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EXPEDITED PUBLICATIONS

Intracoronary Compared With Intravenous Bolus Abciximab Application During Primary Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction

Cardiac Magnetic Resonance Substudy of the AIDA STEMI Trial

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Objectives The aim of the AIDA STEMI (Abciximab i.v. Versus i.c. in ST-elevation Myocardial Infarction) cardiac magnetic resonance (CMR) substudy was to investigate potential benefits of intracoronary versus intravenous abciximab bolus administration on infarct size and reperfusion injury in ST-segment elevation myocardial infarction.

Background The AIDA STEMI trial randomized 2,065 patients to intracoronary or intravenous abciximab and found similar rates of major adverse cardiac events at 90 days with significantly less congestive heart failure in the intracoronary abciximab group. CMR can directly visualize myocardial damage and reperfusion injury, thereby providing mechanistic and pathophysiological insights.

Methods We enrolled 795 patients in the AIDA STEMI CMR substudy. CMR was completed within 1 week after ST-segment elevation myocardial infarction. Central core laboratory–masked analyses for quantified ventricular function, volumes, infarct size, microvascular obstruction, hemorrhage, and myocardial salvage were performed.

Results The area at risk ($p = 0.97$) and final infarct size (16% [interquartile range: 9% to 25%] versus 17% [interquartile range: 8% to 25%], $p = 0.52$) did not differ significantly between the intracoronary and the intravenous abciximab groups. Consequently, the myocardial salvage index was similar (52 [interquartile range: 35 to 69] versus 50 [interquartile range: 29 to 69], $p = 0.25$). There were also no differences in microvascular obstruction ($p = 0.19$), intramyocardial hemorrhage ($p = 0.19$), or ejection fraction ($p = 0.95$) between both treatment groups. Patients in whom major adverse cardiac events occurred had significantly larger infarcts, less myocardial salvage, and more pronounced ventricular dysfunction.

Conclusions This largest multicenter CMR study in ST-segment elevation myocardial infarction patients to date demonstrates no benefit of intracoronary versus intravenous abciximab administration on myocardial damage and/or reperfusion injury. Infarct size determined by CMR was significantly associated with major adverse cardiac events. (Abciximab i.v. Versus i.c. in ST-elevation Myocardial Infarction [AIDA STEMI]; NCT00712101) (J Am Coll Cardiol 2013;61:1447–54) © 2013 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

CMR = cardiac magnetic resonance

IQR = interquartile range

LV = left ventricular

MACE = major adverse cardiac event(s)

MO = microvascular obstruction

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

Randomized studies have consistently shown that treatment with an adjunctive glycoprotein IIb/IIIa inhibitor improves coronary microcirculation and clinical outcome in high-risk ST-segment elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary intervention (PCI) (1,2). Intracoronary abciximab bolus administration results in higher local concentrations and increased levels of platelet glycoprotein IIb/IIIa receptor occupancy compared with standard intravenous application (3). Several meta-analyses suggested a reduction in mortality and target-vessel revascularization with intracoronary abciximab (4–6). However, in the large, randomized AIDA STEMI (Abciximab Intracoronary versus intravenously Drug Application in STEMI) multicenter trial, intracoronary abciximab application did not result in a difference in major adverse cardiac events (MACE) compared with the standard intravenous route (7), but the rate of new congestive heart failure was significantly lower and there was an observed benefit in the female subgroup. Therefore, further analyses are warranted to assess potential benefits of intracoronary abciximab.

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Cardiac magnetic resonance (CMR) is uniquely suited to provide important mechanistic and pathophysiological information on infarct size, myocardial salvage, microvascular obstruction (MO), and intramyocardial hemorrhage (8–10). The aim of the predefined AIDA STEMI CMR multicenter substudy was to investigate potential benefits of intracoronary abciximab application on myocardial damage, reperfusion injury, and left ventricular (LV) function.

