Relationship between Therapeutic Effects on Infarct Size in Acute Myocardial Infarction and Therapeutic Effects on One-year Outcomes: A Patient-Level Analysis of Randomized Clinical Trials

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ABSTRACT

Background: Studies of acute myocardial infarction (AMI) have shown that measured infarct size is related to long-term outcomes such as mortality or heart failure. However, not yet shown is whether a therapeutic effect on infarct size will be reflected in effects of therapy on longer-term outcomes. We used patient-level data from trials of treatments for AMI to assess the relationship between short-term treatment effects on infarct size and treatment effects seen on longer-term outcomes. We hypothesized that a therapy-induced change in infarct size would be related in direction and/or magnitude to the one-year outcome effects of that therapy.

Methods: We combined patient-level data from 10 randomized clinical trials that tested various therapies for ST-elevation MI (STEMI). Infarct size was assessed by sestamibi imaging in 3 trials, and by cardiac magnetic resonance imaging in 7, using standard techniques with analysis in core labs, and was expressed as a percent of left ventricular (LV) mass. Multivariable Cox proportional hazard models predicting one-year outcomes included patients' clinical features and a variable representing the treatment effect on infarct size. The predicted outcomes were hospitalization for heart failure and all-cause mortality over one year of follow-up.

Results: The 10 trials included 2,676 patients. Infarct size was measured at a median of 5 days post-MI. Mean trial infarct size in the control groups in the 10 trials ranged from 16-35% of the LV, and from 12-40% among treatment groups. There was a significant relationship between treatment effect on infarct size and treatment effect on one-year heart failure hospitalization with HR 0.84 (95% CI 0.76 to 0.94, p=0.0013). There was no significant relationship between treatment effect on infarct size and treatment effect on one-year mortality (HR 0.1.00, 95% CI 0.90 to 1.12). The relationship to heart failure hospitalization was stable in sensitivity analyses adjusting for time from MI to infarct size assessment and for considering heart failure as the main outcome and death as a competing risk.

Conclusion: This patient-level analysis of randomized placebo-controlled trials of multiple therapeutics for STEMI suggests that a treatment-induced effect on infarct size is related in direction and quantifiable magnitude to a treatment effect on heart failure hospitalizations. The data enable the consideration of incorporating infarct size assessment into novel trial analytic approaches to assess new therapeutics.

Background

Many studies have documented the importance of infarct size as it relates to longer-term post-AMI outcomes, such as mortality or the onset of heart failure (HF). This concept has informed the design of early studies of new therapies for AMI, with the assumption that a *change* in infarct size associated with a therapy should be linked to a *change* in a patient-related outcome resulting from that therapy, i.e., that infarct size could be used as a surrogate for treatment effects. However, few published data support such an intuitive concept. Thus, we sought to quantitatively evaluate the relationship between short-term therapeutic effect on infarct size and the corresponding therapeutic effect on longer-term patient-related outcomes in AMI trials. We hypothesized that a therapy-induced change in infarct size would be related in direction and/or magnitude to the outcome effect of that therapy.

METHODS: Trial and Patient Inclusion

We combined patient-level data from 10 RCTs that tested various treatments for STEMI. Data were pooled into a common database at the Cardiovascular Research Foundation. This was an independent academic project conceptualized and executed by the authors; study sponsors were not involved in any aspect of this study.

Table 1: Trials Included in the Analysis

Trial	Acronym	Intervention (and Imaging method)
Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberated Debris	EMERALD	distal embolic protection filter vs. control (SPECT)
Acute Myocardial Infarction with HyperOxemic Reperfusion II	AMIHOT-II	post-procedural supersaturated oxygen vs. control (SPECT)
Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency care	IMMEDIATE	pre-hospital intravenous glucose-insulin-potassium infusion vs. placebo prior to primary PCI (SPECT)
Pexelizumab in Conjunction With Angioplasty in Acute Myocardial Infarction	APEX-AMI	pre-procedural intravenous pexelizumab vs. placebo (MRI)
Randomized Leipzig Immediate Percutaneous Coronary Intervention Abciximab IV Versus IC in ST-Elevation Myocardial Infarction	LIPSIAbciximab	intracoronary vs. intravenous bolus of abciximab (MRI)
Prospective, Single-Blind, Placebo-Controlled, Randomized Leipzig Immediate PercutaneouS Coronary Intervention Acute Myocardial Infarction N-ACC	LIPSIA-N-ACC	pre-procedural high-dose N-acetylcysteine vs. placebo (MRI)
Leipzig Immediate Prehospital Facilitated Angioplasty in ST-Segment Myocardial Infarction	LIPSIA-STEMI	pre-hospital tenecteplase vs. control (MRI)
Counterpulsation to Reduce Infarct Size Pre-PCI Acute Myocardial Infarction	CRISP-AMI	pre-procedural intraaortic balloon counterpulsation vs. control (MRI)
Abciximab Intracoronary versus intravenous Drug Application in ST-Elevation Myocardial Infarction	AIDA STEMI	intracoronary vs. intravenous bolus of abciximab (MRI)
Intracoronary Abciximab and Aspiration Thrombectomy in Patients with Large Anterior Myocardial Infarction	INFUSE-AMI	2X2 design to an intralesional bolus of abciximab vs. control, and to thrombus aspiration vs. control (MRI)

