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Intracoronary Abciximab and Aspiration Thrombectomy in Patients With Large Anterior Myocardial Infarction

The INFUSE-AMI Randomized Trial

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Context Thrombus embolization during percutaneous coronary intervention (PCI) in ST-segment elevation myocardial infarction (STEMI) is common and results in suboptimal myocardial perfusion and increased infarct size. Two strategies proposed to reduce distal embolization and improve outcomes after primary PCI are bolus intracoronary abciximab and manual aspiration thrombectomy.

Objective To determine whether bolus intracoronary abciximab, manual aspiration thrombectomy, or both reduce infarct size in high-risk patients with STEMI.

Design, Setting, and Patients Between November 28, 2009, and December 2, 2011, 452 patients presenting at 37 sites in 6 countries within 4 hours of STEMI due to proximal or mid left anterior descending artery occlusion undergoing primary PCI with bivalirudin anticoagulation were randomized in an open-label, 2 × 2 factorial design to bolus intracoronary abciximab delivered locally at the infarct lesion site vs no abciximab and to manual aspiration thrombectomy vs no thrombectomy.

Interventions A 0.25-mg/kg bolus of abciximab was administered at the site of the infarct lesion via a local drug delivery catheter. Manual aspiration thrombectomy was performed with a 6 F aspiration catheter.

Main Outcome Measures Primary end point: infarct size (percentage of total left ventricular mass) at 30 days assessed by cardiac magnetic resonance imaging (cMRI) in the abciximab vs no abciximab groups (pooled across the aspiration randomization); major secondary end point: 30-day infarct size in the aspiration vs no aspiration groups (pooled across the abciximab randomization).

Results Evaluable cMRI results at 30 days were present in 181 and 172 patients randomized to intracoronary abciximab vs no abciximab, respectively, and in 174 and 179 patients randomized to manual aspiration vs no aspiration, respectively. Patients randomized to intracoronary abciximab compared with no abciximab had a significant reduction in 30-day infarct size (median, 15.1%; interquartile range [IQR], 6.8%-22.7%; n=181, vs 17.9% [IQR, 10.3%-25.4%]; n=172; *P*=.03). Patients randomized to intracoronary abciximab also had a significant reduction in absolute infarct mass (median, 18.7 g [IQR, 7.4-31.3 g]; n=184, vs 24.0 g [IQR, 12.1-34.2 g]; n=175; *P*=.03) but not abnormal wall motion score (median, 7.0 [IQR, 2.0-10.0]; n=188, vs 8.0 [IQR, 3.0-10.0]; n=184; *P*=.08). Patients randomized to aspiration thrombectomy vs no aspiration had no significant difference in infarct size at 30 days (median, 17.0% [IQR, 9.0%-22.8%]; n=174, vs 17.3% [IQR, 7.1%-25.5%]; n=179; *P*=.51), absolute infarct mass (median, 20.3 g [IQR, 9.7-31.7 g]; n=178, vs 21.0 g [IQR, 9.1-34.1 g]; n=181; *P*=.36), or abnormal wall motion score (median, 7.5 [IQR, 2.0-10.0]; n=186, vs 7.5 [IQR, 2.0-10.0]; n=186; *P*=.89).

Conclusion In patients with large anterior STEMI presenting early after symptom onset and undergoing primary PCI with bivalirudin anticoagulation, infarct size at 30 days was significantly reduced by bolus intracoronary abciximab delivered to the infarct lesion site but not by manual aspiration thrombectomy.

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Primary percutaneous coronary intervention (PCI) is widely accepted as the most effective reperfusion modality for ST-segment elevation myocardial infarction (STEMI). However, myocardial recovery after primary PCI is often suboptimal despite restoration of coronary blood flow, in part due to thrombus embolization resulting in impaired microvascular perfusion.[1-4] Two strategies proposed to reduce distal embolization after primary PCI are bolus infusion of intracoronary abciximab[5-8] and manual thrombus aspiration.[9-13]

The mechanism through which reduced embolization and improved myo-

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cardial perfusion may improve clinical outcomes is enhanced myocardial salvage. However, conflicting results have been reported as to whether intracoronary abciximab and manual aspiration thrombectomy reduce infarct size or improve clinical outcomes,[5,6,9,12] in part because of differences in patient selection, devices, and study methodology. Moreover, many patients enrolled in these trials had a small amount of myocardium at risk (eg, nonanterior MI); presented up to 12 hours after infarct onset,[7,11] well beyond the time window for effective myocardial salvage[14]; or both. Also, no such prior trial has been performed in patients undergoing primary PCI with bivalirudin as the procedural anticoagulant, which has been shown to reduce major bleeding and improve survival compared with heparin plus a glycoprotein IIb/IIIa inhibitor.[15-17]

We therefore performed a multicenter, prospective trial in which patients presenting early with anterior STEMI and proximal or mid left anterior descending (LAD) artery occlusion undergoing primary PCI with bivalirudin were randomized in a 2×2 factorial design to bolus intracoronary abciximab vs no abciximab and to manual aspiration thrombectomy vs no aspiration.

METHODS

The design of the INFUSE-AMI trial has been previously described.[18] INFUSE-AMI was an open-label, 2×2 factorial, randomized, multicenter, single-blind evaluation of bolus intracoronary abciximab and manual aspiration thrombectomy in patients undergoing primary PCI for anterior STEMI. The study was approved by the institutional review board at each participating center, and all eligible patients signed informed, written consent.