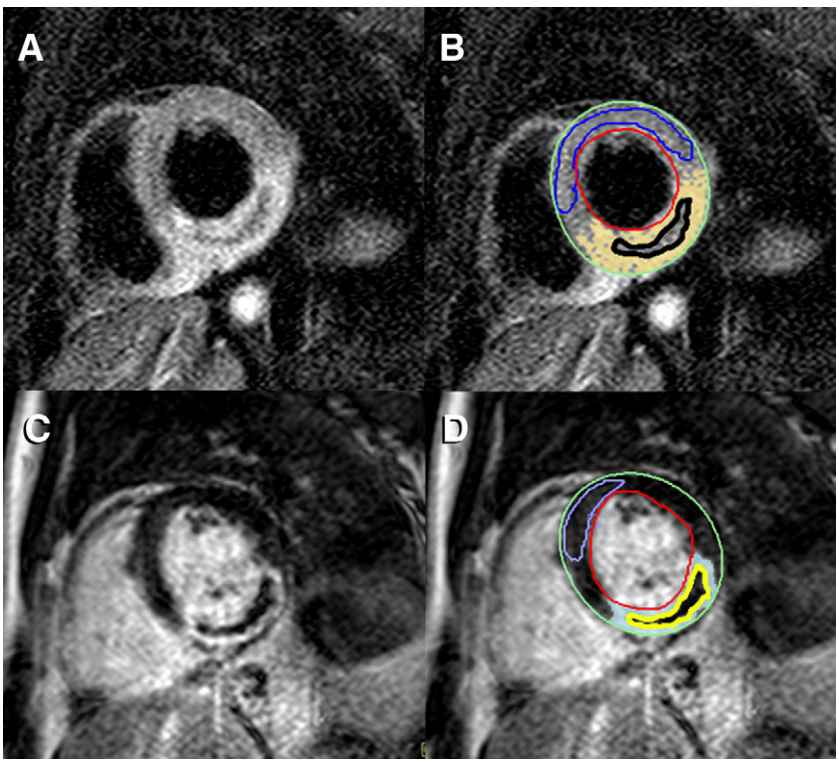

Figure 1 **Assessment of Myocardial Salvage, Infarct Size, Intramyocardial Hemorrhage, and Microvascular Obstruction**

(A) T2-weighted cardiac magnetic resonance image showing high signal intensity of the inferolateral segments (area at risk) with a hypointense core within the area of myocardial edema indicating intramyocardial hemorrhage. **(B)** Computer-aided signal intensity analysis of the T2-weighted image normalized to normal myocardium **(blue contour)**. The **yellow overlay** indicates a signal intensity of >2 SD above remote, uninjured myocardium. The **black contour** indicates the area of intramyocardial hemorrhage. **(C)** Contrast-enhanced image showing high signal intensity reflecting increased contrast accumulation in necrotic myocardium. **(D)** Computer-aided signal intensity analysis of the contrast-enhanced image: **light blue** indicates a signal intensity of >5 SD above remote, uninjured myocardium **(blue contour)**, whereas the **yellow contour** indicates the area of microvascular obstruction. The comparison of edema (area at risk) **(A, B)** with necrosis **(C, D)** shows no relevant myocardial salvage.

Methods

Study design. The design and results of the AIDA STEMI study were previously published (7,11). Briefly, AIDA STEMI was a randomized, open-label, multicenter trial. Patients presenting with STEMI <12 h were randomly assigned in a 1:1 ratio to intracoronary or intravenous abciximab bolus (0.25 mg/kg bodyweight) during PCI with a subsequent 12-h dose-adjusted intravenous infusion.

Patients were enrolled at 22 sites in Germany, with a final enrolled trial population of 2,065 patients. The primary endpoint was a composite of all-cause mortality, recurrent infarction, or new congestive heart failure within 90 days of randomization.

CMR substudy design. Consecutive patients enrolled at 8 sites were included in the CMR substudy. The sites were chosen based on proven expertise in performing CMR examinations in STEMI patients. Per protocol, CMR was performed on days 1 to 10 after the index event for assessment of myocardial salvage, infarct size, presence and extent of MO, and LV ejection fraction and volume. The detailed scan protocol on a clinical 1.5- or 3.0-T magnetic resonance scanner was described previously (11). CMR images were sent on storable media to the CMR core laboratory at the University of Leipzig Heart Center (Leipzig, Germany) for blinded assessment.

