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In an era of rapid ST elevation Myocardial Infarction reperfusion with Primary Percutaneous Coronary Intervention is there a role for adjunct therapeutic hypothermia? A structured literature review

Abstract

Mild hypothermia has been shown to improve neurological outcome and reduce mortality following out of hospital cardiac arrest. In animal models the application of hypothermia with induced coronary occlusion has demonstrated a reduction in infarct size. Consequently, hypothermia has been proposed as a treatment, in addition to Primary Percutaneous Coronary Intervention (PPCI) for ST segment elevation myocardial infarction (STEMI). However, there is incomplete understanding of the mechanism and magnitude of the protective effect of hypothermia on the myocardium, and limited outcomes data. We undertook a structured literature review of therapeutic hypothermia as adjuvant to PPCI for acute STEMI. We examined the feasibility, safety, impact on infarct size and the resultant effect on major adverse cardiac events and mortality. There were12 studies between 1946-2016. With the exception of one study, therapeutic hypothermia for STEMI was reported to be feasible and safe, and its only demonstrable benefit was a modest reduction in post-infarct heart failure events. Evidence to date, however, is from small clinical trials and in an era of low early mortality following PPCI for STEMI, demonstrating a mortality benefit will be challenging. When post-myocardial

infarction left ventricular dysfunction is more frequent, alternative clinical outcomes warrants further investigation.

Introduction

Coronary heart disease (CHD) is the leading cause of mortality in Europe accounting for 1.8 million deaths annually [1]. The incidence of ST elevation myocardial infarction (STEMI) across Europe is estimated to be 44 –142 per 100,000 population with in-hospital mortality rates estimated to be 6-14% [2], [3]. Contemporary STEMI management consists of evidence-based and guideline-indicated therapies including timely reperfusion with primary percutaneous coronary intervention (PPCI). PPCI limits myocardial necrosis, reduces infarct size and improves short and long term prognosis [4]–[6]. Infarct size or degree of left ventricular dysfunction is an important determinant of long-term outcomes following STEMI and has provided the basis for the development of PPCI services globally including projects such as the Stent for Life initiative [7], [8]. Even so, there is a high incidence of post-myocardial infarction left ventricular dysfunction with outcomes such as heart failure and 30-day re-hospitalization remaining prevalent and leading to an expanding populace of chronic heart failure [9]–[13]. The desire to reduce the economic, social and personal cost of ischemic cardiomyopathy has stimulated research interest into early interventions that may prevent downstream heart failure.

Therapeutic Hypothermia and reperfusion injury

Therapeutic hypothermia (TH) can be defined as the process of actively lowering core body temperature in order to decrease end organ injury. TH reduces the risk of death and improves long-term neurological outcome in

patients who suffer out of hospital cardiac arrest (OHCA) and is recommended in national and international guidelines [5], [6], [14]–[18].

Numerous short and long term studies have demonstrated the net beneficial effect of timely PPCI for STEMI, however, the reperfusion process itself can mediate myocardial damage by means of reperfusion injury [19]–[21]. Reperfusion injury is the damage to tissue sustained with restoration of the blood supply after a period of ischaemia. Animal studies have suggested that reperfusion injury can lead to myocardial cell death and increase subsequent infarct size which may account for up to 50% of the total myocardial injury [20].

Porcine and lapine models have suggested that core body temperature is a key determinant of the extent of myocardial necrosis following acute coronary occlusion with subsequent reperfusion [22] and have demonstrated that controlled hypothermia reduces infarct size [23]. The mechanisms of this are unclear and far from complete and underline the knowledge gap around the possible cardio-protective role of TH. Extrapolation and generalization of the mechanisms thought to be responsible for the neuroprotective effect and results from animal studies have led to multiple proposed theories surrounding the cardioprotective role (Table 1).

The difficulty conducting clinical trials in the time-sensitive environment of PPCI, the presence of multiple confounders and lack of large scale

randomized control trials have resulted in the role of TH in cardiovascular outcomes remaining unclear.

