Hypothermia in patients with acute myocardial infarction: a meta-analysis of randomized trials

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Abstract

Background In patients with acute myocardial infarction (MI) receiving percutaneous coronary intervention (PCI), the role of systemic therapeutic hypothermia remains controversial. We sought to investigate the role of systemic therapeutic hypothermia versus standard of care in patients with acute MI treated with PCI.

Methods This is a study-level meta-analysis of randomized trials. The primary outcome was all-cause death. The main secondary outcome was infarct size. Other secondary outcomes were recurrent MI, ischemia-driven target vessel revascularization (TVR), major adverse cardiovascular events, and bleeding.

Results A total of 1012 patients with acute MI receiving a PCI in nine trials (503 randomly assigned to hypothermia and 509 to control) were available for the quantitative synthesis. The weighted median follow-up was 30 days. As compared to controls, patients assigned to hypothermia had similar risk of all-cause death (risk ratio, [95% confidence intervals], 1.25 [0.80; 1.95], $p=0.32$), with a trend toward higher risk of ischemia-driven TVR (3.55 [0.80; 15.87], $p=0.09$) mostly due to acute or subacute stent thrombosis. Although in the overall cohort, infarct size was comparable between groups (standardized mean difference [95% Confidence intervals], 0.06 [−0.92; 1.04], $p=0.92$), patients effectively achieving the protocol-defined target temperature in the hypothermia group had smaller infarct size as compared to controls (p for interaction = 0.016). Treatment strategies did not differ with respect to the other outcomes.

Conclusions As compared to standard of care, systemic therapeutic hypothermia in acute MI patients treated with PCI provided similar mortality with a signal toward more frequent repeat revascularization. Among patients assigned to hypothermia, those effectively achieving the protocol-defined target temperature displayed smaller infarct size.

Trial Registration PROSPERO, CRD42019138754.

Keywords Hypothermia · Meta-analysis · Myocardial infarction · Percutaneous coronary intervention · Randomized trial

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Introduction

Percutaneous coronary intervention (PCI) represents the therapy of choice for reperfusion of patients with ST-segment elevation myocardial infarction (MI) [1, 2]. However, even after timely restoration of blood flow at epicardial level, a substantial proportion of MI patients develop extensive myocardial necrosis [3]. The ischemic process represents one of the most important determinants of myocardial damage in the infarct-related area, being modulated by means of several protective modalities including pharmacological agents, pre- or post-conditioning, and hypothermia [4].

The rationale for hypothermia in patients with acute MI lies on the reduction of energy consumption at cardiac level, which, in turn, has been consistently associated with reduced myocardial infarct size in several animal studies [5]. However, a number of randomized trials, comparing different strategies for systemic therapeutic hypothermia adjunctive to PCI versus standard of care in patients with acute MI, failed to translate these experimental findings in consistent beneficial effects in humans; indeed, while some trials demonstrated the clinical benefit of hypothermia at least in certain subgroups of patients [6], other trials suggested harm [7]. In this regard, the role of systemic therapeutic hypothermia in this setting remains to be defined.

To gain more insight into this topic, we performed a meta-analysis of randomized trials investigating the effect of systemic therapeutic hypothermia in patients with acute MI receiving PCI.

Methods

Search strategy and selection criteria

Details are provided in Supplementary Table 1.

Data collection and assessment of risk of bias

Two investigators (BA and SC) independently assessed publications for eligibility at title and/or abstract level and divergences were resolved by consensus. Studies that met inclusion criteria were selected for further analysis. The same two investigators independently evaluated the risk of bias for each study in accordance with The Cochrane Collaboration method [8]. We did not use scores to evaluate the quality of included trials [9]. This is a meta-analysis of aggregate data: it was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research and no ethical approval was required. This study was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [10] and is registered with PROSPERO, number CRD42019138754.

Outcomes

The primary outcome of the current study was all-cause death. The secondary outcome was infarct size as measured by cardiac imaging. Other outcomes were recurrent MI, ischemia-driven target vessel revascularization (TVR), major adverse cardiovascular events (MACE), and bleeding. All outcomes were evaluated according to the intention-to-treat principle and were collected at the maximum follow-up duration in accordance with the definitions provided in the individual-trial protocols.

