Therapeutic Hypothermia for the Treatment of Acute Myocardial Infarction–Combined Analysis of the RAPID MI-ICE and the CHILL-MI Trials

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In the randomized rapid intravascular cooling in myocardial infarction as adjunctive to percutaneous coronary intervention (RAPID MI-ICE) and 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 studies, hypothermia was rapidly induced in conscious patients with ST-elevation myocardial infarction (STEMI) by a combination of cold saline and endovascular cooling. Twenty patients in RAPID MI-ICE and 120 in CHILL-MI with large STEMIs, scheduled for primary percutaneous coronary intervention (PCI) within <6 hours after symptom onset were randomized to hypothermia induced by rapid infusion of 600–2000 mL cold saline combined with endovascular cooling or standard of care. Hypothermia was initiated before PCI and continued for 1–3 hours after reperfusion aiming at a target temperature of 33°C. The primary endpoint was myocardial infarct size (IS) as a percentage of myocardium at risk (IS/MaR) assessed by cardiac magnetic resonance imaging at 4 ± 2 days. Patients randomized to hypothermia treatment achieved a mean core body temperature of 34.7°C before reperfusion. Although significance was not achieved in CHILL-MI, in the pooled analysis IS/MaR was reduced in the hypothermia group, relative reduction (RR) 15% (40.5, 28.0–57.6 vs. 46.6, 36.8–63.8, p = 0.046, median, interquartile range [IQR]). IS/MaR was predominantly reduced in early anterior STEMI (0–4h) in the hypothermia group, RR = 31% (40.5, 28.8–51.9 vs. 59.0, 45.0–67.8, p = 0.01, median, IQR). There was no mortality in either group. The incidence of heart failure was reduced in the hypothermia group (2 vs. 11, p = 0.009). Patients with large MaR (>30% of the left ventricle) exhibited significantly reduced IS/MaR in the hypothermia group (40.5, 27.0–57.6 vs. 55.1, 41.1–64.4, median, IQR; hypothermia n = 42 vs. control n = 37, p = 0.03), while patients with MaR < 30% did not show effect of hypothermia (35.8, 28.3–57.5 vs. 38.4, 27.4–59.7, median, IQR; hypothermia n = 15 vs. control n = 19, p = 0.50). The prespecified pooled analysis of RAPID MI-ICE and CHILL-MI indicates a reduction of myocardial IS and reduction in heart failure by 1–3 hours with endovascular cooling in association with primary PCI of acute STEMI predominantly in patients with large area of myocardium at risk. (ClinicalTrials.gov id NCT00417638 and NCT01379261).
Methods

Introduction

To reduce infarct size (IS) and associated complications, contemporary therapy in patients with an ongoing ST-elevation myocardial infarction (STEMI) is to restore blood flow in the ischemic myocardium as soon as possible to reduce IS and associated complications. IS is one of the main predictors of both short- and long-term outcome in patients with acute myocardial infarction (AMI) (Miller et al., 1995; Burns et al., 2002). Reducing IS is an important objective of current research to improve outcomes after AMI. Although reperfusion therapy is a prerequisite for myocardial salvage, the process may cause irreversible damage to the myocardium, referred to as reperfusion injury (Kloner, 1993). In addition to reperfusion injury, total ischemic time also contributes to greater IS and increased mortality (Koul et al., 2014).

In experimental studies, mild hypothermia induced before reperfusion of an acute coronary occlusion reduces IS (Duncker et al., 1996; Hale et al., 1997; Hale and Kloner, 1999; Dae et al., 2002; Gotberg et al., 2008; Erlinge, 2011). However, hypothermia has failed to reduce IS if initiated after the onset of reperfusion (Maeng et al., 2006; Gotberg et al., 2008; Erlinge, 2011). In animal models, hypothermia before the start of ischemia can reduce IS by 100%, while hypothermia induced during ischemia may reduce IS by up to 80%. Immediately at reperfusion a 20% IS reduction may be achieved while hypothermia started after reperfusion does not reduce IS (Maeng et al., 2006; Gotberg et al., 2008; Erlinge, 2011).

