Relationship between therapeutic effects on infarct size in acute myocardial infarction and therapeutic effects on 1-year outcomes: A patient-level analysis of randomized clinical trials

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Background While infarct size in patients with ST-segment elevation myocardial infarction (STEMI) has been generally associated with long-term prognosis, whether a therapeutic effect on infarct size has a corresponding therapeutic effect on long-term outcomes is unknown.

Methods Using combined patient-level data from 10 randomized trials of primary percutaneous coronary intervention (PCI) for STEMI, we created multivariable Cox proportional hazard models for one-year heart failure hospitalization and all-cause mortality, which included clinical features and a variable representing treatment effect on infarct size. The trials included 2679 participants; infarct size was measured at a median 4 days post infarction.

Results Mean infarct size among the control groups ranged from 16% to 35% of the left ventricle, and from 12% to 36% among treatment groups. There was a significant relationship between treatment effect on infarct size and treatment effect on 1-year heart failure hospitalization (HR 0.85, 95% CI 0.77-0.93, P = .0006), but not on one-year mortality (HR 0.97, 95% CI 0.89-1.06). The treatment effect between infarct size and heart failure hospitalization was stable in sensitivity analyses adjusting for time from STEMI onset to infarct size assessment, and when considering heart failure as the main outcome and death as a competing risk.

Conclusions We conclude that early treatment-induced effects on infarct size are related in direction and magnitude to treatment effects on heart failure hospitalizations. This finding enables consideration of using infarct size as a valid surrogate outcome measure in assessing new STEMI treatments. (Am Heart J 2017;188:18-25.)

Since pioneering studies documenting the influence of the duration of coronary occlusion on the magnitude of infarction,[1] limiting infarct size in acute myocardial infarction (AMI) by reperfusion and other therapies has been a major target for investigation.[2] Numerous studies have documented the prognostic importance of infarct size as it relates to long-term post-AMI outcomes, including mortality and heart failure.[3] The robustness of this association is supported by the fact that several measures of infarct size, including serum markers of necrosis[4] and imaging tests such as single-photon emission computed tomography (SPECT)[5] and cardiac magnetic resonance (CMR) imaging[6] demonstrate such a relationship. This concept has informed the design of early studies of new therapeutic agents for AMI, with the assumption that infarct size associated with a therapy compared to placebo should be linked to a patient-related outcome resulting from that therapy, that is, that treatment effect on infarct size could be used as a surrogate for treatment effects on longer-term outcomes. However, there are few published data that actually support such an intuitive concept. It does not automatically follow that a treatment effect seen acutely will reliably predict a treatment effect on what seems to be a logically-linked longer-term clinical outcome. Indeed,

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there are many examples in the cardiovascular trial literature in which a therapy effectively directed at a prognostic marker did not result in the expected patient-related outcome, such as suppression of post-AMI premature ventricular contractions by anti-arrhythmic agents,[7] or raising high-density lipoprotein with cholesterol ester transfer protein inhibitors.[8] We therefore sought to quantitatively evaluate the relationship between a short-term therapeutic effect on infarct size and the corresponding longer-term therapeutic effect on patient outcomes. We hypothesized that a therapy-induced change in infarct size would be related in direction and magnitude to the longer-term clinical outcome effect of that therapy. To test this, we evaluated patient-level data from randomized controlled therapeutic trials in AMI.

Methods

As previously described,[9] we combined patient-level data from 10 randomized clinical trials that tested various treatments during primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI).[10-19] Patients were included in the current database if infarct size was measured by either CMR or technetium (Tc)–99 m-sestamibi SPECT within 1 month (outside window 37 days), and if clinical follow-up was reported for ≥6 months. There were a total of 2692 participants meeting these inclusion criteria. Thirteen[13] of these participants did not have data on the randomized treatment assignment, leaving 2679 participants for analysis.

The data from each trial were pooled into a common database at the Cardiovascular Research Foundation (New York, NY). The definitions and adjudicated events from each study were used in the present analysis. This was an independent academic project conceptualized and executed by the authors. The sponsors of the individual trials were not involved in any aspect of this study. Details of the trials and interventions are shown in Supplementary Table I.

Quantitative evaluation of infarct size using standard thresholding techniques was performed in core laboratories blinded to randomized intervention and clinical outcomes data, and expressed as a percent of left ventricular (LV) mass. In 7 trials, infarct size was assessed using CMR with late gadolinium enhancement,[20] and in 3 trials, infarct size was assessed by resting Tc-99 m-sestamibi SPECT imaging using established methodology[5] (see Supplementary Table I).