Statistical analysis

The means of continuous variables and the frequencies or percentages of categorical variables were extracted for exploratory purposes from baseline features of participants enrolled in each included study. Risk ratio (RR) with 95% confidence intervals [95% CI] and Hedges' g bias corrected standardized mean difference (SMD) were used as summary statistics to compare outcomes of interest in patients with acute MI treated with PCI and assigned to either systemic therapeutic hypothermia (hypothermia group) or standard of care (control group). The risk estimates were pooled using the Mantel–Haenszel or inverse variance methods for the random-effect model, and p values < 0.05 were considered statistically significant. The weighted median follow-up duration was calculated based on the sample size of each individual study. Treatment effect was not assessed in trials in which no events were reported within groups. Heterogeneity between trials was quantified using the I^2 statistic; values approaching 25%, 50%, and 75% were suggested to indicate low, moderate, or high heterogeneity, respectively [11]. In addition, we calculated the between-study variance with the Paule–Mandel or DerSimonian–Laird estimator for τ^2, as appropriate, and provided the 95% prediction interval of each pooled estimate [12]. The possibility of small-study effects resulting from publication bias or other biases was examined for the main outcomes by means of visual inspection of funnel plots of the RR or SMD of individual trials against their standard errors and by a test of asymmetry. We performed three sensitivity analyses for the main outcomes:

i) A Chi-square test for treatment-by-subgroup interaction assessed whether the predominant inclusion of patients with anterior acute MI (> 50% of available cohort) or the administration of new P2Y12 inhibitors (either prasugrel or ticagrelor in > 50% of available cohort), a per protocol target temperature ≤ 33 °C, the pre-hospital initiation of

hypothermia, the design (multicentre versus single-centre), and the publication status (full-length manuscript versus meeting presentation) of each included trial were associated with significant changes in the pooled estimates;

ii) An influence analysis assessed the changes in the direction of the summary estimates computed omitting one study at a time

iii) A random-effects meta-regression analysis assessed the modification of treatment effect according to age, proportion of females, and diabetics, door-to-balloon time, and actual body temperature achieved at reperfusion in the investigational arm, proportion of patients achieving the protocol-defined target temperature, and hypothermia duration.

All analyses were performed in R (version 3.3.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

The electronic search identified nine trials, seven with full-length articles [6, 7, 13–17] and two with meeting presentations [18, 19]. A total of 1012 patients with acute MI receiving a PCI were randomly assigned to either hypothermia ($n=503$) or control ($n=509$, Supplementary Fig. 1).

The main characteristics of included trials and the definitions used for the outcomes of interest are described in Supplementary Table 2. All trials but three [6, 16, 17] had a multicentre design. Eight trials enrolled patients with ST-elevation MI and excluded those with cardiogenic shock. One trial (accounting for 4% of the entire cohort available for the current report) enrolled patients with cardiogenic shock and acute MI, regardless of the presence of significant ST elevation at baseline ECG [16]. One trial included only patients with anterior ST-elevation MI [15]. In all trials, patients presenting with acute MI underwent emergency PCI and received peri-procedural antithrombotic therapies according to standard practice at enrolling centers. Patients assigned to hypothermia started the investigational treatment immediately before reperfusion. In one trial, hypothermia was started before hospital arrival by means of body surface cooling pads [17]. In all trials, hypothermia was achieved by means of percutaneous catheters inserted through the femoral vein [6, 13–19] or peritoneum [7]. Five trials reported specific protocols for continuous infusion of cold fluids to speed-up the lowering of core body temperature [6, 7, 14, 15, 17]. The amount of fluids to be administered ranged between 600 and 2000 mL or between 2000 and 4000 mL, depending on the infusion route (either intravenous or peritoneal, respectively). After reperfusion, hypothermia was continued for a period of time ranging between 1 and 24 h. A detailed description of pharmacological protocols for shivering prophylaxis was available in all but two trials [16, 19], and consisted mostly of oral buspirone (30–60 mg) and intravenous infusion of meperidine (1 mg/kg loading, followed by 20–35 mg/h titrated to effect). In three trials [7, 14, 15], the primary endpoint was the feasibility of hypothermia before reperfusion in MI patients receiving PCI. In four trials, the primary endpoints consisted of measures derived from cardiac magnetic resonance imaging (MRI) [6, 7, 14, 15, 17] or single-positron emission computed tomography (SPECT) [18, 19]: cardiac MRI was performed between 2 and 6 days and between 30 and 45 days (as per protocol requirements), whilst SPECT was performed 30 days after PCI. Details of acquisition protocols were available for all cardiac imaging studies. The remaining trials focused on clinical [13] or hemodynamic [16] measures of efficacy. The evaluation of risk of bias and overall quality of included trials are reported in Supplementary Table 3.

The main characteristics of patients included in the original trials are listed in Table 1. Participants were in the majority male, with a median age of 58.0 years [interquartile range, (IQR) 57.0–59.5 years], and about 17% were diabetics. Nearly half of patients presented with acute anterior MI. New P2Y12 inhibitors were administered in less than 40% of patients and a similar proportion of participants received a peri-procedural infusion of glycoprotein IIb/IIIa inhibitors. Interestingly, the proportion of patients treated with coronary stenting increased from 84 to 100% from earlier to contemporary trials. The median door-to-balloon time was longer in the investigational as compared to the control arm (60.5 min, IQR [50.5–95.0] versus 48.0 min, IQR [41.0–92.5], respectively). A proportion of participants between 76% and 100% achieved the protocol-defined target core body temperature. The core body temperature measured at the time of reperfusion was 34.4 °C, IQR [34.0–34.7]. The hypothermia was continued for a median of 3 h after reperfusion.