The two first major clinical trials investigating mild hypothermia using endovascular cooling as an adjunct therapy in AMI failed to show a significant reduction in IS (Dixon et al., 2002; Erlinge et al., 2013). Early and more rapidly induced hypothermia, accomplished by a combination of a rapid infusion of cold saline together with an endovascular cooling catheter, has been examined in the rapid intravascular cooling in myocardial infarction as adjunctive to percutaneous coronary intervention (RAPID MI-ICE) pilot study, which was then per protocol followed by the larger multicenter 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) study. In the RAPID MI-ICE study, hypothermia significantly reduced IS normalized to myocardium at risk (MaR) by 38% (Gotberg et al., 2010). In the following multicenter study (CHILL-MI), hypothermia nonsignificantly reduced IS/MaR by 13%, but a more pronounced effect was seen in post hoc analysis of early (<4 hours from symptom onset to reperfusion) anterior STEMI patients with an IS reduction of 33% (Erlinge et al., 2014).

The aim of this pooled analysis was to examine the combined population of the two prospective randomized clinical trials, RAPID MI-ICE and CHILL-MI that utilized a rapid cooling protocol combining intravenous cold saline and endovascular cooling and to evaluate subgroups that may have greater therapeutic benefit with hypothermia.

The RAPID MI-ICE study was per initial ethics committee approved protocol, designed as a pilot study leading to a larger multicenter trial of treating patients with anterior STEMs with rapidly induced hypothermia. The CHILL-MI study drew on the results from the pilot study, RAPID MI-ICE, and because it mandated a shorter treatment time with hypothermia and also allowed for inferior STEMs, a separate protocol was designed and thence approved in the ethics committee.

Ethics and organization

The studies were performed in accordance with the Declaration of Helsinki and the local ethics committees approved the study protocol. All patients gave written informed consent before inclusion in the studies. The authors had access to all original data.

Study population

Both studies were designed as prospective, randomized, endpoint blinded studies to test the feasibility and safety of an infusion of cold saline together with endovascular hypothermia, using the Accutrol™ catheter and InnerCool RTx endovascular console (Philips Healthcare, San Diego, CA) as an adjunct therapy in patients with STEMI eligible for primary percutaneous coronary intervention (PCI). Men and women between 18 and 75 years of age presenting with an anterior or inferior STEMI with ST-segment elevation of >0.2 mV in two contiguous leads and a duration of symptoms of <6 hours were included. For inferior STEMI an additional ST depression in two contiguous anterior leads for a total ST deviation (inferior ST elevation plus anterior ST depression) of ≥0.8 mV was required. A 2nd EKG was performed in the catheterization laboratory before randomization to ensure persistent ST-elevation. Patients with cardiac arrest, previous AMI, previous PCI or coronary artery bypass grafting (CABG), known congestive heart failure, end stage kidney disease or hepatic failure, recent stroke, coagulopathy, pregnancy, or Killip class II-IV at presentation were excluded.

Protocol

Eligible patients were randomized 1:1 to hypothermia or standard of care after admission and before coronary angiography. Sealed opaque envelopes containing the study group assignment were opened after informed consent. Patients assigned to hypothermia were administered 30 mg of oral buspirone. Meperidine was administered as an intravenous loading dose of 1 mg/kg or 0.5 mg/kg if the patient had received morphine before enrollment in the study. Additional 25 mg intravenous bolus doses of Meperidine were administered as needed to reduce shivering. Hypothermia was initially induced by forced infusion of 4°C cold saline using pressure bags. Volume administered was 600–2000 mL according to a weight-adjusted schedule (10 mL/kg for anterior and 20 mL/kg for inferior STEMI patients).

