. Knowledge on predictors for the occurrence of IMH after STEMI is lacking. The current study aimed to investigate the prevalence and extent of IMH in patients with STEMI and its relation with periprocedural and clinical variables.

Methods and Results—A multicenter observational cohort study was performed in patients with successfully reperfused STEMI with cardiovascular magnetic resonance examination 5.5 ± 1.8 days after percutaneous coronary intervention. Microvascular injury was visualized using late gadolinium enhancement and T2-weighted cardiovascular magnetic resonance imaging for microvascular obstruction and IMH, respectively. The median was used as the cutoff value to divide the study population with presence of IMH into mild or extensive IMH. Clinical and periprocedural parameters were studied in relation to occurrence of IMH and extensive IMH, respectively. Of the 410 patients, 54% had IMH. The presence of IMH was independently associated with anterior infarction (odds ratio, 2.96; 95% CI, 1.73–5.06 [$P < 0.001$]) and periprocedural glycoprotein IIb/IIIa inhibitor treatment (odds ratio, 2.67; 95% CI, 1.49–4.80 [$P < 0.001$]). Extensive IMH was independently associated with anterior infarction (odds ratio, 3.76; 95% CI, 1.91–7.43 [$P < 0.001$]). Presence and extent of IMH was associated with larger infarct size, greater extent of microvascular obstruction, larger left ventricular dimensions, and lower left ventricular ejection fraction (all $P < 0.001$).

Conclusions—Occurrence of IMH was associated with anterior infarction and glycoprotein IIb/IIIa inhibitor treatment. Extensive IMH was associated with anterior infarction. IMH was associated with more severe infarction and worse short-term left ventricular function in patients with STEMI. (*J Am Heart Assoc.* 2017;6:e005651. DOI: 10.1161/JAHA.117.005651.)

Key Words: acute myocardial infarction • cardiac magnetic resonance • intramyocardial hemorrhage • percutaneous coronary intervention • ST-segment elevation myocardial infarction

The recommended treatment for ST-segment elevation myocardial infarction (STEMI) is coronary revascularization by primary percutaneous coronary intervention (PCI) in combination with antithrombotic therapy.¹ PCI and coronary revascularization, however, can cause additional injury in the form of reperfusion arrhythmias, myocardial stunning, and microvascular injury. Microvascular injury, also known as the

no-reflow phenomenon, occurs in up to 40% of patients after successful PCI² and may include microvascular obstruction (MVO) and intramyocardial hemorrhage (IMH) as visualized by cardiac magnetic resonance (CMR) imaging.³ Restoration of blood flow to infarcted or ischemic myocardium inadvertently leads to ultrastructural and functional changes at the microvascular level, including microvascular plugging, platelet

From the Department of Cardiology (R.P.A., R.Y.G.T., P.F.A.T., A.M.B., N.v.R., R.N.) and Department of Epidemiology and Biostatistics (P.M.v.d.V.), VU University Medical Center, Amsterdam, the Netherlands; Centro Nacional Investigaciones Cardiovasculares Carlos III, Madrid, Spain (R.F.-J., G.P., I.G.-L., B.I.); CIBER de Enfermedades Cardiovasculares (CIBERCIV), Madrid, Spain (R.F.-J., G.P., I.G.-L., B.I.); The Zena and Michael A. Wiener CVI, Icahn School of Medicine at Mount Sinai, New York, NY (R.F.-J.); Department of Cardiology, Hospital Universitario de La Princesa, Madrid, Spain (T.B.); IIS-Fundación Jiménez Díaz, Madrid, Spain (B.I.); Department of Cardiology, Maastricht University Medical Center, Maastricht, the Netherlands (M.W.S., S.C.A.M.B.).

*Dr Amier and Dr Tijssen contributed equally to this work.

Correspondence to: Robin Nijveldt, MD, PhD, Department of Cardiology, VU University Medical Center, PO Box 7057 | De Boelelaan 1117, 1081 HV Amsterdam, the Netherlands. E-mail: robin@nijveldt.net

Received January 19, 2017; accepted May 9, 2017.

© 2017 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

Clinical Perspective

What is New?

- This is the first study to link periprocedural additional glycoprotein IIb/IIIa inhibitor treatment to higher occurrence of intramyocardial hemorrhage in patients with reperfused ST-segment elevation myocardial infarction.

What are the Clinical Implications?

- The optimal application of aggressive antithrombotic therapies in patients with ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention remains to be studied, especially in the era of adequate double antiplatelet preloading.
- Anterior infarct location predicted presence and severity of intramyocardial hemorrhage and may prove useful in direct risk stratification.

aggregation, microvascular spasms, inflammatory response, and ischemic and reperfusion damage to the endothelium.^{4,5} Recently, it was shown that these areas of microvascular injury mainly contain areas of microvascular destruction, but also extensive erythrocyte extravasation referred to as reperfusion-induced IMH.^{6–8}

Although microvascular injury and IMH are closely related, it is unclear which factors determine why IMH occurs in certain patients with microvascular injury. IMH might be a feature of larger infarction; however, large infarctions occur without microvascular injury as well, thus patient-related and periprocedural factors are hypothesized to play a role. Recent studies have linked the presence of IMH to larger infarctions with worse left ventricular (LV) functional recovery compared with MVO only.^{9–11} Clarifying which factors promote IMH will increase our understanding of the pathophysiology and might thereby guide future steps to improve patient outcome after STEMI.

Visualization and quantification of infarct characteristics including infarct size, MVO, and IMH, are preferably performed with CMR imaging. With late gadolinium enhancement CMR imaging, infarcted myocardium is assessed by hyperenhancement after contrast administration, and MVO can be seen as a hypointense core within the hyperenhanced region. On T2-weighted CMR imaging, a hypointense core within the hyperintense edematous infarcted myocardium is thought to reflect IMH caused by the paramagnetic effects of hemoglobin breakdown products.⁹

The current study evaluated the prevalence and extent of IMH and the relation of IMH with clinical and procedural parameters in a large group of patients with revascularized STEMI who underwent CMR imaging in the days after infarction. In addition, the relation of IMH with infarct

characteristics and short-term LV functional outcome was assessed.

Methods

In this observational cohort study, prospectively included consecutive patients with STEMI who underwent CMR imaging 4 to 12 days after successful treatment by primary PCI were analyzed. Patient data were derived from previously described cohorts of the VU University Medical Center (PREDICT-MVI database and MVO database),^{12,13} Maastricht University Medical Center (MAST database),¹⁴ and Centro Nacional Investigaciones Cardiovasculares Carlos III (METOCARD-CNIC [Metoprolol in Cardioprotection During an Acute Myocardial Infarction] and Clock database),^{15,16} performed between 2003 and 2014. Written informed consent was obtained from all patients.