Outcomes

A total of 1010 patients (99.8%) were available for evaluation of at least one outcome of interest. Of these, 502 were assigned to hypothermia and 508 patients were assigned to control therapy. The weighted median follow-up was 30 days (range 30–45 days).

Main outcomes (Fig. 1 a, b)

All-cause death was assessed in all patients. Patients assigned to hypothermia versus control showed comparable risk of all-cause death (5.9% versus 4.7%; RR 1.25 [0.80; 1.95], $p=0.32$; $I^2=0\%$). The 95% prediction interval for this outcome contained the null [0.70; 2.24], without evidence of heterogeneity.

Table 1 Main baseline features of patients enrolled in trials included in the study

Trial (registration number)	Patients	Age, years	Female gender	Diabetes mellitus	Anterior MI	Temperature management system; access	Target temperature	Patients achieving target temperature*	Fluids administration protocol	Pharmacological shivering prophylaxis protocol
CHILL-MI (NCT01379261)	120	58.0	21 (17.5)	11 (9.2)	51 (42.5)	Accutrol/InnerCool RTx (ZOLL Medical, Chelmsford, MA, USA); endovascular	33 °C	46 (76.0)	Cold saline 600–2000 mL (10 mL/kg for anterior STEMI; 20 mL/kg for inferior STEMI)	Oral buspirone 30 mg; intravenous meperidine 1 mg/kg loading followed by 25 mg/h infusion as needed
COOL AMI EU (NCT02509832)	50	58.5	7 (14.0)	7 (14.0)	50 (100)	Proteus (ZOLL Medical Corporation, Chelmsford, MA, USA); endovascular	32 °C	23 (92.0)	Cold saline (1000 mL)	Oral buspirone 60 mg; intravenous meperidine 1 mg/kg loading over 15 min followed by 25–35 mg/h infusion titrated to effect
COOL-MI I Pilot (-)	42	55.0	6 (16.7)	10 (23.8)	19 (45.2)	SetPoint (Radiant Medical Inc., Redwood City, CA, USA); endovascular	33 °C	21 (100)	N/A	Oral buspirone 30–60 mg; intravenous meperidine 75–100 mg loading over 15 min followed by 25–30 mg/h infusion titrated to effect
COOL-MI II (NCT00248196)	357	59.5	89 (25.0)	62 (17.5)	153 (43.0)	Reprieve (Radiant Medical Inc; Redwood City, CA, USA); endovascular	33 °C	155 (88.0)	N/A	Oral buspirone 60 mg; intravenous meperidine 25–30 mg/h infusion titrated to effect
ICE-IT I (-)	228	57.0	51 (22.3)	38 (16.7)	99 (43.4)	Celsius Control (Innercool Therapies Inc., San Diego, CA, USA); endovascular	N/R	N/R	N/R	N/R
RAPID-MI-ICE (NCT00417638)	20	60.0	4 (22.2)	3 (16.7)	13 (72.2)	Celsius Control (Innercool Therapies Inc., San Diego, CA, USA); endovascular	33 °C	10 (100)	Cold saline (1000–2000 mL according to physician's discretion)	Oral buspirone 30 mg; intravenous meperidine 1 mg/kg loading followed by 30 mg/h infusion titrated to effect

Table 1 (continued)

Trial (registration number)	Patients	Age, years	Female gender	Diabetes mellitus	Anterior MI	Temperature management system; access	Target temperature	Patients achieving target temperature*	Fluids administration protocol	Pharmacological shivering prophylaxis protocol
SHOCK-COOL (NCT01890317)	40	76.5	14 (35.0)	18 (45.0)	N/R	CoolGard (ZOLL Medical Corporation, Chelmsford, MA, USA); endovascular	33 °C	20 (100)	N/R	N/R
STATIM (NCT01777750)	101	56.5	20 (19.8)	15 (14.8)	52 (51.4)	Pre-hospital: EMCOOLS Flex (EMCOOLS Emergency Medical Cooling Systems, Pfaffstätten, Austria); surface cooling pads In-hospital: Accutrol/ InnerCool RTx (ZOLL Medical, Chelmsford, MA, USA); endovascular	34 °C	38 (81.0)	Cold saline (10 mL/kg for anterior STEMI; 20 mL/kg for inferior STEMI)	Oral buspirone 30 mg; intravenous meperidine 1 mg/kg loading followed by 30 mg/h infusion titrated to effect
VELOCITY (NCT01655433)	54	57.3	8 (14.8)	12 (22.2)	25 (46.3)	Velomedix (Velomedix Inc, Menlo Park, CA, USA); peritoneal	32.5 °C	24 (89.0)	Cold fluid (2500–4000 mL according to peritoneal pressure)	Oral buspirone 30 mg; intravenous meperidine 1 mg/kg loading followed by 25 mg/h infusion titrated to effect

