Received: 26 September 2017 | Revised: 28 November 2017 | Accepted: 30 November 2017
DOI: 10.1111/joic.12485

WILEY Journal Of Interventional Cardiology

Effects of endovascular cooling on infarct size in ST-segment elevation myocardial infarction: A patient-level pooled analysis from randomized trials

Michael Dae MD[1] | William O'Neill MD[2] | Cindy Grines MD[3] | Simon Dixon MD[4] | David Erlinge MD, PhD[5] | Marko Noc MD, PhD[6] | Michael Holzer MD, PhD[7] | Anne Dee PhD[8]

[1] Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, California

[2] Division of Cardiology, Henry Ford Hospital/ Wayne State University, Detroit, Michigan

[3] Division of Cardiology, Northwell Health, Manhasset, New York

[4] Department of Cardiovascular Medicine, Beaumont Health, Royal Oak, Michigan

[5] Department of Cardiology, Lund University, Clinical Sciences, Skane University Hospital, Lund, Sweden

[6] Center for Intensive Internal Medicine, University Medical Center Ljubljana, Slovenia

[7] Department of Emergency Medicine, Medical University of Vienna, Vienna, Austria

[8] Clinical Affairs and Biostatistics, ZOLL Circulation, San Jose, California

Correspondence
Michael Dae, MD, Department of Radiology and Biomedical Imaging, University of California San Francisco, 185 Berry Street, Suite 350, San Francisco, CA 94107.
Email: michael.dae@ucsf.edu

Funding information
ZOLL Circulation

Objectives: This study sought to examine the relationship between temperature at reperfusion and infarct size.

Background: Hypothermia consistently reduces infarct size when administered prior to reperfusion in animal studies, however, clinical results have been inconsistent.

Methods: We performed a patient-level pooled analysis from six randomized control trials of endovascular cooling during primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI) in 629 patients in which infarct size was assessed within 1 month after randomization by either single-photon emission computed tomography (SPECT) or cardiac magnetic resonance imaging (cMR).

Results: In anterior infarct patients, after controlling for variability between studies, mean infarct size in controls was 21.3 (95%CI 17.4-25.3) and in patients with hypothermia <35°C it was 14.8 (95%CI 10.1-19.6), which was a statistically significant absolute reduction of 6.5%, or a 30% relative reduction in infarct size ($P = 0.03$). There was no significant difference in infarct size in anterior ≥35°C, or inferior infarct patients. There was no difference in the incidence of death, ventricular arrhythmias, or re-infarction due to stent thrombosis between hypothermia and control patients.

Conclusions: The present study, drawn from a patient-level pooled analysis of six randomized trials of endovascular cooling during primary PCI in STEMI, showed a significant reduction in infarct size in patients with anterior STEMI who were cooled to <35°C at the time of reperfusion. The results support the need for trials in patients with anterior STEMI using more powerful cooling devices to optimize the delivery of hypothermia prior to reperfusion.

KEYWORDS
hypothermia, infarct size, STEMI

1 | INTRODUCTION

Prompt reperfusion remains the most effective treatment to date for preservation of myocardium following acute coronary occlusion. However, large infarctions still occur despite timely reperfusion, due to reperfusion injury.[1] Numerous treatments have been studied to reduce reperfusion injury, with little success to date.[2] Hypothermia has shown the ability to consistently reduce infarct size when administered prior to reperfusion in preclinical studies.[3–6] Results from clinical trials, however, have been inconsistent.[7–11] One major difference between preclinical and clinical trials is the lack of achievement of an effective degree of cooling prior to reperfusion in patients, as occurred in experimental studies.[12] In the clinical trials to date, a suggestion has been made that patients that achieved a core body temperature less than 35°C prior to reperfusion showed smaller infarcts, at least in those with anterior infarction.[8] However, sample sizes were not sufficient to confirm these findings in individual clinical studies. We therefore performed a patient-level pooled analysis from six randomized trials of endovascular cooling during primary PCI for STEMI in 629 patients, to examine the relationship between temperature at reperfusion and infarct size.

2 | METHODS

2.1 | Study population

This study is a patient-level pooled analysis of six hypothermia trials using endovascular cooling in which infarct size (IS) was assessed by either cardiac magnetic resonance (cMR) or technetium (Tc)-99m sestamibi single-photon emission computed tomography (SPECT) within 1 month after reperfusion at a core laboratory. Adverse events were followed through 30 days.

