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Relationship Between Infarct Size and Outcomes Following Primary PCI

Patient-Level Analysis From 10 Randomized Trials

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ABSTRACT

BACKGROUND Prompt reperfusion in patients with ST-segment elevation myocardial infarction (STEMI) reduces infarct size and improves survival. However, the intuitive link between infarct size and prognosis has not been convincingly demonstrated in the contemporary era.

OBJECTIVES This study sought to determine the strength of the relationship between infarct size assessed early after primary percutaneous coronary intervention (PCI) in STEMI and subsequent all-cause mortality, reinfarction, and hospitalization for heart failure.

METHODS We performed a pooled patient-level analysis from 10 randomized primary PCI trials (total 2,632 patients) in which infarct size was assessed within 1 month after randomization by either cardiac magnetic resonance (CMR) imaging or technetium-99m sestamibi single-photon emission computed tomography (SPECT), with clinical follow-up for ≥6 months.

RESULTS Infarct size was assessed by CMR in 1,889 patients (71.8%) and by SPECT in 743 patients (28.2%). Median (25th, 75th percentile) time to infarct size measurement was 4 days (3, 10 days) after STEMI. Median infarct size (% left ventricular myocardial mass) was 17.9% (8.0%, 29.8%), and median duration of clinical follow-up was 352 days (185, 371 days). The Kaplan-Meier estimated 1-year rates of all-cause mortality, reinfarction, and HF hospitalization were 2.2%, 2.5%, and 2.6%, respectively. A strong graded response was present between infarct size (per 5% increase) and subsequent mortality (Cox-adjusted hazard ratio: 1.19 [95% confidence interval: 1.18 to 1.20]; $p < 0.0001$) and hospitalization for heart failure (adjusted hazard ratio: 1.20 [95% confidence interval: 1.19 to 1.21]; $p < 0.0001$), independent of age, sex, diabetes, hypertension, hyperlipidemia, current smoking, left anterior descending versus non–left anterior descending infarct vessel, symptom-to-first device time, and baseline TIMI (Thrombolysis In Myocardial Infarction) flow 0/1 versus 2/3. Infarct size was not significantly related to subsequent reinfarction.

CONCLUSIONS Infarct size, measured by CMR or technetium-99m sestamibi SPECT within 1 month after primary PCI, is strongly associated with all-cause mortality and hospitalization for HF within 1 year. Infarct size may, therefore, be useful as an endpoint in clinical trials and as an important prognostic measure when caring for patients with STEMI. (J Am Coll Cardiol 2016;67:1674–83) © 2016 by the American College of Cardiology Foundation.

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Cardiovascular mortality has progressively declined over the last 4 decades, in part due to the prompt delivery of reperfusion therapy to patients with ST-segment elevation myocardial infarction (STEMI) (1). By rapidly restoring coronary artery patency in STEMI, fibrinolytic therapy reduces infarct size (IS) and mortality. In this regard, the greater reduction in IS with tissue plasminogen activator compared with streptokinase has been associated with improved survival (2). Compared with fibrinolytic therapy, primary percutaneous coronary intervention (PCI) further reduces IS and improves survival (3,4), contributing to improved population-level outcomes (1,5). However, the benefits of primary PCI are multifactorial, and include restoring epicardial artery patency, which may have salutatory effects in reducing susceptibility to lethal ventricular arrhythmias, preventing expansive left ventricular remodeling, and preserving collateral flow independent of myocardial salvage (the open artery hypothesis) (6). Early data suggested a modest correlation between IS and survival after medical therapy in STEMI (7). The extent to which IS is correlated with outcomes in STEMI has been incompletely characterized in the contemporary primary PCI era. Moreover, whether IS correlates with hospitalization for heart failure (HF) (as would be expected) or reinfarction (which is less intuitive) has not been studied. Given the generally favorable prognosis following primary PCI, most individual studies in which IS has been assessed have been inadequately powered to explore these relationships.

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We therefore performed a patient-level pooled analysis from 10 randomized trials of primary PCI in STEMI to examine the relationship between IS assessed within 1 month after reperfusion and subsequent mortality, reinfarction, and hospitalization for HF within 1-year follow-up.

METHODS

The present study represents a collaborative effort between the principal investigators of randomized trials that enrolled patients with STEMI undergoing primary PCI in whom IS was assessed by either cardiac magnetic resonance (CMR) imaging or technetium (tc)-99m sestamibi single-photon emission computed tomography (SPECT) within 1 month after reperfusion at a core laboratory, and in whom clinical follow-up was performed for ≥6 months (unless death occurred earlier), with adverse events adjudicated by a clinical events committee. Ten such studies were available, and the data from each were pooled into a common database at the Cardiovascular Research Foundation. The objectives were to examine the relationship between IS assessed within 1 month after primary PCI and the occurrence of the prespecified endpoints of all-cause mortality, reinfarction, hospitalization for HF, and combinations thereof. Specifically, our hypothesis was that after adjustment for differences in baseline clinical and angiographic variables, IS would be independently correlated with all-cause mortality and with HF hospitalization, but not necessarily with reinfarction. This was an independent academic project, and the sponsors of the individual studies were not involved.

ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

HF = heart failure

IDI = integrated discriminatory index

IS = infarct size

LAD = left anterior descending

NRI = net reclassification improvement

PCI = percutaneous coronary intervention

SPECT = single-photon emission computed tomography

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction

STUDIES AND DEFINITIONS. The 10 primary PCI trials included in the pooled analysis were (in approximate chronological order of patient enrollment): the EMERALD (Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberated Debris) trial, in which patients undergoing primary PCI were randomized to a distal embolic protection filter versus control group (8); the AMIHOT-II (Acute Myocardial Infarction with HyperOxemic Reperfusion II) trial, in which patients undergoing primary PCI were randomized to post-procedural supersaturated oxygen versus control (9); the IS substudy of the IMMEDIATE (Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency care) trial, in which patients with non-STEMI and STEMI were randomized to receive a pre-hospital intravenous glucose-insulin-potassium infusion versus placebo prior to primary PCI (10); the IS substudy of the APEX-AMI (Pexelizumab in Conjunction With Angioplasty in Acute Myocardial Infarction) trial, in which patients undergoing primary PCI were randomized to intravenous pexelizumab versus placebo (11); the LIPSIA-ABCIXIMAB (Randomized Leipzig Immediate Percutaneous Coronary Intervention Abciximab IV

Squibb, GlaxoSmithKline, Hoffmann-la Roche, Medtronic Foundation, Eli Lilly, Pfizer, Sanofi, Takeda, The Medicines Company, AstraZeneca, Daiichi-Sankyo, Janssen, Salix, Bayer, Gilead, Armetheon, and Medtronic Inc. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Alan S. Jaffe, MD, served as Guest Editor for this paper.

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Versus IC in ST-Elevation Myocardial Infarction) trial, in which patients undergoing primary PCI were randomized to an intracoronary versus intravenous bolus of abciximab (12); the LIPSIA-N-ACC (Prospective, Single-Blind, Placebo-Controlled, Randomized Leipzig Immediate PercutaneouS Coronary Intervention Acute Myocardial Infarction N-ACC) trial, in which patients undergoing primary PCI were randomized to pre-procedural high-dose N-acetylcysteine versus placebo (13); the LIPSIA-STEMI (Leipzig Immediate Prehospital Facilitated Angioplasty in ST-Segment Myocardial Infarction) trial, in which patients with STEMI were randomized to either pre-hospital tenecteplase versus control prior to PCI (14); the CRISP AMI (Counterpulsation to Reduce Infarct Size Pre-PCI Acute Myocardial Infarction) trial, in which patients with anterior STEMI but without cardiogenic shock were randomized to pre-procedural intra-aortic balloon counterpulsation versus control prior to primary PCI (15); the IS substudy of the AIDA STEMI (Abciximab Intracoronary versus intravenous Drug Application in ST-Elevation Myocardial Infarction) trial, in which patients undergoing primary PCI were randomized to an intracoronary versus intravenous bolus of abciximab (16); and the INFUSE-AMI trial, in which patients with anterior STEMI undergoing primary PCI were randomized in a 2 × 2 design to an intralesional bolus of abciximab versus control and to thrombus aspiration versus control (17). The IS core laboratory for each of these studies appears in Online Table 1.

Patients were included in the database in whom IS was measured within 1 month (outside window 37 days) and were by protocol analyzed at an independent core laboratory, masked to randomization assignment and outcomes. No imputations were performed for patients dying before IS assessment or in whom IS was not measured. For studies in which multiple assessments of IS were obtained, the earliest measure was used. A clinical events committee in each study adjudicated death, reinfarction, and hospitalization for HF on the basis of prespecified objective criteria requiring source document confirmation, blinded to IS determination. The definitions and adjudicated events from each study were used in the present analysis. Of note, none of the active therapies in any of the 10 trials significantly reduced IS after primary PCI as tested, except for a modest reduction with intracoronary and intralesional abciximab in 2 studies (12,17), but not in a third (16), and with supersaturated oxygen in AMIHOT-II (9).

STATISTICAL ANALYSES. The effect of IS on subsequent death, reinfarction, and HF hospitalization was assessed using proportional hazards regression. The principal analyses examined the relationship between IS and outcomes from the time of study entry (randomization). For sensitivity analysis, the relationships between IS and adverse outcomes were examined from the time of IS measurement, excluding all events before that time. To account for

TABLE 1 Design Features, Enrollment, and IS Assessment of the Included Trials

	Years of Enrollment	Total Number Enrolled	Number With IS Assessment*	Prior MI	Anterior MI†	IS Test	Days to IS Assessment	Days to Last Follow-Up
EMERALD (8)	2002–2003	501	419 (83.6)	44 (10.5)	168 (40.1)	SPECT	10 (7, 13)	183 (179, 188)
AMIHOT-II (9)	2005–2007	301	287 (95.3)	25 (8.8)	287 (100)	SPECT	16 (14, 18)	366 (353, 374)
IMMEDIATE‡§ (10)	2006–2011	54	37 (68.5)	5 (13.5)	17 (45.9)	SPECT	34 (32, 35)	365 (365, 365)
APEX-AMI‡ (11)	2004–2006	99	94 (94.9)	2 (2.1)	58 (61.7)	CMR	4 (3, 5)	365 (184, 367)
LIPSIA-ABCIXIMAB (12)	2006	154	134 (87.0)	14 (10.4)	65 (48.9)	CMR	2 (2, 3)	188 (184, 194)
LIPSIA-N-ACC (13)	2006–2008	251‖	197 (78.5)	19 (9.6)	85 (43.6)	CMR	3 (2, 4)	190 (185, 244)
LIPSIA-STEMI (14)	2006–2009	162‖	129 (79.6)	6 (4.7)	56 (44.8)	CMR	3 (2, 4)	192 (168, 256)
CRISP AMI (15)	2009–2011	337	260 (77.2)	1 (0.4)	255 (98.1)	CMR	4 (3, 4)	183 (180, 188)
AIDA STEMI‡ (16)	2008–2011	795	771 (97.0)	47 (6.1)	336 (43.6)	CMR	3 (2, 4)	372 (366, 400)
INFUSE-AMI (17)	2009–2011	452	304 (67.3)	3 (1.0)	304 (100)	CMR	6.5 (4, 30)	365 (350.5, 377)