Patients 18 years and older with symptoms consistent with STEMI longer than 30 minutes' duration and 1 mm or greater of ST-segment elevation in 2 or more contiguous leads in V_1-V_4, or new left bundle-branch block, with anticipated symptom-onset-to-device time of 5 hours or less (ie, symptom-to-presentation time, ≤3.5-4 hours) were eligible for enrollment. Principal clinical exclusion criteria included contraindications to study medications or contrast; prior MI, bypass graft surgery, or LAD stenting; planned surgery necessitating antiplatelet agent interruption; contraindication to cardiac magnetic resonance imaging (cMRI); known creatinine clearance less than 30 mL/min/1.73 m^2, dialysis, platelet count less than 100 000 or greater than 700 000 cells/mm^3, or hemoglobin level less than 10 g/dL; recent major bleeding, bleeding diathesis, or current warfarin use; history of intracranial disease; ischemic stroke or transient ischemic attack within 6 months or any permanent neurologic defect; prerandomization cardiogenic shock or cardiopulmonary resuscitation; prior fibrinolysis or IIb/IIIa inhibitor for the present admission; and any comorbid conditions likely to interfere with protocol compliance or associated with less than 1-year survival.

Patients were administered aspirin, 324 mg orally or 250 to 500 mg intravenously, and clopidogrel, 600 mg, or prasugrel, 60 mg, after which emergent coronary arteriography and left ventriculography were performed. Patients undergoing PCI received procedural anticoagulation with bivalirudin (intravenous bolus 0.75 mg/kg plus infusion of 1.75 mg/kg per hour, discontinued at procedure end) without routine glycoprotein IIb/IIIa inhibition. Angiographic eligibility required the infarct lesion to be located in the proximal or mid LAD with visually assessed Thrombolysis in Myocardial Infarction (TIMI) 0-2 flow, and absence of excessive tortuosity, diffuse disease, heavy calcification, or significant left main disease.

Eligible patients were randomized equally to 1 of 4 groups: (1) thrombus aspiration followed by intracoronary bolus abciximab, (2) thrombus aspiration without abciximab, (3) intracoronary bolus abciximab without aspiration, or (4) no abciximab and no aspiration. Telephone randomization in block sizes of 8 within strata was performed using a computerized interactive voice response system balancing for time from symptoms to angiography less than 3 hours vs 3 or more hours and by proximal vs mid LAD occlusion.

Manual thrombus aspiration was performed with a 6 F Export Catheter (Medtronic), the same device used in the TAPAS (Thrombus Aspiration During Percutaneous Coronary Intervention in Acute Myocardial Infarction Study).[9] The protocol specified actively aspirating whenever crossing the lesion or withdrawing the catheter, making several passes until no further thrombus or debris was retrieved. To ensure high intrathrombus drug concentrations, a 0.25-mg/kg bolus of abciximab was administered locally at the site of the infarct lesion via the ClearWay RX Local Therapeutic Infusion Catheter, a microporous "weeping" PTFE balloon mounted on a 2.7F rapid exchange catheter (Atrium Medical). An abciximab infusion after PCI was allowed only for refractory intraprocedural thrombotic complications. Percutaneous coronary intervention was performed using standard techniques, with bare metal or drug-eluting stent implantation at operator discretion. (See video of procedural coronary angiograms of a patient treated with thrombus aspiration followed by intracoronary bolus abciximab at http://www.jama.com.)

After PCI, all patients were treated with aspirin indefinitely and with clopidogrel or prasugrel for at least 1 year. Cardiac MRI was scheduled in all patients at 30 days. Clinical follow-up was scheduled at 30 days and at 1 year. The enrolling research coordinator and local principal investigator performing the index procedure were aware of the study assignments. The patient and all subsequent study personnel, including follow-up nurses, core laboratory technicians, the clinical event adjudication committee, the executive com-

mittee, and the sponsor, were blinded to the randomized treatment.

End Points and Definitions

Baseline patient data for demographic characteristics and medication use, presenting signs and symptoms, laboratory results, 12-lead electrocardiography, and coronary angiography were collected. The primary efficacy end point was infarct size (percentage of total left ventricular mass) at 30 days in patients assigned to intracoronary abciximab vs no abciximab (pooled across the thrombectomy randomization). The major secondary end point was 30-day infarct size in patients assigned to aspiration thrombectomy vs no thrombectomy (pooled across the abciximab randomization). Additional efficacy end points included measures of angiographic reperfusion (TIMI flow, myocardial blush grade [MBG]), ST-segment resolution (STR) at 60 minutes, and 30-day and 1-year clinical outcomes. Cardiac MRI (eMethods and eFigure, available at http://www.jama.com), angiographic, and STR end points were evaluated at independent core laboratories,[2,3] blinded to randomization and outcomes.

Major adverse cardiac events (MACE) were defined as death, reinfarction, new-onset severe heart failure, or rehospitalization for heart failure. Major adverse cardiac and cerebrovascular events (MACCE) were defined as death, reinfarction, stroke, or clinically driven target vessel revascularization (TVR). Bleeding was assessed using the HORIZONS-AMI, TIMI, and GUSTO scales. Detailed definitions of the clinical end points have been previously published.[18] An independent clinical events committee blinded to randomization adjudicated all major end point events using original source documents.

Statistical Methods

The study was powered for infarct size determination at 30 days. A relative reduction in infarct size of 25% with either randomized therapy was considered clinically relevant. Evaluating 408 participants randomized to intracoronary abciximab vs no abciximab provided 80% power to demonstrate a relative 25% reduction in infarct size from 24% to 18% (with SD 21%). To account for loss to follow-up and suboptimal cMRI, enrollment was planned for 452 patients. To preserve α, formal hypothesis testing of the major secondary end point of infarct size in patients randomized to aspiration vs no aspiration was performed only if the primary end point of infarct size with intracoronary abciximab vs no abciximab was significantly reduced.