2.2 | Studies and characteristics

The randomized trials included in the pooled analysis were: COOL MI Pilot,[8] in which patients presenting with anterior or inferior STEMI within 6 h of symptom onset were randomized to primary PCI and cooling to a target temperature of 33°C using an endovascular cooling catheter (Radiant Medical Inc., Redwood City, CA) versus PCI alone. Target temperature was maintained for 3 h post PCI; COOL-MI Pivotal,[7] in which patients presenting with anterior or inferior STEMI within 6 h of symptom onset were randomized to primary PCI and cooling to a target temperature of 33°C using an endovascular cooling catheter (Radiant Medical Inc.) versus PCI alone. Target temperature was maintained for 3 h post PCI; COOL MI II, in which patients presenting with anterior STEMI within 6 h of symptom onset were randomized to primary PCI and cooling to a target temperature of 32°C using an endovascular cooling catheter (Radiant Medical Inc.) versus PCI alone. Target temperature was maintained for 3 h post PCI; ICE-IT,[9] in which patients presenting with anterior or inferior STEMI within 6 h of symptom onset were randomized to primary PCI and cooling to a target temperature of 33°C using an endovascular cooling catheter (Innercool Therapies Inc., San Diego, CA) versus PCI alone. Target temperature was maintained for 6 h post PCI; RAPID MI-ICE,[10] in which patients presenting with anterior or inferior STEMI within 6 h of symptom onset were randomized to primary PCI and cooling to a target temperature of 33°C using an endovascular cooling catheter (Innercool Therapies Inc.) and cold saline infusion versus PCI alone. Target temperature was maintained for 3 h post PCI; and CHILL-MI,[11] in which patients presenting with anterior or inferior STEMI within 6 h of symptom onset were randomized to primary PCI and cooling to a target temperature of 33°C using an endovascular cooling catheter (Innercool Therapies Inc.) and cold saline infusion versus PCI alone. Target temperature was maintained for 1 h post PCI.

Data was available for each individual patient included. The data analysis included the patients with available infarct size and temperature at PCI for cooled patients, and excluded patients with prior-MI. In order to more precisely estimate the effect of hypothermia on infarct size, only patients that received cooling (per-protocol patients) were included. This analysis further refined the assessment of hypothermia trials by categorizing hypothermia patients using temperature at PCI (<35°C and ≥35°) for assessment of hypothermia and infarct size.

2.3 | Statistical analyses

For descriptive analyses, values are presented as mean and standard deviation or median and 25th and 75th quartile depending on a test of normality. Comparison of categorical variables were done with chi-square tests or Fisher's exact tests if number of patients were fewer than five. Continuous variables were compared with ANOVA or the Wilcoxon rank sum test after examining for normality. Relationship between infarct size and hypothermia was assessed through generalized linear models for infarct size that include the group term (Control, <35°C, ≥35°C) as fixed effect and study (RAPID-MI-ICE, CHILL-MI, COOL MI Pilot, COOL MI I, COOL MI II, ICE-IT) as a random effect to account for potential heterogeneity across studies. Unadjusted and adjusted means were calculated. Dunnett-Shu post-hoc test was conducted for multiple comparisons comparing Control with <35°C or Control with ≥35°C. No transformation or imputation was made for infarct size. A sensitivity analysis was conducted using temperature cutoffs at 34.5°C and 34.0°C for hypothermia patients with anterior infarcts.

Separate multivariable models were fitted to evaluate the potential effects of door to balloon time (<90 min, ≥90 min), ischemic time (<4 h, ≥4 h), age (<65 years, ≥65 years), weight status (<25 BMI, ≥25 BMI) as fixed effects on relationship between infarct size and group term using Type III tests. Effect modifications were considered by adding a multiplicative interaction term between group term and the modification factor. Subgroup analyses door to balloon time (<90 min, ≥90 min), ischemic time (<4 h, ≥4 h), age (<65 years, ≥65 years), weight status (<25 BMI, ≥25 BMI), smoking (current smoker vs), TIMI flow pre (0.1 vs 2.3) were conducted by using subsets of the data. All statistical analyses were two-sided with $P<0.05$ considered statistically significant and conducted using SAS 9.3 (SAS Institute, North Carolina).

3 | RESULTS

Description of the trials is presented in Table 1. Slightly less than half of the patients included in this analysis presented with anterior infarcts. Of the patients in the control group, 45% had anterior infarcts, of the hypothermia <35°C group 44%, and of the hypothermia ≥35°C group, 44%. The baseline demographic and clinical characteristics for patients with both anterior and inferior infarcts are presented in Table 2. The majority of the patient population were male, older (>65 years old), had a history of hypertension, and about half were smokers. In the hypothermia ≥35°C patients, history of diabetes was more prevalent ($P = 0.03$), and there was a higher proportion of current smokers ($P = 0.03$). The same pattern of distribution was found in anterior only and inferior only patients (data not shown).

Figures 1–3 present the distribution of infarct size by infarct location. Mean and median infarct sizes were smaller for patients in the hypothermia <35°C group, in combined anterior and inferior, and anterior infarct patients, but not in patients with inferior infarcts. In combined anterior and inferior patients, mean infarct size was 14.4 (SD 14.9) in Controls, 13.8 (SD 14.1) in hypothermia ≥35°C, and 12.3 (SD 12.3) in hypothermia <35°C (Figure 1). In anterior patients, the same pattern exists, where mean infarct size was 21.0 (SD 16.9) in Controls, 19.6 (SD 16.7) in hypothermia ≥35°C, and 15.3 (SD 15.2) in hypothermia (<35°C) (Figure 2). Furthermore, there was a statistically significant absolute difference of 5.77% (27% relative reduction) in anterior infarct size between Control and patients who had a body temperature below 35°C at time of PCI in a simple comparison that excluded patients who did not reach 35°C ($P = 0.02$). Among inferior infarct patients, there was no significant difference between any of the three groups (Figure 3).