Coronary Angiography

Thrombolysis in myocardial infarction (TIMI) grade 3 flow post-PCI was defined as a visually normal flow through the stented coronary artery with normal distal coronary perfusion. Infarctions of the left anterior descending and left main stem coronary artery were defined as anterior myocardial infarction. Findings from coronary angiograms from patients of the METOCARD-CNIC database were adjudicated by an independent clinical events committee.

Cardiovascular Magnetic Resonance

The designs of the CMR protocols of all cohorts were previously published.^{12–14,17} Patients underwent CMR imaging 5.5±1.8 days after PCI, using a 1.5- or 3.0-Tesla clinical magnetic resonance scanner (1.5-T Sonata or Avanto [Siemens] or 1.5-T Intera or 3.0-T Achieva [Philips Medical Systems]).

In summary, balanced steady-state free precession cine imaging was performed in standard long- and short-axis orientations to measure LV volumes and calculate LV ejection fraction. Typical parameters were in-plane resolution 1.6×2.0 mm; slice thickness/slice gap: 5/5 mm, 6/4 mm, 8/0 mm; flip angle 40 to 75°; temporal resolution 35 to 50 ms; and TR/TE 3.4/1.7. Prior to contrast administration, breath-hold T2-weighted spin-echo images were acquired to visualize infarct-related edema and IMH in short-axis orientation covering the whole left ventricle or infarcted area only (defined using 3 long-axis views of T2-weighted CMR imaging).⁹ Typical parameters were TR=2×RR interval; TE 64 ms; and voxel size 1.5×1.8×7 mm. IMH was defined as an area with low (attenuated) signal within the hyperintense

edematous myocardium and was manually delineated and quantified. All IMH analyses were performed by a trained researcher (R.T.), and were later controlled by experienced readers (R.N. or R.F.J.). Measurements of IMH were performed blinded to clinical and other CMR imaging data. In case of disagreement, consensus was reached between the readers. Late gadolinium enhancement imaging was performed using an inversion recovery gradient echo sequence 10 to 15 minutes after administration of 0.2 mmol/kg gadolinium-based contrast agent (Magnevist [Schering] or Dotarem [Guerbet]) in short-axis orientation covering the whole left ventricle. Typical parameters were in-plane resolution 1.5×1.5 mm; slice thickness 5 to 8 mm; TR 3.9 to 9.6 mm; TE 2.4 to 4.4 ms; flip angle 25° ; and TI 250 to 350 ms nulled to normal myocardium. Infarct size was measured using the full-width half maximum method. Areas of hypoenhancement within the hyperenhanced infarcted myocardium were manually delineated and considered MVO. For quantification purposes, areas of MVO were included in the total infarct size.¹³ LV dimensions were indexed to body surface area, which was calculated using the formula of DuBois and DuBois. All CMR data were analyzed using dedicated offline software (QMassMR version 7.6, Medis).

Statistical Methods

All patient data were merged into 1 data set. Continuous variables are presented as mean and SD or median and interquartile range (IQR) when appropriate. Categorical variables are presented as number and percentage. We determined skewness and kurtosis and used Shapiro–Wilk test, box plots, stem-and-leaf plots, and histograms to explore the distribution of continuous variables. In addition to the presence of IMH, the extent of IMH was analyzed. Because of a right-skewed and zero-inflated distribution of IMH extent, patients were categorized into 3 groups: no IMH, mild IMH, and extensive IMH. Extensive versus mild IMH was defined as IMH weighing more versus equal/less than the median (3.76 g) among patients with presence of IMH, respectively. For univariable analysis, we compared means of normally distributed continuous variables between these groups using one-way ANOVA with Tukey post hoc tests for the difference between the groups. Not normally distributed continuous variables were compared using Kruskal–Wallis ANOVA, and post hoc testing was performed with Mann–Whitney *U* tests between groups (if overall ANOVA was significant). Between-group comparison of categorical variables was performed using chi-square test with post hoc testing, with chi-square tests separate for each pair of groups (if the overall chi-square test for 3 groups was significant). *P* values of <0.05 were considered statistically significant. For post hoc testing for differences between the 3 groups (no, mild, and extensive

IMH), Bonferroni correction was applied and *P* values of <0.017 were considered statistically significant. Covariates of interest associated with the occurrence of IMH as well as the occurrence of extensive IMH (versus mild or no IMH) were investigated using multivariable logistic regression. All baseline variables that were significant at $P < 0.10$ on univariable logistic regression analysis were entered into a multivariable model. All statistical analyses were performed using IBM SPSS software package (IBM SPSS Statistics version 22).

Results

Of 445 eligible STEMI patients, 410 patients were included in this pooled individual patient analysis. The main reason for exclusion was lack of or insufficient quality of T2-weighted CMR images. The mean age of the population was 59 ± 11 years, and 343 patients (84%) were men. Baseline characteristics of the study population per study are shown in Table 1 and baseline characteristics of the total study population and per IMH group are shown in Table 2.

A total of 222 patients (54%) had IMH, categorized into 2 groups of 111 patients based on the median IMH (3.76 g) as the cutoff value. Figure 1 shows typical examples of IMH as visualized by T2-weighted CMR imaging in patients without IMH, those with mild IMH, and those with extensive IMH.

Clinical and Periprocedural Parameters Associated With the Presence of IMH

In univariable analysis, male sex (odds ratio [OR], 1.95; 95% CI, 1.15–3.33 [$P=0.014$]), anterior infarction (OR, 4.12; 95% CI, 2.52–6.72 [$P < 0.001$]), lack of TIMI grade 3 flow post-PCI (OR, 1.63; 95% CI, 0.97–2.73 [$P=0.066$]), and treatment with additional glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitor (OR, 3.67; 95% CI, 2.13–6.30 [$P < 0.001$]) were associated with the presence of IMH, while age (OR, 0.98; 95% CI, 0.97–1.00 [$P=0.085$]) and medical history of hypertension (OR, 0.66; 95% CI, 0.45–0.99 [$P=0.044$]) were negatively associated with presence of IMH. In multivariable analysis, anterior infarction (OR, 2.96; 95% CI, 1.73–5.06 [$P < 0.001$]) and treatment with heparin or bivalirudin with additional GPIIb/IIIa inhibitor (OR, 2.67; 95% CI, 1.49–4.80 [$P < 0.001$]) remained significantly associated with IMH (Table 3).