Before angiography, a 14F introducer was inserted in the femoral vein. Through the introducer, a 14F Accutrol™ catheter was placed into the inferior vena cava with the tip of the catheter at the level of the diaphragm. The target temperature was set to 33°C. Core body temperature was assessed using an integrated temperature sensor at the tip of the cooling catheter which helped minimize temperature lag that often occurs in other body compartments such as the bladder, ear, or rectum during rapid core cooling (Bone...
and Feneck, 1988). Following placement and activation of the cooling catheter, coronary angiography and PCI were performed without delay, except for a brief pause to measure core temperature just before advancing the guidewire through the culprit lesion. In the RAPID MI-ICE study, cooling was maintained for 3 hours after reperfusion followed by 3 hours controlled rewarming. In the CHILL-MI study, cooling was maintained for 1 hour after reperfusion followed by spontaneous rewarming. If the PCI procedure took longer than 1 hour, cooling was continued until the end of the procedure.

Loading doses of 500 mg of aspirin and ADP-receptor blockade were given to all patients before cardiac catheterization. Heparin, GP IIb/IIIa inhibitors, and bivalirudin were administered at the discretion of the treating physician.

**Cardiac magnetic resonance imaging**

After 4 ± 2 days, patients underwent a cardiac magnetic resonance imaging (CMR) examination (see Supplementary Materials; Supplementary Data are available online at www.liebertpub.com/ther).

**CMR image analysis**

The analysis of ventricular dimensions, MaR and IS, was performed by a core laboratory (Imacor AB, Lund, Sweden) using a postprocessing software (Segment, v.1.9 R3084; http://segment.heiberg.se) (see Supplementary Materials) (Heiberg et al., 2008, 2010; Sorensson et al., 2010; Ubachs et al., 2012). For the CHILL-MI study, the CMR analysis was performed by a core laboratory (Imacor AB, Lund, Sweden).

**Clinical endpoints**

Clinical endpoints were collected by a clinical report form during index hospitalization at 45 ± 15 days and at 6 months. In addition, clinical events were collected by adverse event and serious adverse event reporting. Hospital charts were monitored by independent monitors for all patients. A blinded clinical events committee evaluated all primary events (death and heart failure) independently.

Heart failure was defined as admission to hospital or attendance at an acute healthcare facility for administration of intravenous diuretic treatment, escalation of diuretic doses, and/or inotropes. Confirmation of heart failure diagnosis is required by chest imaging demonstrating pulmonary congestion or edema, OR patients without available chest imaging, at least one of the following: pulmonary edema (i.e., rales > 1/3 up the lung fields thought to be of cardiac causes), pulmonary capillary wedge pressure > 18 mmHg, BNP > 500 pg/mL (or NT-terminal prohormone BNP > 2500 pg/mL).

**Statistics**

Patient-level data from the two trials were pooled and analyzed as belonging to one trial. All data were analyzed by randomized treatment without imputation of missing data. CMR data were presented using medians and quartiles and analyzed using Wilcoxon nonparametric test for the entire material and within subgroups. Interaction p-values for comparing subgroups or the two trials were obtained using linear models with treatment, subgroup, and interaction as factors. Clinical events up to 45 days were analyzed using Fisher’s exact test. Two-sided p-values below 0.05 were considered to denote statistical significance.

**Results**

One hundred forty patients from 9 sites in 4 countries were included in the meta-analysis, 20 from RAPID MI-ICE and 120 from the CHILL-MI study. Two patients were excluded in the RAPID MI-ICE population (one patient in the normothermia group who underwent emergency CABG after angiography, one patient in the hypothermia group was prevented from immediate angiography due to another STEMI patient at the catheterization laboratory, delaying cooling beyond the prespecified 6 hours duration of ischemia). There were no major differences in baseline characteristics between the groups (Table 1). Time from the onset of symptom to randomization was 138 ± 66 versus 135 ± 59 minutes (mean ± SD, hypothermia vs. control). All but three patients had successful PCI and were included in the final analysis. One patient was reported as having an unsuccessful PCI. TIMI 3 flow was established in 94% of the hypothermia patients and 91% of the control patients, respectively. Thrombus aspiration was performed in 61% and 71% of the patients, respectively. The novel more potent P2Y12-inhibitors ticagrelor or prasugrel were used in 77% and 74% of the patients (hypothermia vs. control, Table 2).