Table 3 presents the unadjusted mean (arithmetic mean) and the adjusted mean of infarct size for anterior, inferior, and all patients (combined anterior and inferior) by group (Control, ≥35°C, <35°C) after controlling for variability across the trials and multiple comparisons. The results reflect a consistent pattern in all patients and anterior patients, where mean infarct size of control was higher than for hypothermia patients, and those patients who reached a body temperature of <35°C at time of PCI had a smaller adjusted mean infarct size than hypothermia patients who had a temperature of ≥35°C at time of PCI. Among all patients, infarct size was different by group ($P = 0.047$) after accounting for study heterogeneity; specifically, there was a statistically significant relative reduction of 20% (absolute adjusted mean infarct size of 15.7% vs 12.5%) between Control and Hypothermia <35°C. Among anterior patients, the relationship was even stronger. There was a marginal to significant association between group and infarct size in both unadjusted and adjusted models ($P = 0.058$, $P = 0.030$, respectively). In addition to a statistically significant relative reduction of 27% observed in

TABLE 1 Study descriptions of study population

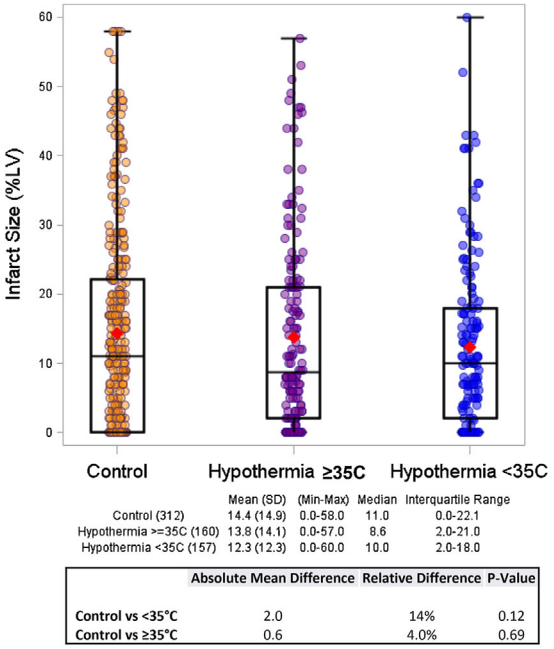
				Infarct size location		
Study	**Infarct size assessment**			**Inferior *N* (%)**	**Anterior *N* (%)**	**All (*N* %)**
ALL		*N* (%)	Control	171 (54.81)	141 (45.19)	312 (49.6)
		N (%)	Hypothermia ≥ 35°C	90 (56.25)	70 (43.75)	160 (25.4)
		N (%)	Hypothermia < 35°C	88 (56.05)	69 (43.95)	157 (25.0)
COOL-MI Pilot (2001)	SPECT at 30 days	*N* (%)	Control	9 (52.94)	8 (47.06)	17 (51.52)
		N (%)	Hypothermia ≥ 35°C	4 (50)	4 (50)	8 (24.24)
		N (%)	Hypothermia < 35°C	4 (50)	4 (50)	8 (24.24)
COOL-MI 1 (2003)	SPECT at 30 days	*N* (%)	Control	76 (56.3)	59 (43.7)	135 (50.19)
		N (%)	Hypothermia ≥ 35°C	43 (53.09)	38 (46.91)	81 (30.11)
		N (%)	Hypothermia < 35°C	37 (69.81)	16 (30.19)	53 (19.7)
ICE-IT (2004)	SPECT at 30 days	*N* (%)	Control	58 (60.42)	38 (39.58)	96 (52.46)
		N (%)	Hypothermia ≥ 35°C	34 (62.96)	20 (37.04)	54 (29.51)
		N (%)	Hypothermia < 35°C	19 (57.58)	14 (42.42)	33 (18.03)
COOL-MI 2 (2006)	SPECT at 30 days	*N* (%)	Control	0 (0)	8 (100)	8 (26.67)
		N (%)	Hypothermia ≥ 35°C	0 (0)	20 (100)	2 (6.67)
		N (%)	Hypothermia < 35°C	0 (0)	2 (100)	20 (66.67)
RAPID-MI-ICE (2009)	CMR at 4 ± 2 days	*N* (%)	Control	2 (22.22)	7 (77.78)	9 (50)
		N (%)	Hypothermia ≥ 35°C	0 (0)	1 (100)	1 (5.56)
		N (%)	Hypothermia < 35°C	3 (37.5)	5 (62.5)	8 (44.44)
CHILL-MI (2013)	CMR at 4 ± 2 days	*N* (%)	Control	26 (55.32)	21 (44.68)	47 (48.96)
		N (%)	Hypothermia ≥ 35°C	9 (64.29)	5 (35.71)	14 (14.58)
		N (%)	Hypothermia < 35°C	25 (71.43)	10 (28.57)	35 (36.46)

TABLE 2 Baseline and clinical characteristics of anterior and inferior STEMI patients