The pooled data were analyzed using two datasets. Dataset 1 included all (n = 2619) participants with data for randomized treatment for whom infarct size was measured within the above noted time window. Dataset 2 added patients enrolled in the study who died prior to the measurement of infarct size, for whom infarct size was imputed for purposes of this analysis to be the largest infarct size measured in that participant's study (total n = 2679). This latter dataset has the advantage of including patients who presumably had infarcts so large that they did not survive, which should reduce bias against inclusion of more severely ill patients. However, it has the disadvantage of using an estimate for those who died before actual infarct size measurement.

Baseline participant characteristics were summarized as means and prevalence estimates for each clinical trial and all studies pooled. One-year outcomes were summarized as the ratio of the total number of events to the number of participants, and were also calculated as raw percentages.

The absolute rate differences between the outcomes in the treatment (T) group versus the control (C) group were calculated to determine the treatment effect for each individual study (C – T), where a positive value indicates a lower, favorable rate of risk for the treatment group compared to the control group, and a negative value indicates a deleterious effect of the treatment on an outcome compared to control. These estimates do not account for time at risk and censoring, and are shown for descriptive purposes only. Mean infarct sizes were calculated for control and treatment participants in each study, as was the treatment effect on infarct size for each study. The difference in the raw means (C – T) was computed for each study such that a positive value for this treatment effect on infarct size would indicate a smaller infarct size with treatment than with placebo, reflecting a treatment that reduced infarct size.

For each participant in each clinical trial, a new variable representing treatment effect on infarct size termed "treatment effect on infarct size" was created for use in Cox proportional models for outcomes. This variable was assigned a value of zero for all control group participants, representing their not having any effect of the study treatment. For participants in the treatment group, the variable was given the value that trial's treatment effect had on infarct size, whether positive (effective treatment), null, or negative (deleterious treatment).

Cox proportional hazards models were used to estimate the association of treatment effect on infarct size with one-year clinical outcomes (using data collected within 400 days of randomization, allowing an extra month for follow-up). The 1-year outcomes of interest were hospitalization for heart failure and all-cause mortality, endpoints we have previously shown are strongly associated with infarct size after primary PCI in STEMI.[9] One study (AMIHOT-II) did not measure heart failure as an outcome. Therefore, effects of treatment on mortality were estimated on the same cohort used for the analysis of the heart failure outcome (AMIHOT-II excluded), and also on the full cohort (including AMIHOT-II), to look for consistency.

For multivariable adjustment in the Cox models, the following covariates were included: age, sex, prior history of AMI, extent of coronary artery disease (left main/multivessel vs. none), and number of days between randomization and infarct size measurement. In Dataset 2, the median within-study number of days between randomization and infarct

Table I. Baseline characteristics for subjects in Dataset 1 and Dataset 2

Analysis Sample/Study*	Number of subjects (n)	Demographics		Medical History		LM/3 Vessel disease		Days from STEMI to scan Median
		Age Mean	Gender % male	Prior MI %	Diabetes mellitus %	Yes %	No %	
DATASET 1								
AIDA STEMI	771	61.5	76%	6.1%	20%	19%	81%	3.0
AMIHOT-II	275	60.8	82%	9.2%	14%	0.0%	100%	16.0
APEX-AMI	94	59.6	83%	2.1%	12%	17%	83%	4.0
CRISP	260	56.1	80%	0.4%	18%	8.8%	91%	4.0
EMERALD	419	59.6	80%	11%	11%	15%	85%	10.0
IMMEDIATE	37	59.3	76%	14%	24%	24%	76%	34.0
INFUSE-AMI	304	60.0	75%	1.0%	8.6%	9.9%	90%	6.5
LIPSIA-ABCIX	133	62.3	80%	11%	27%	14%	86%	2.0
LIPSIA-N-ACC	197	65.9	68%	9.6%	27%	24%	76%	3.0
LIPSIA-STEMI	129	60.9	84%	4.7%	29%	17%	83%	3.0
ALL POOLED	2619	60.7	78%	6.3%	17%	14%	86%	4.0
DATASET 2								
AIDA STEMI	771	61.5	76%	6.1%	20%	19%	81%	3.6
AMIHOT-II	280	60.8	82%	9.4%	15%	0.0%	100%	16.1
APEX-AMI	94	59.6	83%	2.1%	12%	17%	83%	3.8
CRISP	260	56.1	80%	0.4%	18%	8.8%	91%	4.0
EMERALD	430	59.9	79%	11%	12%	16%	84%	10.3
IMMEDIATE	47	62.7	77%	23%	21%	21%	79%	33.6
INFUSE-AMI	316	60.5	74%	0.9%	9.2%	10%	90%	15.4
LIPSIA-ABCIX	137	62.7	80%	11%	28%	16%	84%	2.8
LIPSIA-N-ACC	208	66.4	67%	11%	28%	25%	75%	3.4
LIPSIA-STEMI	136	61.4	82%	4.4%	30%	17%	82%	3.5
ALL POOLED	2679	60.9	77%	6.8%	18%	14%	85%	4.0