All analyses were performed by intention to treat. Missing data were not replaced. However, multiple imputation for missing baseline data and outcomes was performed as a sensitivity analysis for the principal infarct size end points, using the prespecified baseline variables of left ventricular ejection fraction, proximal vs mid left LAD lesion, presence of angiographic collateral vessels, time from symptom onset to first device, sex, and age. Categorical outcomes were compared by χ^2 or Fisher exact test. Continuous variables are presented as median with interquartile range (IQR) and compared by Wilcoxon rank sum test. Analysis of variance models were performed to exclude significant interactions between the 2 levels of randomization. As infarct size is nonnormally distributed, nonparametric testing was used for the principal analysis of the primary and major secondary end points. Infarct size is also reported as mean with standard deviation and compared by *t* test. Kaplan-Meier time-to-event estimates for clinical outcomes were compared with log-rank test. All statistical tests were 2-sided. A *P* value less than .05 was considered significant for all analyses. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc).

RESULTS

Between November 28, 2009, and December 2, 2011, 6318 patients with STEMI were screened at 37 sites in 6 countries (United States, Germany, Poland, Austria, the Netherlands, and the United Kingdom), 452 (7.2%) of whom were randomized (FIGURE). The most common reasons for exclusion were nonanterior MI and symptom-to-treatment time greater than 5 hours. The baseline characteristics of the 4 randomized groups were well matched (TABLE 1).

Procedural data for the patients assigned to intracoronary abciximab vs no abciximab (pooled across the thrombectomy randomization) and those assigned to aspiration thrombectomy vs no thrombectomy (pooled across the abciximab randomization) appear in TABLE 2. A bolus of abciximab was administered to 223 of 229 abciximab-randomized patients (97.4%); in all but 1 patient, abciximab was infused locally to the infarct lesion site through the drug delivery study catheter. Manual thrombus aspiration was performed in 225 of 229 aspiration-randomized patients (98.3%). The prespecified aspiration catheter was used in all but 3 cases, and visible thrombus was retrieved from 78.9% of patients.

Discharge medications included aspirin in 99.1% of patients, clopidogrel in 66.4%, prasugrel in 31.8%, statins in 97.7%, β-blockers in 96.6%, and angiotensin-converting enzyme inhibitors or receptor blockers in 94.1%, with no significant differences between groups.

Myocardial Perfusion and ST-Segment Resolution

Post-PCI TIMI 3 flow, an MBG of 2 or 3, and complete STR at 60 minutes were achieved in 91.4%, 81.4%, and 53.7% of patients, respectively. No significant differences in these measures were present between patients randomized to intracoronary abciximab vs no abciximab or to aspiration thrombectomy vs no thrombectomy (Table 2 and eTable 1).

Infarct Size and Clinical Outcomes

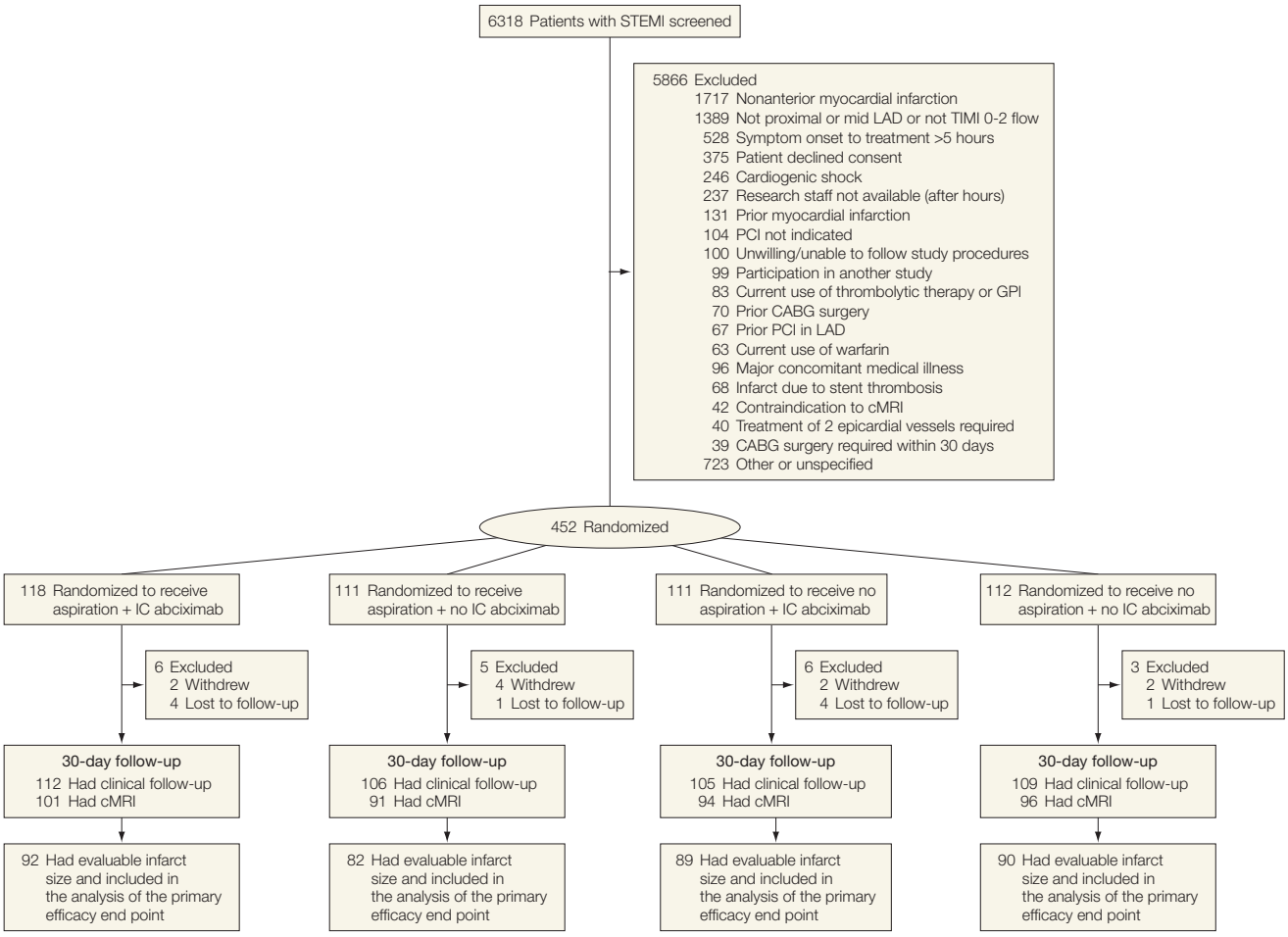
Cardiac MRI was performed in 382 of 439 patients (87.1%) alive at 30 days, from which wall motion and infarct size were analyzable by the core labora-