			Control N = 312	Hypothermia ≥35°C N = 160	Hypothermia <35°C N = 157	P-val*
Gender	N (%)	Female	69 (22.12)	29 (18.13)	38 (24.2)	0.403
	N (%)	Male	243 (77.88)	131 (81.88)	119 (75.8)	
>65 years old	N (%)	No	226 (72.44)	123 (76.88)	116 (73.89)	0.582
	N (%)	Yes	86 (27.56)	37 (23.13)	41 (26.11)	
Diabetes mellitus	N (%)	No	272 (87.74)	127 (79.38)	138 (87.9)	0.032
	N (%)	Yes	38 (12.26)	33 (20.63)	19 (12.1)	
Hypertension	N (%)	No	189 (60.77)	96 (60)	84 (53.5)	0.3
	N (%)	Yes	122 (39.23)	64 (40)	73 (46.5)	
Current smoker	N (%)	No	100 (41.32)	42 (36.21)	65 (52.85)	0.026
	N (%)	Yes	142 (58.68)	74 (63.79)	58 (47.15)	
Prior stroke or transient ischemic attack	N (%)	No	307 (98.4)	156 (97.5)	154 (98.09)	0.808
	N (%)	Yes	5 (1.6)	4 (2.5)	3 (1.91)	
TIMI Flow Grade—prior to PCI 0 or 1	N (%)	No	76 (24.6)	41 (25.63)	42 (28)	0.736
	N (%)	Yes	233 (75.4)	119 (74.38)	108 (72)	
TIMI Flow grade—post pci	N (%)	0	1 (0.3)	2 (1.2)	0 (0)	0.389
	N (%)	1	0 (0)	1 (0.6)	0 (0)	
	N (%)	2	17 (5.5)	10 (6.3)	7 (4.5)	
	N (%)	3	291 (93.3)	146 (91.3)	144 (91.7)	
Door to balloon >90 min	N (%)	No	182 (61.07)	81 (50.63)	89 (57.42)	0.098
	N (%)	Yes	116 (38.93)	79 (49.38)	66 (42.58)	
Ischemic time >4 h	N (%)	No	199 (66.78)	92 (57.5)	103 (66.03)	0.122
	N (%)	Yes	99 (33.22)	68 (42.5)	53 (33.97)	
Height (cm)[a]	Mean (SD)		173.0 (9.3)	174.51	173.9 (9.6)	0.28
Weight (kg)[b]	Mean (SD)		85.57 (15.8)	87.47 (17.3)	86.47 (16.2)	0.488
BMI[c]	Mean (SD)		28.42 (4.3)	28.58 (4.7)	28.42 (5.1)	0.932
Onset to ER (min)[d]	Mean (SD)		130.62 (90.3)	143.17 (97.7)	120.57 (77.2)	0.079
Cooling time (min)[e]	Mean (SD)			14 (17.0)	26.2 (14.9)	
Temperature at start of cooling (degrees C)	Mean (SD)			36.27 (0.5)	35.77 (0.8)	
Temperature at first balloon (degrees C)	Mean (SD)			35.27 (3.4)	34.04 (0.6)	

*The parametric *P*-value is calculated by ANOVA for numerical covariates and chi-square test for categorical covariates.
[a]Data unavailable from 17 patients in Control, 8 patients in Hypothermia <35°C, 19 patients in Hypothermia >35°C.
[b]Data unavailable from 5 patients in Control, 1 patient in Hypothermia <35°C, 2 patients in Hypothermia >35°C.
[c]Data unavailable from 17 patients in Control, 8 patients in Hypothermia <35°C, 19 patients in Hypothermia >35°C.
[d]Data unavailable from 1 patient in Control, 1 patient in Hypothermia <35°C.
[e]Cooling time prior to PCI. Data unavailable from 1 patient in Hypothermia <35°C, 1 patient in Hypothermia >35°C.

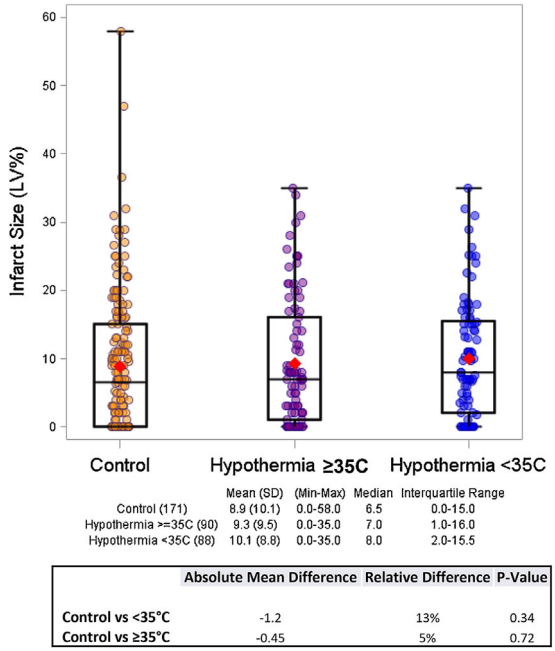
unadjusted mean after controlling for multiple comparison, the adjusted mean in controls was 21.3 (95%CI 17.4-25.3) and patients with Hypothermia <35°C it was 14.8 (95%CI 10.1-19.6), which was an absolute reduction of 6.5%, or a 30% relative reduction in adjusted mean infarct size ($P < 0.05$) controlled for multiple comparison using all data (Table 3). Other models examined showed that additional covariates did not significantly effect relationship for infarct size and group (data not shown). Sensitivity analyses using lower temperature cutoffs for hypothermia groups (<34.5°C or <34°C) in anterior infarcts showed the same pattern of reduction of infarct size with smaller adjusted mean infarct size in the lower temperature group compared to controls (Supplemental Figure S1).



