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Impact of Delay to Reperfusion on Reperfusion Success, Infarct Size, and Clinical Outcomes in Patients With ST-Segment Elevation Myocardial Infarction

The INFUSE-AMI Trial (INFUSE-Anterior Myocardial Infarction)

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Objectives Our aim was to study the impact of delay from symptom onset to first coronary device on infarct size and clinical outcomes at 30 days and 1 year in patients with ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention.

Background Longer delay from symptom onset to reperfusion has been linked to increased mortality and worse clinical outcome. The mechanisms underpinning this association are not entirely clear.

Methods The INFUSE-AMI trial (INFUSE-Anterior Myocardial Infarction) randomized patients with anterior STEMI undergoing primary percutaneous coronary intervention with bivalirudin anticoagulation within 5 h of symptom onset to intralesion (IL) bolus abciximab versus no abciximab and to thrombus aspiration versus no aspiration. The primary endpoint was contrast magnetic resonance infarct size (IS) (percentage of left ventricular mass) at 30 days. Time to reperfusion was classified as <3 versus ≥ 3 h.

Results There were 280 patients (62%) with <3-h delay and 170 patients (38%) with ≥ 3-h delay. Patients with longer delay were significantly older, more often women, and diabetic. Earlier reperfusion was not associated with higher rates of final Thrombolysis In Myocardial Infarction flow grade 3 or myocardial blush grade 2/3, but was an independent predictor of smaller IS ($p = 0.02$ by multivariable linear regression). Mortality at 1 year was reduced in patients with shorter delay to reperfusion (4.0% vs. 9.2%, $p = 0.02$).

Conclusions In patients with large anterior myocardial infarction undergoing relatively early reperfusion, longer delays to reperfusion were associated with larger IS and 1-year mortality, but not with reduced reperfusion success. (The INFUSE - Anterior Myocardial Infarction [AMI] Study; NCT00976521)
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Primary percutaneous coronary intervention (PCI) in patients with ST-segment elevation myocardial infarction (STEMI) results in greater reperfusion success and lower rates of death, reinfarction, and stroke compared with fibrinolysis (1). It is assumed that primary PCI translates into greater myocardial salvage (2), particularly for the late presenters who respond less often to fibrinolysis than earlier presenters (3). Delay from ischemic symptom onset to reperfusion has been shown to be an important predictor of outcomes, to a greater extent for fibrinolysis than for primary PCI (4).

Strategies geared to improve procedural success and reperfusion rates in STEMI have focused on prevention of distal embolization of atherothrombotic debris from the lesion site (5). Intralesion (IL) abciximab (6) and manual thrombus aspiration (7) were tested in this context in the recently completed The INFUSE-AMI trial (INFUSE-Anterior Myocardial Infarction) (8,9). Using the INFUSE-AMI database, we thus sought to evaluate whether the delay from symptom onset to reperfusion affects outcome after primary PCI when these modalities are used and whether the effect is mediated via a larger infarct size (IS), as determined by contrast magnetic resonance (CMR).

Abbreviations and Acronyms

CMR = contrast magnetic resonance
IL = intralesion
IQR = interquartile range
IS = infarct size
LAD = left anterior descending artery
LV = left ventricular
MBG = myocardial blush grade
MI = myocardial infarction
MVO = microvascular obstruction
PCI = percutaneous coronary intervention
SPECT = single-photon emission computed tomography
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombolysis In Myocardial Infarction

Methods

The INFUSE-AMI Study has been described in detail (9). In brief, 452 patients with anterior STEMI and an anticipated symptom onset to reperfusion time of <5 h undergoing primary PCI with bivalirudin anticoagulation were randomized in a 2 × 2 factorial design to an IL abciximab bolus delivered at the site of the infarct lesion via the ClearWay Rx catheter (Atrium Medical, Hudson, New Hampshire) or no abciximab and to thrombus aspiration using the Export catheter (Medtronic, Minneapolis, Minnesota) or no thrombus aspiration. The primary endpoint of the study was IS, measured at 30 days by CMR and expressed as the percentage of left ventricular (LV) mass in patients assigned to IL abciximab or no abciximab, pooled across strata of thrombus aspiration. The secondary major endpoint was IS in patients assigned to aspiration or no aspiration, pooled across strata of IL 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) in a subset of patients to measure extent of microvascular obstruction (MVO), expressed as the percentage of LV mass (9). Major adverse cardiac and cerebral events, consisting of death, reinfarction, stroke, or ischemia-driven target vessel revascularization were recorded at 30 days and 1 year, and bleeding was assessed using various scales from previous clinical trials (10–12).