tory in 372 and 353 patients, respectively (Figure). Patients randomized to intracoronary abciximab compared with no abciximab had a significant decrease in the primary end point of infarct size measured as a percentage of total myocardial mass (median, 15.1% [IQR, 6.8%-22.7%] vs 17.9% [IQR, 10.3%-25.4%]; $P=.03$; mean [SD], 15.2% [9.9%] vs 17.5% [10.2%]; difference, −2.3% [95% CI, −4.4% to −0.2%]; $P=.03$) and absolute infarct mass, but not in abnormal wall motion score (**TABLE 3** and eTable 2).

Patients randomized to aspiration thrombectomy vs no aspiration had no significant difference in infarct size (median, 17.0% [IQR, 9.0%-22.8%] vs median, 17.3% [IQR, 7.1%-25.5%]; $P=.51$; mean [SD], 15.9% [9.7%] vs 16.7% [10.6%]; difference, −0.7% [95% CI, −2.9% to 1.4%]; $P=.49$), absolute infarct mass, or abnormal wall motion score (Table 3 and eTable 2). After multiple imputation to adjust for missing baseline and outcomes data, assignment to intracoronary abciximab vs no abciximab was associated with a nominal reduction in infarct size at 30 days (median, 15.4% [IQR, 7.0%-22.7%] vs 17.6% [IQR, 10.2%-24.7%]; mean difference, −2.0% [95% CI, −4.0% to −0.0%]; $P=.0498$), whereas no significant difference in infarct size was present in patients randomized to manual aspiration vs no aspiration (median, 16.6% [IQR, 8.8%-22.7%] vs 17.4% [IQR, 7.3%-25.2%]; mean difference, −1.1% [95% CI, −3.1% to 0.9%]; $P=.27$).

Cardiac MRI at 30 days was performed in only 2 of 31 patients (6.5%)

Figure. Diagram of Patient Flow in the INFUSE-AMI Trial



More than 1 reason for study exclusion were present in some patients who were not eligible for randomization. Cardiac magnetic resonance imaging (cMRI) at 30 days was not performed in 70 enrolled patients for the following reasons: patient refusal or withdrawn consent for cMRI (n=27); patient inability to complete the cMRI (most commonly for claustrophobia) (n=15); death before the 30-day cMRI (n=13); too ill (n=4); patient forgot (n=4); contrast contraindication (n=2); other (n=5). In addition, despite being performed, the cMRI study was not evaluable for the primary end point of infarct size in 29 patients because of technical issues in image acquisition, including incorrect image sequencing, inadequate inversion recovery time, excessive breathing artifact, and missing slices. CABG denotes coronary artery bypass graft; GPI, glycoprotein IIb/IIIa inhibitor; IC, intracoronary; LAD, left anterior descending coronary artery; PCI, percutaneous coronary intervention; and TIMI, Thrombolysis in Myocardial Infarction.

in whom MACE occurred, in 1 patient treated with intracoronary abciximab with no aspiration, and in 1 patient treated with no abciximab and no aspiration.

No interaction was present between the 2 randomization groups for the 30-day infarct size end point (P=.46), although in a post hoc analysis, median infarct size was lowest in the intracoronary abciximab plus aspiration group compared with the other 3 groups combined (median, 14.7% [IQR, 7.1%-20.6%] vs 17.6% [IQR, 8.1%-25.1%]; P=.03).

No significant differences in any of the major safety or efficacy end points were present between the randomized groups at 30 days (TABLE 4 and eTable 3).

COMMENT

The principal findings from this multicenter, prospective, randomized trial in patients presenting early in the course of a large evolving anterior STEMI undergoing primary PCI with bivalirudin anticoagulation are as follows: (1) bolus intracoronary abciximab delivered to the infarct lesion site significantly but modestly reduced the primary end point of infarct size at 30 days; (2) in contrast, manual aspiration thrombectomy did not significantly reduce infarct size; and (3) indices of myocardial reperfusion, STR, and 30-day clinical event rates were not significantly different between the randomized groups.