	Mean (SD)	(Min-Max)	Median	Interquartile Range
Control (312)	14.4 (14.9)	0.0-58.0	11.0	0.0-22.1
Hypothermia >=35C (160)	13.8 (14.1)	0.0-57.0	8.6	2.0-21.0
Hypothermia <35C (157)	12.3 (12.3)	0.0-60.0	10.0	2.0-18.0

	Absolute Mean Difference	Relative Difference	P-Value
Control vs <35°C	2.0	14%	0.12
Control vs ≥35°C	0.6	4.0%	0.69

FIGURE 1 Distribution of infarct size by group in all anterior and inferior patients. (Highest and lowest values are represented at the ends; lines represent quartiles and median; mean is the red diamond)

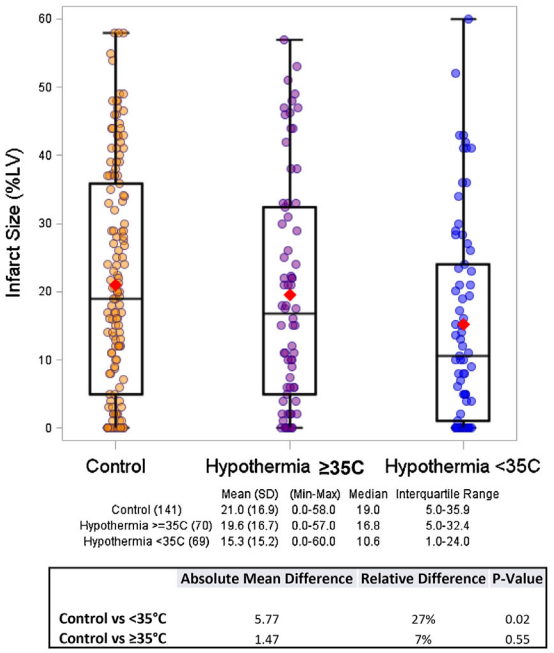


	Mean (SD)	(Min-Max)	Median	Interquartile Range
Control (171)	8.9 (10.1)	0.0-58.0	6.5	0.0-15.0
Hypothermia >=35C (90)	9.3 (9.5)	0.0-35.0	7.0	1.0-16.0
Hypothermia <35C (88)	10.1 (8.8)	0.0-35.0	8.0	2.0-15.5

	Absolute Mean Difference	Relative Difference	P-Value
Control vs <35°C	-1.2	13%	0.34
Control vs ≥35°C	-0.45	5%	0.72

FIGURE 3 Distribution of infarct size by group in inferior patients. (Highest and lowest values are represented at the ends; lines represent quartiles and median; mean is the red diamond)

Table 4 presents interaction analyses that examine effect modification by weight, ischemic time, door to balloon time, and pre-TIMI flow using adjusted means among patients with anterior infarcts with study as a random effect. Overall, we found no effect modification in the factors examined. There was a consistent pattern where adjusted mean of infarct size was smaller in patients reaching <35°C than in Controls or patients who had a higher temperature at time of PCI (Table 4).



	Mean (SD)	(Min-Max)	Median	Interquartile Range
Control (141)	21.0 (16.9)	0.0-58.0	19.0	5.0-35.9
Hypothermia >=35C (70)	19.6 (16.7)	0.0-57.0	16.8	5.0-32.4
Hypothermia <35C (69)	15.3 (15.2)	0.0-60.0	10.6	1.0-24.0

	Absolute Mean Difference	Relative Difference	P-Value
Control vs <35°C	5.77	27%	0.02
Control vs ≥35°C	1.47	7%	0.55

FIGURE 2 Distribution of infarct size by group in anterior patients. (Highest and lowest values are represented at the ends; lines represent quartiles and median; mean is the red diamond)

Incidence of adverse events in Control versus Hypothermia patients for all patients is reported in Table 5. There were no statistically significant differences between Control and Hypothermia patients for death ($P = 0.46$), re-infarction ($P = 1.00$), heart failure/pulmonary edema ($P = 0.72$), ventricular tachycardia ($P = 0.67$), brady-arrhythmias ($P = 0.92$), or bleeding ($P = 0.59$) (Table 5).