*Dataset 1 includes all randomized patients with a measurement of infarct size within 37 days. Dataset 2 also includes patients who died prior to measurement of infarct size, with imputation of both infarct size and days from STEMI to infarct size measurement (see text for details).

measurement was used to impute values for participants who died before the infarct size could be directly measured.

To evaluate whether the proportional hazards assumption was violated, we reviewed fitted spline smoothed curves of coefficients, estimated using Schoenfeld residuals, over the year of follow-up and tested the correlation between weighted residuals and failure times. The assumption was met for each of the death or heart failure models.

We also performed a series of sensitivity analyses to ensure consistency of findings across different scenarios. Sensitivity analyses included[1] removing the day of infarct size assessment as a covariate[2]; including re-infarction as a time dependent covariate in the Cox-models for the outcomes of heart failure and death[3]; analyzing the heart failure outcome using death as a competing risk event; and[4] adjusting for possible within-trial clustering effects by first using the robust sandwich estimator at the treatment within study level, and also by fitting a shared frailty model, using the treatment within study to define the potential cluster. Analyses were done with SAS for Windows, SAS 9.4 (SAS Institute Inc, Cary, NC).

Results

Table I shows the baseline characteristics for each study, and all studies pooled, in each of the two analysis datasets. The pooled population at study entry (dataset 2, n = 2679) included 77% men, average age 61, with prior MI in 7%, diabetes in 18%, and left main or three-vessel coronary artery disease in 14%. Infarct size was assessed at a median of 4 days after STEMI.

One-year clinical outcomes, including the differences between the treatment and control groups for heart failure and mortality, are shown in Table II. The mean infarct sizes for control and treatment groups in each trial, and the treatment effects on infarct size are shown in Table III. Mean infarct sizes among the control groups ranged from 16% to 36% of LV mass, and from 12% to 36% among treatment groups. The treatment effect on infarct size across the 10 studies ranged from −6.5% to 4.3%, and was improved with treatment (smaller infarct size) in 3 trials and worsened (larger infarct size) in 7 trials.

Table IV shows the hazard ratios for treatment effects assessed by infarct size, adjusted for age, gender, diabetes, prior AMI, left main or three-vessel coronary disease, and the number of days elapsed between randomization and infarct size measurement.

The results showed a significant relationship between treatment effect on infarct size and treatment effect on heart failure hospitalization at 1 year. The relationship between treatment effect on infarct size and treatment

Table II. Clinical outcomes for subjects in Dataset 1 and Dataset 2 from each trial