Image analysis. For all quantitative analyses, certified CMR evaluation software was used (cmr^{42}, Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada). Semiautomated computer-aided threshold detection was used to identify regions of edema, hypointense cores, MO, and infarcted myocardium, as previously described (8–10) (Fig. 1).

Infarct size, area at risk, hypointense cores, and MO were expressed as a percentage of LV volume. Salvaged myocardium was quantified as the difference between the volume of increased T2-signal (area at risk) and the volume of delayed enhancement (infarct size), as previously described (9) (Fig. 1). The CMR core laboratory has excellent reproducibility and low interobserver and intraobserver variability for infarct size and myocardial salvage assessment (12).

Statistical analysis. The study was powered for infarct size (a relative reduction in infarct size of 25% was considered clinically relevant). Evaluating 388 patients randomized to intracoronary or intravenous abciximab provided 80% power to demonstrate a relative 25% reduction in infarct size from 24% to 18% (with 21% SD).

Data for continuous variables are presented as the median with the interquartile range (IQR). Categorical variables are presented as frequencies and percentages. Testing for treatment differences was performed with Wilcoxon rank sum tests for continuous variables and chi-square tests for categorical variables.

Predefined subgroup analyses were performed according to the original study protocol (7,11). Hazard ratios with 95% confidence intervals were calculated for binary outcomes. Univariate and stepwise multivariate linear regression analyses were performed to identify predictors of infarct size and myocardial salvage. Multivariate regression was performed using only variables with a p value <0.05 in univariate regression analyses. For univariate analyses, all variables listed in Table 1 were investigated. A 2-tailed p value of <0.05 was considered statistically significant.

Results

Patient characteristics. From July 2008 to April 2011, 795 patients were enrolled in the AIDA STEMI CMR substudy (Fig. 2). Baseline characteristics of the total substudy population and by randomized treatment are presented in Table 1. Patients in the 2 groups had similar baseline characteristics except for hypertension and previous bypass surgery. All other prescribed drugs and study procedures were similar for both groups (Table 1).

CMR findings. The median time between the index event and CMR was 3 days (IQR: 2 to 4 days) for both groups ($p = 0.70$). Most patients underwent CMR on a 1.5-T scanner (97%). The main findings from CMR analyses are presented in Table 2. There were no significant differences in the area at risk, infarct size, and consequently myocardial salvage, as well as for the occurrence and extent of MO ($p = 0.19$) and intramyocardial hemorrhage ($p = 0.19$).

In subgroup analyses, no significant treatment effect on infarct size could be detected (Fig. 3).

Thrombolysis In Myocardial Infarction flow before PCI correlated significantly with infarct size ($r = -0.360$, $p < 0.001$) and the myocardial salvage index ($r = 0.314$, $p < 0.001$). Significant independent predictors of infarct size are displayed in Table 3. Independent predictors of the myocardial salvage index were systolic blood pressure ($p < 0.001$), time from symptom onset to hospital admission for PCI ($p < 0.001$), Killip class on admission ($p < 0.001$), Thrombolysis In Myocardial Infarction flow before PCI ($p < 0.001$), and left anterior descending lesion ($p = 0.03$).

Clinical outcome and relationship of CMR markers and clinical outcome. At 12-month follow-up, there were 13 deaths (3.3%) in the intracoronary and 8 (2.0%) in the intravenous abciximab groups (hazard ratio: 1.69; 95% confidence interval: 0.69 to 4.11; $p = 0.25$). There were also no significant differences in the occurrence of nonfatal reinfarctions ($p = 0.54$) and congestive heart failure ($p = 0.11$). Consequently, MACE at 12-month follow-up were similar (intracoronary 24 [6.2%] vs. intravenous 29 [7.3%] events; hazard ratio: 0.84; 95% confidence interval: 0.48 to 1.46; $p = 0.53$).