METHODS: Assessment of Infarct Size

Quantitative evaluation of infarct size by thresholding techniques was performed in core labs blinded to clinical and outcome data, and expressed as %LV mass. In 7 trials, infarct size was assessed using CMR with late gadolinium enhancement, and in 3 trials it was assessed by resting Tc99m-sestamibi SPECT imaging using established methodology.

METHODS: Statistical Analysis

The pooled data were analyzed using two sets. Dataset 1: all pts for whom an infarct size was measured up to 37days after STEMI. Dataset 2: added those pts who died prior to the measurement of infarct size, for whom infarct size was imputed for the purposes of this analysis to be the largest infarct size measured in that pt's study.

The differences in the raw percent between the outcomes in the treatment (T) group versus the control (C) groups were calculated as the "C minus T (C-T) delta," where a positive value indicates a lower, favorable, (raw) rate of risk for the treatment group compared to the control group. Mean infarct sizes were calculated for control and treatment participants in each study, as was the control minus treatment group difference for each study. The difference in the raw means (C-T) was computed for each study such that a positive value for "delta infarct size" would indicate a smaller infarct size with treatment than with placebo, reflecting a treatment that reduced infarct size.

For each patient within each trial, a variable labeled as "infarct size based treatment" was created for use in the Cox Proportional Hazards (CPH) models for outcomes that represented the treatment effect on infarct size. This variable was assigned a value of zero for all control group participants (in any trial). For participants in the treatment group, the variable had the value of the C-T delta infarct size from the study in which the participant was enrolled. In Dataset 2, for any participant who died before the infarct size was assessed, the maximum infarct size measured in their trial was used as the imputed infarct size.

CPH models were used to estimate the association of infarct size related to treatment with 1-year adjudicated outcomes, hospitalization for HF and all-cause mortality. For multivariable adjustment in the Cox models, a priori, the following factors were chosen as covariates: age, sex, prior MI, coronary disease type (LM/MVD vs. not), and the days between randomization and infarct size assessment.

Table 2: Baseline characteristics for subjects in Dataset 1 and Dataset 2

Analysis Sample++ /Study	Number of subjects	Demographics		Medical History		LM/3 Vessel disease		Days from STEMI to scan Median
		Age	Gender	Prior MI	Diabetes	Yes	No	
	(n)	Mean	% male	% yes	% yes	%	%	
DATASET 1								
AIDA STEMI	771	61.5	76%	6.1%	20%	19%	81%	3.0
AMIHOT2	275	60.8	82%	9.2%	14%	0.0%	100%	16.0
APEX	94	59.6	83%	2.1%	12%	17%	83%	4.0
CRISP-AMI	236	56.4	82%	0.4%	18%	9.3%	91%	14.0
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
LIPSIAbciximab	133	62.3	80%	11%	27%	14%	86%	2.0
LIPSIAN-ACC	212	65.5	69%	9.9%	26%	23%	77%	3.0
LIPSIA STEMI	135	61.1	84%	4.4%	29%	18%	82%	3.0
ALL POOLED	2616	60.7	78%	6.4%	17%	14%	86%	5.0
DATASET 2								
AIDA STEMI	771	61.5	76%	6.1%	20%	19%	81%	3.0
AMIHOT2	280	60.8	82%	9.4%	15%	0.0%	100%	16.0
APEX	94	59.6	83%	2.1%	12%	17%	83%	4.0
CRISP-AMI	236	56.4	82%	0.4%	18%	9.3%	91%	14.0
EMERALD	430	59.9	79%	11%	12%	16%	84%	10.0
IMMEDIATE	47	62.7	77%	23%	21%	21%	79%	34.0
INFUSE-AMI	316	60.5	74%	0.9%	9.2%	10%	90%	6.5
LIPSIAbciximabIX	137	62.7	80%	11%	28%	16%	84%	2.0
LIPSIA N-ACC	223	66.0	68%	11%	27%	23%	77%	3.0
LIPSIA STEMI	142	61.5	82%	4.2%	30%	18%	81%	3.0
ALL POOLED	2676	61.0	77%	6.8%	18%	15%	85%	5.0

++ Dataset 1 includes all randomized patients with a measurement of infarct size within 37 days. Dataset 2 includes all patients in Dataset 1 + 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.