To investigate whether these results were driven by the 2 patient cohorts from CNIC, in which only patients with anterior infarction were included and $>85\%$ received GPIIb/IIIa inhibitor treatment, the univariable and multivariable analyses were repeated without these patients. In multivariable analysis without the METOCARD and Clock patients, both anterior infarction (OR, 3.29; 95% CI, 1.62–6.70 [$P=0.001$]) and

Table 1. Baseline Characteristics Per Study Population

	Patients With STEMI (n=410)	PREDICT-MVI (n=49)	MVO (n=50)	MAST (n=74)	Clock (n=22)	METOCARD-CNIC (n=215)
Age, y	58.5 (±10.8)	60.4 (±9.1)	56.9 (±10.1)	59.2 (±11.2)	57.1 (±7.3)	58.4 (±11.5)
Male sex, No. (%)	343 (84)	37 (76)	44 (88)	57 (77)	17 (77)	188 (87)
BMI	27.1 (±3.5)	27.4 (±3.5)	25.6 (±2.6)	27.4 (±9.6)	27.5 (±3.8)	27.6 (±3.6)
Hypertension, No. (%)	163 (40)	38 (78)	13 (26)	24 (33)	6 (29)	82 (39)
Diabetes mellitus, No. (%)	60 (15)	7 (14)	1 (2)	5 (7)	5 (24)	42 (20)
Hypercholesterolemia, No. (%)	143 (37)	8 (16)	16 (32)	24 (42)	8 (38)	87 (41)
Smoking, No. (%)	318 (78)	41 (84)	33 (66)	65 (88)	16 (76)	163 (77)
Anterior infarction, No. (%)	303 (75)	27 (55)	30 (60)	20 (27)	22 (100)	204 (98)
Time to reperfusion, h	3.0 (2.3–3.9)	2.3 (1.9–2.9)	2.5 (2.0–4.0)	3.3 (2.5–4.2)	3.5 (2.2–6.7)	3.0 (2.4–3.7)
TIMI 3 post-PCI, No. (%)	333 (82)	46 (94)	42 (84)	66 (92)	20 (91)	159 (74)
Aspirin, No. (%)	389 (97)	36 (84)	50 (100)	74 (100)	20 (100)	209 (98)
P2Y12 inhibitors, No. (%)	397 (99)	49 (100)	50 (100)	69 (97)	19 (95)	210 (99)
Antithrombotic therapy PCI						
Heparin only, No. (%)	74 (19)	1 (2)	8 (16)	42 (58)	3 (15)	20 (9)
Bivalirudin only, No. (%)	28 (7)	27 (64)	0 (0)	0 (0)	0 (0)	1 (1)
Additional GPIIb/IIIa inhibitor with heparin or bivalirudin, No. (%)	298 (74)	14 (33)	42 (84)	31 (43)	17 (85)	194 (90)

Data are presented as number (percentage) for dichotomous variables, mean±SD for normally distributed continuous variables, and median (interquartile range) for non-normally distributed continuous variables. BMI indicates body mass index; GPIIb/IIIa inhibitor, glycoprotein IIb/IIIa inhibitor; MVO, microvascular obstruction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction. Study acronyms are explained in the Methods section.

additional GPIIb/IIIa inhibitor (OR 4.14; 95% CI, 1.81–9.45 [$P=0.001$]) remained significantly associated with IMH.

Clinical and Periprocedural Parameters Associated With Extensive IMH

The association of extensive IMH with clinical and periprocedural variables was investigated by comparing patients with extensive IMH with patients with mild or no IMH. In univariable analysis, male sex (OR, 1.86; 95% CI, 0.96–3.62 [$P=0.068$]) and anterior infarction (OR, 3.85; 95% CI, 1.97–7.54 [$P<0.001$]) were associated with extensive IMH, while age (OR, 0.98; 95% CI, 0.96–1.00 [$P=0.047$]) and hypertension (OR, 0.55; 95% CI, 0.34–0.87 [$P=0.012$]) were negatively associated with extensive IMH. In multivariable analysis, anterior infarction (OR, 3.76; 95% CI, 1.91–7.43 [$P<0.001$]) remained significantly associated with extensive IMH, and hypertension (OR, 0.60; 95% CI, 0.37–0.99 [$P=0.045$]) remained significantly negatively associated with extensive IMH (Table 4).

Analogous to the previous prediction model, these analyses were repeated without the METOCARD and Clock patients, for abovementioned reasons. In multivariable analysis without the METOCARD and Clock patients, anterior infarction (OR, 4.50; 95% CI, 1.92–10.53 [$P=0.001$]) remained significantly associated with extensive IMH.

Furthermore, subanalysis was performed in all patients to assess whether extensive IMH was associated with medical therapy before hospital admission. In univariable analysis, statin treatment (OR, 0.33; 95% CI, 0.14–0.75 [$P=0.008$]) was negatively associated with extensive IMH. After correction for age and sex, no significant relation remained for statin treatment and extensive IMH.

Association Between IMH and CMR Parameters

CMR examinations were performed at 5.5 ± 1.8 days after PCI, similar for patients with and without IMH. Figure 2 shows that IMH occurred already in the very early phase after STEMI and is detectable with CMR imaging as soon as 1 to 2 days post-PCI. Infarct size, MVO, and LV functional parameters were compared between the 3 patient groups, ie, no IMH, mild IMH, and extensive IMH. The relationship of CMR parameters of infarct severity and short-term LV functional outcome with the extent of IMH are shown in Table 5.

MVO was seen on late gadolinium enhancement CMR imaging in 279 patients (69%), and IMH was seen on T2-weighted CMR imaging in 222 patients (54%). Fifty-seven patients (14%) showed MVO without IMH and no patients showed IMH without MVO; late gadolinium enhancement CMR

Table 2. Baseline Characteristics Per IMH Group

	Patients With STEMI (n=410)	No IMH (n=188)	Mild IMH (n=111)	Extensive IMH (n=111)	P Value
Age, y	58.5 (±10.8)	59.5 (±10.6)	58.6 (±10.4)	56.7 (±11.4)	0.11
Male sex, No. (%)	343 (84)	148 (79)	96 (87)	99 (89)	0.039
BMI	27.1 (±3.5)	27.0 (±3.8)	27.0 (±3.3)	27.3 (±3.2)	0.76
Hypertension, No. (%)	163 (40)	85 (46)	45 (41)	33 (30)	0.031
Diabetes mellitus, No. (%)	60 (15)	29 (15)	20 (18)	11 (10)	0.21
Hypercholesterolemia, No. (%)	143 (37)	61 (35)	49 (45)	33 (31)	0.083
Smoking, No. (%)	318 (78)	144 (77)	85 (77)	89 (81)	0.71
Anterior infarction, No. (%)	303 (75)	114 (61)	92 (84)	97 (90)	<0.001
Time to reperfusion, h	3.0 (2.3–3.9)	3.0 (2.3–3.9)	3.1 (2.4–4.1)	2.8 (2.2–3.7)	0.16
TIMI 3 post-PCI, No. (%)	333 (82)	159 (86)	88 (79)	86 (78)	0.17
Aspirin, No. (%)	389 (97)	176 (97)	109 (98)	104 (96)	0.69
P2Y12 inhibitors, No. (%)	397 (99)	184 (100)	109 (98)	104 (96)	0.29
Antithrombotic therapy PCI, No. (%)					<0.001
Heparin only	74 (19)	50 (28)	8 (7)	16 (15)	
Bivalirudin only	28 (7)	22 (12)	3 (3)	3 (3)	
Additional GPIIb/IIIa inhibitor with heparin or bivalirudin	298 (74)	108 (60)	100 (90)	90 (83)	