Patients in whom MACE occurred had significantly larger infarcts, less myocardial salvage, and more pronounced LV dysfunction (Table 4). Intramyocardial hemorrhage and MO as markers of severe reperfusion injury were more frequent in patients with MACE without reaching statistical significance.

Table 1 Patient Characteristics

Variable	Total CMR Substudy (n = 795), Main Trial (n = 2,065)	Intracoronary Abciximab (n = 394), Main Trial (n = 1,032)	Intravenous Abciximab (n = 401), Main Trial (n = 1,033)	p Value
Age, yrs	62 (51–71)	63 (51–71)	61 (51–71)	0.23
Male	603/795 (76)	287/394 (73)	316/401 (79)	0.05
Cardiovascular risk factors				
Current smoking	339/727 (47)	161/364 (44)	178/363 (49)	0.19
Hypertension	540/792 (68)	284/393 (72)	256/399 (64)	0.01
Hypercholesterolemia	304/787 (39)	147/391 (38)	157/396 (40)	0.56
Diabetes mellitus				
Any	160/792 (20)	87/392 (22)	73/400 (18)	0.17
Insulin requiring	74/792 (9)	40/392 (10)	34/400 (9)	0.41
BMI, kg/m^2	27.3 (24.9–30.3)	27.4 (24.9– 30.1)	27.3 (24.8– 30.5)	0.78
Previous infarction	48/794 (6)	23/393 (6)	25/401 (6)	0.82
Previous PCI	67/795 (8)	35/394 (9)	32/401 (8)	0.65
Previous CABG	11/795 (1)	2/394 (1)	9/401 (2)	0.04
Anterior infarction	363/758 (48)	180/382 (47)	183/376 (49)	0.67
Systolic blood pressure, mm Hg	130 (117–147)	130 (116–145)	130 (117–150)	0.74
Diastolic blood pressure, mm Hg	80 (70–88)	80 (70–86)	80 (70–90)	0.19
Heart rate, beats/min	76 (67–87)	76 (67–86)	76 (67–88)	0.16
Creatinine clearance, ml/min*	94 (73–118)	92 (72–120)	96 (74–117)	0.28
Time from symptom onset to PCI hospital admission, min	180 (109–310)	164 (108–300)	190 (110–335)	0.30
Door-to-balloon time, min	30 (22–42)	30 (22–43)	29 (22–42)	0.31
Killip class on admission				0.37
1	699/795 (88)	341/394 (87)	358/401 (89)	
2	59/795 (7)	35/394 (9)	24/401 (6)	
3	20/795 (3)	11/394 (3)	9/401 (2)	
4	17/795 (2)	7/394 (2)	10/401 (3)	
No. of diseased vessels				0.08
1	422/795 (53)	211/394 (54)	211/401 (53)	
2	225/795 (28)	121/394 (31)	104/401 (26)	
3	148/795 (19)	62/394 (16)	86/401 (21)	
Infarct-related artery				0.53
Left anterior descending	347/795 (44)	166/394 (42)	181/401 (45)	
Left circumflex	97/795 (12)	51/394 (13)	46/401 (12)	
Right coronary artery	344/795 (43)	175/394 (44)	169/401 (42)	
Left main	5/795 (1)	2/394 (1)	3/401 (1)	
Bypass graft	2/795 (<1)	0/394 (0)	2/401 (1)	
TIMI flow grade before PCI				0.11
0	445/795 (56)	225/394 (57)	220/401 (55)	
I	104/795 (13)	41/394 (10)	63/401 (16)	
II	129/795 (16)	71/394 (18)	58/401 (15)	
III	117/795 (15)	57/394 (15)	60/401 (15)	
Stent implanted	777/795 (98)	385/394 (98)	392/401 (98)	0.84
Thrombectomy	190/795 (24)	99/394 (25)	91/401 (23)	0.42
Drug-eluting stent	335/793 (42)	164/392 (42)	171/401 (43)	0.77
Bare metal stent	69/793 (59)	234/392 (60)	235/401 (59)	0.81
TIMI flow grade post-PCI				0.59
0	12/794 (2)	6/394 (2)	6/400 (2)	
I	19/794 (2)	9/394 (2)	10/400 (3)	
II	62/794 (8)	36/394 (9)	26/400 (7)	
III	701/794 (88)	343/394 (87)	358/400 (90)	
Intra-aortic balloon pump	35/795 (4)	17/394 (4)	18/401 (5)	0.91

