JACC: CARDIOVASCULAR INTERVENTIONS VOL. 6, NO. 7, 2013

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC. http://dx.doi.org/10.1016/j.jcin.2013.03.013

Relationship Between Myocardial Reperfusion, Infarct Size, and Mortality

The INFUSE-AMI (Intracoronary Abciximab and Aspiration Thrombectomy in Patients With Large Anterior Myocardial Infarction) Trial

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Objectives This study sought to compare infarct size (IS) measured by magnetic resonance imaging in patients with successful (myocardial blush grade [MBG] 2/3) versus unsuccessful (MBG 0/1) microcirculatory reperfusion in the INFUSE-AMI (Intracoronary Abciximab and Aspiration Thrombectomy in Patients With Large Anterior Myocardial Infarction) trial.

Background Successful microcirculatory reperfusion, defined angiographically by MBG 2 or 3, is associated with improved outcomes in patients with ST-segment elevation myocardial infarction. The precise mechanism underlying this association is not well defined.

Methods The INFUSE-AMI trial randomized 452 patients with anterior ST-segment elevation myocardial infarction to intracoronary bolus abciximab delivered locally at the infarct lesion versus no abciximab, and to manual thrombus aspiration versus no aspiration. The primary endpoint was IS (percentage of left ventricular mass) at 30 days.

Results MBG 2/3 was achieved in 367 patients (81.4%). IS was significantly lower in patients with MBG 2/3 than in those with MBG 0/1 (median: 16.7% [interquartile range (IQR): 7.0 to 22.7] vs. 19.5% [IQR: 11.1 to 29.2]; $p = 0.002$). Intracoronary abciximab further reduced IS in patients with MBG 2/3 (median: 14.4% [IQR: 5.4 to 20.9] vs. 17.4% [IQR: 10.5 to 23.8]; $p = 0.01$). MBG 2/3 was associated with ~30% reduction in infarct mass ($p = 0.002$) and ~90% reduction in microvascular obstruction on day 5. Ejection fraction was higher with MBG 2/3 at 30 days: median: 50.3% (IQR: 43.8 to 57.8) versus 46.9% (IQR: 37.5 to 54.0); $p = 0.004$. At 30 days, the rate of death was significantly lower (1.7% vs. 8.3%; $p = 0.0008$) in the MBG 2/3 group.

Conclusions MBG 2/3 occurs in 80% of ST-segment elevation myocardial infarction patients treated with primary percutaneous coronary intervention and is associated with smaller infarct size, less microvascular obstruction, improved ejection fraction, and significantly lower 30-day mortality. (Intracoronary Abciximab and Aspiration Thrombectomy in Patients With Large Anterior Myocardial Infarction [INFUSE-AMI]; NCT00976521) (J Am Coll Cardiol Intv 2013;6:718–24) © 2013 by the American College of Cardiology Foundation

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Outcomes after acute ST-elevation myocardial infarction (STEMI) are directly linked to the rapidity and success of reperfusion. Primary percutaneous coronary intervention (PCI) is superior to fibrinolytic therapy largely because it achieves a higher rate of successful reperfusion, defined as obtaining optimal epicardial (TIMI [Thrombolysis In Myocardial Infarction] flow grade 3) and myocardial (myocardial blush grade [MBG] 2 or 3) flow at the end of the procedure (1). It is assumed that the improved outcomes associated with primary PCI are related to greater myocardial salvage and, hence, a smaller infarct size (IS) (2). IS assessment is complex because of the various stages of damage and remodeling occurring in the first few weeks. Initially, reperfused myocardium is edematous, which may artificially increase the measured infarct size early on. As remodeling occurs and edema resolves, it is easier to determine the exact and final IS. Yet, the correlation between achieving optimal reperfusion, particularly at the myocardial level, and IS has not been studied in great detail (3). In particular, there are no data correlating MBG with later IS, as assessed by contrast-enhanced cardiac magnetic resonance (CMR) at 30 days, after remodeling has occurred and microvascular obstruction (MVO) (4) has resolved (5,6).