**Table 1. Clinical and Angiographic Data**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypothermia (n = 70)</th>
<th>Control (n = 68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>58</td>
<td>59</td>
</tr>
<tr>
<td>Women</td>
<td>15 (21%)</td>
<td>10 (15%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20 (29%)</td>
<td>9 (15%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9 (13%)</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>11 (16%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>31 (44%)</td>
<td>28 (41%)</td>
</tr>
<tr>
<td>Anterior STEMI</td>
<td>29 (41%)</td>
<td>35 (51%)</td>
</tr>
<tr>
<td>Inferior STEMI</td>
<td>41 (59%)</td>
<td>33 (49%)</td>
</tr>
</tbody>
</table>

p = NS (not significant) for all comparisons. Data are presented as mean ± SD.

SD, standard deviation; STEMI, ST-elevation myocardial infarction.

**Table 2. Medication and Procedures**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypothermia (n = 70)</th>
<th>Control (n = 68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial TIMI flow 0/1</td>
<td>61 (87%)</td>
<td>56 (82%)</td>
</tr>
<tr>
<td>Initial TIMI flow 2/3</td>
<td>9 (13%)</td>
<td>12 (18%)</td>
</tr>
<tr>
<td>TIMI 3 flow post PCI</td>
<td>66 (94%)</td>
<td>62 (91%)</td>
</tr>
<tr>
<td>Thrombectomy</td>
<td>43 (61%)</td>
<td>48 (71%)</td>
</tr>
<tr>
<td>GpIIb/IIIa</td>
<td>20 (29%)</td>
<td>28 (41%)</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>38 (54%)</td>
<td>33 (49%)</td>
</tr>
<tr>
<td>Ticagrelor/Prasugrel</td>
<td>54 (77%)</td>
<td>50 (74%)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>70 (100%)</td>
<td>68 (100%)</td>
</tr>
<tr>
<td>Buspirone 30 mg</td>
<td>44 (71%)</td>
<td>0</td>
</tr>
<tr>
<td>Meperidine/Pethidine</td>
<td>114 ± 67 mg</td>
<td>0</td>
</tr>
</tbody>
</table>

TIMI, thrombolysis in myocardial infarction; PCI, percutaneous coronary intervention.
TABLE 3. Induction of Hypothermia

| Mean core temp at reperfusion: | 34.7°C |
| Mean catheter cooling rate:    | 6°C/hour |
| Patients ≤ 35.0°C at reperfusion: | 80% |
| Symptom to randomization        |          |
| Hypothermia                     | 138 (±66) |
| Control                         | 135 (±59) |
| Randomization to balloon         |          |
| Hypothermia                     | 42 min   |
| Control                         | 34 min   |
| Increased time to reperfusion in hypothermia group | 8 min |

Hypothermia treatment

Baseline tympanic temperature was similar in the two groups (36.1°C±0.7°C vs. 36.1°C±0.7°C). After randomization to the hypothermia group, cold saline was started after 7 minutes and endovascular cooling after 30 minutes (mean). Hypothermia treatment caused an increase in randomization-to-balloon time of 8 minutes from 34 to 42 minutes (Table 3). Average temperature at reperfusion was 34.7°C±0.6°C. At the time of reperfusion, a core body temperature of ≤35°C was achieved in 80% of the patients randomized to hypothermia. Cold saline infusion and endovascular cooling were successfully used in 69 of the 70 patients. Intravenous Meperidine was administered at the catheterization laboratory to prevent shivering in all patients in the hypothermia group with a mean total dose of 113±65 mg. Buspirone was administered to 96% of the patients. Mean saline volume was comparable between CHILL-MI and RAPID MI-ICE (1325±523 mL vs. 1540±430 mL).