Continued on the next page

Table 1 Continued

Variable	Total CMR Substudy (n = 795), Main Trial (n = 2,065)	Intracoronary Abciximab (n = 394), Main Trial (n = 1,032)	Intravenous Abciximab (n = 401), Main Trial (n = 1,033)	p Value
Concomitant medications				
Beta-blockers	759/793 (96)	373/393 (95)	386/400 (97)	0.27
ACE inhibitors/AT-1 antagonist	754/793 (95)	372/393 (95)	382/400 (96)	0.58
Aspirin	795/795 (100)	394/394 (100)	401/401 (100)	
Clopidogrel	678/768 (88)	330/381 (87)	348/387 (90)	0.15
Prasugrel	179/608 (29)	92/310 (30)	87/298 (2)	0.90
Clopidogrel, prasugrel, or both	775/775 (100)	385/385 (100)	390/390 (100)	
Clopidogrel or prasugrel preloading	458/793 (58)	226/394 (57)	232/399 (58)	0.88
Statins	752/793 (95)	367/393 (93)	385/400 (96)	0.07
Aldosterone antagonist	91/793 (12)	49/393 (13)	42/400 (1)	0.39
Completion of abciximab infusion	748/794 (94)	370/393 (94)	378/401 (94)	0.94

Values are median (interquartile range) or n/N (%). *Creatinine clearance was calculated by the Cockcroft-Gault formula.

ACE = angiotensin-converting enzyme; AT-1= angiotensin 1; BMI = body mass index; CABG = coronary artery bypass graft; CMR = cardiac magnetic resonance; PCI = primary percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

Discussion

The AIDA STEMI CMR substudy is the largest multicenter CMR study to assess markers of myocardial damage and reperfusion injury in reperfused STEMI patients. The principal finding is that in patients with STEMI undergoing primary PCI, intracoronary compared with intravenous abciximab bolus administration did not result in a difference in infarct size, myocardial salvage, LV function, or extent of reperfusion injury, confirming the lack of difference in MACE. Furthermore, infarct size was significantly associated with outcome.

The main mechanism through which intracoronary abciximab may improve myocardial perfusion and clinical outcome is the higher drug concentration, resulting in increased local platelet inhibition, displacement of platelet-bound fibrin, and dissolution of thrombi (13,14). Previous studies demonstrated the superiority of intracoronary over intravenous abciximab injection with respect to various surrogate endpoints of effective reperfusion (4–6,15,16), and these benefits were associated with improved survival in 3 different meta-analyses (4–6). However, the recently completed AIDA STEMI trial, powered for clinical out-