We therefore set out to analyze the relationship between angiographic markers of successful reperfusion in STEMI patients and IS measured at 30 days after PCI, using the recently performed INFUSE-AMI (Intracoronary Abciximab and Aspiration Thrombectomy in Patients With Large Anterior Myocardial Infarction) randomized clinical trial.

Methods

INFUSE-AMI has been described in detail (7). In brief, 452 patients with anterior STEMI and anticipated symptom onset to reperfusion time of <5 h undergoing primary PCI with bivalirudin anticoagulation were randomized in a 2 × 2 factorial design to intracoronary (IC) abciximab delivered locally at the site of the infarct lesion via the ClearWay Rx catheter (Atrium Medical, Hudson, New Hampshire) versus no abciximab or to thrombus aspiration using the Export catheter (Medtronic, Minneapolis, Minnesota) versus no thrombus aspiration. The primary endpoint of the study was IS, measured at 30 days by CMR and expressed as a percentage of left ventricular (LV) mass in patients assigned to IC abciximab versus no abciximab, pooled across strata of thrombus aspiration. The secondary major endpoint was IS in patients assigned to aspiration versus no aspiration, pooled across strata of intracoronary abciximab. All patients received aspirin and clopidogrel or aspirin and prasugrel. In a subset of patients, CMR was also performed at 5 days after myocardial infarction (MI) to measure the extent of MVO, again expressed as a percentage of LV mass.

All images were acquired on a commercially available 1.5-T scanner after each site was qualified by reviewing 2 recent CMR cases performed using the imaging protocol pre-specified for the trial. The CMR exam consisted of 2 components: 1) cine-CMR imaging for LV volumes and systolic function; and 2) delayed-enhancement CMR imaging for evaluation of IS, MVO, and LV mass. Cine-CMR imaging was performed using a 2-dimensional breath-held, steady-state, free-precession sequence (parameters: 1) shortest repetition/echo time; 2) 8-mm slice thickness without gaps; 3) image matrix = 128 to ~256 × 192 to ~256; 4) field of view = 35 to 40 cm; 5) flip angle = 45° to ~70°; 6) in-plane spatial resolution >2.5 × 2.0 mm, bandwidth 125 kHz; and 7) temporal resolution <50 ms). Delayed-enhancement CMR imaging was performed using a 2D breath-held segmented inversion-recovery gradient-echo sequence 10 min after 0.2mmol/kg gadolinium contrast injection (parameters: 1) shortest repetition/echo time; 2) 8-mm slice thickness without gaps; 3) image matrix = 128 to ~256 × 192 to ~256; 4) field of view = 35 to 40 cm; 5) flip angle = 15°; 6) in-plane spatial resolution greater than 2.5 × 2.5 mm; 7) 2-signal averaging; and 8) bandwidth = 32 to 64 kHz). All CMR images were analyzed at an independent core laboratory (Cardiovascular Research Foundation, New York, New York) without knowledge of treatment assignment. Quantitative analysis was performed using the U.S. Food and Drug Administration–approved ReportCard software (version 4.0 NeoSoft LLC, Waukesha, Wisconsin). LV volumes were determined by manually tracing the endocardial borders, excluding the papillary muscles, at end diastole and end systole on all short-axis cine-CMR images. LV mass (the area between the epicardial and endocardial borders) and infarct area (the white area within the black myocardium) were segmented on