The present study was designed to maximize the likelihood that a reduction in infarct size could be demonstrated with intracoronary abciximab, aspiration thrombectomy, or both, if indeed such a reduction truly exists. Two of the strongest baseline determinates of infarct size are anterior MI location and abnormal TIMI flow.[19] We therefore limited enrollment to patients with proximal or mid LAD occlusion (and without prior MI) and operator-assessed baseline TIMI 0-2 flow. We also restricted enrollment to patients who could be treated early, in whom the time window for effective myocardial salvage had not closed.[14] Indeed, the median time from symptom onset to hospital arrival was only 99 minutes, and the median door-to-device time was 45 minutes. The study population thus represents a highly selected cohort of patients with large anterior MI (those with the greatest clinical need), in whom infarct size reduction should be feasible given early presentation and rapid treatment.

We assessed infarct size by cMRI, which strongly correlates with subsequent mortality.[4,20,21] To reduce sample size, prior studies using cMRI have typically measured infarct size early after reperfusion (2-7 days), a period during which substantial myocardial edema is present that may be mischaracterized as nonviable myocardium.[22,23] We therefore powered the present trial for assessment of the primary infarct size end point at 30 days (when much of the myocardial edema has resolved), a time

Table 1. Baseline Characteristics of the Randomized Groups

	Patients, No./Total No. (%)			
	Aspiration + IC Abciximab (n = 118)	No Aspiration + IC Abciximab (n = 111)	Aspiration + No Abciximab (n = 111)	No Aspiration + No Abciximab (n = 112)
Age, median (IQR), y	60.0 (52.0-66.0)	56.0 (49.0-68.0)	62.0 (53.0-73.0)	62.5 (52.5-71.0)
Male sex	84/118 (71.2)	84/111 (75.7)	85/111 (76.6)	81/112 (72.3)
Body mass index, median (IQR)[a]	26.6 (23.9-29.7)	26.3 (23.8-29.4)	26.8 (24.3-30.5)	26.6 (24.0-28.7)
Killip class				
I	99/118 (83.9)	96/111 (86.5)	82/110 (74.5)	90/112 (80.4)
II	8/118 (6.8)	6/111 (5.4)	13/110 (11.8)	13/112 (11.6)
III	2/118 (1.7)	2/111 (1.8)	0/110	2/111 (1.8)
Hypertension	37/118 (31.4)	30/111 (27.0)	39/111 (35.1)	36/112 (32.1)
Hyperlipidemia	20/117 (17.1)	19/111 (17.1)	18/111 (16.2)	14/112 (12.5)
Diabetes mellitus	15/118 (12.7)	9/111 (8.1)	19/110 (17.3)	8/112 (7.1)
Prior myocardial infarction	0/118	3/110 (2.7)	1/110 (0.9)	0/112
Prior percutaneous coronary intervention	2/118 (1.7)	2/110 (1.8)	3/111 (2.7)	3/112 (2.7)
Cigarette smoking, current	52/117 (44.4)	53/109 (48.6)	46/109 (42.2)	55/112 (49.1)
Symptom to hospital arrival, median (IQR), min	92.5 (65.0-152.0)	100.5 (75.0-158.0)	107.0 (66.5-152.5)	98.0 (67.0-136.0)
Hospital arrival to first device, median (IQR), min[b]	43.0 (30.0-64.0)	48.0 (36.0-69.0)	42.0 (30.0-61.0)	46.5 (34.0-70.5)
Symptom onset to first device, median (IQR), min[b]	141 (120-221)	166 (126-233)	151 (117-205)	160 (126-217)
Infarct artery lesion location[c]				
Proximal left anterior descending	74/118 (62.7)	76/111 (68.5)	68/111 (61.3)	74/112 (66.1)
Mid left anterior descending	49/118 (41.5)	44/111 (39.6)	47/111 (42.3)	48/112 (42.9)
Left ventricular ejection fraction, median (IQR), %[d]	40.0 (35.0-49.0)	40.0 (35.0-48.0)	40.0 (38.0-50.0)	40.0 (31.0-50.0)

Abbreviations: IC, intracoronary; IQR, interquartile range.
[a] Calculated as weight in kilograms divided by height in meters squared.
[b] Balloon angioplasty, local drug delivery, or aspiration.
[c] Some patients had both proximal and mid left anterior descending lesions.
[d] From contrast left ventriculography during the index procedure.

more specific for identification of truly infarcted myocardium.[23] Myocardial reperfusion was assessed by several complementary parameters, including post-PCI TIMI flow, MBG, and STR.[2,3] In addition, bivalirudin was used as the procedural anticoagulant to minimize bleeding and improve survival.[15-17] Under these optimal conditions, 30-day infarct size was significantly reduced by intracoronary abciximab but not by manual aspiration thrombectomy, representing the primary and major secondary end points of the trial, respectively.

Table 2. Procedural Outcomes and Reperfusion Indices for the Pooled Randomized Groups