4 | DISCUSSION

The present study, drawn from a patient-level pooled analysis of six randomized trials of endovascular cooling during primary PCI in STEMI, showed a significant reduction in infarct size in patients with anterior STEMI who were cooled to <35°C at the time of reperfusion. After controlling for variability between studies, there was a clinically and statistically significant absolute reduction of 6.5%, or a 30% relative reduction in infarct size compared to Controls. The relationship between hypothermia group and infarct size was not modified by weight status, ischemic time, door to balloon time, or pre-TIMI flow. These variables were thought pertinent to the outcomes of the study. The ability of endovascular catheters to achieve sufficient cooling may be affected by weight status. Ischemic time and door to balloon time, particularly with significant delays due to the cooling procedure, may affect the results. The mean difference in door to balloon time between controls and hypothermia patients was 6 min (control—

TABLE 3 Unadjusted and adjusted mean* (95%CI) of Infarct Size

Model	Control mean (95%CI)	Hypothermia ≥35°C mean (95%CI)	Hypothermia <35°C mean (95%CI)	*P*-val
All				
Unadjusted	14.4 (12.8-15.9)	13.8 (11.6-16.0)	12.3 (10.1-14.6)	0.343
Adjusted*	15.7 (11.8-19.7)	15.7 (11.4–20.0)	12.5 (8.3-16.6)**	0.047
Anterior				
Unadjusted	21.0 (18.3-23.8)	19.6 (15.7-23.4)	15.3 (11.4-19.2)**	0.058
Adjusted*	21.3 (17.4-25.3)	20.4 (15.4-25.3)	14.8 (10.1-19.6)**	0.030
Inferior				
Unadjusted	8.9 (7.4-10.3)	9.3 (7.3-11.3)	10.1 (8.0-12.1)	0.634
Adjusted*	9.4 (6.2-12.5)	10.1 (6.6-13.5)	9.8 (6.4-13.2)	0.833

*Adjusted by random effect of study.
**$P < 0.05$ compared to Control after post-hoc adjustment (Dunnett-Hsu).

86 ± 60 min vs hypothermia—92 ± 49 min, $P = 0.20$). Pre-TIMI flow allows the assessment of treatment response in patients with persistent occlusion versus spontaneous reperfusion prior to PCI. The presence of collateral flow and cumulative disease burden may also influence outcomes, however, this data was not available for consideration. There was no difference in deaths, ventricular arrhythmias, or re-infarction due to stent thrombosis between hypothermia and control patients

Numerous strategies to reduce reperfusion injury have been unsuccessful to date.[2,13] Hypothermia has been shown to be an effective therapy to help prevent reperfusion injury in preclinical studies when administered prior to reperfusion, regardless of the species tested.[3–6] This has led to the assessment of hypothermia in clinical trials as a means to reduce reperfusion injury in patients. Challenges to overcome for inducing hypothermia in STEMI patients included the ability to control shivering in awake patients,[14] and developing a means to rapidly reduce core body temperature in the much larger thermal mass in patients compared to most experimental models. The clinical studies included in this pooled analysis used endovascular cooling to lower core body temperature, and all were successful in controlling shivering using a combination of oral buspirone, intravenous meperidine, and surface warming. The results of these trials were mixed, and not as successful as was found in experimental studies. In all of the clinical trials, there was no significant difference in infarct size between hypothermia patients and controls. Post-hoc analysis of one of the early endovascular cooling trials (COOL-MI) suggested that patients with anterior STEMI who were cooled to less than 35°C prior to reperfusion showed smaller infarct size relative to controls, implying a dose response relationship.[7] Preclinical studies have also reported a dose response whereby moderate (32°C) therapeutic hypothermia showed a strong dose-dependent infarct size reduction and favorable hemodynamic outcomes versus mild (35°C) hypothermia.[15] Our results support the suggestion that patients with anterior STEMI who were cooled to less than 35°C prior to reperfusion (mean temperature at PCI was 34°C) had significantly smaller infarcts compared to controls, and to patients

TABLE 4 Adjusted mean (95%CI) of infarct size in subgroups* in anterior STEMI patients

	Control	Hypothermia ≥35°C	Hypothermia <35°C	Interaction *P*-val*
Weight				0.59
BMI ≤ 25 ($n = 63$)	21.8 (14.3-29.4)	25.2 (16.1-34.3)	13.3 (4.0-22.6)	
BMI >25 ($n = 203$)	21.4 (18.2-24.5)	19.2 (14.5-24.0)	15.6 (10.9-20.3)	
Ischemic Time				0.86
≤4 h ($n = 174$)	19.9 (15.7-24.2)	18.4 (12.8-24.0)	13.7 (8.6-18.8)	
>4 h (97)	22.3 (15.6-29.0)	22.2 (14.5-30.0)	18.7 (10.5-26.9)	
Door to balloon time				0.86
≤90 min ($n = 149$)	21.4 (17.2-25.7)	19.9 (13.9-25.9)	14.9 (9.3-20.5)	
>90 min ($n = 121$)	19.4 (12.5-26.2)	20.1 (12.5-27.6)	14.9 (7.3-22.5)	
Pre-TIMI flow				0.61
Pre-TIMI flow 0 or 1 ($n = 196$)	24.0 (20.8-27.1)	21.4 (16.7-26.1)	19.4 (14.2-24.6)	
Pre-TIMI flow 2 or 3 ($n = 76$)	12.7 (6.1-19.3)	15.6 (8.3-23.0)	7.8 (0.7-14.9)	

*Models are adjusted by random effect of study; interaction term consists of stratification factor and hypothermia treatment