Data are presented as number (percentage) for dichotomous variables, mean±SD for normally distributed continuous variables, and median (interquartile range) for non-normally distributed continuous variables. P values are shown for overall difference between the patient groups (no, mild, and extensive intramyocardial hemorrhage [IMH], respectively). BMI indicates body mass index; GPIIb/IIIa inhibitor, glycoprotein IIb/IIIa inhibitor; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.

imaging was not available in 5 patients, all of whom showed no IMH.

Patients with extensive IMH had larger absolute and indexed infarct size compared with patients with mild or no IMH (all $P<0.001$). The extent of MVO, both absolute and indexed to LV mass, was significantly larger in

patients with extensive IMH compared with mild or no IMH (both $P<0.01$). Furthermore, patients with extensive IMH had lower LV ejection fraction and larger LV dimensions, both absolute and indexed to body surface area, compared with patients with mild or no IMH (all $P<0.001$).

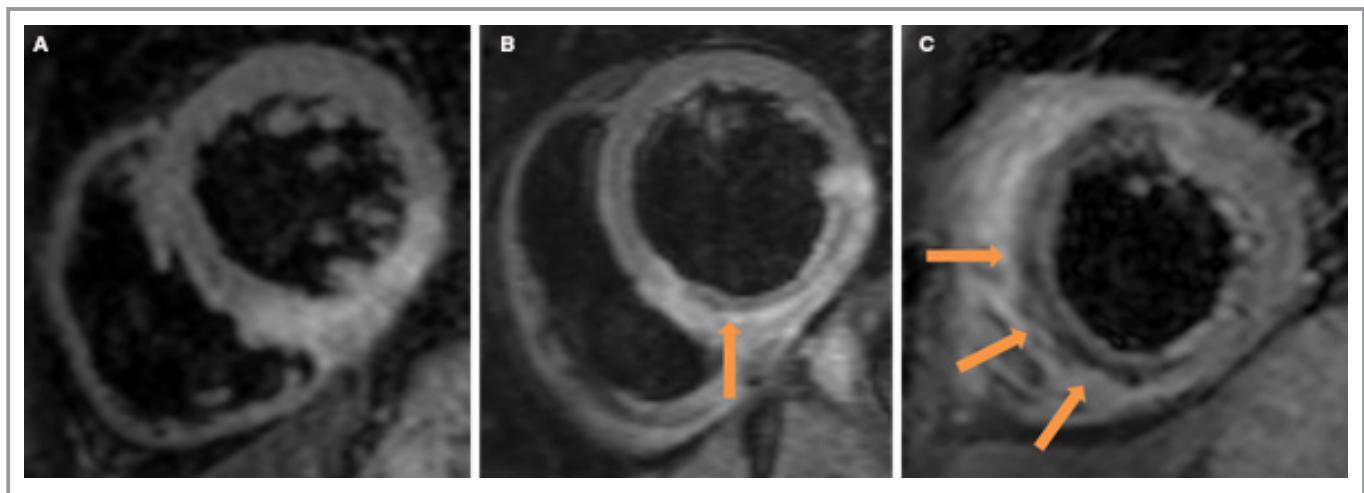


Figure 1. Typical cardiac magnetic resonance imaging examples of (A) a patient without intramyocardial hemorrhage (IMH), (B) a patient with mild IMH, and (C) a patient with extensive IMH. IMH is visible on T2-weighted cardiovascular magnetic resonance images as a hypointense core within the hyperintense infarcted region.

Table 3. Univariable and Multivariable Logistic Regression Analysis for Presence of IMH

	Univariable			Multivariable*		
	OR	95% CI	P Value	OR	95% CI	P Value
Age, y	0.98	0.97–1.00	0.085	0.99	0.97–1.00	0.20
Male sex	1.95	1.15–3.33	0.014	1.39	0.76–2.57	0.29
BMI	1.01	0.96–1.07	0.65			
Hypertension	0.66	0.45–0.99	0.044	0.84	0.53–1.34	0.46
Diabetes mellitus	0.90	0.52–1.57	0.72			
Hypercholesterolemia	1.13	0.75–1.72	0.55			
Smoking	1.13	0.71–1.81	0.61			
Anterior infarction	4.12	2.52–6.72	<0.001	2.96	1.73–5.06	<0.001
Time to reperfusion, h	0.95	0.86–1.05	0.32			
TIMI <3 post-PCI	1.63	0.97–2.73	0.066	1.18	0.68–2.07	0.55
Aspirin	1.01	0.30–3.36	0.99			
P2Y12 inhibitors	0.23	0.03–2.00	0.18			
Antithrombotic therapy PCI						
Bivalirudin only (vs heparin only)	0.57	0.20–1.58	0.28	0.66	0.23–1.96	0.46
Additional GPIIb/IIIa inhibitor with heparin or bivalirudin (vs heparin only)	3.67	2.13–6.30	<0.001	2.67	1.49–4.80	0.001

BMI indicates body mass index; GPIIb/IIIa inhibitor, glycoprotein IIb/IIIa inhibitor; IMH, intramyocardial hemorrhage; OR, odds ratio; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

*Multivariable analysis of significant univariable parameters with $P < 0.10$.

Compared with patients without IMH, patients with mild IMH had larger absolute and indexed infarct size (both $P < 0.001$), higher prevalence of MVO ($P < 0.001$), and greater absolute extent of MVO ($P = 0.001$). Regarding LV functional parameters, patients with mild IMH had lower LV ejection fraction ($P < 0.001$) and larger absolute and indexed LV end-systolic volume ($P = 0.013$ and 0.005 , respectively).

To investigate whether the abovementioned relations were driven by higher presence of anterior infarction in the patients with IMH, the relation of CMR parameters with extent of IMH was also assessed in patients with anterior infarction only. All of the abovementioned relations between CMR parameters and the extent of IMH remained intact with equal or greater statistical significance.