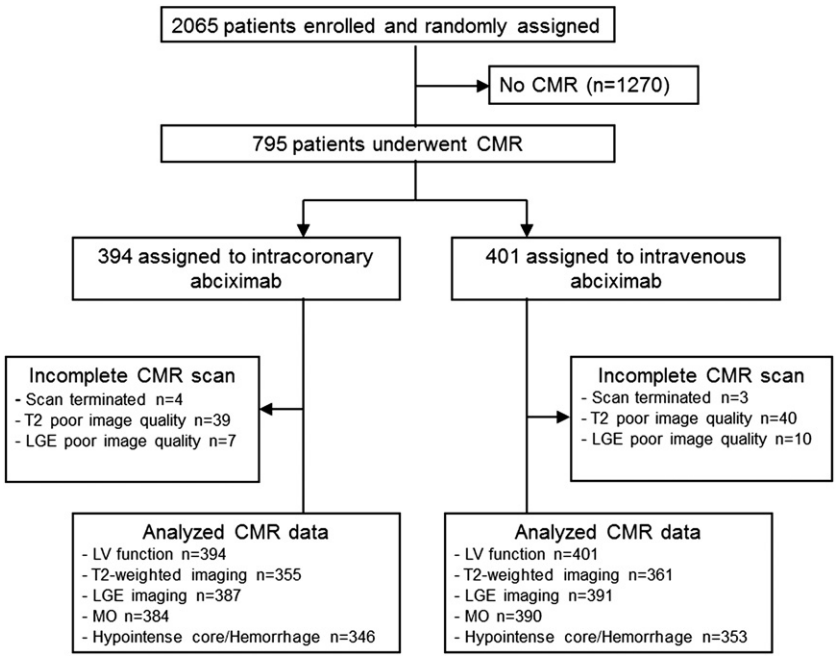

Figure 2 Study Profile

CMR = cardiac magnetic resonance; LGE = late gadolinium enhancement; LV = left ventricular; MO = microvascular obstruction.

Table 2 Cardiovascular Magnetic Resonance Results

Characteristic	Total CMR Substudy	Intracoronary Abciximab	Intravenous Abciximab	p Value
Area at risk (edema), % LV	35 (25–48)	35 (25–47)	35 (26–48)	0.97
Infarct size, % LV	17 (8–25)	16 (9–25)	17 (8–25)	0.52
Myocardial salvage, % LV	17 (9–27)	18 (10–26)	16 (8–27)	0.43
Myocardial salvage index	51 (33–69)	52 (35–69)	50 (29–69)	0.25
Late MO present	381/774 (49)	180/384 (47)	201/390 (52)	0.19
Late MO, % LV	0 (0–1.8)	0 (0–1.4)	0.2 (0–1.9)	0.22
Hypointense core present (hemorrhage)	243/699 (35)	112/346 (32)	131/353 (37)	0.19
Hypointense core, % LV	0 (0–1.4)	0 (0–1.0)	0 (0–1.5)	0.22
LV ejection fraction, %	51 (43–58)	51 (43–58)	50 (43–58)	0.95
LV end-diastolic volume, ml	146 (120–173)	146 (118–175)	146 (121–170)	0.83

Values are median (interquartile range) or n/N (%).
CMR = cardiac magnetic resonance; LV = left ventricular; MO = microvascular obstruction.

comes, found nearly identical MACE rates, whereas fewer patients in the intracoronary group had new congestive heart failure (7). Subgroup analyses showed the consistency of the results in all subgroups except for women. The reduction in new congestive heart failure events might have been a consequence of improved perfusion and reduction in infarct size by intracoronary abciximab. The use of CMR in this substudy allowed us to obtain further mechanistic insight into the potential benefits of intracoronary abciximab on reperfusion. In accordance with the clinical findings, CMR showed almost identical results in both groups. Similarly, in female patients, there was no effect on infarct size or myocardial salvage. Thus, no pathophysiological and biological rationale is apparent for the lower incidence of