Abbreviations and Acronyms

CMR = cardiac magnetic resonance
IC = intracoronary
IQR = interquartile range
IS = infarct size
LV = left ventricular
MBG = myocardial blush grade
MI = myocardial infarction
MVO = microvascular obstruction
PCI = percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombolysis In Myocardial Infarction

he has served on the advisory boards for and has received honoraria from Abbott Vascular, Boston Scientific, Medtronic, Atrium, Bristol-Myers Squibb, sanofi-aventis, Merck & Co., Inc., Janssen, Eli Lilly, Daiichi Sankyo, The Medicines Company, and AstraZeneca. Dr. Gibson is a consultant to AstraZeneca, Baxter Healthcare, Bayer Corporation, Cardiovascular Medical Communications, CSL Behring, Cytori Therapeutics, Daiichi Sankyo Company, Inc., Eli Lilly and Company, Exeter Group, Genentech, Inc., GlaxoSmithKline, Janssen Pharmaceuticals, Johnson & Johnson Corporation, Ortho McNeil, St. Jude Medical, The Medines Company, Ischemix, Inc., Merck & Co., Portola Pharmaceuticals, Inc., and Regado Biosciences, Inc.; and has received research/grant support from Angel Medical Corporation, Atrium Medical Systems, Bayer Corp., Ikaria, Inc., Janssen Pharmaceuticals, Johnson & Johnson Corporation, Lantheus Medical Imaging, Merck & Co., Portola Pharmaceuticals, Roche Diagnostics, Sanofi-Aventis, Stealth Peptides, Inc., St. Jude Medical, Volcano Corp., and Walk Vascular. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received February 8, 2013; accepted March 14, 2013.

Table 1. Baseline Characteristics of the Study Patients According to Final MBG

	Final MBG 0/1	Final MBG 2/3	p Value
Patient characteristics			
Age, yrs	61.5 (53.0–72.5)	61.0 (51.0–70.0)	0.30
Male	73.8 (62/84)	73.8 (271/367)	1.00
BMI, kg/m^2	26.2 (24.0–29.5)	26.7 (24.0–29.4)	0.96
Heart rate, beats/min	79.0 (65.0–90.0)	77.0 (66.0–88.0)	0.32
Systolic blood pressure, mm Hg	138.5 (119.0–150.0)	140.0 (120.0–155.0)	0.26
Killip classification			
I	72.6 (61/84)	83.3 (305/366)	0.02
II	14.3 (12/84)	7.7 (28/366)	0.054
III	4.8 (4/84)	0.5 (2/366)	0.01
LVEF, %, investigator estimate	39.0 (30.0–45.0)	40.0 (35.0–50.0)	0.0005
Medical history			
Medically treated hypertension	33.3 (28/84)	30.8 (113/367)	0.65
Medically treated hyperlipidemia	16.7 (14/84)	15.3 (56/366)	0.76
Diabetes mellitus	13.3 (11/83)	10.9 (40/367)	0.54
Insulin-treated	6.0 (5/83)	2.5 (9/366)	0.15
Prior myocardial infarction	1.2 (1/82)	0.8 (3/367)	0.55
Prior PCI	1.2 (1/83)	2.5 (9/367)	0.70
Congestive heart failure	4.8 (4/84)	0.0 (0/365)	0.001
Smoking	51.2 (43/84)	63.0 (228/362)	0.05
Peripheral vascular disease	1.2 (1/84)	1.6 (6/366)	1.00
History of renal insufficiency	1.2 (1/84)	0.8 (3/367)	0.56
History of stroke or TIA	2.4 (2/84)	1.4 (5/367)	0.62
Randomization strata			
Symptom onset to first angiogram			0.03
<3 h	59.5 (50/84)	71.4 (262/367)	
≥3 h	40.5 (34/84)	28.6 (105/367)	
LAD infarct lesion			0.58
Proximal LAD	61.9 (52/84)	65.1 (239/367)	
Mid LAD	45.2 (38/84)	40.9 (150/367)	

Values are median (IQR) or % (n/N).