Markers of reperfusion were assessed at independent, blinded core electrocardiography (ST-segment resolution) and angiography (Thrombolysis In Myocardial Infarction [TIMI] flow, corrected TIMI frame counts, and myocardial blush grade [MBG]) core laboratories at the Cardiovascular Research Foundation, using standard definitions (10). MBG was assessed according to the densitometric method, which evaluates the maximal intensity of contrast penetrating the infarct zone, compared with unaffected territories (13). TIMI flow grade 3 was considered successful epicardial reperfusion, and MBG grade 2/3 was considered successful microcirculatory (myocardial) reperfusion (14).

Statistical analysis. Continuous variables are presented as mean with SD or median with interquartile range and were compared with the Wilcoxon rank sum test. Categorical variables are presented as proportions and were compared with the chi-square or Fisher exact test. Survival curves for time-to-event variables were constructed on the basis of all available follow-up data with Kaplan-Meier methodology and were compared using the log-rank test. Multivariable linear regression was performed to determine the independent predictors of 30-day IS. The following variables were entered into the model: symptom to first device time (as a continuous variable), age, sex, diabetes, hypertension, hyperlipidemia, current smoker, body mass index, baseline white blood cell count, estimated creatinine clearance, proximal versus mid left anterior descending artery (LAD) location, number diseased epicardial coronary arteries, collaterals present, baseline TIMI flow grade 0/1 versus flow grade 2/3, final TIMI flow grade 3 versus flow grade <3, IL abciximab randomization, aspiration randomization, and interaction term TIMI flow × delay (<3 h vs. ≥3 h). Significance level was set at 0.05. All analyses were performed with SAS software version 9.2 (SAS Institute, Cary, North Carolina).

Results

The primary endpoint of the study was previously reported (9). IL abciximab compared with no IL abciximab reduced 30-day IS by 16%, from 17.9% (interquartile range [IQR]: 10.3% to 25.4%) to 15.1% (IQR: 6.8% to 22.7%) ($p = 0.03$). There was no significant difference in IS with thrombus aspiration.

Among the 450 patients enrolled in the study with reperfusion timing data, 280 (62%) had a <3-h delay from symptom onset to first device and 170 (38%) had a delay

Table 1. Baseline Clinical Characteristics Stratified by Delay to Reperfusion

	Delay to Reperfusion <3 h (n = 280)	Delay to Reperfusion ≥3 h (n = 170)	p Value
Patient characteristics			
Age, yrs	60.0 (51.0–69.0)	62.0 (53.0–73.0)	0.02
Male	81.4 (228/280)	61.2 (104/170)	<0.0001
BMI, kg/m^2	26.6 (24.0–29.4)	26.8 (23.9–29.4)	0.78
Heart rate, beats/min	75.0 (65.0–86.5)	80.0 (70.0–90.0)	0.005
Systolic BP, mm Hg	138.0 (120.0–154.0)	140.0 (122.5–156.5)	0.19
Killip class I	79.2 (221/279)	85.3 (145/170)	0.11
LVEF, % (investigator estimate)	40.0 (35.0–50.0)	40.0 (35.0–50.0)	0.96
LVEF <40%	31.6 (83/263)	31.4 (49/156)	0.97
Medical history			
Medically treated hypertension	30.4 (85/280)	33.5 (57/170)	0.48
Medically treated hyperlipidemia	15.8 (44/279)	15.3 (26/170)	0.89
Diabetes mellitus	8.6 (24/279)	15.3 (26/170)	0.03
Insulin treated	6.1 (17/278)	12.9 (22/170)	0.01
Previous myocardial infarction	2.5 (7/279)	1.8 (3/170)	0.75
Previous PCI	0.0 (0/280)	0.0 (0/170)	N/A
Previous CABG	25.9 (68/263)	17.9 (29/162)	0.06
Family history of premature CAD	1.1 (3/279)	0.6 (1/169)	1.00
Previous congestive heart failure	2.5 (7/279)	1.8 (3/170)	0.75
Smoking	62.5 (172/275)	57.1 (97/170)	0.25
Peripheral vascular disease	1.4 (4/279)	1.8 (3/170)	1.00
History of stroke or TIA	1.1 (3/279)	1.2 (2/170)	1.00
History of renal insufficiency	0.7 (2/280)	0.0 (0/169)	0.53