Macrovascular	Decreases post-ischaemic hyperaemia [24]
Microvascular	Reduces no-reflow phenomenon and microvascular obstruction [25] [26]
Metabolic	Decreased ulitisation of high energy phosphate and glucose [27], [28]
	Reduction in lactate production [27]
Cellular	Reduces apoptosis [29]–[31]
	Maintenance of integrity of myocardial cell membranes and collagen structure in connective tissues [29] [32]
Intracellular	Maintenance of myocardial mitochondrial function [29] [32] [31]
	Prevents intracellular calcium overload and improves intracellular pH homeostasis [33]
	Decreases free radical and cytotoxin generation [30], [34], [35]
Platelet	Inhibits platelet aggregation [36]

Table 1: Proposed mechanisms of myocardial protection with therapeutic hypothermia

Aims

To examine the published literature concerning systemic TH in the context of acute STEMI without OHCA and report on:

- Feasibility and delivery
- Safety
- Efficacy
    - Effect on Infarct size

- Outcome data

Methods

A systematic search of literature was performed across Embase, ISI Web of Science, Medline, Medline In-Process, Cochrane Central Register of Controlled trials and Pubmed from 1st January 1946 through to 23rd May 2016. The search was limited to original articles in human adults written in English. The following search terms were used STEMI, ST segment elevation*, ST myocardial, ST infarction*, ST coronary, Myocardial infarction, Systemic hypothermia, induced hypothermia, lowering temperature, rapid cooling, catheter* cooling, treat* hypothermi*, initia* hypothermi*, induce* hypothermi*, therap* hypothermi*, Coronary angioplast*, coronary angiogra*, PPCI, PCI, PTCA, percutaneous coronary intervention*, Balloon Angioplasty. References in the captured studies were reviewed for potentially relevant articles not identified by the above search.

Articles were included if they were original, described the administration pf systemic TH to patients following STEMI and reported on any of : (a) the feasibility of TH, (b) the effect of TH on infarct size, (c) the impact of TH on cardiovascular morbidity or MACE, and (d) the safety of TH. Patients who experienced an OHCA were excluded and duplicate publications removed. Two reviewers (C.S. and R.B.) independently appraised each abstract against the inclusion and exclusion criteria.