Values are n (%) or median (25th, 75th percentile). *Completed within 37 days of reperfusion and analyzable at the core laboratory, in patients with ≥6 months of follow-up or earlier death. Thus, some patients in the original reports may not be included in the present study if IS was assessed beyond the 37-day window or if 6-month follow-up was not complete (unless death occurred earlier). †As defined by left anterior descending infarct artery. ‡IS substudy of the main trial. §Patients with both non–ST-segment elevation acute coronary syndromes and STEMI were enrolled in IMMEDIATE. Only STEMI patients are included in this analysis. ‖Twenty-two patients from LIPSIA-STEMI were also enrolled in LIPSIA-N-ACC (as allowed per protocol), 21 of whom otherwise met the inclusion criteria for this study. These 21 records are only represented once in the current pooled database.

AIDA STEMI = Abciximab Intracoronary versus intravenous Drug Application in ST-Elevation Myocardial Infarction; AMIHOT-II = Acute Myocardial Infarction with Hyperoxemic Reperfusion II; APEX-AMI = Pexelizumab in Conjunction With Angioplasty in Acute Myocardial Infarction; CMR = cardiac magnetic resonance; CRISP AMI = Counterpulsation to Reduce Infarct Size Pre-PCI Acute Myocardial Infarction; EMERALD = Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberated Debris; IMMEDIATE = Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency care; IS = infarct size; LIPSIA-ABCIXIMAB = Randomized Leipzig Immediate Percutaneous Coronary Intervention Abciximab IV Versus IC in ST-Elevation Myocardial Infarction; LIPSIA-N-ACC = Prospective, Single-Blind, Placebo-Controlled, Randomized Leipzig Immediate PercutaneouS Coronary Intervention Acute Myocardial Infarction N-ACC; LIPSIA-STEMI = Leipzig Immediate Prehospital Facilitated Angioplasty in ST-Segment Myocardial Infarction; MI = myocardial infarction; SPECT = single-photon emission computed tomography.

potential heterogeneity across studies, the standard errors in the regression equations were adjusted by including a random effect for study. IS was determined in patients with versus without events during follow-up, and time to first event analyses were examined according to IS quartiles. The area under the receiver-operating curve (C-statistic) was derived from a logistic regression model. The C-statistics relating IS to outcomes as assessed by CMR and SPECT were compared by the Student *t* test.

Categorical variables were compared using the chi-square test or a Fisher exact test if the expected cell frequencies were <5. Continuous variables are displayed as median (25% quartile, 75% quartile) and were compared using the Student *t* test or the Wilcoxon rank sum test if the assumption of normality was violated. Time-to-event data are displayed as Kaplan-Meier estimates. The following variables that were common in all of the datasets were entered into each proportional hazards regression model: age, sex, diabetes, hypertension, hyperlipidemia, current smoking, left anterior descending (LAD) versus non-LAD infarct vessel, symptom-to-first device time, baseline TIMI (Thrombolysis In Myocardial Infarction) flow 0/1 versus 2/3, and IS. The proportional hazards assumption was tested by evaluating the interaction term of each covariate by time. If the regression coefficient for any of these interaction terms was significant, the corresponding survival functions were graphed, and as long as these functions did not cross the variable they were included in the model.

Two analyses were used to assess the improvement in the prediction of death, reinfarction, hospitalization for HF, and the composite of death or hospitalization for HF from the inclusion of IS in multivariable regression models. First, a comparison of C-statistics that were derived from logistic regression results was performed. Second, the net reclassification improvement index (NRI) and integrated discrimination improvement (IDI) (18) were calculated to assess the added predictive value of IS. The reduced model for these analyses included age, sex, diabetes, hypertension, hyperlipidemia, current smoking, LAD versus non-LAD infarct vessel, symptom-to-first device time, and baseline TIMI flow 0/1 versus 2/3. The full model included these same 9 variables plus IS.

NRI indicates the extent to which subjects are more appropriately classified as being high risk versus low risk in multivariable models with versus without the new variable. IDI indicates the extent to which the new variable differentiates individuals along a continuum of predicted risk. If the addition of IS leads to prediction of higher probabilities of events for subjects that have events and lower probabilities of events for subjects that do not, NRI and IDI will be positive and significant. If the addition of IS leads to the opposite case, both measures will be negative and significant. Nonsignificant values imply that IS is neither helpful nor harmful. All p values are 2-sided, and $p < 0.05$ was considered statistically significant. All analyses were performed with SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

TRIALS AND PATIENTS. The design features of the 10 randomized primary PCI trials included in the pooled analysis are shown in Table 1. A total of

TABLE 2 Clinical, Angiographic, and Procedural Characteristics of the 2,632 Patients

Clinical features	
Age, yrs	60.2 (51.2, 70.0)
Male	2,045/2,632 (77.7)
Diabetes mellitus	456/2,622 (17.4)
Hypertension	1,366/2,628 (52.0)
Hyperlipidemia	525/2,295 (22.9)
Current smoker	1,093/2,564 (42.6)
Prior MI	166/2,628 (6.3)
Angiographic features	
Infarct artery	
LAD	1,631/2,625 (62.1)
RCA	779/2,625 (29.7)
LCX	206/2,625 (7.8)
Baseline TIMI flow	
0/1	1,592/2,491 (63.9)
2	375/2,491 (15.1)
3	524/2,491 (21.0)
Procedural details	
GP IIb/IIIa inhibitor used	1,352/2,175 (62.2)
Stent implanted	2,539/2,594 (97.9)
Post-PCI TIMI flow	
0/1	85/2,567 (3.3)
2	173/2,567 (6.7)
3	2,309/2,567 (89.9)
Time intervals	
Symptom-to-door, min	110 (66, 186)
Door-to-device, min	42 (27, 80)
Symptom-to-device, min	190 (134, 277)
Discharge medications	
Aspirin	2,597/2,629 (98.8)
ADP receptor antagonist	2,294/2,351 (97.6)
Beta-blocker	2,485/2,625 (94.7)
ACEI or ARB	2,338/2,624 (89.1)
Statin	2,496/2,626 (95.0)

Values are median (25th, 75th percentile) or n/N (%).