Discussion

Infarct characteristics and LV functional outcome, as assessed by CMR imaging, are increasingly used as surrogate outcome measures for prognosis after myocardial infarction, even when studying the effect of new interventions. The presence of microvascular injury, regardless of successful epicardial revascularization, confers a poorer prognosis for patients.^{9,10,18} Both MVO and IMH are features of the larger concept of microvascular injury^{6–8} and have been linked to

poorer prognosis after STEMI,^{9,11} even independent from infarct size.¹⁹ Moreover, the presence of IMH on top of MVO confers an even poorer prognosis than the presence of MVO only.^{10,20} Therefore, an increasing number of studies are focusing on understanding IMH within the concept of microvascular injury after STEMI. This study is the first to investigate the relation of periprocedural factors with the presence and extent of IMH and is the largest patient series thus far.

The main findings of the study are: (1) IMH occurs in 54% of patients with successfully reperfused STEMI, whereas MVO occurs in 70%; (2) the presence of IMH is independently associated with anterior infarct location and periprocedural administration of additional GPIIb/IIIa inhibitor; (3) extensive IMH is independently associated with anterior infarct location; and (4) the presence and extent of IMH are associated with more severe infarction and worse short-term LV functional parameters.

The most striking finding of this study is the strong independent association of the presence of IMH with additional GPIIb/IIIa inhibitor treatment. Although a causal relationship cannot be assumed because of the observational nature of the study, it is conceivable that more aggressive antithrombotic strategies might induce IMH. Several studies have shown modest infarct size reduction after additional

Table 4. Univariable and Multivariable Logistic Regression Analysis for Extensive IMH (Extensive vs Mild or No IMH)

	Univariable			Multivariable*		
	OR	95% CI	P Value	OR	95% CI	P Value
Age, y	0.98	0.96–1.00	0.047	0.98	0.96–1.00	0.11
Male sex	1.86	0.96–3.62	0.068	1.34	0.66–2.69	0.42
BMI	1.02	0.96–1.09	0.46			
Hypertension	0.55	0.34–0.87	0.012	0.60	0.37–0.99	0.045
Diabetes mellitus	0.56	0.28–1.13	0.10			
Hypercholesterolemia	0.70	0.44–1.13	0.14			
Smoking	1.26	0.73–2.18	0.41			
Anterior infarction	3.85	1.97–7.54	<0.001	3.76	1.91–7.43	<0.001
Time to reperfusion, h	0.94	0.83–1.07	0.35			
TIMI <3 post-PCI	1.44	0.84–2.46	0.19			
Aspirin	0.64	0.18–2.23	0.48			
P2Y12 inhibitors	0.36	0.07–1.79	0.21			
Antithrombotic therapy PCI						
Bivalirudin only (vs heparin only)	0.44	0.12–1.63	0.22			
Additional GPIIb/IIIa inhibitor with heparin or bivalirudin (vs heparin only)	1.57	0.86–2.88	0.15			

BMI indicates body mass index; GPIIb/IIIa inhibitor, glycoprotein IIb/IIIa inhibitor; IMH, intramyocardial hemorrhage; OR, odds ratio; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.
 *Multivariable analysis of significant univariable parameters with $P < 0.10$.

GPIIb/IIIa inhibitor treatment during PCI; however results on long-term LV functional recovery and major adverse cardiac events remain conflicting^{21–23} and no additional mortality reduction was shown after GPIIb/IIIa inhibitor treatment in patients with STEMI who had adequate dual antiplatelet preloading.²⁴ We found additional GPIIb/IIIa inhibitor treatment to be associated with higher incidence of IMH. Also, animal models have shown increased incidence of IMH with use of additional intracoronary GPIIb/IIIa inhibitors,²⁵ and a recent study in patients with STEMI showed potent inhibition of platelet aggregation following GPIIb/IIIa inhibitors to be related to IMH occurrence.²⁶ We postulate that the discordance of infarct size reduction without a conclusive effect on long-term clinical outcome might partially be explained by a higher incidence of IMH in patients treated with additional GPIIb/IIIa inhibitors.

Anterior infarction was also independently associated with the presence of IMH. Anterior infarctions generally lead to poorer clinical outcome, ie, lower LV ejection fraction, higher incidence of heart failure, and higher mortality rate compared with inferior infarctions. Occlusion of the left main stem or left anterior descending coronary artery often results in larger infarctions, which in previous studies has been linked to the presence of microvascular injury, including IMH.^{10,13} Nevertheless, infarct size is only known (days) after PCI when

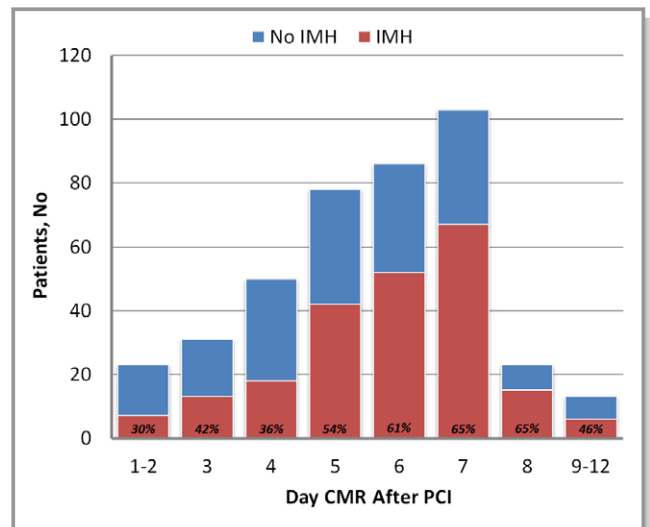


Figure 2. Number of patients with intramyocardial hemorrhage (IMH) on the days cardiovascular magnetic resonance (CMR) imaging was performed following percutaneous coronary intervention, illustrating that IMH occurs already in the very early phase after ST-segment elevation myocardial infarction (STEMI) and is detectable with CMR imaging as soon as 1 to 2 days after STEMI. Red column: patients with IMH with percentage of total patients displayed. Blue column: patients without IMH.