Table 3 – HF and Mortality Outcomes for Patients in Dataset 1 and Dataset 2

Analysis Sample/Study	Heart Failure					All-Cause Mortality				
	Raw Event % (and ratio)				C-T Delta *	Raw Event % (and ratio)				C-T Delta
	Control		Treatment			Control		Treatment		
DATASET 1										
AIDA STEMI	1.6%	(6/383)	4.1%	(16/388)	*-2.5%*	2.9%	(11/383)	2.1%	(8/388)	*0.8%*
AMIHOT2						1.5%	(1/68)	1.4%	(3/207)	*0.1%*
APEX	0.0%	(0/46)	0.0%	(0/48)	*0.0%*	2.2%	(1/46)	0.0%	(0/48)	*2.2%*
CRISP-AMI	2.4%	(3/124)	3.6%	(4/112)	*-1.2%*	1.6%	(2/124)	0.0%	(0/112)	*1.6%*
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%*
LIPSIAbciximab	0.0%	(0/61)	2.8%	(2/72)	*-2.8%*	0.0%	(0/61)	1.4%	(1/72)	*-1.4%*
LIPSIAN-ACC	2.9%	(3/103)	6.4%	(7/109)	*-3.5%*	3.9%	(4/103)	5.5%	(6/109)	*-1.6%*
LIPSIA STEMI	1.5%	(1/65)	5.7%	(4/70)	*-4.2%*	3.1%	(2/65)	1.4%	(1/70)	*1.7%*
DATASET 2										
AIDA STEMI	1.6%	(6/383)	4.1%	(16/388)	*-2.5%*	2.9%	(11/383)	2.1%	(8/388)	*0.8%*
AMIHOT2						1.5%	(1/68)	3.8%	(8/212)	*-2.3%*
APEX	0.0%	(0/46)	0.0%	(0/48)	*0.0%*	2.2%	(1/46)	0.0%	(0/48)	*2.2%*
CRISP-AMI	2.4%	(3/124)	3.6%	(4/112)	*-1.2%*	1.6%	(2/124)	0.0%	(0/112)	*1.6%*
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%*
LIPSIAbciximab	0.0%	(0/63)	4.1%	(3/74)	*-4.1%*	3.2%	(2/63)	4.1%	(3/74)	*-0.9%*
LIPSIA N-ACC	4.6%	(5/108)	8.7%	(10/115)	*-4.1%*	8.3%	(9/108)	10.4%	(12/115)	*-2.1%*
LIPSIA STEMI	3.0%	(2/67)	8.0%	(6/75)	*-5.0%*	6.0%	(4/67)	8.0%	(6/75)	*-2.0%*

**C-T Delta indicates the unadjusted risk difference, 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)*

Table 4 – Mean Infarct Size for Control, Treatment, and Control minus Treatment

Analysis Sample/Study *	Total N	Control (C) Group Infarct Size: Mean (n)	Treatment (T) Infarct Infarct Size: Mean (n)	C-T Delta Infarct Size
Dataset 1 (n=2616)				
AIDA STEMI	771	17.8 (n= 383)	18.1 (n= 388)	-0.3
AMIHOT2	275	27.0 (n= 68)	23.0 (n= 207)	4
APEX	94	16.3 (n= 46)	12.0 (n= 48)	4.3
CRISP-AMI	236	35.4 (n= 124)	40.5 (n= 112)	-5.1
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
LIPSIAbciximab	133	17.9 (n= 61)	24.8 (n= 72)	-6.9
LIPSIA N-ACC	212	16.8 (n= 103)	17.8 (n= 109)	-1
LIPSIA STEMI	135	17.2 (n= 65)	21.1 (n= 70)	-3.9
Dataset 2 (n=2676)				
AIDA STEMI	771	17.8 (n= 383)	18.1 (n= 388)	-0.3
AMIHOT2	280	27.0 (n= 68)	24.2 (n= 212)	2.8
APEX	94	16.3 (n= 46)	12.0 (n= 48)	4.3
CRISP-AMI	236	35.4 (n= 124)	40.5 (n= 112)	-5.1
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
LIPSIAbciximab	137	19.2 (n= 63)	25.7 (n= 74)	-6.5
LIPSIA N-ACC	223	18.2 (n= 108)	19.3 (n= 115)	-1.1
LIPSIA STEMI	142	18.5 (n= 67)	23.7 (n= 75)	-5.2

+ C-T Delto Infarct size indicates the unadjusted difference in 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 5 : Adjusted Hazard Ratio for Infarct Size Based (C-T) Treatment Effect on Outcomes