Overall numbers (proportions) and mean values are reported; (STE)MI: (ST-elevation)myocardial infarction

N/A not applicable, *N/R* not reported, *CHILL-MI* rapid endovascular catheter core cooling combined with cold saline as an adjunct to percutaneous coronary intervention for the treatment of acute myocardial infarction, *COOL AMI EU* a multicenter, prospective, randomized-controlled trial to assess cooling as an adjunctive therapy to percutaneous intervention in patients with acute myocardial infarction, *COOL-MI II* cooling as an adjunctive therapy to percutaneous intervention in patients with acute myocardial infarction, *ICE-IT I* Intravascular Cooling Adjunctive to Percutaneous Coronary Intervention (part 1) , *RAPID-MI-ICE* a randomized, controlled study of the use of central venous catheter core cooling combined with cold saline, and rewarming as an adjunct to percutaneous coronary intervention for the treatment of acute myocardial infarction, *SHOCK-COOL* Randomized Pilot Study of Mild Hypothermia in Cardiogenic Shock Complicating Myocardial Infarction, *STATIM* strategic target temperature management in myocardial infarction, *VELOCITY* Pilot Study to evaluate ultrafast hypothermia before reperfusion in patients with acute ST-elevation myocardial infarction

*Patients effectively receiving hypothermia among those randomized; in case the number (proportion) of patients effectively achieving target temperature was not available in the original trial, the number (proportion) of patients achieving a temperature ≤ 35 °C has been provided