BMI = body mass index; IQR = interquartile range; LAD = left anterior descending artery; LVEF = left ventricular ejection fraction; MBG = myocardial blush grade; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

the delayed-enhancement CMR images (8). To determine regional systolic function, the LV was divided into 16 segments, and wall motion abnormalities were visually classified as normal (score 0), hypokinetic (score 1), akinetic (score 2), dyskinetic (score 3), and summed. Percentage of infarct mass was calculated as infarct mass divided by total myocardial mass. Correlations for interobserver variability were 0.9930 for infarct mass and 0.9699 for total myocardial mass. Correlations for intraobserver variability were 0.9953 and 0.9870, respectively.

Major adverse cardiac and cerebrovascular events including death, reinfarction, stroke, or ischemia-driven target vessel revascularization were recorded at 30 days, and bleeding was assessed using the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction), TIMI, and GUSTO (Global Use of Strategies To Open Occluded Coronary Arteries) scales (9).

Markers of reperfusion were assessed at independent, blinded core electrocardiography (ST-segment resolution) and angiographic (TIMI flow, corrected TIMI frame counts, and MBG) core laboratories at the Cardiovascular Research Foundation, using standard definitions (10–12). MBG was assessed according to the densitometric method, which evaluates the maximal intensity of contrast penetrating the infarct zone, in comparison to unaffected territories. TIMI flow grade 3 was considered successful epicardial reperfusion, and MBG grade 2/3 was considered successful microcirculatory (myocardial) reperfusion (13).

Statistical analysis. Continuous variables are presented as mean ± SD or median with interquartile range (IQR) and were compared with the Wilcoxon rank-sum test. Categorical variables are presented as proportions and were compared with the chi-square or Fischer exact test. IS was not distributed normally and is represented only as median values.

Table 2. Procedural Characteristics of the Study Patients According to Final MBG

	Final MBG 0/1	Final MBG 2/3	p Value
Target lesion % diameter stenosis	100.0 (99.0–100.0)	100.0 (95.0–100.0)	0.35
Target lesion reference vessel diameter	3.0 (3.0–3.5)	3.0 (3.0–3.5)	0.50
Target lesion length, mm	19.0 (15.0–27.0)	16.0 (12.0–24.0)	0.04
Pre-PCI thrombus	92.9 (79/85)	84.8 (313/369)	0.05
Pre-PCI collaterals	28.6 (24/84)	26.3 (97/369)	0.67
Stents per lesion, n	1.0 (1.0–2.0)	1.0 (1.0–1.0)	0.0005
>1	33.3 (29/87)	16.3 (61/374)	0.0003
Total stent length, mm	24.0 (18.0–35.0)	23.0 (16.0–30.0)	0.053
Stent type			
DES only	67.4 (58/86)	80.5 (301/374)	0.008
BMS only	31.4 (27/86)	19.5 (73/374)	0.02
DES and BMS	1.2 (1/86)	0.0 (0/374)	0.19
Final % diameter stenosis	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.30
Side branch treated, any	89.4 (76/85)	79.4 (293/369)	0.03
Final distal embolization	8.2 (7/85)	1.1 (4/369)	0.001
Aspiration performed	48.8 (41/84)	52.6 (193/367)	0.53
ClearWay Rx catheter used	51.2 (43/84)	49.3 (181/367)	0.76
If randomized to ClearWay, IC abciximab infused	83.0 (44/53)	81.6 (177/217)	0.81
Thrombus aspiration followed by local infusion of abciximab	21.4 (18/84)	24.3 (89/367)	0.58
Local infusion of abciximab followed by thrombus aspiration	4.8 (4/84)	1.6 (6/367)	0.10
Local infusion of abciximab and no thrombus aspiration	26.2 (22/84)	23.7 (87/367)	0.63
Thrombus aspiration and no local infusion of abciximab	21.4 (18/84)	26.2 (96/367)	0.37
No local infusion of abciximab and no thrombus aspiration	26.2 (22/84)	24.3 (89/367)	0.71
Acute success	71.4 (60/84)	94.0 (343/365)	<0.0001
Lesion success	75.9 (63/83)	95.0 (345/363)	<0.0001
Procedure success	71.4 (60/84)	94.0 (343/365)	<0.0001