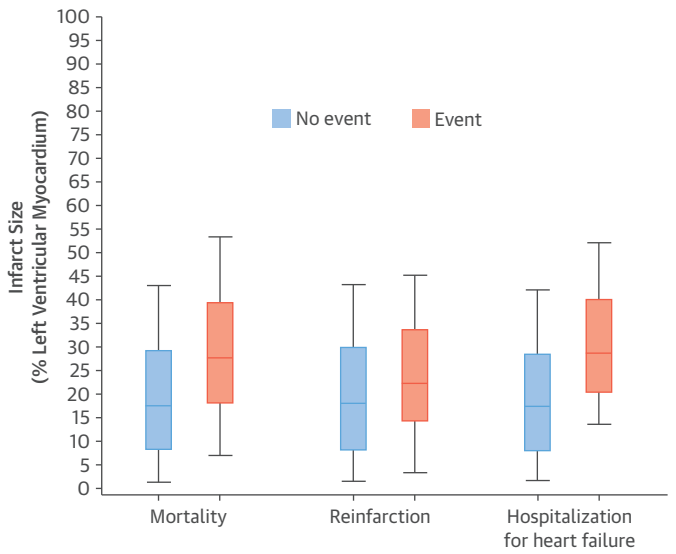
ACEI = angiotensin-converting enzyme inhibitor; ADP = adenosine diphosphate; ARB = angiotensin receptor blocker; GP = glycoprotein; LAD = left anterior descending; LCX = left circumflex; MI = myocardial infarction; PCI = percutaneous coronary intervention; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction.

3,084 unique patients with STEMI were enrolled between 2002 and 2011, of whom 2,632 (85.3%) underwent IS assessment within 1 month that was analyzable at the study core laboratory. IS was assessed by CMR in 7 of the studies (1,889 patients, 71.8% of the total) and by SPECT in 3 of the studies (743 patients, 28.2% of the total). The median (25th, 75th percentile) time to IS measurement was 4 days (3, 10 days). Clinical follow-up was pre-specified through 6 months in 5 of the trials and through 1 year in 5 trials. The aggregate median (25th, 75th percentile) duration from time of study entry to last clinical follow-up for all 10 trials was 352 days (185, 371 days).

Baseline features of the 2,632 study patients are shown in **Table 2**. Median symptom-to-first device time was 190 min (134, 277 min), and the LAD was the infarct vessel in nearly two-thirds of patients. Baseline TIMI flow was 0/1 in 63.9% of patients, and approximately 90% of patients had TIMI 3 flow after PCI. Guideline-directed medical therapies were prescribed in >90% of patients at discharge.

RELATIONSHIP BETWEEN IS AND ADVERSE EVENTS. The median IS (% of left ventricular myocardial mass) was 17.9% (8.0%, 29.8%). The Kaplan-Meier estimated 1-year rates of all-cause mortality, reinfarction, and HF hospitalization after study entry were 2.2% (54 events), 2.5% (60 events), and 2.6% (58 events), respectively. In unadjusted analyses, a relationship was present among IS and all-cause mortality, reinfarction, and hospitalization for HF (**Figure 1**). When considered in quartiles of IS, a graded response was present between IS and subsequent all-cause mortality and HF hospitalization, but not for reinfarction (**Figure 2**, **Central Illustration**). Similar relationships held when follow-up time was measured from the date of IS assessment (Online Figure 1). **Table 3** shows the C-statistics for these relationships, which were similar for IS assessment by CMR and SPECT. By multivariable analysis, IS was a strong independent predictor of all-cause mortality, HF hospitalization, and the composite occurrence of all-cause mortality or HF hospitalization, but not for reinfarction (**Table 4**, Online Table 2). The NRI for the full versus reduced model was significant for all-cause mortality, HF hospitalization, and mortality or HF hospitalization, but not for reinfarction (**Table 4**, Online Table 2). The IDI was significant in this comparison for HF hospitalization and for mortality or HF hospitalization. These findings were similar when only patients without prior myocardial infarction (MI) were analyzed (Online Tables 3 and 4). The C-statistics for the full versus reduced models were significantly greater for prediction of HF hospitalization and death or HF hospitalization with IS added in all patients and in the those without prior MI (**Table 4**, Online Tables 2 to 4). The relationship between IS and all-cause mortality or HF hospitalization was consistent across multiple subgroups, but was somewhat stronger for anterior compared with nonanterior infarcts (**Figure 3**, Online Figure 2).