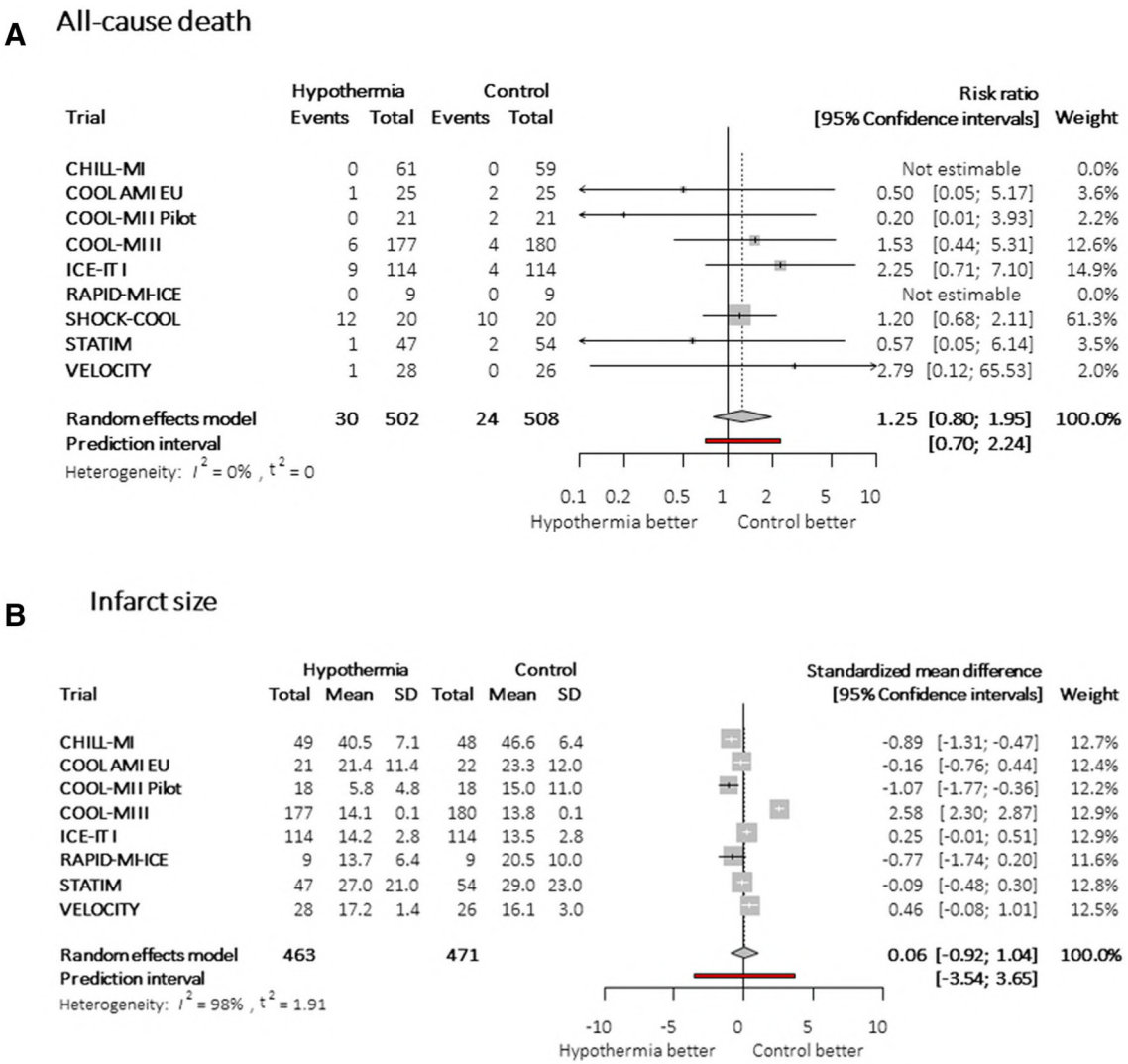

Fig. 1 Forest plots for primary and main secondary outcomes with systemic therapeutic hypothermia versus control. Risk ratio for all-cause death (a) and standardized mean difference for infarct size (b) with systemic therapeutic hypothermia versus control. The diamonds indicate the point estimate and the left and the right ends of the lines the [95% Confidence intervals]

Infarct size was measured in 934 patients (92.4% of the entire cohort with available clinical data). Patients assigned to hypothermia versus control showed comparable infarct size (range: 5.8–40.5% versus 13.5–46.6% of the left ventricle; SMD = 0.06 [− 0.92, 1.04], $p = 0.92$; $I = 98\%$). The 95% prediction interval for this outcome contained the null [− 3.54; 3.65], with evidence of high heterogeneity. Of interest, the risk estimate for infarct size was independent from the type of imaging used (cardiac MRI versus SPECT; p for interaction [p_{int}] = 0.39).

Other outcomes (Supplementary Fig. 2 A–D)

Recurrent MI was assessed in 970 patients (96.0% of the entire cohort with available clinical data). Patients assigned to hypothermia versus control showed comparable risk of recurrent MI (1.2% versus 0.8%; RR 1.31 [0.40; 4.30], $p = 0.66$; $I^2 = 0\%$).

Ischemia-driven TVR was assessed in 744 patients (73.6% of the entire cohort with available clinical data). Patients assigned to hypothermia versus control showed a trend toward higher risk for ischemia-driven TVR (2.4% versus 0.2%; RR 3.55 [0.80; 15.87], $p = 0.09$; $I^2 = 0\%$). Of note, there was only one ischemia-driven TVR event reported in the control group [17], and more than half of ischemia-driven TVR in the hypothermia group were due to acute or subacute stent thrombosis (ST). In this regard, by omitting the Strategic Target Temperature Management in Myocardial Infarction (STATIM) trial [17], hypothermia associated with a significantly higher risk of

ischemia-driven TVR (RR 6.71 [1.23; 36.6], $p = 0.028$; $I^2 = 0\%$).

MACE was assessed in 701 patients (69.4% of the entire cohort with available clinical data). Patients assigned to hypothermia versus control showed comparable risk of MACE (5.7% versus 3.7%; RR 1.44 [0.61; 3.38], $p = 0.40$; $I^2 = 7\%$).

Bleeding was assessed in 425 patients (42.0% of the entire cohort with available clinical data). Patients assigned to hypothermia versus control showed comparable risk of bleeding (7.1% versus 4.3%; RR 1.46 [0.79; 2.70], $p = 0.22$; $I^2 = 0\%$). The 95% prediction interval for all these outcomes contained the null, without evidence of significant heterogeneity.

Sensitivity analyses for main outcomes

In the influence analysis, no single study significantly altered the direction of the summary estimates for all-cause death and infarct size (Supplementary Fig. 3 A, B). We found no evidence for small-study effects (Supplementary Fig. 4 A, B).

There was no evidence of treatment-by-subgroup interaction regarding all-cause death and infarct size and the proportion of patients with anterior acute MI ($p_{int} = 0.42$ and 0.53, respectively), receiving new P2Y12 inhibitors ($p_{int} = 0.41$ and 0.34, respectively), per protocol target temperature ≤ 33 °C ($p_{int} = 0.41$ and 0.83, respectively), pre-hospital initiation of hypothermia ($p_{int} = 0.51$ and 0.78, respectively), trial design ($p_{int} = 0.62$ and 0.48, respectively), and publication status ($p_{int} = 0.27$ and 0.13, respectively).

The meta-regression analysis showed that the higher the proportion of patients achieving the protocol-defined target temperature, the lower the infarct size in the hypothermia group ($p_{int} = 0.016$, Supplementary Table 4).

Discussion

This is the most comprehensive meta-analysis of study-level data investigating MI patients treated with PCI and randomly allocated to either systemic therapeutic hypothermia or standard of care. The main findings of this study can be summarized as follows:

i) Hypothermia is associated with similar mortality with a signal toward more frequent repeat revascularization, mainly due to ST, as compared to control therapy;
ii) There is a significant temperature-by-infarct size interaction demonstrating a reduced infarct size in patients achieving the protocol-defined target temperature.