Assessment of IS and myocardium at risk

CMR data were missing in 17% of the patients and were equally distributed between the groups. The reasons for missing CMR data were claustrophobia, CMR not available/image quality unsatisfactory, patient not willing, CMR stopped at the patient’s request, chronic back pain, incorrecty randomized, and rib fracture after cardiopulmonary resuscitation. There was no difference between the hypothermia and control groups with regard to the timing of the CMR examination (3.8±1.3 days vs. 3.6±1.4 days, hypothermia vs. control).

Analysis of interaction between the two studies demonstrated no significant interaction for the IS/MaR results (p=0.20). The primary endpoint of IS/MaR was reduced for patients in the hypothermia group, relative reduction (RR) 15% (40.5 28.0–57.6 vs. 46.6 36.8–63.8, median, inter quartile range [IQR]), hypothermia n=57 vs. control n=56 p=0.046 (Fig. 1). The RR in IS/MaR in the anterior infarcts was 29% (40.9, 14.6–62.6 vs. 57.2, 42.4–67.3, median, IQR), hypothermia n=20 vs. control n=27, p=0.08 (Fig. 2a). The RR for IS/MaR in the inferior infarcts was 12% (35.7, 27, 2–56.8 vs. 40.6, 26.8–59.5, median, IQR), hypothermia n=36 vs. control n=28, p=0.43 (Fig. 2b). The absolute reduction in IS to the left ventricular mass (IS/LV) was 6.2% in early anterior STEMI, p=0.15.

![Infarct size/Myocardium at Risk](image)

**FIG. 1.** Infarct size as percent of myocardium at risk. Infarct size as percent of myocardium at risk by treatment (median, IQR, 5–95%). Infarct size in % of myocardium at risk (IS/MaR), relative risk reduction (RR). A: All patients (control n=39, hypothermia n=42, p=0.049) B: All patients with anterior STEMI 0–4h (control n=17, hypothermia n=24, p=0.046). IQR, interquartile range; IS/MaR, infarct size as a percentage of myocardium at risk; STEMI, ST-elevation myocardial infarction.

Exploratory analyses of factors influencing the effect of hypothermia

Although no subgroup demonstrated a significant p-value for interaction, subgroup analyses were performed to aid the understanding of what patient groups might benefit most from the treatment and to help design future confirmatory studies.

Patients with a large MaR defined as >30% of LV had a significantly reduced IS/MaR of 26.5% by hypothermia (40.5, 27.0–57.6 vs. 55.1, 41.1–64.4, median, IQR; hypothermia n=42 vs. control n=37, p=0.03) and absolute reduction in IS/LV of 5.1% by hypothermia (22.5, 10.3–23.5 vs. 17.4, 16.0–28.8, median, IQR; hypothermia n=42 vs. control n=37, p=0.03).

Patients with smaller MaR (<30% of LV) did not show any benefit of hypothermia in either IS/MaR (35.8, 28.3–57.5 vs. 38.4, 27.4–59.7, median, IQR; hypothermia n=15 vs. control n=19, p=0.50) or IS/LV (10.6, 6.9–16.2 vs. 11.8, 8.5–15.3, median, IQR; hypothermia n=16 vs. control n=20, p=0.50).

Patients with short symptom to reperfusion time (<3 hours) had a significantly reduced IS/MaR of 24% by hypothermia (35.5, 27.0–54.0 vs. 46.6, 38.0–63.3, median, IQR; hypothermia n=39 vs. control n=36, p=0.03), while patients with longer symptom to reperfusion time (3–6 hours) did not have any effect of hypothermia (47.3, 35.8–61.6 vs. 49.9, 33.6–64.6, median, IQR; hypothermia n=18 vs. control n=19, p=0.69).

IS/MaR was especially reduced in early anterior STEMI (0–4h) in the hypothermia group, RR=31% (40.5, 28.8–51.9
Combination hypothermia was well tolerated in all patients. PCI operators and nurses found the protocol easy to implement with minimal disruption to normal catheter laboratory workflow. The primary clinical endpoint of adjudicated death and heart failure was significantly reduced in the hypothermia group at 45 days (2 vs. 11 events, \( p = 0.009 \), Fig. 3). The trend was consistent over the two trials, with 0 versus 3 events in RAPID MI-ICE and 2 versus 8 events in CHILL-MI. Heart failure was only present in patients with anterior infarcts. Since there was no mortality in either group, the reduction in events consisted entirely of fewer adjudicated heart failure events in the hypothermia group. There was no difference in rates of pneumonia, ventricular arrhythmias, bradycardia, reinfarction, stroke, or major bleeding between the groups (Table 4).