Values are median (IQR) or % (n/N). Acute success is defined as lesion and procedure success. Lesion success is defined as achievement of a final in-stent residual diameter stenosis of <50% (by QCA) and TIMI (Thrombolysis In Myocardial Infarction) flow grade 3 using any percutaneous method. Procedure success is defined as achievement of a final in-stent diameter stenosis of <50% (by QCA) using the assigned device and with any adjunctive devices. ClearWay Rx catheter is manufactured by Atrium Medical (Hudson, New Hampshire).

BMS = bare-metal stent; DES = drug-eluting stent; IC = intracoronary; QCA = quantitative coronary angiography; other abbreviations as in Table 1.

Significance level was set at 0.05. All analyses were performed with SAS (version 9.2, SAS Institute, Cary, North Carolina).

Results

Of the 452 enrolled patients, MBG could be assessed at the core laboratory in 451 patients (99.7%). MBG 2/3 was achieved in 367 patients (81.4%). Baseline characteristics according to final MBG are shown in Table 1. Compared with patients with MBG 0/1 after PCI, those with final MBG 2/3 were more likely to present earlier than 3 h from symptom onset, less likely to have current or previous heart failure, and more likely to have higher ejection fraction before PCI.

Procedural characteristics of the study population according to final MBG are shown in Table 2. Patients with unsuccessful microcirculatory reperfusion had significantly longer lesions, with more thrombus, and required more stents than those in whom successful myocardial reperfusion was achieved. The former group also had significantly more side branches treated and more distal embolization, resulting in overall significantly lower rates of procedural success (71.4% vs. 94%; $p < 0.001$). There were no differences between the groups with respect to performance of aspiration thrombectomy or IC administration of abciximab or the order in which these procedures were performed. MBG 2/3 was achieved in 184 of 228 (80.7%) and 183 of 223 (82.1%) of the IC abciximab and no abciximab groups, respectively; $p = 0.71$. MBG 2/3 was achieved in 83.4% (191 of 229) vs. 79.3% (176 of 222) of patients treated with and without thrombus aspiration, respectively; $p = 0.26$.

Failure to restore microcirculatory reperfusion (MBG 0/1) was also associated with a lower rate of final TIMI flow grade 3 (75% vs. 95.1%; $p < 0.0001$) and higher TIMI frame counts (Table 3). Of note, however, there was no difference in the rates of ST-segment resolution in patients with MBG 0/1 versus MBG 2/3 (Table 3). Among patients with an open microcirculation, 54 had MBG 2 and 313 had

Table 3. Markers of Reperfusion and IS According to Final MBG

	Final MBG 0/1	Final MBG 2/3	p Value
Final TIMI flow grade 3	75.0 (63/84)	95.1 (349/367)	<0.0001
Corrected TIMI frame counts	42 (32–55)	34 (28–44)	0.0005
ST-segment resolution*	67.0 (41.3–85.0)	72.9 (45.6–87.8)	0.26
>70%	47.4 (37/78)	53.3 (177/332)	0.35
30%–70%	33.3 (26/78)	29.5 (98/332)	0.51
<30%	19.2 (15/78)	17.2 (57/332)	0.67
CMR at 30 days, n = 371			
IS, % of LV mass	19.5 (11.1–29.2)	16.7 (7.0–22.7)	0.002
Infarct mass, g	28.2 (14.3–39.4)	19.9 (7.8–31.2)	0.002
Total abnormal wall motion score	10.0 (5.0–12.0)	7.0 (2.0–10.0)	0.002
LV ejection fraction	46.9 (37.5–54.0)	50.3 (43.8–57.8)	0.004
CMR at 5 days, n = 168			
Any MVO	83.3 (20/24)	51.7 (73/144)	0.003
Total MVO, g	2.6 (0.5–5.1)	0.2 (0.0–3.7)	0.02
MVO size, % of infarct mass	6.8 (3.3–11.0)	1.5 (0.0–9.4)	0.05
Total abnormal wall motion score	10.0 (8.0–12.0)	8.0 (4.0–10.0)	0.005

Values are median (IQR) or % (n/N). *Based on sum of leads with positive ST-segment elevation.
IS = infarct size; LV = left ventricle; CMR = cardiac magnetic resonance; MVO = microvascular obstruction; other abbreviations as in Tables 1 and 2.