Values are % (n) or median (interquartile range).
BMI = body mass index; BP = blood pressure; CABG = coronary artery bypass grafting; CAD = coronary artery disease; LVEF = left ventricular ejection fraction; N/A = not available; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

Table 2. Procedural Characteristics Stratified by Delay to Reperfusion

	Delay to Reperfusion <3 h (n = 280)	Delay to Reperfusion ≥3 h (n = 170)	p Value
Total ischemic time, min	128.0 ± 28.0	240.5 ± 38.6	<0.0001
Door-to-device time, min	42.0 (32.0–59.5)	53.0 (38.0–83.0)	<0.0001
Baseline TIMI flow grade			0.52
0 or 1	70.7 (198/280)	73.5 (125/170)	
2 or 3	29.3 (82/280)	26.5 (45/170)	
Final TIMI flow grade			
0 or 1	1.8 (5/280)	2.4 (4/170)	0.73
2 or 3	98.2 (275/280)	97.6 (166/170)	0.73
3	92.5 (259/280)	89.4 (152/170)	0.76
Final myocardial blush grade			
0 or 1	17.9 (50/280)	20.1 (34/169)	0.55
2 or 3	82.1 (230/280)	79.9 (135/169)	0.55
2	11.8 (33/280)	12.4 (21/169)	0.84
3	70.4 (197/280)	67.5 (124/169)	0.52
Corrected TIMI frame count	20.00 (16.00–26.00)	20.00 (16.00–25.00)	0.67

Values are % (n), mean ± SD, or median (interquartile range).
TIMI = Thrombolysis In Myocardial Infarction.

≥3 h. As shown in Table 1, patients with longer ischemic time were more likely to be older and women and have higher heart rate and diabetes mellitus. Approximately two-thirds of the subjects in each group had proximal LAD occlusion (p = 0.11). Total ischemic time was 128.0 ± 28.0 min versus 240.5 ± 38.6 min, respectively (p = 0.0001). Longer door-to-device time was responsible for only ~11 min of this delay (Table 2). Patients with longer delays were also more likely to have Q waves on a pre-PCI electrocardiogram (55.0% vs. 37.2%, p = 0.0002).

A shorter delay to reperfusion was not associated with higher rates of final TIMI flow grade 3 or MBG 2/3 (Table 2). IS at 30 days (percentage of LV mass) was marginally smaller in patients with a shorter delay to reperfusion (16.4%; IQR: 6.5% to 22.9% vs. 18.1%; IQR: 10.5% to 24.8%, respectively; p = 0.07) (Table 3). By linear regression, earlier reperfusion was an independent predictor of smaller 30-day IS (Table 4). In the 5-day CMR substudy, there was no difference in MVO or other CMR parameters as a function of time to reperfusion.

As shown in Table 5 and Figures 1 and 2, patients with longer delay to reperfusion had significantly higher rates of major adverse cardiac and cerebral events at 30 days and 1 year, driven by higher rates of cardiac and all-cause death. There were no significant differences between the groups with respect to bleeding complications, MI, new-onset or recurrent severe heart failure, or stent thrombosis.

To better understand the complex relationship between delay to reperfusion and outcome, we examined MBG 2/3, ST-segment resolution >70%, IS, and 1-year death in patients grouped in 6-h delay groups (Fig. 3A). There were 3, 99, 178, 84, 73, and 12 patients with time from symptom onset to delay of 0 to 1, 1 to 2, 2 to 3, 3 to 4, 4 to 5, and 5 to 6 h, respectively. There was a statistically significant (p = 0.02) trend for greater (albeit modest) average 30-day IS with increasing delay, as well as a significant trend toward higher mortality (p = 0.03). These results were confirmed in the subset of 254 patients with TIMI flow grade 0/1 at baseline angiography and follow-up CMR at 30 days, for whom delay to reperfusion was the most meaningful (Fig. 3B).