### Other endpoints

Ejection fraction analyzed by CMR at 4 ± 2 days did not differ between groups. The area under the curve or peak

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**FIG. 2.** Infarct size by infarct location. Predefined subgroup analysis of infarct size as percent of myocardium at risk by treatment and location, full analysis set (median, IQR, 5–95%). (a) Anterior STEMI (control \( n = 27 \), hypothermia \( n = 20 \), \( p = 0.08 \)). (b) Inferior STEMI (control \( n = 28 \), hypothermia \( n = 36 \), \( p = 0.43 \)). (c) All patients with anterior STEMI 0-4h (control \( n = 17 \), hypothermia \( n = 24 \), \( p = 0.046 \)).

**FIG. 3.** Death and heart failure. Main clinical endpoint of death and heart failure at day 45. There were no deaths. Heart failure events were monitored and adjudicated by a blinded central adjudication committee.

**TABLE 4. CLINICAL EVENTS**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypothermia (( n = 70 ))</th>
<th>Control (( n = 68 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality at 45 days</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2 (3%)</td>
<td>11 (16%)</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>VT/VF</td>
<td>5 (7%)</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>4 (6%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6 (9%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>2 (3%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

\(^{a}p = 0.009\).

VT/VF, ventricular tachycardia/ventricular fibrillation.
concentration for troponin T or CKMB did not differ between the groups. NT-proBNP at 4±2 days was also similar between the groups.

**Discussion**

This combined population of two similar trials (RAPID MI-ICE and CHILL-MI) examining a rapid cooling protocol using the combination of intravenous cold saline and endovascular cooling in patients treated with primary PCI for STEMI, indicates that hypothermia may reduce IS in myocardium at risk. This result is supported as the key clinical endpoint of death and heart failure was significantly and consistently reduced in the two trials. In further exploratory analyses, we found that patients with large infarcts (MaR > 30%) and shorter symptom onset to reperfusion times (0–3 hours) benefitted the most from hypothermia therapy. Previous studies have suggested, based on preclinical models that these are two key variables to consider in cardioprotective trial design (Yellon and Hausenloy, 2007).

**Safety**

The safety of using endovascular cooling alone has previously been demonstrated in conscious patients with AMI (Dixon et al., 2002; Kandzari et al., 2004; Erlinge et al., 2013). The rationale of using a combination of cold saline together with endovascular cooling was to achieve a rapid induction of hypothermia as early as possible during the ischemic period without delaying reperfusion therapy. However, an intravenous infusion of cold saline could possibly lead to an increase in acute heart failure and pulmonary congestion in patients with AMI. In this population without previous congestive heart failure on presentation, despite large myocardial infarctions, clinical signs of heart failure were reduced in the hypothermia group. There were no differences in the rates of pneumonia, ventricular arrhythmias, bradycardia, reinfarction, stroke, or major bleeding between the groups and most importantly there were no deaths in either group, indicating that cooling is safe.

**Feasibility**

In a previous experimental study, it has been demonstrated that a combination of cold saline infusion and an endovascular cooling catheter can accomplish a reduction in core body temperature to ≤35°C within 5–10 minutes in 40–50 kg swine (Gotberg et al., 2008). In the present pooled analysis, inducing hypothermia with a combination of cold saline infusion and endovascular cooling was clinically feasible and achieved a rapid reduction in core body temperature in awake patients with STEMI without a major delay in time to reperfusion (8 minutes). In patients randomized to hypothermia, 80% reached the target temperature of ≤35°C.