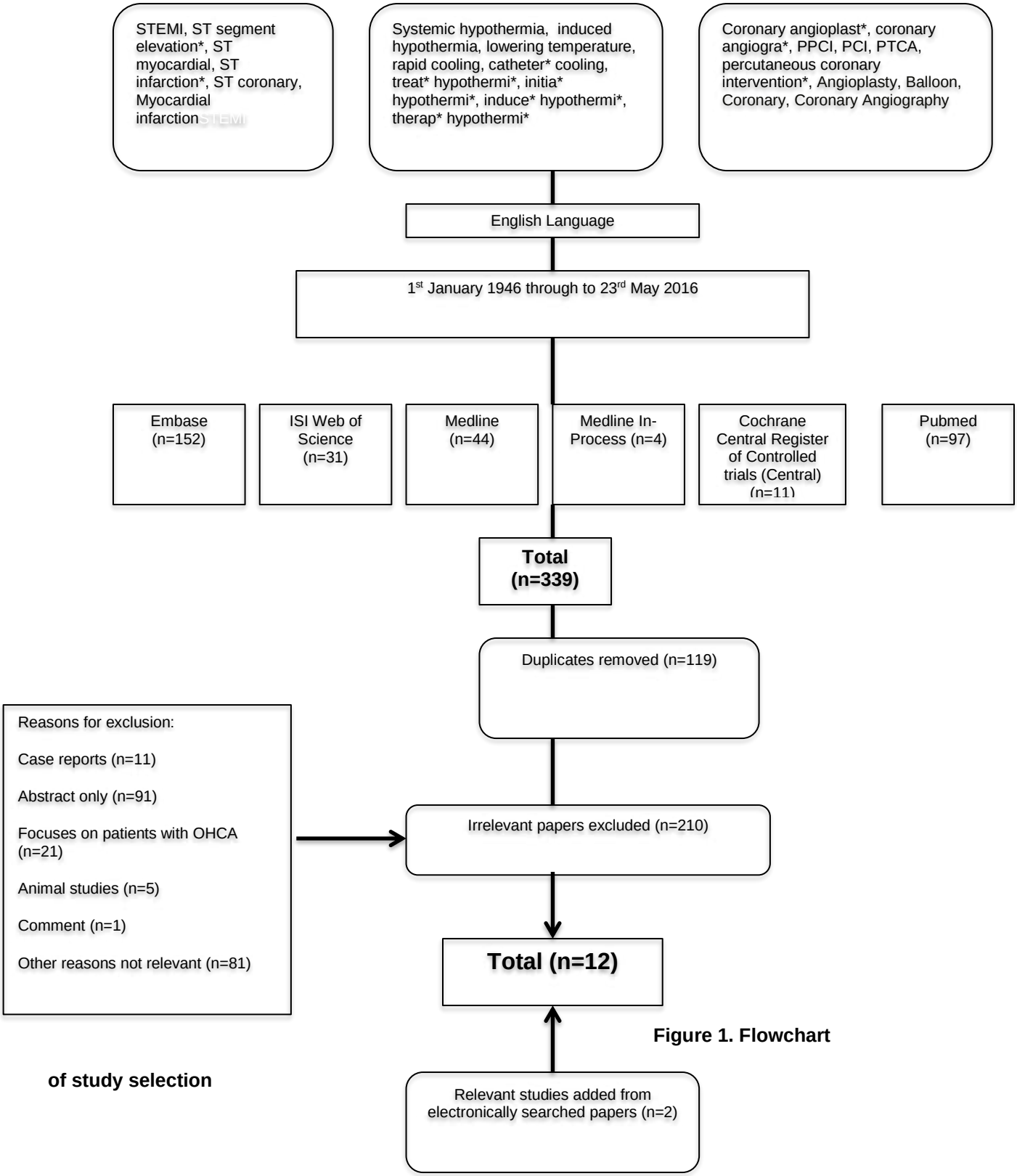

Figure 1. Flowchart of study selection

Results

Of 339 articles identified, there were 119 duplicates and 210 studies were removed as they did not meet the inclusion criteria (Figure 1). Two studies were found from the reference lists of papers already included in the study and included for review. Therefore, a total of ten original studies and two pooled analysis studies formed the basis of the review (Table 1). The technique of TH represents new challenges unique to the acute interventional cardiology team as it is an adjunct therapy in a time sensitive environment. It should not be allowed to significantly impair the time to reperfusion nor render reperfusion techniques more difficult as any delay in the time to reperfusion is associated with adverse outcomes [37]. Studies to date have examined the potential impact on feasibility, safety and outcomes (Table 2)

	Sample size (n)	Type of study	Age (years) (mean +/-SD)		Male (%)		DM (%)		HT (%)		Current smokers (%)		Previous MI (%)		Hyperlipidaemia (%)		Site of infarct (%)		Door to Balloon (mins) (mean =/- SD)	
			TH	C	TH	C	TH	C	TH	CI	TH	C	TH	C	TH	C	TH	C	TH	C
Dixon et al [38]	42	RCT	52±9	58±14	90	76	19	29	25	27	67	52	14	5	43	24	Ant=40 Inf= 60	Ant=48 Inf=52	87±30	104±44
COOL MI [39]	392	RCT	60±12	59±12	75	80	17	18	47	39	44	48	10	12	31	30	Ant=42 Inf=58	Ant=44 Inf=56	110±41	92±47
ICE IT [40]	228	RCT	57±13	57±12	77		16		50		50		1		NR		Ant=43 Inf=57	Ant=43 Inf=57	106	96
LOWTEMP [41]	20	Cohort	63*		80		NR		NR		NR		NR		NR		Ant= 50 Npn ant=50		NR	
NICAMI [42]	11	Cohort	62±11		91		0		36		55		NR		54		Ant=27 Non ant=73		NR	
RAPID MI ICE [43]	18	RCT	62±10	58±7	62	58	11	22	33	22	33	56	NR		11	0	Ant=67 Inf=33	Ant= 78 Inf=22	43±7	40±6
Testori et al [44]	19	Cohort	51*		95		5		53		32		NR		16		Ant=47 Post=53		59*	
CHILL MI [45]	120	RCT	57*	59*	79	86	13	5	28	12	46	39	NR		16	2	Ant=38 Inf=62	Ant= 48 Inf= 52	42±16	33±21
Blatt et al [46]	21	Cohort with historical control	69±7	65±1	75	69	38	46	63	85	63	31	38	46	75	54	Ant= 88 Inf= 12	Ant= 69 Inf= 31	79±21	82±26
VELOCITY [47]	54	RCT	57*	58*	89	81	21	23	50	35	43	44	0	0	36	23	Ant= 46	Ant= 46	62	47

C= Control; NR = Not Reported; * = Median; Ant = Anterior STEMI; Inf = Inferior STEMI