Table 3. CMR Parameters at 5 and 30 Days Stratified by Delay to Reperfusion

	Delay to Reperfusion <3 h	Delay to Reperfusion ≥3 h	p Value
CMR at 5 days	110	59	
Total MVO, g	0.8 (0.0–3.8)	0.7 (0.0–3.8)	0.85
MVO (% of total myocardial mass)	0.56 (0.00–2.39)	0.48 (0.00–2.57)	0.97
MVO (% of total infarct mass)	3.3 (0.0–9.6)	2.9 (0.0–8.9)	0.92
Total abnormal wall motion score	8.0 (4.0–10.0)	9.0 (6.0–11.0)	0.25
Total infarct mass, g	31.8 (13.6–50.5)	32.1 (19.2–46.2)	0.77
Infarct size, % of LV mass	21.0 (11.2–30.6)	23.5 (15.9–33.2)	0.13
LVEF, %	48.1 (41.1–54.1)	47.5 (40.3–52.4)	0.36
CMR at 30 days	N = 229	N = 130	
Total myocardial mass, g	130.9 (110.7–154.2)	127.3 (103.3–151.1)	0.08
Total infarct mass, g	21.4 (7.3–34.2)	20.5 (12.8–31.1)	0.77
Infarct size, % of LV mass	16.4 (6.5–22.9)	18.1 (10.5–24.8)	0.07
Total abnormal wall motion score	6.4 ± 4.9 (238)	7.2 ± 4.7 (133)	0.09
LVEDV, ml	175.5 (150.6–207.0)	167.9 (137.5–209.0)	0.13
LVEF, %	49.8 ± 10.8 (230)	48.7 ± 9.5 (130)	0.34

Values are n or median (interquartile range), or mean ± SD.
CMR = contrast magnetic resonance; LV = left ventricular; LVEF = left ventricular ejection fraction; LVEDV = left ventricular end-diastolic volume; MRI = magnetic resonance imaging; MVO = microvascular obstruction.

Among the 372 patients who survived to 30 days and underwent CMR (263 with a delay <3 h and 109 with a delay ≥3 h), there were no significant differences in the rates of 1-year death (1.9% vs. 1.9%, p = 0.97) or death/MI (2.3% vs. 2.8%, p = 0.78). These data suggest that most of the mortality risk in the longer delay group was manifested earlier than 30 days (as also seen in Fig. 2).

Table 4. Independent Predictors of 30-Day Infarct Size by Linear Regression Analysis

Multivariate Predictors	Coefficient	SE	p Value
Intercept	−9.39	4.05	0.0213
Baseline WBC count	0.54	0.13	0.0001
Abciximab infusion	−2.58	1.01	0.0108
Symptom onset to first device time, min	0.02	0.01	0.0175
Proximal LAD location	5.39	1.07	<0.0001
Baseline TIMI 0/1	6.07	1.11	<0.0001
Age	0.13	0.05	0.0038
Sex, male	2.09	1.22	0.0880

LAD = left anterior descending artery; TIMI = Thrombolysis In Myocardial Infarction; WBC = white blood cell.

Discussion

In the present analysis from the INFUSE-AMI Study, we studied the impact of delay to reperfusion on infarct size and clinical outcomes in patients with STEMI. The main findings are that in patients with large anterior STEMI presenting relatively early after symptom onset, longer delays to reperfusion were not associated with decreased reperfusion success or greater MVO, but were associated with increased IS and mortality. These findings were confirmed in the subset with TIMI flow grade 0/1 in the infarct-related artery at baseline angiography.

The relationship between delays to reperfusion and clinical outcomes after STEMI has been analyzed extensively after treatment with both fibrinolysis and primary PCI. Because symptom onset may be difficult to time precisely

Table 5. Clinical Outcomes at 30 Days and 1 Year Stratified by Delay to Reperfusion

	30 Days			1 Year		
Event	Delay to Reperfusion <3 h	Delay to Reperfusion ≥3 h	p Value*	Delay to Reperfusion <3 h	Delay to Reperfusion ≥3 h	p Value*
MACCE†	2.2 (6)	7.2 (12)	0.009	6.2 (17)	13.5 (22)	0.008
Death	1.4 (4)	5.4 (9)	0.02	4.0 (11)	9.2 (15)	0.02
Cardiac death	1.4 (4)	5.4 (9)	0.02	2.5 (7)	8.6 (14)	0.004
MI	0.4 (1)	1.3 (2)	0.28	0.7 (2)	1.3 (2)	0.57
Death/MI	1.8 (5)	6.0 (10)	0.02	0.8 (2)	0.0 (0)	0.29
Bleeding (TIMI major or minor)	2.2 (6)	2.5 (4)	0.86	3.7 (10)	4.3 (6)	0.95
New-onset severe heart failure	3.2 (9)	4.8 (8)	0.41	5.1 (14)	6.8 (11)	0.45
Any revascularization	1.1 (3)	2.5 (4)	0.26	3.9 (10)	6.6 (10)	0.19
Stent thrombosis (def + prob)	1.1 (3)	1.3 (2)	0.89	1.1 (3)	2.6 (4)	0.27

Values are % (n). *p Value from the log-rank test. †MACCE defined as a composite of all-cause death, reinfarction (Q-wave and non–Q-wave), ischemia-driven target vessel revascularization, or stroke.
Def = definite; MACCE = major adverse cardiac and cerebrovascular event(s); MI = myocardial infarction; prob = probable; TIMI = Thrombolysis In Myocardial Infarction.