	Heart failure					All-cause mortality				
	Raw event % (and ratio)					Raw event % (and ratio)				
Analysis sample/study	Control		Treatment		C-T Delta*	Control		Treatment		C-T Delta*
Dataset 1										
AIDA STEMI	1.6%	(6/383)	4.1%	(16/388)	−2.5%	2.9%	(11/383)	2.1%	(8/388)	0.8%
AMIHOT-II	-	-	-	-	-	1.5%	(1/68)	1.4%	(3/207)	0.1%
APEX-AMI	0.0%	(0/46)	0.0%	(0/48)	0.0%	2.2%	(1/46)	0.0%	(0/48)	2.2%
CRISP	3.0%	(4/135)	3.2%	(4/125)	−0.2%	2.2%	(3/135)	0.0%	(0/125)	2.2%
EMERALD	0.5%	(1/198)	1.8%	(4/221)	−1.3%	0.5%	(1/198)	1.8%	(4/221)	−1.3%
IMMEDIATE	4.5%	(1/22)	0.0%	(0/15)	4.5%	0.0%	(0/22)	0.0%	(0/15)	0.0%
INFUSE-AMI	2.8%	(4/145)	1.3%	(2/159)	1.5%	3.4%	(5/145)	1.9%	(3/159)	1.5%
LIPSIA-ABCIX	0.0%	(0/61)	2.8%	(2/72)	−2.8%	0.0%	(0/61)	1.4%	(1/72)	−1.4%
LIPSIA-N-ACC	2.1%	(2/94)	6.8%	(7/103)	−4.7%	4.3%	(4/94)	5.8%	(6/103)	−1.5%
LIPSIA-STEMI	1.7%	(1/60)	5.8%	(4/69)	−4.1%	3.3%	(2/60)	1.4%	(1/69)	1.9%
Dataset 2										
AIDA STEMI	1.6%	(6/383)	4.1%	(16/388)	−2.5%	2.9%	(11/383)	2.1%	(8/388)	0.8%
AMIHOT-II	-	-	-	-	-	1.5%	(1/68)	3.8%	(8/212)	−2.3%
APEX-AMI	0.0%	(0/46)	0.0%	(0/48)	0.0%	2.2%	(1/46)	0.0%	(0/48)	2.2%
CRISP	3.0%	(4/135)	3.2%	(4/125)	−0.2%	2.2%	(3/135)	0.0%	(0/125)	2.2%
EMERALD	0.5%	(1/205)	1.8%	(4/225)	−1.3%	3.9%	(8/205)	3.6%	(8/225)	0.3%
IMMEDIATE	3.6%	(1/28)	0.0%	(0/19)	3.6%	21.4%	(6/28)	21.1%	(4/19)	0.3%
INFUSE-AMI	2.7%	(4/150)	1.2%	(2/166)	1.5%	6.7%	(10/150)	6.0%	(10/166)	0.7%
LIPSIA-ABCIX	0.0%	(0/63)	4.1%	(3/74)	−4.1%	3.2%	(2/63)	4.1%	(3/74)	−0.9%
LIPSIA-N-ACC	4.0%	(4/99)	9.2%	(10/109)	−5.2%	9.1%	(9/99)	11.0%	(12/109)	−1.9%
LIPSIA-STEMI	3.2%	(2/62)	8.1%	(6/74)	−4.9%	6.5%	(4/62)	8.1%	(6/74)	−1.6%

Dataset 1 includes all randomized patients with a measurement of infarct size within 37 days. Dataset 2 includes patients who died prior to measurement of infarct size, with imputation of both infarct size and days from STEMI to infarct size measurement as described in the text.
* C-T Delta indicates the unadjusted risk difference between the Treatment and Control groups, where a positive value indicates the event rate is higher in the control group than the treatment group (Treatment better) and a negative value indicates the event rate is higher in the treatment group compared to the control group (Control better).

effect on one-year all-cause mortality was not significant. The respective hazard ratios for heart failure hospitalization and mortality for Dataset 1 were 0.87 (P = .01) and 0.99 (P = .87), and for Dataset 2 were 0.85 (P = .0006) and 0.97 (P = .51). Thus, the inclusion or exclusion of participants who died prior to infarct size assessment did not appreciably affect the results.

Sensitivity analyses were performed investigating whether the treatment hazard ratios changed with removal of elapsed time from randomization to scan, by adding recurrent AMI as a covariate, and investigating if the treatment effect on heart failure would be different if mortality was considered as a competing risk. Because treatment effects were estimated at the study level, adjustments were also made to the models to account for within-study clustering. Results were stable across different sensitivity analyses as shown in Tables V and VI.

Discussion

The present study of patient-level data from 10 randomized controlled trials of treatment interventions during primary PCI in patients with STEMI suggests that therapeutic effects on infarct size, as measured by noninvasive CMR or SPECT imaging within days after treatment, is related in direction and magnitude to the longer-term (one-year) therapeutic effect on hospitalization for heart failure. In contrast, no such relationship was present between the treatment effect on infarct size and subsequent one-year all-cause mortality. These findings have implications for the potential to incorporate infarct size as a surrogate outcome in trials of new therapies for AMI.