Table 5. CMR Parameters of LV Function and Infarct Characteristics

	No IMH (n=188)	Mild IMH (n=111)	Extensive IMH (n=111)	P Value No vs Mild IMH	P Value No vs Extensive IMH	P Value Mild vs Extensive IMH
Infarct size, g	11.0 (4.1–21.1)	25.7 (16.7–35.2)	45.5 (32.9–57.4)	<0.001	<0.001	<0.001
Infarct size, %LV	9.9 (3.6–17.8)	22.9 (16.9–30.6)	36.9 (29.1–45.4)	<0.001	<0.001	<0.001
Presence of MVO, No. (%)	57 (31)	111 (100)	111 (100)	<0.001	<0.001	NA
Extent of MVO, mL	0.9 (0.6–1.7)	1.7 (0.9–3.2)	6.6 (3.3–9.0)	0.001	<0.001	<0.001
Extent of MVO, %LV	0.85 (0.6–1.5)	1.7 (0.9–3.1)	5.1 (3.2–8.2)	<0.001	<0.001	<0.001
LVEF	51 (±9)	46 (±8)	39 (±8)	<0.001	<0.001	<0.001
LVEDV, mL	166 (137–192)	167 (141–194)	188 (166–214)	0.56	<0.001	<0.001
LVEDVi, mL/m ²	83 (74–97)	86 (73–98)	96 (88–107)	0.32	<0.001	<0.001
LVESV, mL	80 (64–99)	90 (72–110)	111 (95–137)	0.013	<0.001	<0.001
LVESVi, mL/m ²	40 (34–50)	46 (37–56)	58 (50–67)	0.005	<0.001	<0.001

Data are presented as number (percentage) for dichotomous variables, mean±SD for normally distributed continuous variables, and median (interquartile range) for non-normally distributed continuous variables. CMR indicates cardiac magnetic resonance; IMH, intramyocardial hemorrhage; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEDVi, indexed left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVESVi, indexed left ventricular end-systolic volume; MVO, microvascular obstruction; NA, not applicable.

cardiac imaging is performed, rendering it unsuitable for immediate risk stratification at the catheterization laboratory, whereas infarct location is immediately revealed at the time of the procedure (or even prior to PCI on the presenting ECG). When designing therapies or strategies aimed at minimizing IMH, infarct location might prove useful as part of a risk score to directly identify high-risk patients suited for additional therapy.

Medical history of hypertension before hospitalization was independently associated with a lower risk of extensive IMH. On a pathophysiological level, our results are difficult to interpret because medical history of hypertension is not a true reflection of vascular exposure to hypertension, as patients with undetected and therefore untreated hypertension are misclassified. On the one hand, this relationship is counter-intuitive, as hypertension has previously been linked to coronary (micro)vascular remodeling and endothelial dysfunction.²⁷ In addition, both hypertension and IMH have been linked to adverse prognoses following STEMI. On the other hand, our results might reflect a possible protective effect of the medication these patients already received before hospital admission, ie, angiotensin-converting enzyme inhibitors and statins. Subanalysis in our study showed no significant relationship between medical therapy before admission (β -blocker, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, statin, or calcium channel blocker) and extensive IMH, after correction for age and sex. Taking into consideration that medical history of hypertension was not independently associated with presence of IMH and borderline significantly associated with extensive IMH, we believe this finding should be interpreted with caution.

Lastly, our results show IMH to be associated with more severe infarction, as shown by poorer LV function, larger LV dimensions, larger infarct size, and greater extent of MVO on short-term CMR imaging. These results were not driven by a higher incidence of anterior infarction in patients with IMH, as the associations remained significant when assessed separately in patients with anterior infarction only. These findings are in agreement with those from previous studies.^{7,11,19,20} Long-term follow-up of these patients is necessary to investigate LV functional recovery and mortality/major adverse cardiac events.

Limitations

Several factors leading to potential bias should be addressed. Two studies (Clock and METOCARD) included anterior infarction only. Also, the use of additional GPIIb/IIIa inhibitors differed among the included study cohorts (33–100%), reflecting the development over time and a growing tendency for application in selected patients only in the era of adequate dual antiplatelet preloading. The choice for GPIIb/IIIa inhibitor treatment is generally left to the discretion of the interventional cardiologist and if patients received additional GPIIb/IIIa inhibitors because microvascular injury was already suspected based on suboptimal epicardial flow restoration, the effect of GPIIb/IIIa inhibitors on IMH might be an overestimation. However, TIMI flow <3 post-PCI was not independently associated with presence or extent of IMH. Also, in consideration of these possible sources of selection bias, additional analyses were performed, as described in the Results section, all supporting our conclusions.

Furthermore, the METOCARD trial showed benefit of periprocedural β -blocker administration on infarct size and MVO.²⁸ No significant differences in IMH occurrence ($P=0.36$) or IMH extent ($P=0.097$) were found between patients with and without intravenous periprocedural β -blockers in the METOCARD trial. These data were not recorded in the other studies and therefore β -blocker administration was not included in our analysis.

As microvascular injury, including IMH, shows a dynamic time course after STEMI, the timing of CMR imaging after PCI (range 1–12 days) might have influenced the detection and quantification of IMH.^{29,30} We cannot exclude the possibility that IMH was underestimated in some patients.

Lastly, in our study, T2-weighted CMR imaging was used for IMH detection. There is no consensus yet on which method should be preferred for IMH detection in patients with STEMI, T2-weighted CMR imaging or T2*CMR imaging. T2* sequences might be more sensitive and reliable in detecting the presence of IMH^{31,32}; however, spatial resolution is generally poorer than in T2-weighted sequences, which limits the quantification of IMH extent. Until consensus has been reached, both methods are frequently used to this end.

Conclusions

Additional GPIIb/IIIa inhibitor administration during PCI was independently associated with development of IMH, which warrants further investigation regarding the optimal application of aggressive antithrombotic therapies. Anterior infarction was independently associated with occurrence of IMH and higher risk of extensive IMH. These predictors might prove useful in the future identification of patients requiring additional treatment during PCI. In agreement with previous studies, IMH was associated with more severe infarction; however, long-term follow-up is required to assess the relation with functional and clinical outcome.

Acknowledgments

We thank the staff members of the catheterization laboratory, the CMR imaging personnel, and the research nurses for their skilled assistance during the various procedures.

Sources of Funding

The PREDICT-MVI study was supported in part by unrestricted research grants from Volcano Corporation and Biotronik. The METOCARD-CNIC was mainly sponsored by the CNIC through competitive CNIC translational grant 012009 and by an independent research grant from the Spanish National Ministry of Health and Social Policy (EC10042), a Mutua

Madriena Foundation grant (AP86952011), and a master research agreement between Philips Healthcare and CNIC. Dr Ibanez is supported by competitive grants from the Institute of Health Carlos III and the European Regional Development Fund (ERDF/FEDER) (PI13/01979 and RD12/0042/0054). Dr Fernández-Jiménez holds a FICNIC fellowship from the Fundació Jesús Serra, the Fundación Interhospitalaria de Investigación Cardiovascular (FIC), and the Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC). The CNIC is supported by the MINECO and the Pro CNIC Foundation, and is a Severo Ochoa Center of Excellence (MINECO award SEV-2015-0505).

Disclosures

None.