Table no 2: Baseline characteristics of the study populations

Feasibility and Delivery

Ten studies examined the feasibility of TH and the issue of attaining a target temperature prior to revascularization (Table 3). Techniques employed were;

external cooling with surface pads (n=1), cooling via an endovascular catheter (which cools or warms the saline circulating through it without the need to infuse fluids n=4), combinations of endovascular and infusion of chilled saline (n=2), surface pads and endovascular catheters (n=1), chilled saline infusion with a hypothermia inducing suit (n=1) and peritoneal lavage with chilled lactated Ringer's solution (n=1) [38]–[44], [46], [47]. These methods have been previously demonstrated to be effective for temperature management in post cardiac arrest patients [48], [49]. All studies aimed for mild therapeutic hypothermia (target core temperature <35^{o}Farenheit or Celsius? prior to reperfusion in the majority), achievement of which varied from 72% to 100% [39], [41]. The disparity in achievement of the target temperature was attributed to causes such as technical difficulty, device malfunction, kinking of the catheter and first medical contact to reperfusion time being slow [38], [44]. In four studies all participants reached the pre-specified target temperature [41]–[43], [46]. Attainment of target temperature was demonstrated regardless of the cooling technique used. The authors of the Rapid Endovascular Catheter Core Cooling Combined With Cold Saline as an Adjunct to Percutaneous Coronary Intervention for the Treatment of Acute Myocardial Infarction (CHILL-MI) trial reported that PCI operators and nurses found the study protocol easy to implement [45]. Dixon et al. the insertion of the cooling catheter to be a rapid process that could occur either in the catheter laboratory or the emergency room [38].

Study	**Target core temperature**	**Percentage attaining target temperature**	**Method of cooling**
Dixon et al [38]	33℃	95%	Endovascular catheter cooling
COOL MI [39]	33℃	72%	Endovascular catheter cooling
ICE IT [40]	32-34℃	NA	Endovascular catheter cooling

LOWTEMP [41]	32-34℃	100%	Endovascular catheter cooling
NICAMI [42]	34.5℃	100%	Surface Cooling pads
RAPID MI-ICE [43]	<35℃^	100%	Endovascular catheter cooling and infusion of normal saline at 4℃
Testori et al [44]	<35℃^	78%	Endovascular catheter and surface cooling pads
CHILL MI [45]	33℃	76% ∞	Endovascular catheter cooling and infusion of normal saline at 4℃
Blatt et al [46]	32-34℃*	100%	Hypothermic suit and infusion of normal saline at 4℃
VELOCITY [47]	32.5℃	96%	Automated peritoneal lavage system

^ prior to reperfusion; * applied for 12 hours; ∞ Population attaining temperature below 35°C

Table no 3. Target temperature, percentage of study population who attained the target temperature and methods of cooling in the various studies

Safety

Shivering

Shivering is a particular concern with TH especially in this cohort of patients as it increases oxygen consumption, circulating catecholamines and cardiac output [50]. Hypothermia induced shivering and cold intolerance were minimised in a number of studies using pharmacological agents such as oral buspirone (a serotonin 1A partial agonist) and/or intravenous meperidine (an opioid) [38], [39], [41]–[45], [47]. These agents have been shown to suppress shivering without causing respiratory depression and act synergistically [51]. In addition to pharmacological therapy, some studies used forced air blankets[38], [39], [43], [47]. Blatt et al used a different method with muscle relaxants and sedation with midazolam in order to minimize shivering [46]. No studies reported having to terminate cooling due to shivering or cold intolerance, but in the Feasibility of Endovascular Cooling as an Adjunct to Primary Percutaneous Coronary Intervention (LOWTEMP) study, those who had shivering refractory to pharmacological therapy and external warming

measures, were treated by increasing the temperature of the external thermoregulatory unit until the symptoms resolved [41].