Notwithstanding the encouraging preclinical data [20, 21], randomized trials investigating the outcomes of hypothermia in patients with acute MI receiving PCI have been largely inconclusive. Indeed, although hypothermia has proven to be feasible and safe in this clinical setting, its clinical benefit has yet to be demonstrated [22]. The current analysis does not support a clinical difference between patients with acute MI treated with PCI assigned to hypothermia versus those who did not. On one hand, the comparable risk of death, MI, and bleeding observed between treatment groups is reassuring and highlights once more that hypothermia could be implemented during acute MI with neither clinically relevant delay in reperfusion nor major adverse outcomes. On the other hand, despite the fact that we pooled the largest cohort of patients from randomized-controlled trials dealing with the study research question [22, 23], individuals at high-risk for adverse outcomes, such as those with previous MI or presenting with acute heart failure or hemodynamic impairment, were poorly represented in primary trials and this cohort. Of note, roughly 44% of deaths observed in this meta-analysis occurred among participants of the Randomized Pilot Study of Mild Hypothermia in Cardiogenic Shock Complicating Myocardial Infarction (SHOCK-COOL) trial [16], which enrolled patients with cardiogenic shock complicating acute MI.

Infarct size, as measured with cardiac imaging, represents a valuable prognostic marker in clinical trials designed to test the efficacy of reperfusion therapies for acute MI [24]. In the present analysis, infarct size was not reduced in the overall cohort of MI patients receiving hypothermia before PCI. However, patients in the hypothermia group effectively achieving the protocol-defined target temperature showed a significant reduction of infarct size, without effect modification depending on duration of hypothermia. Despite the intrinsic limitations of subgroup analyses, this result is relevant for a couple of reason. Animal models of acute MI showed that hypothermia could significantly reduce infarct size during the ischemic rather than during the reperfusion phase [25]. In line with these considerations, the myocardial damage in patients with acute MI could be prevented by effectively reducing the temperature in the infarct-related area before reperfusion [26]. In this context, while the infusion of cold fluids adjunctive to percutaneous cooling systems represents an important tool to speed-up the reduction of core body temperature during the early MI phase, the required volume overload may be detrimental in certain patients presenting hemodynamic impairment. For this reason, the possibility of faster and selective intracoronary hypothermia in MI patients scheduled for emergency PCI has recently attracted considerable interest and is subject to investigation in a randomized-controlled clinical trial (NCT03447834) [27].

Remarkably, as compared to control therapy, hypothermia was associated with numerically more frequent repeat

revascularizations. Five out of nine events occurring in the hypothermia group were due to ST [7, 15]. This finding requires an in-depth discussion. Preclinical evidence has correlated hypothermia with increased platelet activation [28], and previous retrospective data in patients with acute MI and cardiac arrest [29] or cardiogenic shock [30] showed a clustering of ST in patients treated with hypothermia. Although the signal toward higher risk of ST with hypothermia might be mechanistically plausible, the baseline critical illness rather than hypothermia per se might have increased the risk of ST observed previously [31]. In addition, being ST multifactorial in nature, the revascularization techniques (including suction devices and the type of stents), and ancillary therapies of MI patients, which varied considerably among included studies, might contribute to the observed risk. Of interest, the majority of trials pooled in our meta-analysis excluded patients with cardiac arrest or cardiogenic shock. In addition, one-third of thrombotic events were observed among patients treated with peritoneal hypothermia [7]. Only one case of ST had increased platelet activation at point-of-care testing [15]. Future trials should specifically examine the possible causative association between hypothermia, platelet aggregation, and subsequent risk of ST in contemporary practice, addressing whether there is a particular hazard with certain temperature management systems as compared to others.

Study limitations

A number of limitations should be taken into account when interpreting the results of this study.

i) This is a study-level meta-analysis and an individual patient data analysis would be preferable for at least two reasons: first, to adequately investigate a potential benefit of hypothermia according to infarct location and time to presentation after symptoms onset, as previously reported [22, 23]; and, second, to assess a treatment effect modification with hypothermia dependent on clinical and procedural factors other than those investigated in this meta-analysis.
ii) In the absence of double blinding, possible bias in the adjudication of outcome events among treatment groups cannot be ruled out.
iii) In the primary trials, patients were included over a time span of 15 years. In this regard, the clinical, pharmacological, and interventional management of participants varied considerably across the trials and their impact on the analyzed outcomes remains to be addressed.
iv) The overwhelming majority of included trials had a follow-up length of 30 days, which is insufficient to address the long-term prognostic impact of hypothermia in this setting.
v) Although different temperature management systems with variable cooling performance (average °C reduction/unit of time) were included in this analysis, their comparative efficacy and safety was not investigated.

Conclusions

In patients with acute MI undergoing PCI, systemic therapeutic hypothermia did not reduce mortality compared with the standard of care. Patients achieving the protocol-defined target temperature showed reduced infarct size compared with patients who did not achieve this target. The signal toward more frequent repeat revascularization with hypothermia and the potential cardio-protective role of local rather than systemic hypothermia in this setting require further investigation.