FIGURE 1 IS in Patients With and Without Adverse Events During the 1-Year Clinical Follow-Up (From Time of Study Entry)



The **whiskers** of the plot extend from the 10th to 90th percentile. The **line inside the box** is the median and the **top and bottom of the box** represent the 1st and 3rd quartiles. Median (25th, 75th percentile) infarct size (IS) (% left ventricular myocardial mass) was greater in patients with versus without all-cause mortality (28.3% [17.9%, 39.5%] vs. 17.6% [8.0%, 29.5%], respectively; $p < 0.0001$), reinfarction (21.7% [14.8%, 33.3%] vs. 17.9% [8.0%, 29.8%], respectively; $p = 0.03$), and hospitalization for heart failure (29.1% [20.2%, 40.0%] vs. 17.3% [8.0%, 28.0%], respectively; $p < 0.0001$).

DISCUSSION

The present study, drawn from a patient-level pooled analysis of 10 randomized trials of primary PCI in STEMI, establishes the presence of a strong independent relationship among IS measured within 1 month after reperfusion and all-cause death, hospitalization for HF, and the composite occurrence of all-cause death or HF hospitalization within 1 year. The results were similar for IS assessed by both CMR and tc-99m sestamibi SPECT, were robust whether events prior to IS assessment were included or excluded, and were consistent across numerous subgroups. Importantly, IS assessed several days after primary PCI significantly contributed to the classification of the risk of death, HF hospitalization, and death or HF hospitalization during 1-year follow-up and improved

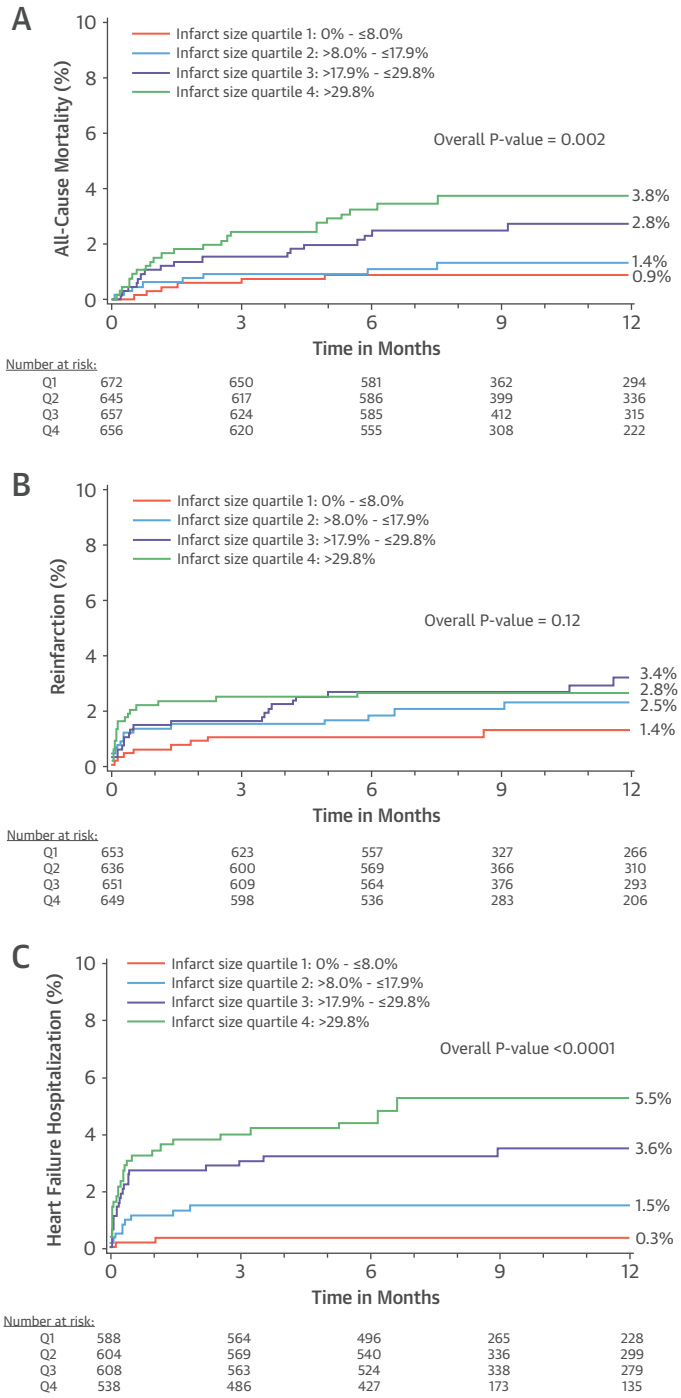
discrimination for assessment of the risk of subsequent HF hospitalization and death or HF hospitalization. Conversely, IS was not an independent predictor of reinfarction after primary PCI in STEMI.

Previous studies in the fibrinolytic era reported an association between IS as measured by tc-99m sestamibi SPECT and mortality (7,19). Notably, however, these analyses were not adjusted for the coexistence of other high-risk clinical and angiographic features in patients with a large infarction that may also have affected survival. In the present patient-level pooled analysis from a very large cohort of patients undergoing contemporary reperfusion therapy with primary PCI, a strong, monotonic relationship was present between IS and mortality after STEMI. After adjustment for baseline covariates, every 5% increase in IS was independently associated with a 19% increase in 1-year all-cause mortality. In this regard, 3 of the strongest baseline determinants of IS in patients undergoing primary PCI are anterior infarct location (LAD infarct artery), pre-PCI TIMI 0/1 flow, and symptom onset-to-first device time (20), variables that also strongly correlate with mortality after primary PCI (6,21–24). In the multivariable model adjusting for these risk factors as well as IS, IS as well as baseline TIMI flow correlated with survival, suggesting that the influence of anterior infarct location and prolonged symptom-to-device time on mortality may be affected through increased IS. Advanced age and medically-treated diabetes mellitus also remained as independent predictors of all-cause mortality after adjusting for IS, whereas hyperlipidemia was associated with greater survival (possibly because of its correlation with statin use).