Door-to-Balloon Time

Given delays to revascularization can negatively impact prognosis there are concerns surrounding the effect of instituting TH on door to balloon times (DTB) [table 2]. The Cooling as an Adjunctive Therapy to Percutaneous Intervention in Patients With Acute Myocardial Infarction (COOL-MI) [39], Intravascular Cooling Adjunctive to Percutaneous Coronary Intervention for Acute Myocardial Infarction (ICE-IT) [40] and CHILL-MI [45] studies showed increases in mean door-to-balloon times of 18, 10 and 9 minutes, respectively for patients who received TH compared with those who did not receive TH although there was no statistically significant increase in DTB times in these studies. In a study of twenty one patients, Blatt and colleagues used a historic control cohort to demonstrate no significant difference in median hospital reperfusion times of in the TH group compared with the control group (79±21 vs. 86±21 minutes, $p<0.22$) [46]. Most recently, the VELOCITY study, which used peritoneal lavage as the ICE ing method, showed a statistically significant increase in the median door-to-balloon times in the TH group (47 vs. 62 minutes, $p=0.007$) [47].

Clinical Events (excluding MACE/mortality)

The process of TH was reported to be well tolerated in most studies without causing any evidence of significant hemodynamic compromise [38]–[40],

[44]–[46] (Table 4.). Episodes of ventricular tachycardia/ventricular fibrillation corrected by electrical DC cardioversion were reported, but not directly attributed to TH [38], [40]–[47]. The cooling devices did not hamper the electrical DC cardioversion. Bradycardia was reported in three studies [38], [41], [45]. Three patients in the LOWTEMP study developed bradycardia which responded to either temporary or permanent pacing but was not directly attributed to TH [41]. Episodes of major bleeding or bleeding requiring blood transfusion were reported to be <5% in the majority of studies, though higher in the Blatt et al (25%) cohort of patients with cardiogenic shock [38], [41], [43]–[47]. The incidence of infection or fever was also low throughout the studies with no statistical significantly difference between intervention and control arms demonstrated [43], [45], [47].

		Clinical Events at follow up period (%)											
Study		Ventricular tachycardia/ fibrillation	Bradycardia	Infection/ Fever	Major bleeding	MACE	Death	Reinfarction	Repeat PCI	Stent thrombosis	Heart failure	Pulmonary oedema	Stroke/TIA
Dixon et al [38]	Cooling n=21	3 (14%)	3 (14%)	NR	1 (5%)	0	0	0	0	NR	NR	1 (5%)	0
	Control n=21	6 (29%)	4 (19%)	NR	0	2 (10%)	2 (10%)	0	2 (10%)	NR	NR	0	0
COOL MI [39]	Cooling n=177	NA	NA	NA	NA	11 (6%)	6 (3%)	NA	NA	NA	NA	NA	NA
	Control n= 180	NA	NA	NA	NA	7 (4%)	4 (2%)	NA	NA	NA	NA	NA	NA
ICE IT [40]	Cooling n=114	NA	NA	32 (28%)	NA	10 (9%)	9 (8%)	2 (2%)	NA	NA	0	NA	0
	Control n=114	NA	NA	29 (25%)	NA	6 (5%)	5 (4%)	0	NA	NA	3 (3%)	NA	0
LOWTEMP [41]	Cooling n=18	1 (6%)	3 (17%)	NR	0	NR	1 (6%)	0	NR	NR	NR	NR	0
NICAMI [42]	Cooling n=11	1 (9%)	0	NR	NR	NR	0	NR	NR	NR	NR	NR	NR
RAPID MI-ICE [43]	Cooling N=9	0	0	3 (33%)	0	0	0	0	NR	NR	0	NR	0
	Control N=9	2 (22%)	0	0	0	0	0	0	NR	NR	3 (33%)	NR	0
Testori et al [44]	Cooling N=19	2 (11%)	0	3 (16%)	0	NR	1 (5%)	0	NR	NR	NR	NR	0
CHILL MI [45]	Cooling N=61	5 (8%)	2 (3%)	3 (5%)	0	NR	0	1 (2%)	NR	NR	2 (3%)	1 (2%)	0
	Control N=59	2 (3%)	1 (2%)	1 (2%)	1 (2%)	NR	0	0	NR	NR	8 (14%)	2 (3%)	0
Blatt et al [46]	Cooling N=8	NR	NR	3 (38%)	2 (25%)	NR	4 (50%)	NR	NR	1 (13%)	NR	NR	NR
	Control N=13	NR	NR	3 (23%)	3 (23%)	NR	6 (46%)	NR	NR	2 (15%)	NR	NR	NR

VELOCITY [47]	Cooling N=28	1 (4%)	NR	1 (4%)	1 (4%)	4 (14%)	1 (4%)	4 (14%)	3 (11%)	3 (11%)	NR	NR	NR
	Control N=26	0	NR	0	0	0	0	0	0	0	NR	NR	NR

VT = Ventricular tachycardia; VF = Ventricular fibrillation; NR = Not reported; NA = Data not available

Table 4: Clinical events noted in ten original studies

Efficacy

Effect on infarct size (IS)

Reviewed studies have utilized single-photon emission computed tomography (SPECT) and cardiac magnetic resonance (CMR) imaging to determine infarct size.