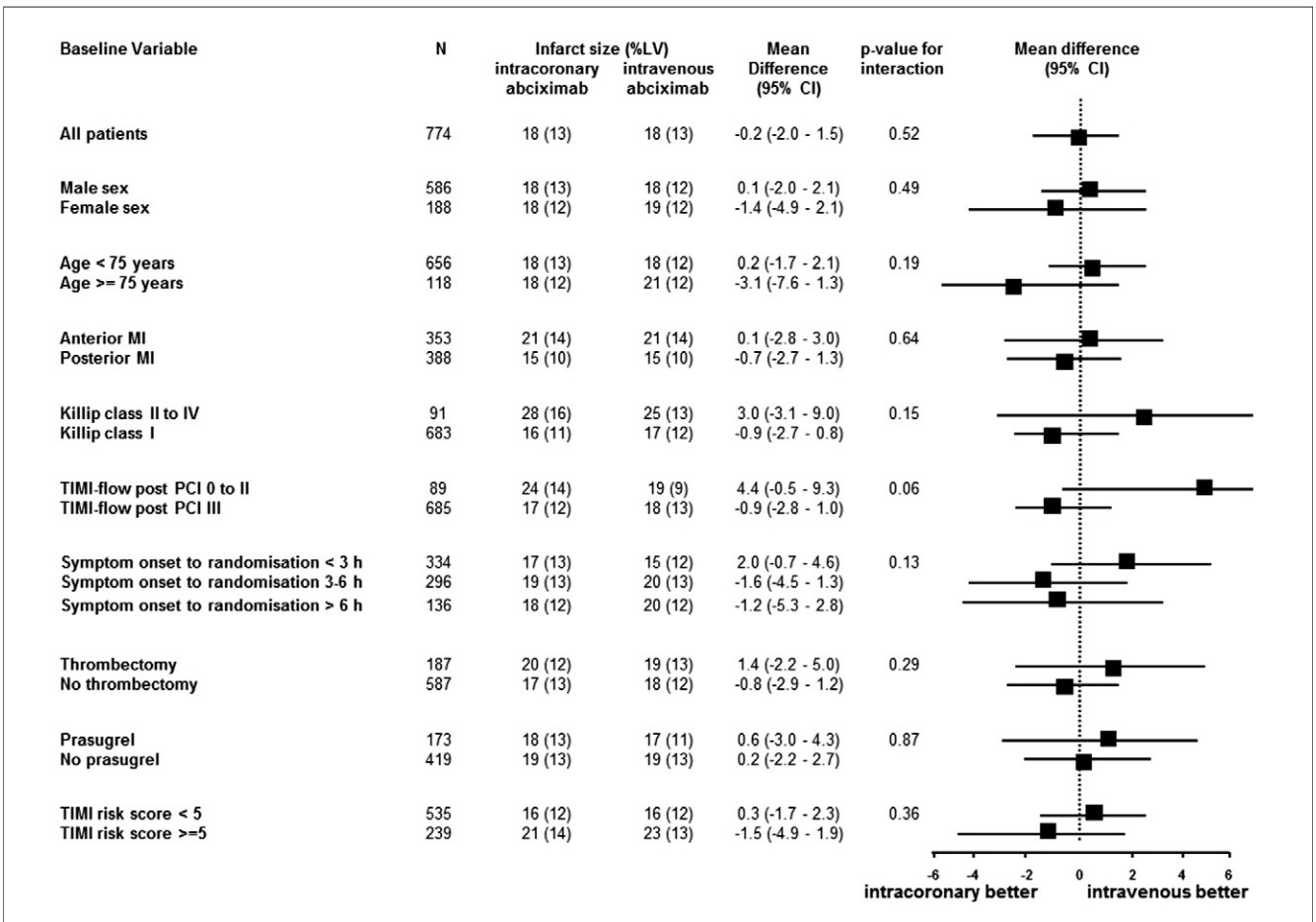

Figure 3 Forest Plot Subgroup Analyses for Infarct Size

CI = confidence interval; LV = left ventricular volume; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

congestive heart failure or for women, as suggested by the clinical results of the AIDA STEMI trial.

Compared with previous studies, AIDA STEMI included younger patients undergoing faster reperfusion with better antiplatelet activation control (4–6). The INFUSE-AMI (Intracoronary Abciximab Infusion and Aspiration Thrombectomy in Patients Undergoing Percutaneous Coronary Intervention for Anterior ST-Segment Elevation Myocardial Infarction) trial differed in several ways from the AIDA STEMI trial and all other previous studies (15). First, bolus intracoronary abciximab was compared with placebo. Second, only early presenting patients (<4 h) with anterior STEMI were enrolled. Third, bivalirudin was used for anticoagulation during PCI. Fourth, a dedicated local drug delivery balloon was used, whereas in almost all previous trials, intracoronary abciximab was infused proximally through the guide catheter. The use of a local drug delivery balloon may result in higher intraclot abciximab concentrations with prolonged drug residence time, enhanced platelet disaggregation, and thrombus resolution (14). However, overall, the magnitude of the absolute infarct size reduction with intracoronary abciximab in the INFUSE-AMI trial was modest (mean reduction, 2.3% LV volume) and was not accompanied by other markers of reperfusion success, and long-term follow-up needs to demonstrate whether this translates into improved clinical outcomes. In contrast to INFUSE-AMI, our twice as large AIDA STEMI CMR substudy did not find a significant infarct size reduction even in the subgroup of patients with early reperfused (<4 h) anterior infarcts (intracoronary: 19.0% LV volume [IQR: 10.6% to 28.5%]; intravenous: 19.2% LV volume [IQR: 7.2% to 28.8%]; p = 0.53).