In randomized clinical trials of treatments for AMI, clinical endpoints which mechanistically reflect infarct size include mortality and hospitalization for heart failure. However, with improvements in prognosis with expeditious reperfusion therapy, the relatively low frequencies of these events in contemporary studies pose substantial logistical challenges in designing trials meant to detect further reductions of a positive intervention. For example, assuming a 5% rate of the composite of all-cause mortality in the control arm, approximately 15,500 participants would be required to detect a 25% reduction by a new treatment with 90% power.

The scale, duration, and expense of such trials have encouraged the utilization of surrogate biomarkers, either alone or as part of composite endpoints. However,

Table III. Mean infarct size for control, treatment, and control minus treatment group difference from each trial

Analysis sample/study	Total N	Control (C) group infarct size: Mean (n)	Treatment (T) infarct size: Mean (n)	C-T delta infarct size*
Dataset 1 (n = 2619)				
AIDA STEMI	771	17.8 (n = 383)	18.1 (n = 388)	–0.3
AMIHOT-II	275	27.0 (n = 68)	23.0 (n = 207)	4
APEX-AMI	94	16.3 (n = 46)	12.0 (n = 48)	4.3
CRISP	260	36.2 (n = 135)	42.0 (n = 125)	–5.8
EMERALD	419	14.3 (n = 198)	17.2 (n = 221)	–2.9
IMMEDIATE	37	12.1 (n = 22)	12.5 (n = 15)	–0.4
INFUSE-AMI	304	20.6 (n = 145)	18.1 (n = 159)	2.4
LIPSIA-ABCIX	133	17.9 (n = 61)	24.8 (n = 72)	–6.9
LIPSIA-N-ACC	197	16.3 (n = 94)	18.1 (n = 103)	–1.8
LIPSIA-STEMI	129	16.2 (n = 60)	21.4 (n = 69)	–5.2
Dataset 2 (n = 2679)				
AIDA STEMI	771	17.8 (n = 383)	18.1 (n = 388)	–0.3
AMIHOT-II	280	27.0 (n = 68)	24.2 (n = 212)	2.8
APEX-AMI	94	16.3 (n = 46)	12.0 (n = 48)	4.3
CRISP	260	36.2 (n = 135)	42.0 (n = 125)	–5.8
EMERALD	430	16.2 (n = 205)	18.2 (n = 225)	–1.9
IMMEDIATE	47	22.0 (n = 28)	22.1 (n = 19)	–0.1
INFUSE-AMI	316	21.5 (n = 150)	19.5 (n = 166)	2.1
LIPSIA-ABCIX	137	19.2 (n = 63)	25.7 (n = 74)	–6.5
LIPSIA-N-ACC	208	17.8 (n = 99)	19.7 (n = 109)	–1.9
LIPSIA-STEMI	136	17.4 (n = 62)	23.6 (n = 74)	–6.2

Dataset 1 includes all randomized patients with a measurement of infarct size within 37 days. Dataset 2 includes patients who died prior to measurement of infarct size, with imputation of both infarct size and days from STEMI to infarct size measurement as described in the text.
* C-T Delta Infarct size indicates the unadjusted difference between the Treatment and Control group means, where a positive value indicates the infarct size is larger in the control group than the treatment group (Treatment better) and a negative value indicates the infarct size larger in the treatment group compared to the control group (Control better).

Table IV. Adjusted hazard ratios (HR) for infarct size based (C-T) treatment effect on outcomes

Outcome	Adjusted HR (95% CI)*	*P*	Raw outcome % (difference)
Dataset 1			
Heart failure hospitalization	0.87 (95% CI 0.79-0.97)	.01	2.5% (58/2332)
All-cause mortality	1.03 (95% CI 0.89-1.18)	.71	2.1% (50/2337)
All-cause mortality (with AMIHOT-II data)	0.99 (95% CI 0.88-1.12)	.87	2.0% (53/2604)
Dataset 2			
Heart failure hospitalization	0.85 (95% CI 0.77-0.93)	.0006	2.8% (67/2387)
All-cause mortality	0.99 (95% CI 0.90-1.09)	.78	4.4% (105/2392)
All-cause mortality (with AMIHOT-II data)	0.97 (95% CI 0.89-1.06)	.50	4.2% (113/2664)

* Adjusted HR and *P*value from Cox Proportional Hazard Models where covariates included age, gender, DM, prior MI, and left main/3-vessel disease (yes/no) and the number of days elapsed between day of randomization and the day of the infarct size assessment.

although such strategies increase statistical power and thus enable smaller trials, the legitimacy of surrogates as being clinically meaningful is a valid concern. Demonstrating an association between a biomarker and subsequent prognosis is not sufficient to establish it as a surrogate. It must also be shown that interventions which improve (or worsen) the biomarker measure have a similar directional impact and magnitude of effect on the related clinical endpoint, a much more difficult threshold to meet.