Single-photon emission computed tomography (SPECT)

Early studies, using SPECT, failed to show a statistically significant reduction in infarct size at 30 days [38]–[40] (Table 5). Dixon et al [38] reported a non-significant reduction in median infarct size in patients who received cooling compared with the control group (2% vs. 8% of the left ventricle, p = 0.80). This study was underpowered to test for the effect of TH and was mainly hypothesis generating. Similarly, the COOL MI [39] and ICE-IT [40] studies did not show a significant difference in left ventricular infarct size with TH (COOL-MI: 13.8% vs.14.1%, p=0.45; ICE-IT: 10.2% vs. 13.2%, p=0.14). Post-hoc subgroup analysis of the COOL-MI study found that patients with an anterior myocardial infarction who obtained the target temperature prior to PPCI had a reduction in infarct size (9.3% of vs. 18.2%, p=0.05) [39]. A similar trend was also demonstrated in the ICE-IT trial (12% vs. 22.7%, p=0.09) [40].

Cardiac magnetic resonance imaging

The Rapid Intravascular Cooling in Myocardial Infarction as Adjunctive to Percutaneous Coronary Intervention (RAPID MI-ICE) [43] study used cardiac magnetic resonance imaging at 4±2 days after initiation of TH to assess infarct size. In this study, there was a trend towards reduction in infarct size although this did not reach statistical significance, however, when normalized against the myocardium at risk, (defined as the myocardial tissue in the perfusion bed distally to the culprit lesion of the infarct-related coronary artery), there was a 38% reduction in the infarct size between TH and control groups (29.8±12.6% vs. 48±21.6%, p=0.041). A pooled dataset of ICE-IT and RAPID MI-ICE demonstrated a 24% reduction in infarct size as a percentage of left ventricular myocardium (p<0.049) [52]. This was predominantly due to significantly reduced infarct size among those with anterior myocardial infarctions (30%, p=0.04) and was not demonstrated for inferior myocardial infarctions. For those who achieved the target temperature (<35℃) prior to revascularisation there was a significant reduction in infarct size for both anterior (33%, p=0.03) and inferior (42%, p=0.04) myocardial infarctions. In the CHILL-MI trial median infarct size normalised to myocardium at risk was lower in the TH group in comparison to controls but did not reach statistical significance (40.5% vs. 46.6%; p=0.15) [45].

Combined analysis of the RAPID MI-ICE and CHILL MI demonstrated a relative reduction in infarct size normalized to myocardium at risk of 15% (40.5 vs. 46.6; p=0.046) in the study population treated with TH [42]. The

effect was most pronounced for those with early anterior STEMI (0-4h) who exhibited a relative risk reduction in infarction size normalized to myocardium at risk of 31%. Patients with a large area of myocardium at risk (>30% of the left ventricle) who received TH also exhibited a significant reduction in infarct size normalized to myocardium at risk compared with controls (40.5 vs. 55.1, p = 0.03).

The Evaluation of Ultrafast Hypothermia Before Reperfusion in STEMI Patients (VELOCITY) trial failed to show any significant difference between the effects of TH compared with control in median infarct size (% left ventricular mass) with peritoneal lavage [39]. This remained the case when adjusted against the area at risk. The findings were evident at both 3-5 days (17.2% TH vs. 16.1% control; P=0.54) and at 30 days (12.5% TH vs. 11.8% control; P=0.43). This remained the case even when adjusting for infarct site or time from symptom onset to hospital arrival although the number of patients undergoing post infarction imaging were small (n=46) [39].