Two updated meta-analyses including the AIDA STEMI results found no benefit in clinical outcome with intracoronary abciximab administration, including mortality and reinfarction (17,18). However, a significant relationship between the patient risk profile and mortality could be observed. Thus, there are still open questions worth studying such as the appropriate patient group (e.g., exclusively high-risk patients with high thrombus burden and large myocardium at risk), the means of intracoronary abciximab administration (role of selective delivery systems), and concomitant medication.

Table 3 Predictors of Infarct Size in Multivariate Regression Analysis

	Multivariate Analysis: Final Model		
	Coefficients		
Dependent Variable Infarct Size (% LV)	B	SE	p Value
Heart rate, beats/min (continuous)	0.10	0.03	<0.001
Systolic blood pressure, mm Hg (continuous)	−0.07	0.02	<0.001
Killip class on admission, 1 (I) 2 (II) 3 (III, IV)	4.05	0.84	<0.001
No. of diseased vessels, 1–3	2.36	0.59	<0.001
Right coronary artery lesion, 0 (no) 1 (yes)	−2.85	1.07	0.01
TIMI flow before PCI: 0–3	−3.43	0.35	<0.001
Symptom onset to PCI hospital admission, min (continuous)	0.01	0.00	0.02

The final model explained 28% of the observed variance (adjusted R^2).
Abbreviations as in Table 1.

Table 4 Relationship of CMR Markers and Clinical Outcome at 12 Months

Characteristic	MACE	No MACE	p Value
Infarct size, % LV	24 (18–31) [50]	16 (8–24) [78]	<0.001
Myocardial salvage index	37 (23–55) [44]	52 (33–69) [644]	0.01
Late MO present	28/50 (56)	350/718 (49)	0.32
Late MO, % LV	0.6 (0–2.7) [50]	0 (0–1.6) [718]	0.09
Hypointense core present (hemorrhage)	19/47 (40)	222/645 (34)	0.47
Hypointense core, % LV	0 (0–2.1) [47]	0 (0–1.3) [645]	0.36
LV ejection fraction, %	40 (33–47) [53]	51 (44–58) [736]	<0.001

Values are median (interquartile range) [n] or n/N (%).
MACE = major adverse cardiac events; other abbreviations as in Table 2.

Our CMR substudy findings provide an important perspective on the use of CMR as an endpoint in reperfusion studies in acute STEMI. The current study is the largest multicenter, multivendor investigation to evaluate the prognostic significance of myocardial damage and reperfusion injury as determined by CMR (15,19–21). Our data demonstrate that MACE occurrence in reperfused STEMI patients is directly related to infarct size, which strengthens its use as a strong surrogate endpoint for clinical trials investigating the success of reperfusion strategies. Future studies on improved myocardial reperfusion should therefore consider CMR to provide a thorough evaluation and understanding of therapeutic effects, improve risk stratification, and ultimately prognosis.

Study limitations. The present study was conducted at 8 different centers using different CMR vendors. However, all centers carefully followed the same protocol, and all data were centrally analyzed by an experienced core laboratory. Second, a significant portion of patients had incomplete CMR scans. Because the proportion was identical in both groups, a potential selection bias is limited.

Conclusions

In this largest CMR multicenter study to date in STEMI patients undergoing primary PCI, intracoronary compared with intravenous abciximab application did not result in a difference in myocardial damage, LV function, or reperfusion injury. Nevertheless, infarct size was significantly associated with MACE.

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Key Words: angioplasty ■ cardiac magnetic resonance imaging ■ glycoprotein IIb/IIIa inhibition ■ infarction ■ infarct size.