**Infarct size**

Using CMR for assessing IS/MaR is a validated method in patients with AMI (Carlsson et al., 2009; Sorensson et al., 2010; Ubachs et al., 2012) and has been used to describe the natural course of infarct evolution in man (Hedstrom et al., 2009). This methodology reduces the sample size needed in clinical trials to show significant effects of cardioprotective interventions. Therapeutic hypothermia reduced IS/MaR by 15% in the entire study population. Of note, the effect was of pronounced benefit in patients with large infarctions (24% reduction of IS/MaR) and patients with shorter duration from symptom onset to reperfusion (27% reduction of IS/MaR).

The combined group identified in the CHILL-MI and the RAPID MI-ICE trials with anterior STEMI and a duration of <4 hours had a 31% reduction in IS/MaR and an absolute reduction in IS/LV of 6.2%. This is noteworthy because an absolute IS reduction of 5.1% in the STOP-AMI trial translated into reduced mortality and is accepted as a clinically meaningful result for cardioprotection trials (Schonig et al., 2000). It would be interesting to further explore the potential cardioprotective effects of hypothermia in a new study focusing only on anterior STEMI with short duration (<4 hours from symptom onset to PCI), especially in light of the several cardioprotective studies previously focusing on this subset of STEMI patients (Hausenloy et al., 2010; Stone et al., 2012).

**Other endpoints**

The main clinical endpoint, a combination of death and heart failure, was significantly reduced in the therapeutic hypothermia group, explained solely by a reduction in heart failure since there were no deaths in either arm. Since all the heart failure events occurred in patients with anterior STEMI, the reduction in heart failure could be the result of a more pronounced IS reduction in anterior STEMIs.

**Limitations**

This is a combined analysis of two studies with similar, but not exactly the same protocol (hypothermia duration 3 hours or 1 hour). Although there was no significant heterogeneity in the interaction test, the CHILL-MI trial showed a numerically smaller and nonsignificant reduction of IS than the pilot study. Since the decision to go forward with the larger study was taken knowing the pilot study results, the pooled analysis might have a bias toward larger effect. The patients were not at the highest risk since patients older than 75, those with Killip Class II-IV, or cardiac arrest were excluded.

It is plausible that part of the hyperenhanced myocardium on CMR acquired at 4±2 days can be due to edema, since it has recently been shown that there is a significant decrease in hyperenhanced myocardium during the first week after infarction (Engblom et al., 2009). There was, however, no difference in the timing of the CMR examination between the hypothermic patients and the controls. Furthermore, MaR was similar between treatment groups. CMR data were missing in 17% of the patients, equally distributed between the groups and of similar magnitude as observed in other CMR-based trials (Stone et al., 2012). The exploratory and secondary analysis should be evaluated with caution due to risk for type I error.

**Implications**

Our data suggest that hypothermia may have the largest benefit in early presenters (<3–4 hours) with larger infarcts (MaR > 30%). In the CHILL-MI trial, 91% of LAD infarcts and only 51% of RCA/LCX infarcts had MaR > 30%, which suggest future clinical trials to be focused on anterior STEMI. Contrary to our hypothesis, the possible benefits of hypothermia do not seem to be influenced by angiographic findings (IRA spontaneous reperfusion, degree of collaterals to
IRMA when occluded) on admission coronary angiogram. These are important findings for future randomized clinical trials.

The combined cooling methods are very effective, safe, and can be easily adopted by STEMI centers as an adjunct to primary PCI. Since lower temperature at reperfusion has, according to animal data, incremental salvage potential, more powerful cooling methods (< 34°C) should be developed and investigated.

Conclusions

The pooled analysis of RAPID MI-ICE and CHILL-MI indicates that hypothermia induced by a combination of cold saline infusion and endovascular cooling in STEMI patients might reduce IS and the incidence of heart failure. This potential effect seems to be most pronounced in patients with large anterior infarctions who present early after symptom onset. These findings warrant confirmation by a larger scale prospective trial of endovascular cooling in the routine care of AMI focusing on the potential target population with large anterior myocardial infarction.

Acknowledgment

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