	Patients, No./Total No. (%)					
	Intracoronary Abciximab[a] (n = 229)	No Intracoronary Abciximab[a] (n = 223)	*P* Value	Aspiration Thrombectomy[b] (n = 229)	No Aspiration Thrombectomy[b] (n = 223)	*P* Value
Unfractionated heparin administered before cardiac catheterization	142/229 (62.0)	145/223 (65.0)	.51	145/229 (63.3)	142/223 (63.7)	.94
Bivalirudin administered	229/229 (100.0)	222/223 (99.6)	.99	228/229 (99.6)	223/223 (100.0)	.99
Abciximab administered	223/229 (97.4)	5/223 (2.2)	<.001	116/229 (50.7)	112/223 (50.2)	.93
Aspiration performed	119/229 (52.0)	115/223 (51.6)	.93	225/229 (98.3)	9/223 (4.0)	<.001
Number of lesions treated, mean (SD)	1.1 (0.4)	1.2 (0.4)	.28	1.2 (0.4)	1.2 (0.4)	.64
Drug-eluting stents implanted	171/229 (74.7)	157/223 (70.4)	.31	170/229 (74.2)	158/223 (70.9)	.42
Total stent length, median (IQR), mm	24.0 (18.0-34.0)	23.0 (17.0-32.5)	.13	23.5 (18.0-32.0)	24.0 (18.0-35.0)	.30
Maximum stent diameter, median (IQR), mm	3.0 (3.0-3.5)	3.0 (3.0-3.5)	.75	3.0 (3.0-3.5)	3.0 (3.0-3.5)	.20
TIMI flow before PCI[c]						
0/1	166/229 (72.5)	158/223 (70.9)	.70	168/229 (73.4)	156/223 (70.0)	.42
2/3	63/229 (27.5)	65/223 (29.1)	.70	61/229 (26.6)	67/223 (30.0)	.42
TIMI flow after PCI[c]						
0/1	7/229 (3.1)	2/223 (0.9)	.18	4/229 (1.7)	5/223 (2.2)	.75
2	13/229 (5.7)	17/223 (7.6)	.41	13/229 (5.7)	17/223 (7.6)	.41
3	209/229 (91.3)	204/223 (91.5)	.94	212/229 (92.6)	201/223 (90.1)	.36
Corrected TIMI frame count after PCI, median (IQR)[c]	20 (16-26)	20 (16-26)	.62	20 (16-26)	20 (16-26)	.40
MBG 0/1 after PCI[c]	44/228 (19.3)	40/223 (17.9)	.71	38/229 (16.6)	46/222 (20.7)	.26
MBG 2/3 after PCI[c]	184/228 (80.7)	183/223 (82.1)	.71	191/229 (83.4)	176/222 (79.3)	.26
ST-segment resolution at 60 min, median (IQR), %[c,d]	69.8 (46.0-85.5)	74.1 (52.6-88.2)	.30	71.2 (45.2-87.2)	74.4 (55.8-87.4)	.37
Complete, >70%	101/202 (50.0)	108/187 (57.8)	.13	101/199 (50.8)	108/190 (56.8)	.23
Partial, 30%-70%	73/202 (36.1)	49/187 (26.2)	.04	65/199 (32.7)	57/190 (30.0)	.57
Absent, <30%	28/202 (13.9)	30/187 (16.0)	.55	33/199 (16.6)	25/190 (13.2)	.34

Abbreviations: MBG, myocardial blush grade; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.
[a] Pooled, either with or without aspiration thrombectomy.
[b] Pooled, either with or without intracoronary abciximab.
[c] Core laboratory assessed.
[d] In patients with baseline ST-segment elevation in 2 or more contiguous leads.

Table 3. Thirty-Day Cardiac Magnetic Resonance Imaging Results for the Pooled Randomized Groups

	Intracoronary Abciximab[a] (n = 188)	No Intracoronary Abciximab[a] (n = 184)	*P* Value	Aspiration Thrombectomy[b] (n = 186)	No Aspiration Thrombectomy[b] (n = 186)	*P* Value
Infarct size, median [IQR], % of total LV mass[c]	15.1 [6.8-22.7] (n = 181)	17.9 [10.3-25.4] (n = 172)	.03	17.0 [9.0-22.8] (n = 174)	17.3 [7.1-25.5] (n = 179)	.51
Total LV myocardial mass, median [IQR], g	128.6 [106.6-152.4] (n = 181)	130.4 [109.9-155.9] (n = 172)	.55	128.3 [108.9-149.8] (n = 174)	132.0 [107.6-156.1] (n = 179)	.50
Infarct mass, median [IQR], g	18.7 [7.4-31.3] (n = 184)	24.0 [12.1-34.2] (n = 175)	.03	20.3 [9.7-31.7] (n = 178)	21.0 [9.1-34.1] (n = 181)	.36
Total abnormal wall motion score, median [IQR]	7.0 [2.0-10.0] (n = 188)	8.0 [3.0-10.0] (n = 184)	.08	7.5 [2.0-10.0] (n = 186)	7.5 [2.0-10.0] (n = 186)	.89
Left ventricular ejection fraction, median [IQR], %	50.2 [44.2-57.9] (n = 182)	48.9 [42.3-56.7] (n = 179)	.22	49.6 [43.3-56.8] (n = 181)	49.5 [41.8-57.6] (n = 180)	.66

Abbreviations: cMRI, cardiac magnetic resonance imaging; LV, left ventricular.
[a] Pooled, either with or without aspiration thrombectomy
[b] Pooled, either with or without intracoronary abciximab.
[c] Primary end point.

These results need to be placed in the context of previous studies. Two earlier randomized trials demonstrated infarct size reductions with intracoronary compared with intravenous abciximab (despite enrollment of patients with nonanterior MI presenting up to 12 hours after symptoms),[5,6] and a meta-analysis of 6 randomized trials (1246 patients) reported enhanced survival with intracoronary abciximab.[7] However, the recently completed AIDA-STEMI trial, which with 2065 randomized patients was powered for clinical outcomes, found nearly identical rates of MACE (and biomarker-assessed infarct size) with bolus intracoronary and intravenous abciximab.[8]