Among potentially valid biomarker endpoints in patients with STEMI, infarct size is attractive because it has a plausible direct pathophysiologic link to important clinical outcomes, and can be reliably measured noninvasively early after infarct onset.[5,20] Additionally, infarct size measured as percent of the LV is a continuous (as opposed to dichotomous) variable, which allows greater discrimination and enhanced statistical power. This approach also is attractive because in using acute treatments for STEMI, it results in one measure of infarct size for each patient. This provides a specific defined measure of treatment effect, in contrast to serum biomarkers (such as natriuretic peptides in heart failure trials) that require assessment longitudinally over time in

Table V. Sensitivity analyses

	Primary Analysis Result		Days elapsed between day of randomization and the day the scan removed as covariate		Reinfarction added as time-dependent covariate (excludes data from IMMEDIATE trial*)		Death analyzed as competing risk	
Dataset 1	Adjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Heart failure hospitalization	0.87 (95% CI 0.79-0.97)	.01	0.88 (95% CI 0.79-0.97)	.01	0.88 (95% CI 0.79-0.99)	.03	0.88 (95% CI 0.80-0.96)	.007
All-cause mortality	1.03 (95% CI 0.89-1.18)	.71	1.03 (95% CI 0.90-1.19)	.65	0.97 (95% CI 0.83-1.13)	.69		
All-cause mortality (with AMIHOT-II data)	0.99 (95% CI 0.88-1.12)	.87	1.00 (95% CI 0.89-1.12)	.97	0.92 (95% CI 0.80-1.06)	.25		
Dataset 2								
Heart failure hospitalization	0.85 (95% CI 0.77-0.93)	.0006	0.85 (95% CI 0.77-0.93)	.0005	0.87 (95% CI 0.79-0.97)	.009	0.85 (95% CI 0.78-0.93)	.0003
All-cause mortality	0.99 (95% CI 0.90-1.09)	.78	1.01 (95% CI 0.92-1.11)	.86	1.01 (95% CI 0.89-1.15)	.84		
All-cause mortality (with AMIHOT-II data)	0.97 (95% CI 0.89-1.06)	.50	1.00 (95% CI 0.92-1.09)	>.99	1.04 (95% CI 0.92-1.16)	.53		

*The IMMEDIATE Trial did not capture MI as an outcome, and therefore data from that trial were excluded in the sensitivity analysis that included MI as a time dependent covariate in the models for the other outcomes.

analyses their correspondence to clinical outcomes. The use of infarct size as a surrogate endpoint in STEMI trials may substantially reduce clinical trial size requirements, potentially accelerating testing and regulatory approval of new therapies. While incorporating an imaging test would engender additional costs related to the imaging itself as well as central analysis and quality control, this could potentially be balanced by the reduction in the overall sample size required to test the intervention in a rigorous manner.

Prompt reperfusion following STEMI onset reduces infarct size and improves short-term and long-term survival.[2,3] In addition, the reduction in infarct size with primary PCI compared to fibrinolytic therapy may in part underlie the benefit of the mechanical approach.[21,22] However, a link between a therapeutic effect of reduction in infarct size and subsequent reduction in morbidity or mortality has not been previously demonstrated in the contemporary era. Evidence of this relationship is foundational to incorporating infarct size as a component of a composite endpoint in AMI trials.

Using the patient-level data from the same 10 trials used in this study, we have recently demonstrated a powerful association between infarct size and subsequent prognosis. Specifically, infarct size, measured by CMR or SPECT within 30 days of STEMI after primary PCI, was strongly predictive of all-cause mortality and hospitalization for heart failure within one year.[9] After adjusting for age, gender, diabetes, hypertension, hyperlipidemia, current smoking, left anterior descending (LAD) vs. non-LAD infarct vessel, symptom-to-first device time, and baseline TIMI flow 0/1 vs. 2/3, the relationships between infarct size (per 5% increase) to the 1-year occurrence of heart failure hospitalization and all-cause mortality were HR 1.20 [95% CI 1.19, 1.21], and HR 1.19 [1.18, 1.20] respectively, both $P < .0001$. Those results set the stage for the current analysis, demonstrating that a therapeutic-induced effect on infarct size is related to a quantifiable therapeutic effect on an outcome (heart failure hospitalization) of similar direction and magnitude. These data suggest that treatment effects on infarct size would plausibly reflect treatment effects on more established clinical endpoints, in particular heart failure hospitalization.