TABLE 5 Incidence of adverse events

	Control		Hypothermia		
	(Events/Total)	Incidence	(Events/Total)	Incidence	*P*-value*
Deaths	11/351	0.03	17/381	0.04	0.46
Re-infarction	3/249	0.01	3/279	0.01	1.00
Heart failure/pulmonary edema	16/279	0.06	21/309	0.07	0.72
Ventricular tachycardia	46/279	0.16	46/309	0.15	0.67
Brady-arrythmias	46/270	0.17	51/301	0.17	0.92
Bleeding	29/267	0.11	38/300	0.13	0.59

*Chi-square or Fisher's exact test.

who were cooled to a temperature ≥ 35°C prior to reperfusion (mean temperature 35.2°C). This relationship between lower temperature at PCI and smaller infarct size was consistent and not affected by ischemic time, door to balloon time, or pre-TIMI flow.

Hypothermia influences numerous mechanisms leading to cell protection during ischemia and reperfusion,[12] and has the unique advantage of delivery to the ischemic bed in the absence of antegrade flow, prior to reperfusion, due to conduction cooling from the blood pool to the myocardium.[3] In contrast, pharmaceutical agents can only reach the ischemic territory after reperfusion, or potentially via collateral blood flow. Preclinical studies have shown that induction of cooling after reperfusion fails to reduce infarct size.[16]

There were no major safety issues with hypothermia compared to the normothermia control patients. There was no difference in deaths, ventricular arrhythmias, or re-infarction due to stent thrombosis. The 6.5% absolute infarct size reduction in patients with anterior STEMI, if reproduced in future adequately powered clinical trials will likely result in significant improvement in clinical outcome. Stone et al, in a recent pooled analysis of infarct size and clinical outcomes showed that for every 5% decrease in absolute infarct size, there is a 20% reduction in risk of hospitalization for heart failure or mortality.[17]

The results in this study reinforce the value of achieving sufficient cooling prior to reperfusion, and support efforts to improve the technology to cool faster and more effectively. To this end, the recently reported COOL AMI EU pilot study, which used a more powerful cooling system in patients with anterior STEMI, showed an absolute 7% (relative 30%) decrease in infarct size in the per protocol population, warranting the value in performing a fully powered randomized control trial to confirm this signal.[18]

4.1 | Strengths and limitations

All of the studies used endovascular catheter cooling in the inferior vena cava, and a similar strategy for controlling shivering. As opposed to the use of a meta-analysis of aggregate data from published studies, raw patient-level data was available from all of the clinical trials included. Infarct size was measured by cMR and SPECT imaging in core laboratories that were blinded to randomization assignment. Differences in methodology between SPECT and cMR may introduce variability in the results. Despite the fact that cMR has higher spatial resolution than SPECT, and is more sensitive in detecting small regions of subendocardial infarction, prior studies have shown fairly comparable infarct size results between the two modalities.[19,20] Lund et al[19] compared infarct size measurements with cMR and SPECT in 60 consecutive patients at 6 ± 3 days post intervention for STEMI. Mean infarct size was not significantly different between cMR and SPECT (20.7 ± 11.5% vs 19.4 ± 14.3%, $P = 0.26$). Hadamitzky et al[20] evaluated 281 patients with STEMI using cMR and SPECT a median of 4.9 and 4.3 days after primary PCI. The difference between cMR and SPECT (13.9 ± 11.5% vs 15.1 ± 17.2%, $P = 0.35$) was not significant when using a quantitative threshold for infarction of four standard deviations above remote myocardium for cMR, while the Pearson's correlation coefficient r was 0.75. Further, infarct size measurements from 4 days to 30 days post MI may introduce variability. A recent report of a pooled analysis of infarct size by cMR (1889 patients) and SPECT (743 patients), concluded that infarct size measured by cMR or SPECT within 1 month after primary PCI is strongly associated with all-cause mortality and hospitalization for heart failure within 1 year.[17] In this pooled analysis, however, a significant reduction of infarct size in patients cooled to <35°C persisted in spite of variability in the imaging methodology.

The results were most positive in the anterior STEMI population. Anterior infarcts are larger, and likely provide greater accuracy for detecting changes due to treatment when measured by imaging methodology such as SPECT or cMR.[21] Further, patients presenting with anterior infarction carry the highest mortality risk, risk for heart failure post infarction, and are in the greatest need for timely reperfusion and adjunctive cardioprotection against reperfusion injury.[22] Overall, the results support the need for larger RCTs in patients with anterior STEMI using more powerful cooling devices to optimize the ability of hypothermia to reduce infarct size.

ACKNOWLEDGMENTS

This study was funded in part by ZOLL Circulation.

DISCLOSURE STATEMENT

Dr. Dae serves as Medical Director for ZOLL Circulation. Anne Dee serves as Senior Biostatistician for ZOLL Circulation. Drs. Noc, and Holzer, and

Erlinge are members of a clinical advisory board for ZOLL Circulation. Drs. O'Neill, Dixon, and Grines, report no financial disclosures.