However, in addition to enrolling only anterior STEMI patients presenting early, our trial differs from these earlier studies in several important ways.2 First, all prior studies of intracoronary vs intravenous abciximab included a 12-hour post-PCI abciximab infusion in both groups. Procedural anticoagulation with bivalirudin without routine glycoprotein IIb/IIIa inhibition in the control group of INFUSE-AMI thus isolated the effects of bolus-only abciximab. In this regard, some[24] but not all[25] studies have suggested that infarct size might be reduced by adding abciximab to heparin. Second, in all prior trials (including AIDA-STEMI), intracoronary abciximab was infused proximally through the guide catheter, limiting its penetration into occlusive thrombus and allowing preferential drug flow to lower resistance pathways (such as the left circumflex artery) and blowback into the aorta. In contrast, the local drug delivery catheter used in the present study directly achieves high intraclot concentrations of abciximab at the site of LAD occlusion and prolongs drug residence time, which may enhance platelet disaggregation and thrombus resolution.[26-28] In the present study, an abciximab bolus delivered directly to the infarct lesion site (without a 12-hour infusion) reduced infarct size at 30 days (the primary end point of the study) in patients with anterior STEMI reperfused early.

Regarding aspiration thrombectomy, in TAPAS, 1071 patients with anterior and nonanterior STEMI who presented within 12 hours of symptom onset at a single center were randomized to manual aspiration (using the same catheter as studied in the present

Table 4. Clinical Efficacy and Safety End Points at 30 Days for the Pooled Randomized Groups

	No. of Events (%)[a]					
	Intracoronary Abciximab[b] (n = 229)	No Intracoronary Abciximab[b] (n = 223)	*P* Value	Aspiration Thrombectomy[c] (n = 229)	No Aspiration Thrombectomy[c] (n = 223)	*P* Value
Efficacy End Points						
MACCE	11 (4.8)	7 (3.2)	.36	7 (3.1)	11 (5.0)	.31
MACE	16 (7.0)	15 (6.8)	.91	15 (6.6)	16 (7.2)	.81
Death	8 (3.5)	5 (2.3)	.42	7 (3.1)	6 (2.7)	.81
Reinfarction	1 (0.5)	2 (0.9)	.56	1 (0.5)	2 (0.9)	.55
New-onset severe heart failure	7 (3.1)	10 (4.5)	.44	8 (3.5)	9 (4.1)	.77
Rehospitalization for heart failure	0	2 (0.9)	.15	0	2 (0.9)	.15
Stroke	1 (0.4)	0	.32	0	1 (0.5)	.31
Clinically driven TVR	2 (0.9)	3 (1.4)	.65	1 (0.5)	4 (1.8)	.17
Stent thrombosis, definite or probable	2 (0.9)	2 (0.9)	.99	3 (1.4)	1 (0.5)	.33
Acute, <24 h	0	0		0	0	
Subacute, 1-30 d	2 (0.9)	2 (0.9)	.99	3 (1.4)	1 (0.5)	.33
Bleeding End Points						
HORIZONS-AMI major bleeding	11 (4.9)	8 (3.6)	.50	9 (4.0)	10 (4.6)	.79
TIMI major or minor bleeding	5 (2.2)	4 (1.8)	.75	3 (1.3)	6 (2.8)	.30
TIMI major	5 (2.2)	1 (0.5)	.11	2 (0.9)	4 (1.8)	.40
TIMI minor	0	3 (1.4)	.08	1 (0.5)	2 (0.9)	.55
GUSTO bleeding, any	15 (6.75)	12 (5.5)	.58	12 (5.3)	15 (6.8)	.51
GUSTO severe	10 (4.4)	9 (4.1)	.84	9 (4.0)	10 (4.5)	.77
GUSTO moderate	3 (1.3)	0	.09	2 (0.9)	1 (0.5)	.58
GUSTO mild	2 (0.9)	3 (1.4)	.64	1 (0.4)	4 (1.8)	.17
Any blood product transfusion	4 (1.8)	1 (0.5)	.18	2 (0.9)	3 (1.4)	.64
Thrombocytopenia, in-hospital[d]	2/196 (1.0)	2/179 (1.1)	.99	1/186 (0.5)	3/189 (1.6)	.62

Abbreviations: GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries; HORIZONS-AMI, Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction; MACE, major adverse cardiac events; MACCE, major adverse cardiac and cerebrovascular events: TIMI, Thrombolysis in Myocardial Infarction; TVR, target vessel revascularization.

[a] Data are Kaplan-Meier estimates.

[b] Pooled, either with or without aspiration thrombectomy.

[c] Pooled, either with or without intracoronary abciximab.

[d] <100 000 cells/mm^3 in patients with a baseline platelet count >150 000 cells/mm^3 (n=384).

trial) vs no aspiration before primary PCI; aspiration resulted in modest improvements in MBG and STR but a marked reduction in 1-year mortality.[9,10] Other trials of manual aspiration thrombectomy have reported conflicting results,[11,12] and in contrast to single-center studies, multicenter aspiration trials have largely been negative.[13] Moreover, in TAPAS, aspiration did not reduce infarct size as measured by cardiac biomarkers,[9] calling into question the mechanism underlying the survival benefit. The present multicenter trial, in which only patients presenting early with anterior MI and coronary anatomy optimal for aspiration were enrolled, and in which cMRI was used to assess infarct size at 30 days, was specifically designed to overcome many of the limitations from these earlier studies. The fact that manual thrombus aspiration did not reduce infarct size (the major secondary end point) in our study makes a substantial clinical benefit unlikely, questioning its routine use in STEMI.

Our study has several limitations. First, the trial was single-blind, with the operator knowing the randomization assignment. Thus, while some bias cannot be excluded, the patient and follow-up personnel were unaware of the treatments provided, and the study used numerous core laboratories and a clinical events committee blinded to treatment assignment. The major findings of the study were not altered in a sensitivity analysis in which multiple imputation was used to adjust for missing baseline and infarct size data.