Table 4. 30-Day Clinical Outcomes in the Study Population According to Final MBG

	Final Blush 0/1	Final Blush 2/3	p Value
Death, reinfarction, TVR, or stroke	10.7 (9)	2.5 (9)	0.0004
Death, reinfarction, CHF	11.9 (10)	5.5 (20)	0.03
Death	8.3 (7)	1.7 (6)	0.0008
Target vessel reinfarction	1.3 (1)	0.6 (2)	0.48
Death or reinfarction	9.5 (8)	2.0 (7)	0.0004
Bleeding	5.0 (4)	1.4 (5)	0.04
TIMI major	3.7 (3)	0.8 (3)	0.04
TIMI minor	1.3 (1)	0.6 (2)	0.48
New onset severe heart failure	3.7 (3)	3.6 (13)	0.96
Rehospitalization for heart failure	1.3 (1)	0.3 (1)	0.24
TIA	1.3 (1)	0.0 (0)	0.03
Stroke	0.0 (0)	0.3 (1)	0.64
Any revascularization	2.5 (2)	1.4 (5)	0.46
Stent thrombosis, definite or probable	1.3 (1)	0.8 (3)	0.71

Values are Kaplan-Meier estimates expressed as % (n events).
CHF = congestive heart failure; TVR = target vessel revascularization; other abbreviations as in Tables 1 and 2.

MBG 3 (12% and 69.4% of all patients, respectively). These 2 groups did not differ significantly with respect to baseline characteristics. Patients with MBG 2, compared with those with MBG 3, however, did have lower rates of TIMI flow grade 3 (85.2% vs. 96.8%; p = 0.0003), lower procedural success (82.7% vs. 95.8%; p = 0.0002), and similar rates of ST-segment resolution.

The primary study endpoint, IS at 30 days (assessed in 352 patients, 78% of the cohort), was significantly lower in patients with MBG 2/3 than in those with MBG 0/1 (median: 16.7% [IQR: 7.0 to 22.7] vs. 19.5% [IQR: 11.1 to 29.2]; p = 0.002) (Table 3). A similar proportion of patients in both groups had CMR for primary endpoint evaluation—78% and 80%, respectively. In the 5-day IS substudy, there was also ~30% lower infarct mass (p = 0.002) and ~90% lower amount of myocardium with MVO present. In patients with serial CMR at 5 and 30 days (n = 166), infarct mass declined by nearly 30% in both groups (p = 0.65). Total abnormal wall motion score was significantly lower in patients with MBG 2/3 than in those with MBG 0/1, both at 5 days (p = 0.005) and at 30 days (p = 0.002). Ejection fraction at 30 days was higher in MBG 2/3 than in MBG 0/1 patients at 30 days: median: 50.3% (IQR: 43.8 to 57.8) versus 46.9% (IQR: 37.5 to 54.0); p = 0.004. There were no significant differences in LV remodeling or function between days 5 and 30 in patients with MBG 0/1 versus 2/3. There was no significant difference in IS between MBG 2 and MBG 3 (median: 17.5% [IQR: 9.8 to 25.1] vs. 16.2% [IQR: 6.7 to 22.3]; p = 0.32).