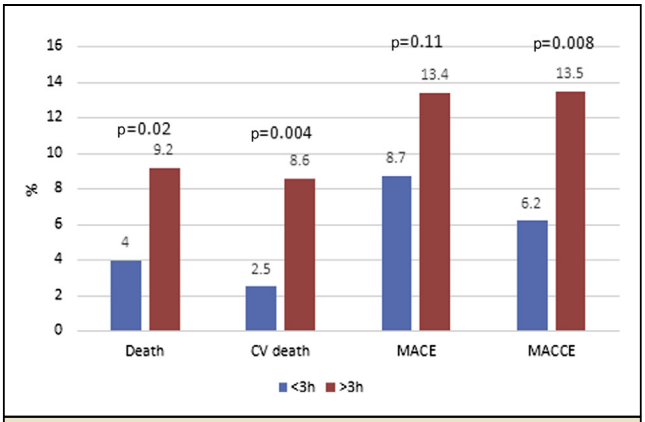

Figure 1. Mortality and Morbidity Rates at 1 Year According to Reperfusion Delay (<3 vs. ≥3 h)

Patients undergoing reperfusion within 3 h of symptom onset had significantly lower rates of all-cause death, cardiovascular death, major adverse cardiac events, and major adverse cardiac and cerebrovascular events than patients with later reperfusion. MACCE = major adverse cardiac and cerebrovascular events (all cause death, reinfarction [Q-wave and non–Q-wave], ischemia-driven target vessel revascularization, or stroke); MACE = major adverse cardiac events (death, reinfarction, new-onset heart failure, or rehospitalization for heart failure); CV = death/cardiovascular death.

and because infarct-artery patency may be restored before initiation of pharmacological or mechanical reperfusion therapy, most of the emphasis has been placed on the delay attributable to systems of care (i.e. "door-to-device" [15] or "door-to-needle" [16]). Consequently, professional guidelines recommend that reperfusion be achieved within a certain interval, indexed to first medical contact rather than to symptom onset (17,18). Yet, in this context, 2 series examining changes in door-to-device time in the past decade in >50,000 patients concluded that continuing reduction in the hospital-related delay to reperfusion had little effect on mortality (19,20). Delayed door-to-balloon times may reflect greater patient illness and complexity, such as the need to stabilize heart failure or treat ventricular arrhythmias before cardiac catheterization. Administrative registry databases are typically unable to account for many of these events, and all potential confounders are not collected in even the most rigorously performed clinical trials. Thus, total ischemic time (symptom onset to balloon or first device) may be a better metric to examine the effect of time on clinical outcomes.

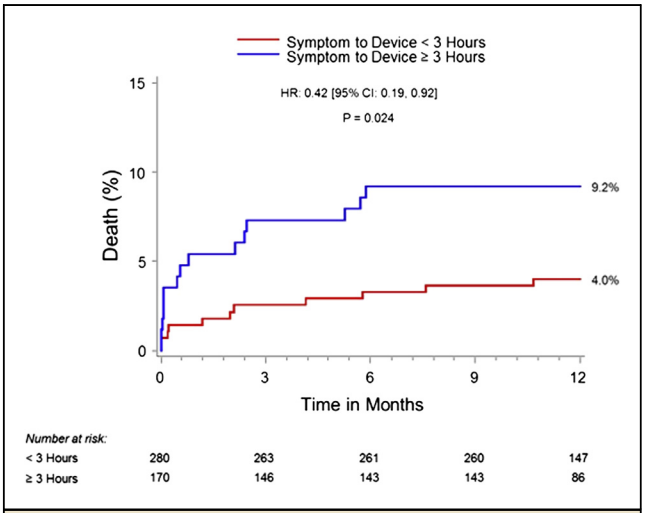

Figure 2. Cumulative Survival at 1 Year According to Reperfusion Delay (<3 vs. ≥3 h)

Patients undergoing reperfusion within 3 h of symptom onset **(red line)** had significantly lower rates of death at 1 year than patients with later reperfusion **(blue line)**. The curves separated early, by 30 days, and remained parallel thereafter. CI = confidence interval; HR = hazard ratio.