Second, by design, the study cohort was highly selected, with only 7.2% of screened STEMI patients enrolled. However, because only patients with the greatest potential for infarct size reduction were randomized, it is unlikely that intracoronary abciximab or aspiration would be more effective in a broader population.

Third, crossing the lesion with the drug delivery catheter prior to abciximab infusion may have mechanically dislodged thrombus downstream, perhaps explaining why infarct size was lowest in the combined aspiration/abciximab group. A larger study is required to confirm this observation.

Fourth, manual aspiration catheters with a larger internal diameter than the one used in the present trial are now available. However, the device used in this study was associated with reduced mortality in TAPAS. Moreover, studies have not shown greater thrombus retrieval or improved myocardial perfusion with larger bore devices,[29] and use of a larger aspiration catheter in a prior randomized trial was associated with increased infarct size.[12]

Fifth, infarct size assessment by cMRI at 30 days was available in only 353 of 452 patients (78.1%), with the most common reasons for missing data being patient death prior to 30 days, inability to tolerate the procedure, patient refusal or withdrawal, and study site technical issues with image acquisition. Of note, however, the 78.1% acquisition rate in the present study at 30 days is similar to 81.6% cMRI infarct size acquisition rate at 3 to 5 days reported from the recently published CRISP AMI trial.[30]

In addition, although infarct size at 30 days was reduced with intracoronary abciximab, early markers of microcirculatory reperfusion (MBG and STR) were not improved. This discordance may reflect different ascertainment times given infarct evolution over 30 days (especially as edema is substantially reduced during this time) and variable accuracy of different biomarkers. The comparable 30-day clinical event rates between groups is consistent with the early MBG and STR results.[2,3] Moreover, the magnitude of the absolute reduction in infarct size with intracoronary abciximab, while statistically significant, was modest (mean reduction, 2.3%; 95% CI, 0.2% to 4.4%, of total left ventricular mass, less than the 6% which was considered clinically relevant during planning of the study). As a result, the increase in left ventricular ejection fraction noted in abciximab-treated patients compared with those not receiving abciximab did not reach statistical significance. Larger trials are required to determine whether the degree of infarct size reduction at 30 days achieved with intracoronary abciximab in the present study translates into improved late clinical outcomes without increasing bleeding.

In conclusion, among patients with large anterior STEMI presenting early after infarct onset and undergoing primary PCI with bivalirudin anticoagulation, infarct size was reduced by bolus intracoronary abciximab delivered to the site of the infarct lesion, but not by manual aspiration thrombectomy.

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INFUSE-AMI Trial (A 2×2 Factorial, Randomized, Multicenter, Single-Blind Evaluation of Intracoronary Abciximab Infusion and Aspiration Thrombectomy in Patients Undergoing Percutaneous Coronary Intervention for Anterior ST-Segment Elevation Myocardial Infarction) Organization and Participating Investigators: *Executive Committee:* Gregg W. Stone (Principal Investigator), Columbia University Medical Center, New York Presbyterian Hospital, and the Cardiovascular Research Foundation, New York, NY; C. Michael Gibson (Co-Principal Investigator), Harvard Medical School and Beth Israel Deaconess Medical Center, Boston, MA; David A. Cox, Lehigh Valley Hospital, Allentown, PA; Rajesh Dave, Holy Spirit Cardiovascular Institute, Holy Spirit Hospital, Camp Hill, PA; Dariusz Dudek, Samodzielna Pracownia Hemodynamiki i Angiokardiografii, Kraków, Poland; Cindy L. Grines, William Beaumont Hospital, Royal Oak, MI; Alexandra J. Lansky, Yale University, New Haven, CT; Gabriel Steg, Hopital Bichat-Claude Bernad Service de Cardiologie, Paris, France; Thomas Stuckey, LeBauer Cardiovascular Research Foundation, Moses Cone Hospital, Greensboro, NC; Jochen Wöhrle, University of Ulm, Ulm, Germany. *European Country Leaders:* Thomas Neunteufl, Austria; Jochen Wöhrle, Germany; Jacques Koolen, the Netherlands; Dariusz Dudek, Poland; Anthony Gershlick, United Kingdom. *Data Monitoring:* Genae Associates (Antwerp, Belgium), Krakow Cardiovascular Research Institute (Krakow, Poland), Bailer Research (San Ramon, California). *Clinical Events Committee:* Cardiovascular Research Foundation; Shing Chiu Wong (Chair), Cornell-Weill Medical Center; Steven Marx, Columbia University Medical Center; Ozgen Dogan, Columbia University Medical Center; Kevin Dunsky, Mount Sinai Hospital, New York, NY. *Data Management and Analysis:* Cardiovascular Research Foundation; Roxana Mehran (Director), Helen Parise (Biostatistics). *Data and Safety Monitoring Board:* Bernard J. Gersh (Chair), Mayo Clinic, Rochester, MN; David Faxon, Brigham and Women's Hospital, Boston; Tim Collier, London School of Hygiene and Tropical Medicine, London, UK. *Coronary Angiographic Core Laboratory Analysis:* Cardiovascular Research Foundation, Ecaterina Cristea (Director), Sorin J. Brener. *Cardiac MRI Core Laboratory Analysis:* Cardiovascular Research Foundation, Steven D. Wolff (Director), Akiko Maehara (Co-Director). *Electrocardiographic Core Laboratory Analysis:* Cardiovascular Research Foundation, Jose Dizon (Director), Ecaterina Cristea.

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