HF represents the most common cause of patient hospitalization in the United States and Europe, accounting for >1 million admissions annually (25,26). Prior MI is present in up to 30% of patients with HF hospitalization, which imposes an extraordinary economic burden on the health care system (27). Although the mechanistic link between IS and HF hospitalizations is intuitive, such a relationship has not been previously demonstrated in studies while simultaneously accounting for other baseline confounders. The present study demonstrates that IS measured within 1 month after primary PCI for STEMI is a strong independent predictor of hospitalization for HF. Advanced age, female sex, smoking, and hyperlipidemia were also associated with hospitalization for HF.

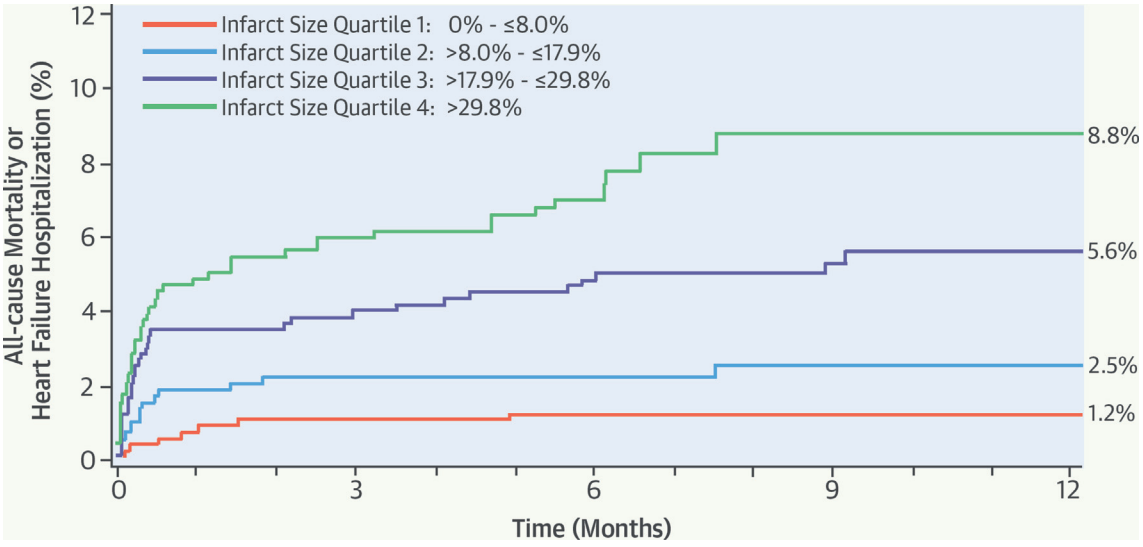
A strong graded response was present between IS and the composite occurrence of all-cause mortality or hospitalization for HF, with 1-year estimated rates of 1.2% in the quartile of patients with the smallest

FIGURE 2 Time to First Event Analysis (From Time of Study Entry) According to Quartiles of IS



(A) All-cause mortality, **(B)** reinfarction, and **(C)** heart failure hospitalization. A strong graded response between infarct size (IS) and adverse outcomes during 1-year follow-up was present for all-cause mortality and heart failure hospitalization, but not for reinfarction.

CENTRAL ILLUSTRATION **IS and Prognosis After Primary PCI: All-Cause Mortality or HF Hospitalization**



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Time-to-first event analysis (from time of study entry) according to quartiles of infarct size (IS) for the composite endpoint of all-cause mortality or heart failure (HF) hospitalization. Within 1 year, all-cause mortality or heart failure hospitalization occurred >7× as frequently in the quartile of patients with the highest IS (>29.8% of the left ventricle) compared with the quartile of patients with the lowest IS (≤8.0% of the left ventricle). PCI = percutaneous coronary intervention.

IS versus 8.8% in the quartile of patients with the largest IS, a >7-fold increase. By multivariable analysis, every 5% increase in IS contributed to a 20% increase in the relative hazard for all-cause mortality or hospitalization for HF within 1 year after primary PCI. These data suggest that interventions that reduce IS might favorably affect prognosis in STEMI (assuming no counterbalancing off-target negative effects). In this regard, the greater degree of myocardial salvage and smaller IS with primary PCI as compared with fibrinolytic therapy may in part underlie the survival advantage of the mechanical approach (3,4). However, the present study cannot establish causality, and further analyses (which are ongoing) are required to determine whether IS meets the strict criteria to be considered a true surrogate for death and/or HF hospitalization after primary PCI in STEMI (28,29).

TABLE 3 C-Statistics for the Relationships Between Infarct Size and Adverse Events During Follow-Up

1-Year Endpoint	C-Statistic (95% CI)	p Value*
All-cause mortality (n = 2,630)	0.66 (0.58–0.73)	
CMR (n = 1,887)	0.64 (0.56–0.73)	0.51
SPECT (n = 743)	0.71 (0.52–0.90)	
Reinfarction (n = 2,592)	0.58 (0.51–0.65)	
CMR (n = 1,886)	0.59 (0.50–0.67)	0.81
SPECT (n = 706)	0.60 (0.47–0.72)	
Heart failure hospitalization (n = 2,340)	0.71 (0.65–0.77)	
CMR (n = 1,884)	0.70 (0.64–0.76)	0.88
SPECT (n = 456)	0.72 (0.58–0.86)	

*p values are for the comparisons between CMR and SPECT.
CI = confidence interval; other abbreviations as in Table 1.