De Luca et al. (21) examined the total ischemic time in a large cohort of STEMI patients treated with primary PCI. After adjusting for age, sex, diabetes mellitus, and previous revascularization, every additional 30 min of reperfusion delay increased 1-year mortality by 8% (hazard ratio: 1.01 to 1.15, p = 0.04). In an analysis of 2 large STEMI trials encompassing >4,500 patients, Brodie et al. (22) highlighted the interaction between delay from symptom onset to presentation and delay from arrival to reperfusion. Only in patients with a short delay to presentation (≤90 min from symptom onset) did a shorter delay to reperfusion affect 1-year mortality (1.9% vs. 3.8%, p = 0.029 vs. 4.0% vs. 4.6%, p = 0.47 in those who presented later). The present contemporary study supports the relationship between early reperfusion and improved survival after primary PCI in patients with large anterior STEMI.

Despite a wealth of clinical data from these randomized and observational studies, little information exists regarding the mechanism for the higher mortality associated with delayed reperfusion. In a randomized trial of fibrinolysis versus primary PCI in which IS was assessed by technetium-99 sestamibi single-photon emission computed tomography (SPECT) imaging, IS was independent of total ischemic time with PCI but not with fibrinolysis (3). Conversely, in a previous analysis of predictors of infarct size determined by SPECT scintigraphy in nearly 1,200 patients at a median of 23 days after primary PCI, Stone et al. (23) identified LAD infarct, longer door-to-device time, male sex, and pre-PCI TIMI flow grade 0/1 as the principal correlates of IS (all p < 0.001). In the INFUSE-AMI Study, delay from symptom onset to reperfusion was an independent predictor of larger IS at 30 days (as measured by CMR, which is more sensitive than SPECT for the detection of small areas of infarction) and correlated with 1-year mortality. We have also previously shown from this study that 30-day IS correlated with subsequent death between 30 days and 1 year (3.4% vs. 0.0% in patients with larger than vs. equal to or smaller than the median IS of 17%, respectively, p = 0.02)