The differences observed in MBG were associated with significantly better clinical outcomes, as shown in Table 4. Specifically, at 30 days, the rate of death was significantly reduced in the MBG 2/3 versus 0/1 group (1.7% vs. 8.3%; p = 0.0008). The MBG 2/3 group also had significantly less major bleeding, but similar rates of reinfarction, stent thrombosis, heart failure, and target vessel revascularization.

Because IC abciximab lowered IS without affecting rates of MBG 2/3, we explored whether its effect was different in the 2 MBG groups (Table 5). There was no interaction between abciximab effect on IS and final MBG (p = 0.12). There were no significant differences in MVO at 5 days and in clinical outcome at 30 days between patients who did or did not receive IC abciximab within each group of final MBG.

Discussion

This is, to our knowledge, the largest study to evaluate the relationship between angiographic markers of reperfusion, particularly MBG, IS, and short-term outcomes after primary PCI in STEMI. It is also the first to evaluate this relationship with respect to convalescent IS, assessed at 30 days. The important lessons from this analysis are as follows: 1) Angiographically successful myocardial reperfusion, expressed as MBG 2 or 3, was associated with a lower IS (15% as proportion of LV mass and 30% as absolute mass). This difference is probably an underestimation of the real difference, as all patients who died did not get cMRI at 30 days. 2) Angiographically successful reperfusion was also associated with a 30% lower rate of MVO, detected by CMR at 5 days after MI and a substantially lower abnormal wall motion score. 3) As in prior studies, the reduction in IS was linked to a substantially lower mortality at 30 days. These observations point to the critical importance of

Table 5. IS and Clinical Outcome According to Final MBG and Abciximab Administration

	MBG 0/1 + Abciximab	MBG 0/1 – Abciximab	p Value	MBG 2/3 + Abciximab	MBG 2/3 – Abciximab	p Value
IS, % LV mass	21.1 (12.7–29.1)	19.2 (10.2–29.2)	0.73	14.4 (5.4–20.9)	17.4 (10.5–23.8)	0.01
Infarct mass, g	30.1 (14.5–40.7)	26.7 (14.3–36.8)	0.55	17.6 (6.3–28.9)	22.8 (11.1–34.1)	0.009
Total abnormal wall motion score	9.5 (5.0–12.0)	10.0 (4.0–11.0)	0.73	5.0 (1.0–10.0)	8.0 (3.0–10.0)	0.04
LV ejection fraction	46.0 (37.8–53.2)	47.0 (37.2–54.5)	0.85	51.3 (45.1–58.8)	49.3 (42.9–57.0)	0.13
Death, MI, TVR, or stroke	13.6 (6)	7.5 (3)	0.35	2.8 (5)	2.2 (4)	0.75
Death, MI, CHF	13.6 (6)	10.0 (4)	0.57	5.0 (9)	6.1 (11)	0.63
Death	11.4 (5)	5.0 (2)	0.28	1.7 (3)	1.7 (3)	0.99
Bleeding, TIMI major or minor	4.8 (2)	5.1 (2)	0.97	1.6 (3)	1.1 (2)	0.66

Values are median (IQR) or % (n).
MI = myocardial infarction; other abbreviations as in Tables 1, 3, and 4.

achieving effective myocardial reperfusion in STEMI. These data also may provide the mechanistic link between the previously reported independent association between MBG and mortality (14). Also of note, in the present study, the robust association between MBG (a measure of microvascular integrity) and IS were independent of ST-segment resolution (a measure of myocyte integrity [15]).