In contrast to all-cause mortality and HF hospitalization, the relationship between IS and reinfarction was weak, and lost significance when adjusted for measured confounders. As reinfarction is one of the most common causes of death after primary PCI (30,31), the present study suggests that reducing reinfarction (e.g., by preventing stent thrombosis) may improve prognosis in STEMI independent of measures taken to enhance myocardial recovery.

STUDY LIMITATIONS. First, the included trials varied in enrollment criteria, and were weighted toward anterior infarct location and large infarctions. However, the positive correlation between IS and all-cause mortality or HF hospitalization was present in high- and low-risk groups (including those stratified according to infarct artery, time to intervention, and TIMI flow pre- and post-PCI), but was somewhat

stronger in patients with anterior compared with nonanterior MI. Second, the definitions of the endpoints and their method of ascertainment and adjudication varied somewhat between studies. Several variables related to either IS or survival in past studies, such as Killip class and angiographic collaterals, were not uniformly available and were thus not included in the present study. Similarly, left ventricular ejection fraction was not assessed in many patients, and thus its prognostic utility could not be compared with IS. Third, although all endpoints were adjudicated by an independent committee in each trial on the basis of source criteria documentation, it remains possible that the clinician evaluating the patient, and ordering the tests required for endpoint ascertainment, may have been biased by knowledge of IS. Moreover, adjudication of mortality type was not uniformly performed in all studies, and it is likely that the relationship between IS and cardiac mortality would have been even stronger than for all-cause mortality. Fourth, although IS was measured early (median 4 days), deaths occurring before IS could be assessed are not included in these analyses, and imputation was not used to replace missing data or IS measurements. However, as early deaths usually occur in patients with proximal coronary artery occlusion, the present conclusions would likely have been strengthened had IS been available in these patients. Fifth, although the C-statistics relating IS determined by CMR and SPECT to adverse events during follow-up were similar, the present study was not designed to evaluate the relative prognostic utility of these 2 imaging modalities. In this regard, CMR is more sensitive than tc-99m sestamibi SPECT imaging in detecting small regions of subendocardial infarction (32), although such infarcts may have limited prognostic effect. Further study comparing modalities to assess IS and myocardial salvage is warranted, as recommended by a recent workshop organized by the National Heart, Lung, and Blood Institute (33). Despite these limitations, the present study is the largest and most robust examination of the relationship between IS and prognosis after reperfusion therapy to date.

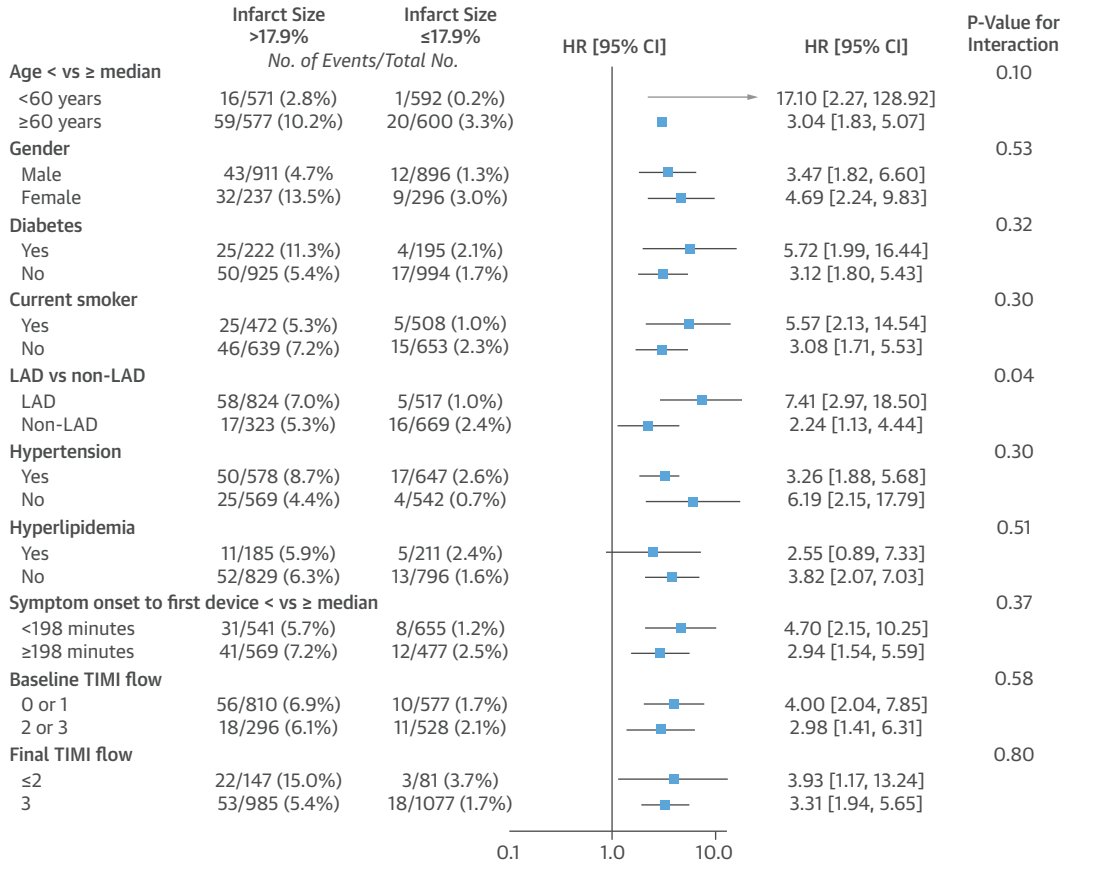
Finally, whether the improvement in the predictive models warrants the time and costs of the tests required to assess IS can be difficult to judge statistically. However, for death or HF hospitalization, the NRI of 0.536 suggests that the addition of IS substantially contributes to improved classification, and the IDI of 0.21 suggests a net 2.1% increase and decrease in the predicted 1-year probabilities of death or HF hospitalization for patients experiencing and not experiencing an event, respectively, which given the seriousness of these events, is clinically relevant.