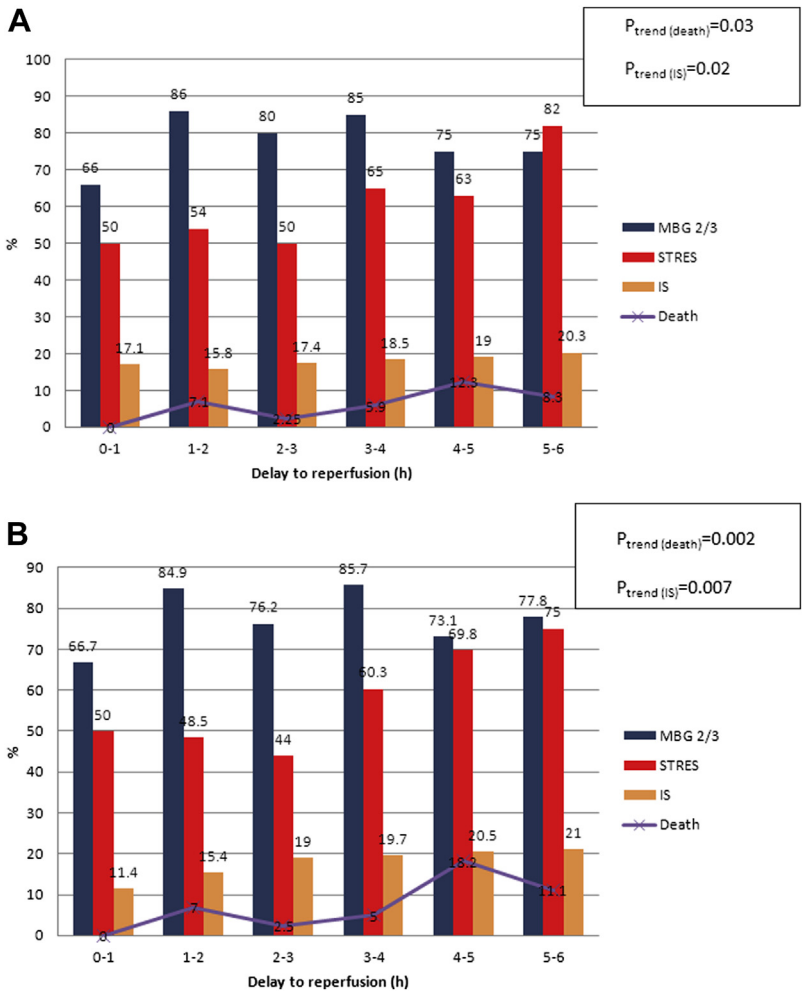

Figure 3. Average Infarct Size and Frequency of Myocardial Blush Grade 2/3, Complete (>70%) ST-Segment Resolution or 1-Year Death According to Hourly Intervals of Reperfusion Delay

(A) Average infarct size (IS) (percentage of left ventricular mass) and frequency of myocardial blush grade (MBG) 2/3, complete (>70%) ST-segment resolution (STRES), or 1-year death according to hourly intervals of reperfusion delay. Dividing the delay to reperfusion into hourly intervals, we tabulated the average infarct size **(orange columns)** assessed by cardiac magnetic resonance, frequency of obtaining MBG grade 2 or 3 **(blue columns)** and of having >70% ST-segment resolution **(red columns)** in each of these intervals. The mortality rate at 1 year is overlaid on these values **(purple line)**. There was a significant trend toward greater infarct size and mortality as time to reperfusion increased, without differences in frequencies of favorable angiographic or electrocardiographic outcomes. **(B)** Average IS (percentage of left ventricular mass) and frequency of MBG 2/3, complete (>70%) STRES or 1-year death according to hourly intervals of reperfusion delay. Analyzing only patients with baseline Thrombolysis In Myocardial Infarction 0-1 flow in the infarct artery and dividing the delay to reperfusion into hourly intervals, we tabulated average infarct size **(orange columns)** assessed by cardiac magnetic resonance and the frequency of obtaining an MBG of 2 or 3 **(blue columns)** and of having >70% STRES **(red columns)** in each of these intervals. The mortality rate at 1 year is overlaid on these values **(purple line)**. There was a significant trend toward greater IS and mortality as time to reperfusion increased, without differences in frequencies of favorable angiographic or electrocardiographic outcomes.

(24). These data reinforce the relationship between IS and mortality after primary PCI and suggest that efforts to reduce the time delay to reperfusion in patients with large anterior STEMI presenting relatively early are warranted.

Previous studies have shown that earlier time to reperfusion with primary PCI is associated with greater reperfusion success, as assessed by MBG 2/3 (25). This was not observed in the present study, in which all patients were reperfused relatively early. Thus, the reduction in IS in patients reperfused early in the present study was not due to better myocardial perfusion, but more likely to interruption of the infarct wave front from the subendocardium to the subepicardium, before becoming transmural (26).

Study limitations. In addition to the larger IS in patients with longer delay to reperfusion, differences in baseline characteristics, such as age, diabetes, and other unmeasured

confounders may have contributed to the higher mortality in these patients, which mostly occurs early after STEMI. The limited number of deaths in the present study precludes a comprehensive multivariable analysis to determine the predictors of survival. Moreover, many patients who died did not have IS assessment because they did not reach the 30-day CMR time point. We recognize that the lack of association between delay to reperfusion and MBG or ST-segment resolution may represent the consequence of a homogeneous STEMI population treated within a short interval from symptom onset. The present study also represents a post-hoc analysis from a carefully controlled, randomized trial designed to determine the effect of intralesional abciximab delivery and thrombus aspiration on IS. Although patient enrollment was stratified for delay to presentation of <3 or >3 h, the analysis was not corrected for the propensity to present in each of these categories. Thus, these results should be considered hypothesis generating.

Conclusions

Despite these limitations, the present study demonstrates that among patients with a large anterior MI presenting relatively early after symptom onset and treated by contemporary primary PCI, longer delay to reperfusion is linked to greater IS and higher mortality. This effect appears not to be mediated by less successful reperfusion. As median door-to-device times have now been reduced in many hospital systems to <60 min, if STEMI outcomes are to be further improved, the emphasis should shift to aggressive public education focusing on minimizing the delay to presentation and ensuring access to reperfusion for all eligible patents.