The link demonstrated in this study between therapeutic effects on infarct size and heart failure hospitalization is highly plausible, as larger infarcts are associated with greater LV dysfunction and remodeling, and the development of clinical heart failure.[23] The absence of such a link between treatment effect on infarct size and treatment effect on all-cause mortality, despite strong prognostic data, may have several explanations. A proportion of deaths after AMI are from non-cardiac causes,[24] which are presumably not related to infarct size. Another important cause of death post-MI is recurrent MI, which was not related to infarct size in our previous analysis.[9] It is also possible that some of the interventions tested had adverse effects that otherwise offset the benefits of infarct size reduction on survival (but not on heart failure hospitalization).

The current data showing that a treatment-induced effect on infarct size is associated with a longer-term effect on heart failure hospitalizations suggest that this imaging biomarker might be incorporated in future STEMI trials, allowing investigation of new agents with

Table VI. Additional sensitivity analyses

Dataset 1	Primary analysis using a robust sandwich estimator to adjust for within study/treatment group clustering HR (95% CI)	*P*	Primary analysis using a random effect for study/treatment group to adjust for clustering HR (95% CI)	*P*
Heart failure hospitalization	0.87 (95% CI 0.79-0.96)	.007	0.86 (95% CI 0.75-0.99)	.03
All-cause mortality	1.03 (95% CI 0.93-1.14)	.60	1.03 (95% CI 0.89-1.18)	.71
All-cause mortality (with AMIHOT-II data)	0.99 (95% CI 0.90-1.09)	.84	0.99 (95% CI 0.88-1.12)	.87
Dataset 2				
Heart failure hospitalization	0.85 (95% CI 0.77-0.93)	.0003	0.83 (95% CI 0.73-0.95)	.007
All-cause mortality	0.99 (95% CI 0.86-1.13)	.84	1.01 (95% CI 0.89-1.15)	.86
All-cause mortality (with AMIHOT-II data)	0.97 (95% CI 0.86-1.09)	.61	1.00 (95% CI 0.89-1.12)	.94

smaller sample sizes. Infarct size could serve as part of a composite measure. For example, one such approach might be the use of the Finkelstein-Schoenfeld method,[25] whereby treatment and control group patients could be compared sequentially on outcomes of death, cardiac arrest, heart failure hospitalization and infarct size. This gives higher priority to the more established clinical outcome endpoints, but also allows for smaller, but still rigorous, clinical trials with plausible interpretability of results. Smaller sample sizes (and thus more efficient trial execution) could expand the repertoire of trial designs beyond the traditional large event driven randomized controlled trial, as could other approaches gaining higher profile such as registry-based randomized controlled trials.[26]

Limitations of the present study should be considered. We included all trials available to this investigative group with patient-level data for both infarct size and long-term outcomes, but for uniformity of the treatment effect context included only those studies with patients undergoing primary PCI for STEMI. It is uncertain whether the relationships described herein hold for adjunctive treatments in other settings (eg, after fibrinolytic therapy, or in non-STEMI, or when comparing different reperfusion strategies). Moreover, although the pooled dataset we utilized represents the largest study of its kind, among the component studies modest reductions in infarct size were present in only 3 studies,[11,13,19] and none were large enough to demonstrate significantly reduced mortality. Although the core laboratories and clinical events committees were blinded, the trials were open-label and we cannot exclude some degree of investigator bias. Finally, while patient-level data were used from these 10 trials in this analysis, by necessity, we created a trial-level variable representing the overall treatment effect on infarct size measured in that trial. However, this allows the testing of whether patients' estimated infarct size change as a function of actual treatment received, adjusted for the other important clinical characteristics in the multivariable regression, are related in direction and magnitude to the long-term clinical outcomes.

In conclusion, the present patient-level analysis of randomized controlled trials of multiple treatments in patients with STEMI undergoing primary PCI suggests that a treatment-induced effect on infarct size is related in direction and quantifiable magnitude to a treatment effect on heart failure hospitalizations. This enables consideration of incorporating infarct size assessment into the evaluation of new therapeutic interventions in STEMI.

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