TABLE 4 Significant Multivariable Predictors of Adverse Events From Time of Study Entry

	Adjusted HR (95% CI)	p Value	NRI	p Value	IDI	p Value
All-cause mortality						
Infarct size, per 5% increase	1.19 (1.18–1.20)	<0.0001	0.474	0.004	0.015	0.07
Age, per decade increase	2.66 (2.59–2.73)	<0.0001				
Female	1.50 (0.81–2.75)	0.19				
Hypertension	1.27 (0.57–2.84)	0.55				
Current smoking	1.02 (0.45–2.30)	0.96				
Symptom onset to device time	1.00 (1.00–1.00)	0.20				
Baseline TIMI flow 0/1	1.82 (1.06–3.12)	0.03				
LAD infarct artery	1.05 (0.35–3.18)	0.93				
Diabetes	2.31 (1.54–3.47)	<0.0001				
Hyperlipidemia	0.57 (0.33–0.99)	0.05				
AUC for model with infarct size = 0.86, without infarct size = 0.83; p = 0.19						
Reinfarction						
Infarct size, per 5% increase	1.02 (1.01–1.04)	0.55	0.184	0.22	0.000	0.98
Age, per decade increase	1.19 (1.17–1.22)	0.07				
Female	0.61 (0.26–1.48)	0.28				
Hypertension	0.95 (0.47–1.93)	0.90				
Current smoking	2.00 (1.16–3.45)	0.01				
Symptom onset to device time	1.00 (1.00–1.00)	0.16				
Baseline TIMI flow 0/1	0.58 (0.30–1.14)	0.11				
LAD infarct artery	1.49 (0.74–3.02)	0.26				
Diabetes	2.78 (1.83–4.21)	<0.0001				
Hyperlipidemia	0.80 (0.40–1.62)	0.54				
AUC for model with infarct size = 0.66, without infarct size = 0.66; p = 0.91						
Heart failure hospitalization						
Infarct size, per 5% increase	1.20 (1.19–1.21)	<0.0001	0.689	<0.0001	0.015	0.03
Age, per decade increase	1.87 (1.83–1.90)	<0.0001				
Female	3.13 (1.97–4.96)	<0.0001				
Hypertension	1.10 (0.61–1.97)	0.76				
Current smoking	1.95 (1.01–3.78)	0.05				
Symptom onset to device time	1.00 (1.00–1.00)	0.25				
Baseline TIMI flow 0/1	1.27 (0.56–2.87)	0.57				
LAD infarct artery	1.09 (0.61–1.93)	0.78				
Diabetes	0.84 (0.46–1.54)	0.58				
Hyperlipidemia	1.66 (1.04–2.67)	0.03				
AUC for model with infarct size = 0.83, without infarct size = 0.78; p = 0.03						
Death or heart failure hospitalization						
Infarct size, per 5% increase	1.20 (1.19–1.21)	<0.0001	0.536	<0.0001	0.021	0.004
Age, per decade increase	2.10 (2.06–2.14)	<0.0001				
Female	2.13 (1.34–3.38)	0.001				
Hypertension	1.12 (0.73–1.70)	0.60				
Current smoking	1.57 (1.16–2.13)	0.004				
Symptom onset to device time	1.00 (1.00–1.00)	0.20				
Baseline TIMI flow 0/1	1.40 (0.73–2.66)	0.31				
LAD infarct artery	1.05 (0.72–1.52)	0.80				
Diabetes	1.34 (0.97–1.84)	0.08				
Hyperlipidemia	0.97 (0.57–1.68)	0.91				
AUC for model with infarct size = 0.83, without infarct size = 0.78; p = 0.01						

AUC = area under the curve; HR = hazard ratio; IDI = integrated discrimination improvement; NRI = net reclassification index; other abbreviations as in Table 2.

FIGURE 3 Relationship Between IS and the Composite Endpoint of All-Cause Mortality or HF Hospitalization During 1-Year Clinical Follow-Up (From Time of Study Entry) in 10 Subgroups



Outcomes were examined in patients with large versus small infarct size (IS) (above or below the median of 17.9%). Interaction p values are for comparison of the hazard ratios in each subgroup. HF = heart failure; LAD = left anterior descending; TIMI = Thrombolysis In Myocardial Infarction.

Additional studies are also warranted to determine the extent to which other readily available CMR parameters, including microvascular obstruction, left ventricular ejection fraction, and left ventricular volumes, might provide incremental prognostic value to IS determination.

CONCLUSIONS

IS measured by CMR or tc-99m sestamibi SPECT within 1 month after primary PCI is strongly associated with all-cause mortality and hospitalization for HF within 1 year. IS may therefore be useful as an endpoint in clinical trials and as an important prognostic measure when caring for patients with STEMI.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with STEMI, assessment of IS by CMR imaging or tc-99m sestamibi SPECT imaging within 1 month after primary PCI is related to hospitalization for HF and all-cause mortality over the course of the next year.

TRANSLATIONAL OUTLOOK: Prospective studies are needed to determine whether therapeutic interventions that reduce IS improve event-free survival after primary PCI for patients with STEMI.

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KEY WORDS angioplasty, infarct size, myocardial infarction, prognosis

APPENDIX For supplemental figures and tables, please see the online version of this article.