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REFERENCES

1. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003;361:13–20.
2. Schomig A, Kastrati A, Dirschinger J, et al. Coronary stenting plus platelet glycoprotein IIb/IIIa blockade compared with tissue plasminogen activator in acute myocardial infarction. Stent versus Thrombolysis for Occluded Coronary Arteries in Patients with Acute Myocardial Infarction Study Investigators. N Engl J Med 2000;343:385–91.
3. Schomig A, Ndrepepa G, Mehilli J, et al. Therapy-dependent influence of time-to-treatment interval on myocardial salvage in patients with acute myocardial infarction treated with coronary artery stenting or thrombolysis. Circulation 2003;108:1084–8.
4. Maeng M, Nielsen PH, Busk M, et al. Time to treatment and three-year mortality after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction-a DANish trial in acute myocardial infarction-2 (DANAMI-2) substudy. Am J Cardiol 2010;105:1528–34.
5. Henriques JP, Zijlstra F, Ottervanger JP, et al. Incidence and clinical significance of distal embolization during primary angioplasty for acute myocardial infarction. Eur Heart J 2002;23:1112–7.
6. Thiele H, Schindler K, Friedenberger J, et al. Intracoronary compared with intravenous bolus abciximab application in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary INtervention: the randomized Leipzig Immediate Percutaneous Coronary Intervention Abciximab IV Versus IC in ST-Elevation Myocardial Infarction trial. Circulation 2008;118:49–57.
7. Svilaas T, Vlaar PJ, van der Horst IC, et al. Thrombus aspiration during primary percutaneous coronary intervention. N Engl J Med 2008;358:557–67.
8. Gibson CM, Maehara A, Lansky AJ, et al. Rationale and design of the INFUSE-AMI study: 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. Am Heart J 2011;161:478–86.e7.
9. Stone GW, Maehara A, Witzenbichler B, et al. Intracoronary abciximab and aspiration thrombectomy in patients with large anterior myocardial infarction: the INFUSE-AMI randomized trial. JAMA 2012;307:1817–26.
10. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. TIMI Study Group. N Engl J Med 1985;312:932–6.
11. Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008;358:2218–30.
12. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. The GUSTO Angiographic Investigators. N Engl J Med 1993;329:1615–22.
13. van 't Hof AW, Liem A, Suryapranata H, Hoorntje JC, de Boer MJ, Zijlstra F. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. Zwolle Myocardial Infarction Study Group. Circulation 1998;97:2302–6.
14. Poli A, Fetiveau R, Vandoni P, et al. Integrated analysis of myocardial blush and ST-segment elevation recovery after successful primary angioplasty: real-time grading of microvascular reperfusion and prediction of early and late recovery of left ventricular function. Circulation 2002;106:313–8.
15. Cannon CP, Gibson CM, Lambrew CT, et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. JAMA 2000;283:2941–7.
16. Boersma E. Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients. Eur Heart J 2006;27:779–88.
17. Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;33:2569–619.
18. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e78–140.
19. Flynn A, Moscucci M, Share D, et al. Trends in door-to-balloon time and mortality in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. Arch Intern Med 2010;170:1842–9.
20. Wang TY, Fonarow GC, Hernandez AF, et al. The dissociation between door-to-balloon time improvement and improvements in other acute myocardial infarction care processes and patient outcomes. Arch Intern Med 2009;169:1411–9.
21. De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. Circulation 2004;109:1223–5.

22. Brodie BR, Gersh BJ, Stuckey T, et al. When is door-to-balloon time critical? Analysis from the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) and CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trials. J Am Coll Cardiol 2010;56:407–13.
23. Stone GW, Dixon SR, Grines CL, et al. Predictors of infarct size after primary coronary angioplasty in acute myocardial infarction from pooled analysis from four contemporary trials. Am J Cardiol 2007;100:1370–5.
24. Stone GW, Maehara A, Witzenbichler B, et al. Intralesional abciximab and thrombus aspiration in patients with large anterior myocardial infarction: one-year results from the INFUSE-AMI trial. Circ Cardiovasc Interv 2013;6:L526–34.
25. Brener SJ, Moliterno DJ, Aylward PE, et al. Reperfusion after primary angioplasty for ST-elevation myocardial infarction: predictors of success and relationship to clinical outcomes in the APEX-AMI angiographic study. Eur Heart J 2008;29:1127–35.
26. Reimer KA, Vander Heide RS, Richard VJ. Reperfusion in acute myocardial infarction: effect of timing and modulating factors in experimental models. Am J Cardiol 1993;72:13G–21G.

Key Words: ischemic time ■ infarct size ■ myocardial blush grade ■ outcome ■ STEMI.