REFERENCES

1. Yellon DM, Hausenloy DJ. Myocardial reperfusion injury. *N Eng J Med*. 2007;357:1121–1135.
2. Hausenloy DJ, Botker HE, Engstrom T, et al. Targeting reperfusion injury in patients with ST-segment elevation myocardial infarction: trials and triblations. *Eur Heart J*. 2017;38:935–941.
3. Dae MW, Gao DW, Sessler DI, Chair K, Stillson CA. Effect of endovascular cooling on myocardial temperature, infarct size, and cardiac output in human-sized pigs. *Am J Physiol Heart Circ Physiol*. 2002;282:H1584–H1591.
4. Hale SL, Dave RH, Kloner RA. Regional hypothermia reduces myocardial necrosis even when instituted after the onset of ischemia. *Basic Res Cardiol*. 1997;92:351–357.
5. Miki T, Liu T, Cohen M, Downey J. Mild hypothermia reduces infarct size in the beating rabbit heart. *Basic Res Cardiol*. 1998;93:372–383.
6. Götberg M, Olivecrona GK, Engblom H, et al. Rapid short-duration hypothermia with cold saline and endovascular cooling before reperfusion reduces microvascular obstruction and myocardial infarct size. *BMC Cardiovasc Disord*. 2008;8:7.
7. O'Neil W. A prospective randomized trial of mild systemic hypothermia during PCI treatment of ST elevation MI; the COOL MI trial. Presented at: 15th Annual Transcatheter Cardiovascular Therapeutics; 16 September 2003; Washington DC, USA.
8. Dixon SR, Whitbourn RJ, Dae MW, et al. Induction of mild systemic hypothermia with endovascular cooling during primary percutaneous coronary intervention for acute myocardial infarction. *J Am Coll Cardiol*. 2001;40:1928–1934.
9. Grines C. Intravascular cooling adjuctive to percutaneous coronary intervention for acute myocardial infarction; The ICE-IT trial. Presented at: 16th Annual Transcatheter Cardiovascular Therapeutics; 27 October 2004; Washington DC, USA.
10. Götberg M, Olivecrona GK, Koul S, et al. A pilot study of rapid cooling by cold saline and endovascular cooling before reperfusion in patients with ST-elevatin myocardial infarction. *Circ Cardiovasc Interv*. 2010;3:400–407.
11. Erlinge D, Götberg M, Noc M, et al. Rapid endovascular catheter core cooling combined with cold saline as an adjunct to percutaneous coronary intervention for the treatment of acute myocardial infarction. The CHILL-MI trial. *J Am Coll Cardiol*. 2014;63:1957–1965.
12. Dae M. Hypothermia and percutaneous coronary intervention during acute myocardial infarction. *Interv Cardiol*. 2012;4:235–243.
13. Haunseloy DJ, Yellon DM. Myocardial ischemia-reperfusion injury: a neglected therapeutic target. *J Clin Invest*. 2013;123:92–100.
14. Mokhtarani M, Mahgoub AN, Morioka N, et al. Buspirone and meperidine synergistically reduce the shivering threshold. *Anest Analg*. 2001;93:1233–1239.
15. Dash R, Mitsutake Y, Pyun W, et al. Dose-dependent cardioprotection of moderate (32°C) versus mild (35°C) therapeutic hypothermia in a porcine acute ischemia-reperfusion injury model. *JACC Cardiovasc Interv*. in press.
16. Maeng M, Mortensen U, Kristensen J, Kristiansen SB, Andersen HR. Hypothermia during reperfusion does not reduce myocardial infarct size in pigs. *Basic Res Cardiol*. 2006;101:61–68.
17. Stone GW, Selker HP, Thiele H, et al. Relationship between infarct size and outcomes following primary PCI: Patient-level analysis from 10 randomized trials. *J Am Coll Cardiol*. 2016;67:1674–1683.
18. Noc M, Erlinge D, Neskovic A, et al. COOL AMI EU pilot trial: a multicenter, prospective, randomized controlled trial to assess cooling as an adjunctive therapy to percutaneous intervention in patients with acute myocardial infarction. *EuroIntervention*. 2017;13:e531–e539.
19. Lund GK, Stork A, Saeed M, et al. Acute myocardial infarction: evaluation with first-pass enhancement and delayed enhacement MR imaging compared with ^{201}Tl SPECT imaging. *Radiology*. 2004;232:49–57.
20. Hadamitzky M, Langhans B, Hausleiter J, et al. Prognostic value of late gadolinium enhancement in cardiovascular magnetic resonance imaging after acute ST-elevation myocardial infarction in comparison with single-photon emission tomography using Tc99m-Sestamibi. *Eur Heart J Cardiovasc Imaging*. 2014;15:216–225.
21. Gibbons R, Araoz P. Does infarct size matter? *J Am Coll Cardiol*. 2016;67:1684–1686.
22. Heusch G. Critical issues for the translation of cardioprotection. *Circ Res*. 2017;120:1477–1486.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Dae M, O'Neill W, Grines C, et al. Effects of endovascular cooling on infarct size in ST-segment elevation myocardial infarction: A patient-level pooled analysis from randomized trials. *J Interven Cardiol*. 2018;31:269–276. https://doi.org/10.1111/joic.12485