Author contributions BA, GN, AL, ALL, DB, SK, EX, AK, and SC were involved in study conception and design. SC performed the data analysis. BA, K-LL, MJ, UL, and AK supervised the data analysis. BA together with AL, GN, AK, and SC wrote the first draft of the manuscript. BA, GN, AL, ALL, DB, SK, EX, K-LL, MJ, UL, HT, AK, and SC were involved in data acquisition and revised the manuscript for important intellectual contents. All authors had full access to all the data, including statistical reports and tables and approved the manuscript for final submission.

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Compliance with ethical standards

Conflict of interest MJ is consultant for Biotronik and OrbusNeich. The other authors declare no potential conflict of interest.

Patient consent Not required.

References

1. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Juni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO (2018) 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J. https://doi.org/10.1093/eurheartj/ehy394
2. Neumann JT, Gossling A, Sorensen NA, Blankenberg S, Magnussen C, Westermann D (2020) Temporal trends in incidence and outcome of acute coronary syndrome. Clin Res Cardiol. https://doi.org/10.1007/s00392-020-01612-1
3. Ndrepepa G, Kastrati A (2016) Mechanical strategies to enhance myocardial salvage during primary percutaneous coronary intervention in patients with STEMI. EuroIntervention 12(3):319–328
4. Davidson SM, Ferdinandy P, Andreadou I, Botker HE, Heusch G, Ibanez B, Ovize M, Schulz R, Yellon DM, Hausenloy DJ, Garcia-Dorado D (2019) Multitarget strategies to reduce myocardial ischemia/reperfusion injury. J Am Coll Cardiol 73(1):89–99