Study	Imaging assessment	Patients assessed (%)	Time of assessment (days)	Results Cooling (IS)	Results Control (IS)	P-value
Dixon et al [36]	SPECT#	86%	30	2% of LV (median)	8% of LV (median)	P=0.80
COOL MI [37]	SPECT#	NR	30	14.1% of LV (median)	13.8% of LV (median)	P=0.45
ICE IT [38]	SPECT#	NR	30	10% of LV (mean)	13% of LV (mean)	P=0.14
LOWTEMP [α] [41]	SPECT#	90%	30	4.0% of LV (median)	NA	NA
NICAMI [α] [42]	SPECT^	NR	Within 30	23% of LV (mean)	NA	NA
RAPID MI-ICE [43]	CMR	100%	4±2	13.7% of LV mass (mean)	20.5% of LV mass (mean)	P=0.08
Erlinge et al. [48]*	SPECT# CMR	100%	30 (SPECT) 4±2 (CMR)	10.7% of LV mass (mean)	14.1% of LV mass (mean)	P=0.049
CHILL MI [45]	CMR	81%	4±2	40.5% (IS normalised to MaR)	46.6% (IS normalised to MaR)	P=0.15
Erlinge et al. [53]*	CMR	100%	4±2	40.5% (IS	46.6% (IS	P =0.046

				normalised to MaR)	normalised to MaR)	
VELOCITY [47]	CMR	85%	3-5	17.2% of LV mass (median)	16.1% of LV mass (median)	P=0.54

[α] Feasibility study

*Pooled analysis

#99mTc-sestamibi SPECT imaging

^99mTc-tetrofosmin SPECT imaging

LV = Left ventricle

CMR = Cardiac magnetic resonance

MaR= Myocardium at risk, IS= Infarct size

NR = not reported

Table no 5. Studies using imaging to assess Infarct size (IS)

Major Adverse Cardiac Events (MACE) and Mortality

Dixon and colleagues performed the first multi-centre RCT that investigated the impact of TH on MACE (n=42) [38] (Table 4). At 30 days MACE was observed in none of the treated and 10% of the control patients (p=NS). Similarly, the COOL-MI study (n=357) failed to show a significant difference in MACE at 30 days (6.2% in the TH group versus 3.9% in the control group, p=0.45) [39]. No difference was reported in the rates of in-hospital adverse events such as pulmonary oedema, shock or arrhythmia.

The ICE-IT study (n=228) showed no difference in MACE at 30 days (p=0.29) and 12 months (p=0.77) [40]. In total, nine deaths were reported in the TH arm and four in the control arm (p=0.15). To date the only trial to have demonstrated a difference in MACE was CHILL-MI, the primary clinical end

point of adjudicated death and heart failure was significantly reduced in the hypothermia arm versus control arm at 45 days (2 vs. 8 events in the study populations, p=0.047) [45]. Of note, there were no deaths in either arm – with the reduction in events being accounted for by fewer heart failure events. The RAPID MI-ICE trial did not report any MACE at 30 days in either arm of the trial [43].

The VELOCITY trial demonstrated a significant increase in its primary composite safety end point (0% control vs. 21.4% TH; P=0.01) and MACE (0% control vs. 14.3% TH; P=0.047) at 30 days [44]. This appeared to be driven predominantly by an increase in stent thrombosis events in the TH group (0 control vs. 3 TH).

Discussion

With the exception of one study, the use of systemic TH prior to percutaneous intervention for STEMI in conscious patients was shown to be feasible with a comparable safety profile with control groups regardless of the method used. In the VELOCITY study, the use of TH was associated with an increased risk of adverse events particularly stent thrombosis [47]. Hypothermia may reduce the efficacy of ADP antagonists [54], [55] as well as delaying gastric absorption of anti-platelet agents [56] so has the potential to increase stent

thrombosis. The impact of TH on stent thrombosis has been mixed in practice. Rates of stent thrombosis in the literature vary but have been reported to be as high as 31% within 30 days at one center [57]. Although 80% of these patients received bare metal stents and observational data shows comparable rates of stent thrombosis with TH to that expected in standardly treated primary PCI patients [58]. None of the other studies in the review demonstrated this trend which therefore raises questions about the safety of peritoneal lavage in instituting hypothermia. Although Poldermann et al. did not report any cases of stent thrombosis utilising this technique [59]. Interestingly approximately a third of patients in the VELOCITY study were given clopidogrel, which has significantly worse platelet inhibition when given in conjunction with TH compared to prasugrel or ticagrelor [60]. This is in contrast to the CHILL MI study where the vast majority (89%) received either prasugrel or ticagrelor.