References

- O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso JE, Tracy CM, Woo YJ, Zhao DX. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127:529–555.
- Zhao B, Li J, Luo X, Zhou Q, Chen H, Shi H. The role of von Willebrand factor and ADAMTS13 in the no-reflow phenomenon: after primary percutaneous coronary intervention. *Tex Heart Inst J*. 2011;38:516–522.
- Frohlich GM, Meier P, White SK, Yellon DM, Hausenloy DJ. Myocardial reperfusion injury: looking beyond primary PCI. *Eur Heart J*. 2013;34:1714–1722.
- Jaffe R, Charron T, Puley G, Dick A, Strauss BH. Microvascular obstruction and the no-reflow phenomenon after percutaneous coronary intervention. *Circulation*. 2008;117:3152–3156.
- Jaffe R, Dick A, Strauss BH. Prevention and treatment of microvascular obstruction-related myocardial injury and coronary no-reflow following percutaneous coronary intervention: a systematic approach. *JACC Cardiovasc Interv*. 2010;3:695–704.
- Betgem RP, de Waard GA, Nijveldt R, Beek AM, Escaned J, van Royen N. Intramyocardial haemorrhage after acute myocardial infarction. *Nat Rev Cardiol*. 2015;12:156–167.
- Hamirani YS, Wong A, Kramer CM, Salerno M. Effect of microvascular obstruction and intramyocardial hemorrhage by CMR on LV remodeling and outcomes after myocardial infarction: a systematic review and meta-analysis. *JACC Cardiovasc Imaging*. 2014;7:940–952.
- Robbers LF, Eerenberg ES, Teunissen PF, Jansen MF, Hollander MR, Horrevoets AJ, Knaapen P, Nijveldt R, Heymans MW, Levi MM, van Rossum AC, Niessen HW, Marcu CB, Beek AM, van Royen N. Magnetic resonance imaging-defined areas of microvascular obstruction after acute myocardial infarction represent microvascular destruction and haemorrhage. *Eur Heart J*. 2013;34:2346–2353.
- Beek AM, Nijveldt R, van Rossum AC. Intramyocardial hemorrhage and microvascular obstruction after primary percutaneous coronary intervention. *Int J Cardiovasc Imaging*. 2010;26:49–55.
- Eitel I, Kubusch K, Strohm O, Desch S, Mikami Y, de Waha S, Gutberlet M, Schuler G, Friedrich MG, Thiele H. Prognostic value and determinants of a hypointense infarct core in T2-weighted cardiac magnetic resonance in acute reperfused ST-elevation-myocardial infarction. *Circ Cardiovasc Imaging*. 2011;4:354–362.
- Husser O, Monmeneu JV, Sanchis J, Nunez J, Lopez-Lereu MP, Bonanad C, Chaustre F, Gomez C, Bosch MJ, Hinarejos R, Chorro FJ, Riegger GA, Llacer A, Bodi V. Cardiovascular magnetic resonance-derived intramyocardial hemorrhage after STEMI: influence on long-term prognosis, adverse left ventricular remodeling and relationship with microvascular obstruction. *Int J Cardiol*. 2013;167:2047–2054.