Several small studies have previously examined the relationship between MBG and IS. In a series of 31 patients undergoing primary PCI in whom CMR was performed within the first 7 days and at 3 months after MI (16), those with suboptimal reperfusion (TIMI myocardial perfusion grade <3) had larger infarct areas both early ($p = 0.02$) and late ($p = 0.03$), compared with patients with normal TIMI myocardial perfusion grade. The remodeling process was also less favorable in the former group ($p = 0.03$). Vincente et al. (17) studied 39 patients with STEMI treated with primary PCI who achieved TIMI flow grade 3 and complete ST-segment resolution. MBG 0/1 had poor sensitivity (53.8%) and modest specificity (75%) for MVO, which was the sole predictor of unfavorable LV remodeling (17). Using CMR as the gold standard for IS, Riedle et al. (18) studied 95 patients with STEMI and non-STEMI and compared quantitative with qualitative MBG. They showed a near perfect correlation between quantitative MBG and IS, which is consistent with the data provided in our report. In a small cohort of 27 patients, Porto et al. (5) showed that increasing MBG grade correlated with CMR IS ($p = 0.043$) and MVO ($p = 0.001$), whereas ST-segment resolution >70% did not correlate with either. In contrast, Nijveldt et al. (3) examined 60 patients treated with primary PCI for STEMI and correlated CMR (days 2 to 9), electrocardiogram, and angiographic findings. They found that early (first pass) and late (gadolinium-enhancement) MVO (present in 57% of the patients) correlated with incomplete ST-segment resolution, but not with TIMI flow grade or MBG. Late MVO predicted changes in diastolic volumes at 4 months. In the largest series before this report, Marra et al. (19) confirmed our findings that MBG 2/3 (achieved in 61% of their 294 patients) correlated with smaller enzymatic IS and lower rate of MVO ($p < 0.001$ for both). In their study, CMR was performed early, within the first week after STEMI (19).

Our study, by virtue of its size and specific population included (large anterior MI), extends, and broadens these observations. Because we analyzed IS at 5 and 30 days, we could assess both the earlier process (MVO, edema) and the later convalescent IS after substantial edema resolution. The relative changes in infarct mass between the 5- and 30-day CMR did not differ between the 2 groups of MBG, which is consistent with the concept that myocardial salvage occurs early after reperfusion. The overall decline in infarct mass between the 2 studies represents the process of remodeling and resolution of edema, which initially may give the impression of a larger MI.

These data further clarify the overall INFUSE-AMI results. Because the patients who did and did not receive IC abciximab had similar rates of MBG 2/3, we can conclude that abciximab does not enhance myocardial perfusion per se, but rather it contributes to IS reduction by favorably affecting microthrombi present in the capillaries (and possibly by reducing associated inflammation) (20,21).

Study limitations. First, our study was powered for IS and not for MBG, and thus the observed rates between randomized groups should be considered exploratory. Second, more than 20% of the enrolled patients, and all those who died within 30 days, did not have CMR, and thus did not contribute to the actual data reported in this paper. As such, we could not really explore the relationship between IS and death. As described previously (7), imputations of IS performed as sensitivity analyses did not affect the overall trial result. Longer-term follow-up (currently ongoing to 1 year) is required to examine the late implications of MBG and 30-day IS. Third, the lack of association between ST-segment resolution and MBG requires additional exploration, as the electrocardiographic parameters have been validated in numerous datasets as powerful predictors of myocardial salvage and of clinical outcome, and our MBG 0/1 was recorded in only a small proportion of our patients (22). Finally, these study results are confined currently to patients with left anterior descending artery infarcts.

Conclusions

Despite these caveats, we conclude that angiographically defined successful myocardial reperfusion—MBG grade 2 or 3—occurred in ~80% of patients treated with contemporary primary PCI, independent of IC abciximab administration or thrombectomy. Achieving MBG 2/3 after primary PCI was associated with smaller IS (particularly evident when IC abciximab was also administered to the infarct lesion site via the ClearWay Rx catheter), smaller MVO area, lower abnormal wall motion score, and improved ejection fraction. All these improved markers of reperfusions translated into significantly lower 30-day mortality, as compared with patients in whom microcirculatory reperfusion was not successful. Thus, physicians should be adequately trained to assess MBG and evaluate this measure at the end of PCI for prognostic purposes.

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Key Words: infarct size ■ myocardial blush grade ■ ST-segment elevation myocardial infarction ■ thrombus aspiration.