Another concern with TH is its potential impact on door-to-balloon times, given that treatment delays have a negative impact on infarct size and mortality [61]. Although door to balloon times were longer in the TH groups, these were often modest and did not reach statistical significance. Notably the mean delay in reperfusion times conferred by TH, in the larger randomized studies, has been reduced from 18 minutes in the earliest trial to 9 minutes in the most recent, implying a learning curve effect. [39], [45]. Initial data from a UK hospital which is part of the Case Series Clinical Study suggesting that delivering efficient TH is feasible and associated with a one minute delay in door to balloon times[62], [63].

The impact of TH on infarct size and MACE has been inconsistent and largely disappointing. Larger RCTs (COOL-MI, ICE-IT and CHILL-MI) have not demonstrated any statistically significant difference in infarct size. Although subgroup and pooled analysis data hint at a potential benefit in those where target temperature is attained prior to revascularization, present early with anterior STEMI or have a large area of myocardium at risk [39], [52], [53]. Equally, no trial has demonstrated a mortality benefit with TH. The only observed benefit in MACE seen has been a significant reduction in the incidence of heart failure in the CHILL MI study. These findings are not in keeping with the success demonstrated in animal models where induction of TH prior to reperfusion can limit infract size and microvascular injury [64], [65]. The timing of TH appears to be crucial as early institution during the ischaemic period leads to a reduction in infarct size [66] and this is true even in the absence of reperfusion [67]. Given nearly 15% of the population in the CHILL-MI trial had a time from symptom onset to reperfusion of greater than four hours [45] and only three quarters of the patients in the larger studies [39], [45] achieved TH (≤35°C) prior to reperfusion this is an important consideration in future trials. A very recent development is the use of local intracoronary saline to achieve hypothermia delivered at the index procedure to attain rapid focused area of hypothermia [68]. Although still an experimental technique it may also offer the benefit of negating the systemic consequences of TH namely shivering and an enhanced adrenergic response.

Contemporary outcomes for those undergoing PPCI for STEMI in the absence of OHCA are good with current treatment strategies and so trying to elicit short-term improvements in clinical endpoints is difficult. Recruitment to trials has been poor as illustrated by small trial populations in multi-centre studies, with potential impact on door to balloon times a concern as well as selection bias. For example, the CHILL MI trial excluded patients over 75 or those with previous PCI, coronary artery bypass grafting or known heart failure, this high-risk population potentially have the most to gain from reduction in infarct size. Several other cofounders within the studies existed as the type/generation of drug eluting stent deployed was not clear and the administration of heparin, glycoprotein IIb/IIIa inhibitors and bivalirudin was at the discretion of the treating physician [45], [47].

For all the studies reviewed, the length of clinical follow up was short and this may, therefore, have underestimated detection of the development of heart failure which is often insipient after STEMI [11]. Equally, functional imaging in the earlier randomized studies was by SPECT and the low spatial resolution of SPECT may reduce delineation of small infarcts in a quarter of patients and this is particularly important with modern reperfusion therapies when assessing infarct size [69]. Equally the COOL-MI and ICE-IT studies only measured total infarct size and not the percentage of the area subtended and therefore may underestimate potential effect. Imaging was only ever performed early post infarct with longest delay to left ventricular assessment being 30 days. This is important as early cardiac magnetic resonance imaging may underestimate the potential for functional recovery seen at one year [70]

which suggests that future studies should also perform delayed imaging in order to assess longer term outcomes.

Conclusion

In this structured literature review of six RCT's, four cohort studies and two pooled analyses, we found that with the exception of one study, achieving TH in awake patients undergoing percutaneous coronary intervention for ST elevation myocardial is feasible and safe. To date, there is no evidence from RCTs to support a reduction in mortality with TH during PPCI for STEMI. However, the most recent RCT has shown a reduction in heart failure at day 45. Determination of the pathophysiological mechanisms and macroscopic factors such as left ventricular function are important in determining the utility and understanding of TH.

Clearly, large scale investigation is necessary given encouraging results from animal studies and subset and pooled analysis suggesting a benefit of TH in those presenting early with anterior STEMI or with a large area of myocardium at risk. Attainment of target temperature prior to and combined with rapid revascularization may provide a clinically viable and therapeutic target. The current lack of high level evidence for TH suggests that it should not be widely adopted, however, a randomized trial powered to detect short and long term outcomes as well as addressing possible safety concerns is indicated.

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