5. Hausenloy DJ, Yellon DM (2013) Myocardial ischemia-reperfusion injury: a neglected therapeutic target. J Clin Invest 123(1):92–100
6. Erlinge D, Gotberg M, Lang I, Holzer M, Noc M, Clemmensen P, Jensen U, Metzler B, James S, Botker HE, Omerovic E, Engblom H, Carlsson M, Arheden H, Ostlund O, Wallentin L, Harnek J, Olivecrona GK (2014) 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: a randomized controlled study of the use of central venous catheter core cooling combined with cold saline as an adjunct to percutaneous coronary intervention for the treatment of acute myocardial infarction. J Am Coll Cardiol 63(18):1857–1865
7. Nichol G, Strickland W, Shavelle D, Maehara A, Ben-Yehuda O, Genereux P, Dressler O, Parvataneni R, Nichols M, McPherson J, Barbeau G, Laddu A, Elrod JA, Tully GW, Ivanhoe R, Stone GW (2015) Prospective, multicenter, randomized, controlled pilot trial of peritoneal hypothermia in patients with ST-segment- elevation myocardial infarction. Circ Cardiovasc Interv 8(3):e001965
8. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 343:d5928
9. Juni P, Witschi A, Bloch R, Egger M (1999) The hazards of scoring the quality of clinical trials for meta-analysis. JAMA 282(11):1054–1060
10. Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 151(4):264–269
11. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327(7414):557–560
12. IntHout J, Ioannidis JP, Rovers MM, Goeman JJ (2016) Plea for routinely presenting prediction intervals in meta-analysis. BMJ Open 6(7):e010247
13. Dixon SR, Whitbourn RJ, Dae MW, Grube E, Sherman W, Schaer GL, Jenkins JS, Baim DS, Gibbons RJ, Kuntz RE, Popma JJ, Nguyen TT, O'Neill WW (2002) Induction of mild systemic hypothermia with endovascular cooling during primary percutaneous coronary intervention for acute myocardial infarction. J Am Coll Cardiol 40(11):1928–1934
14. Gotberg M, Olivecrona GK, Koul S, Carlsson M, Engblom H, Ugander M, van der Pals J, Algotsson L, Arheden H, Erlinge D (2010) A pilot study of rapid cooling by cold saline and endovascular cooling before reperfusion in patients with ST-elevation myocardial infarction. Circ Cardiovasc Interv 3(5):400–407
15. Noc M, Erlinge D, Neskovic AN, Kafedzic S, Merkely B, Zima E, Fister M, Petrovic M, Cankovic M, Veress G, Laanmets P, Pern T, Vukcevic V, Dedovic V, Sredniawa B, Swiatkowski A, Keeble TR, Davies JR, Warenits AM, Olivecrona G, Peruga JZ, Ciszewski M, Horvath I, Edes I, Nagy GG, Aradi D, Holzer M (2017) COOL AMI EU pilot trial: a multicentre, prospective, randomised controlled trial to assess cooling as an adjunctive therapy to percutaneous intervention in patients with acute myocardial infarction. EuroIntervention 13(5):e531–e539
16. Fuernau G, Beck J, Desch S, Eitel I, Jung C, Erbs S, Mangner N, Lurz P, Fengler K, Jobs A, Vonthein R, de Waha-Thiele S, Sandri M, Schuler G, Thiele H (2019) Mild hypothermia in cardiogenic shock complicating myocardial infarction. Circulation 139(4):448–457
17. Testori C, Beitzke D, Mangold A, Sterz F, Loewe C, Weiser C, Scherz T, Herkner H, Lang I (2019) Out-of-hospital initiation of hypothermia in ST-segment elevation myocardial infarction: a randomised trial. Heart 105(7):531–537
18. O'Neill WW (2003) COOL-MI: cooling as an adjunctive therapy to percutaneous intervention in patients with acute myocardial infarction. In: Presented at Transcatheter Cardiovascular Therapeutics Conference 2003, Washington DC, USA, September, 2003
19. Grines CL (2004) ICE-IT-1: intravascular cooling adjunctive to percutaneous coronary intervention for acute myocardial infarction (part 1): a preliminary review of results. In: Presented at Transcatheter Cardiovascular Therapeutics Conference 2004, Washington DC, USA, September, 2004
20. Dae MW, Gao DW, Sessler DI, Chair K, Stillson CA (2002) Effect of endovascular cooling on myocardial temperature, infarct size, and cardiac output in human-sized pigs. Am J Physiol Heart Circ Physiol 282(5):H1584–1591
21. Tissier R, Ghaleb B, Cohen MV, Downey JM, Berdeaux A (2012) Myocardial protection with mild hypothermia. Cardiovasc Res 94(2):217–225
22. Villablanca PA, Rao G, Briceno DF, Lombardo M, Ramakrishna H, Bortnick A, Garcia M, Menegus M, Sims D, Makkiya M, Mookadam F (2016) Therapeutic hypothermia in ST elevation myocardial infarction: a systematic review and meta-analysis of randomised control trials. Heart 102(9):712–719
23. Saunderson CED, Chowdhary A, Brogan RA, Batin PD, Gale CP (2016) In an era of rapid STEMI reperfusion with primary percutaneous coronary intervention is there a role for adjunct therapeutic hypothermia? A structured literature review. Int J Cardiol 223:883–890
24. Ndrepepa G, Mehilli J, Schwaiger M, Schuhlen H, Nekolla S, Martinoff S, Schmitt C, Dirschinger J, Schomig A, Kastrati A (2004) Prognostic value of myocardial salvage achieved by reperfusion therapy in patients with acute myocardial infarction. J Nucl Med 45(5):725–729
25. Olivecrona GK, Gotberg M, Harnek J, Van der Pals J, Erlinge D (2007) Mild hypothermia reduces cardiac post-ischemic reactive hyperemia. BMC Cardiovasc Disord 7:5
26. Otterspoor LC, van Nunen LX, van't Veer M, Johnson NP, Pijls NHJ (2017) Intracoronary hypothermia before reperfusion to reduce reperfusion injury in acute myocardial infarction: a novel hypothesis and technique. Ther Hypothermia Temp Manag 7(4):199–205
27. El Farissi M, Keulards DCJ, van't Veer M, Zelis JM, Berry C, De Bruyne B, Engstrom T, Frobert O, Piroth Z, Oldroyd KG, Tonino PAL, Pijls NHJ, Otterspoor LC (2019) Selective intracoronary hypothermia in patients with ST-elevation myocardial infarction. Rationale and design of the EURO-ICE Trial. EuroIntervention. https://doi.org/10.4244/EIJ-D-19-00471
28. Straub A, Krajewski S, Hohmann JD, Westein E, Jia F, Bassler N, Selan C, Kurz J, Wendel HP, Dezfouli S, Yuan Y, Nandurkar H, Jackson S, Hickey MJ, Peter K (2011) Evidence of platelet activation at medically used hypothermia and mechanistic data indicating ADP as a key mediator and therapeutic target. Arterioscler Thromb Vasc Biol 31(7):1607–1616
29. Penela D, Magaldi M, Fontanals J, Martin V, Regueiro A, Ortiz JT, Bosch X, Sabate M, Heras M (2013) Hypothermia in acute coronary syndrome: brain salvage versus stent thrombosis? J Am Coll Cardiol 61(6):686–687
30. Orban M, Mayer K, Morath T, Bernlochner I, Hadamitzky M, Braun S, Schulz S, Hoppmann P, Hausleiter J, Tiroch K, Mehilli J, Schunkert H, Massberg S, Laugwitz KL, Sibbing D, Kastrati A (2015) The impact of therapeutic hypothermia on on-treatment platelet reactivity and clinical outcome in cardiogenic shock patients undergoing primary PCI for acute myocardial infarction: results from the ISAR-SHOCK registry. Thromb Res 136(1):87–93
31. Shah N, Chaudhary R, Mehta K, Agarwal V, Garg J, Freudenberger R, Jacobs L, Cox D, Kern KB, Patel N (2016) Therapeutic hypothermia and stent thrombosis: a nationwide analysis. JACC Cardiovasc Interv 9(17):1801–1811