12. Teunissen PF, de Waard GA, Hollander MR, Robbers LF, Danad I, Biesbroek PS, Amier RP, Echavarría-Pinto M, Quiros A, Broyd C, Heymans MW, Nijveldt R, Lammertsma AA, Raijmakers PG, Allaart CP, Lemkes JS, Appelman YE, Marques KM, Bronzwaer JG, Horrevoets AJ, van Rossum AC, Escaned J, Beek AM, Knaapen P, van Royen N. Doppler-derived intracoronary physiology indices predict the occurrence of microvascular injury and microvascular perfusion deficits after angiographically successful primary percutaneous coronary intervention. *Circ Cardiovasc Interv.* 2015;8:e001786.
13. Nijveldt R, Beek AM, Hirsch A, Stoel MG, Hofman MB, Umans VA, Algra PR, Twisk JW, van Rossum AC. Functional recovery after acute myocardial infarction: comparison between angiography, electrocardiography, and cardiovascular magnetic resonance measures of microvascular injury. *J Am Coll Cardiol.* 2008;52:181–189.
14. Bekkers SC, Backes WH, Kim RJ, Snoep G, Gorgels AP, Passos VL, Waltenberger J, Crijns HJ, Schalla S. Detection and characteristics of microvascular obstruction in reperfused acute myocardial infarction using an optimized protocol for contrast-enhanced cardiovascular magnetic resonance imaging. *Eur Radiol.* 2009;19:2904–2912.
15. Ibanez B, Macaya C, Sanchez-Brunete V, Pizarro G, Fernandez-Friera L, Mateos A, Fernandez-Ortiz A, Garcia-Ruiz JM, Garcia-Alvarez A, Iniguez A, Jimenez-Borreguero J, Lopez-Romero P, Fernandez-Jimenez R, Goicolea J, Ruiz-Mateos B, Bastante T, Arias M, Iglesias-Vazquez JA, Rodriguez MD, Escalera N, Acebal C, Cabrera JA, Valenciano J, Perez de PA, Fernandez-Campos MJ, Casado I, Garcia-Rubira JC, Garcia-Prieto J, Sanz-Rosa D, Cuellas C, Hernandez-Antolin R, Albarran A, Fernandez-Vazquez F, de la Torre-Hernández JM, Pocock S, Sanz G, Fuster V. Effect of early metoprolol on infarct size in ST-segment-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention: the effect of metoprolol in cardioprotection during an acute myocardial infarction (METOCARD-CNIC) trial. *Circulation.* 2013;128:1495–1503.
16. Pizarro G, Fernandez-Friera L, Fuster V, Fernandez-Jimenez R, Garcia-Ruiz JM, Garcia-Alvarez A, Mateos A, Barreiro MV, Escalera N, Rodriguez MD, de Miguel A, Garcia-Lunar I, Parra-Fuertes JJ, Sanchez-Gonzalez J, Pardillos L, Nieto B, Jimenez A, Abejon R, Bastante T, Martinez de Vega V, Cabrera JA, Lopez-Melgar B, Guzman G, Garcia-Prieto J, Mirellis JG, Zamorano JL, Albarran A, Goicolea J, Escaned J, Pocock S, Iniguez A, Fernandez-Ortiz A, Sanchez-Brunete V, Macaya C, Ibanez B. Long-term benefit of early pre-reperfusion metoprolol administration in patients with acute myocardial infarction: results from the METOCARD-CNIC trial (effect of metoprolol in cardioprotection during an acute myocardial infarction). *J Am Coll Cardiol.* 2014;63:2356–2362.
17. Ibanez B, Fuster V, Macaya C, Sanchez-Brunete V, Pizarro G, Lopez-Romero P, Mateos A, Jimenez-Borreguero J, Fernandez-Ortiz A, Sanz G, Fernandez-Friera L, Corral E, Barreiro MV, Ruiz-Mateos B, Goicolea J, Hernandez-Antolin R, Acebal C, Garcia-Rubira JC, Albarran A, Zamorano JL, Casado I, Valenciano J, Fernandez-Vazquez F, de la Torre JM, de Perez PA, Iglesias-Vazquez JA, Martinez-Tenorio P, Iniguez A. Study design for the “effect of metoprolol in cardioprotection during an acute myocardial infarction” (METOCARD-CNIC): a randomized, controlled parallel-group, observer-blinded clinical trial of early pre-reperfusion metoprolol administration in ST-segment elevation myocardial infarction. *Am Heart J.* 2012;164:473–480.
18. Carrick D, Haig C, Rauhalmi S, Ahmed N, Mordi I, McEntegart M, Petrie MC, Eteiba H, Hood S, Watkins S, Lindsay M, Mahrous A, Ford I, Tzemos N, Sattar N, Welsh P, Radjenovic A, Oldroyd KG, Berry C. Prognostic significance of infarct core pathology revealed by quantitative non-contrast in comparison with contrast cardiac magnetic resonance imaging in reperfused ST-elevation myocardial infarction survivors. *Eur Heart J.* 2016;37:1044–1059.
19. Ganame J, Messalli G, Dymarkowski S, Rademakers FE, Desmet W, Van de Werf F, Bogaert J. Impact of myocardial haemorrhage on left ventricular function and remodelling in patients with reperfused acute myocardial infarction. *Eur Heart J.* 2009;30:1440–1449.
20. Carrick D, Haig C, Ahmed N, McEntegart M, Petrie MC, Eteiba H, Hood S, Watkins S, Lindsay MM, Davie A, Mahrous A, Mordi I, Rauhalmi S, Sattar N, Welsh P, Radjenovic A, Ford I, Oldroyd KG, Berry C. Myocardial hemorrhage after acute reperfused ST-segment-elevation myocardial infarction: relation to microvascular obstruction and prognostic significance. *Circ Cardiovasc Imaging.* 2016;9:e004148.
21. Stone GW, Maehara A, Witzenbichler B, Godlewski J, Parise H, Dambrink JH, Ochal A, Carlton TW, Cristea E, Wolff SD, Brener SJ, Chowdhary S, El-Omar M, Neunteufl T, Metzger DC, Karwoski T, Dizon JM, Mehran R, Gibson CM. Intracoronary abciximab and aspiration thrombectomy in patients with large anterior myocardial infarction: the INFUSE-AMI randomized trial. *JAMA.* 2012;307:1817–1826.
22. Thiele H, Wöhrle J, Hambrecht R, Rittger H, Birkemeyer R, Lauer B, Neuhaus P, Brosteanu O, Sick P, Wiemer M, Kerber S, Kleinertz K, Eitel I, Desch S, Schuler G. Intracoronary versus intravenous bolus abciximab during primary percutaneous coronary intervention in patients with acute ST-elevation myocardial infarction: a randomised trial. *Lancet.* 2012;379:923–931.
23. Navarese EP, Kozinski M, Obonska K, Margheri M, Gurbel PA, Kubica J, De LG. Clinical efficacy and safety of intracoronary vs. intravenous abciximab administration in STEMI patients undergoing primary percutaneous coronary intervention: a meta-analysis of randomized trials. *Platelets.* 2012;23:274–281.
24. Witkowski A, Maciejewski P, Wasek W, Malek LA, Niewada M, Kaminski B, Drzewiecki J, Kosmider M, Kubica J, Ruzyllo W, Peruga JZ, Dudek D, Opolski G, Dobrzycki S, Gil RJ; Collaborators SR. Influence of different antiplatelet treatment regimens for primary percutaneous coronary intervention on all-cause mortality. *Eur Heart J.* 2009;30:1736–1743.
25. Buszman PP, Wojakowski W, Milewski K, Debinski M, Pajak J, Aboodi MS, Jackiewicz W, Kawka M, Bochenek A, Prats J, Granada JF, Kaluza GL, Buszman PE. Controlled reperfusion with intravenous bivalirudin and intracoronary abciximab combination therapy in the porcine myocardial infarction model. *Thromb Res.* 2012;130:265–272.
26. Malek LA, Klopotoski M, Spiewak M, Wozniak K, Was J, Misko J, Ruzyllo W, Witkowski A. Platelet reactivity and intramyocardial hemorrhage in patients with ST-segment elevation myocardial infarction. *Clin Appl Thromb Hemost.* 2014;20:553–558.
27. Camici PG, Crea F. Coronary microvascular dysfunction. *N Engl J Med.* 2007;356:830–840.
28. Garcia-Prieto J, Villena-Gutierrez R, Gomez M, Bernardo E, Pun-Garcia A, Garcia-Lunar I, Crainiciuc G, Fernandez-Jimenez R, Sreeramkumar V, Bourio-Martinez R, Garcia-Ruiz JM, Serrano del Valle A, Sanz-Rosa D, Pizarro G, Fernandez-Ortiz A, Hidalgo A, Fuster V, Ibanez B. Neutrophil stunning by metoprolol reduces infarct size. *Nat Commun.* 2017;8:14780.
29. Carrick D, Haig C, Ahmed N, Rauhalmi S, Clerfond G, Carberry J, Mordi I, McEntegart M, Petrie MC, Eteiba H, Hood S, Watkins S, Lindsay MM, Mahrous A, Welsh P, Sattar N, Ford I, Oldroyd KG, Radjenovic A, Berry C. Temporal evolution of myocardial hemorrhage and edema in patients after acute ST-segment elevation myocardial infarction: pathophysiological insights and clinical implications. *J Am Heart Assoc.* 2016;5:e002834. 10.1161/JAHA.115.002834.
30. Fernandez-Jimenez R, Garcia-Prieto J, Sanchez-Gonzalez J, Agüero J, Lopez-Martin GJ, Galan-Arriola C, Molina-Iracheta A, Doohan R, Fuster V, Ibanez B. Pathophysiology underlying the bimodal edema phenomenon after myocardial ischemia/reperfusion. *J Am Coll Cardiol.* 2015;66:816–828.
31. Kandler D, Lucke C, Grothoff M, Andres C, Lehmkuhl L, Nitzsche S, Riese F, Mende M, de Waha S, Desch S, Lurz P, Eitel I, Gutberlet M. The relation between hypointense core, microvascular obstruction and intramyocardial haemorrhage in acute reperfused myocardial infarction assessed by cardiac magnetic resonance imaging. *Eur Radiol.* 2014;24:3277–3288.
32. Hansen ES, Pedersen SF, Pedersen SB, Kjaergaard U, Schmidt NH, Botker HE, Kim WY. Cardiovascular MR T2-STIR imaging does not discriminate between intramyocardial haemorrhage and microvascular obstruction during the subacute phase of a reperfused myocardial infarction. *Open Heart.* 2016;3:e000346.