Outcome	HR (95% CI) ++	p-value	Raw outcome % (ratio)
Dataset 1			
Hospitalization for Heart Failure	**0.88 (95% CI 0.78 to 0.99)**	**0.0272**	**2.5% (58/ 2330)**
All-cause Mortality	1.03 (95% CI: 0.88 to 1.20)	0.6922	2.1% (49/2334)
All-cause Mortality (with AMIHOT2 data)	0.99 (95% CI 0.87 to 1.12)	0.8468	2.0% (52/ 2601)
Dataset 2			
Hospitalization for Heart Failure	**0.84 (95% CI 0.76 to 0.94)**	**0.0013**	**2.8% (67/ 2385)**
All-cause Mortality	1.00 (95% CI 0.90 to 1.12)	0.9355	4.4% (104/ 2389)
All-cause Mortality (with AMIHOT2 data)	0.98 (95% CI 0.90 to 1.08)	0.7476	4.2% (112/ 2661)

Covariates included age, gender, DM, prior MI, and NEW LM/3 vessel disease (yes/no) and the number of days elapsed between day of randomization and the day the imaging study used to measure MI size was performed.
++ Adjusted Hazard Ratio (HR) and p-value from Cox Proportional Hazard Models

Table 6: Sensitivity Analyses

	Primary Analysis Result	p-value	Days elapsed between day of randomization and the day the scan removed as covariate	p-value	MI added as Time dependent covariate (excludes data from IMMEDIATE TRIAL***)	p-value	Death analyzed as Competing risk	p-value
Dataset 1 *	HR (95% CI) ++		HR (95% CI) ++		HR (95% CI) ++		HR (95% CI) ++	
Heart Failure	0.88 (95% CI 0.78 to 0.99)	0.0272	0.88 (95% CI 0.79 to 0.99)	0.0275	0.89 (95% CI 0.79 to 1.00)	0.0568	0.88 (95% CI 0.80 to 0.97)	0.0104
All-cause Mortality	1.03 (95% CI: 0.88 to 1.20)	0.6922	1.04 (95% CI: 0.89 to 1.21)	0.6491	1.00 (95% CI 0.86 to 1.17)	0.9743		
All-cause Mortality (with AMIHOT2 data)	0.99 (95% CI 0.87 to 1.12)	0.8468	1.00 (95% CI 0.88 to 1.13)	0.9711	0.93 (95% CI 0.81 to 1.07)	0.2957		
Dataset 2 **								
Heart Failure	0.84 (95% CI 0.76 to 0.94)	0.0013	0.84 (95% CI 0.76 to 0.93)	0.0012	0.88 (95% CI 0.79 to 0.98)	0.0172	0.85 (95% CI 0.77 to 0.93)	0.0004
All-cause Mortality	1.00 (95% CI 0.90 to 1.12)	0.9355	1.02 (95% CI 0.91 to 1.13)	0.7654	1.05 (95% CI 0.92 to 1.19)	0.4925		
All-cause Mortality (with AMIHOT2 data)	0.98 (95% CI 0.90 to 1.08)	0.7476	1.01 (95% CI 0.92 to 1.10)	0.9051	1.06 (95% CI 0.94 to 1.19)	0.3783		

++ Hazard Ratio (95% confidence interval) , unless noted otherwise, adjusted for age, gender, DM, prior MI, and NEW LM/3 vessel disease (yes/no) and the number of days elapsed between day of randomization and the day the imaging study used to measure MI size was performed.
* Subset 1 includes all subjects with STEMI who had imaging done to measure infarct size and used in outcome analysis. The AMIHOT2 trial did not capture the HF outcome, and are included from the outcome analyses unless noted otherwise.
** Subset 2 includes Subset 1 subjects plus subjects that died before the imaging study was measured. For these subjects, the infarct size was imputed as the maximum infarct size measured in any subject from that the trial they were enrolled in. The elapsed time to when the infarct size was measures was imputed as the mean number of days until when the scan was done from the trial they were enrolled in.
*** 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.

Limitations

- Representativeness of these trials which were available to the investigative team
- Only involved STEMI, not all ACS
- Created a new variable to represent group-level effect on infarct size for individual patients, to allow assessment of influence of infarct size on individual outcomes, with adjustment for co-variates

Conclusion

This analysis, using patient-level data from 10 randomized controlled trials of treatment interventions for STEMI, suggests that therapeutic effect on infarct size, measured by noninvasive imaging, is related in direction and magnitude to the longer-term (one-year) therapeutic effect on hospitalization for heart failure. The data have implications for the potential to incorporate infarct size as part of a composite outcome in trials of new therapies for AMI.