

Review Article

Benefit Absence of Therapeutic Moderate Hypothermia in the Treatment of Cardiac Arrest: A Systematic Review and Meta-Analysis

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Abstract: Background: Hyperthermia is frequent after cardiac arrest, and is associated with poor vital and neurological prognosis. In the last few years there have been published some studies that show benefits with moderate hypothermia in these patients, and other studies haven't shown such benefits. Aim: To collect all clinical trials evaluating the utility of moderate therapeutic hypothermia in survivors of a cardiac arrest. Method: A comprehensive search of clinical trials evaluating moderate hypothermia in patients who survive a cardiac arrest was carried out. The mortality and quality of life of the survivors were evaluated. The quality of the included studies, the publication bias and the heterogeneity of the results were evaluated. Results: there is no significant reduction in mortality (RR 0.97, 95% CI 0.93-1.01) or increase in quality of life (RR 1.07, 95% CI 0.94-1.21) of the patients undergoing moderate hypothermia versus those not treated with that. There are no different results in patients with cardiac arrest with defibrillable and non – defibrillable rhythms, with the different used cooling methods, or even with the induction of intra – cardiac arrest hypothermia. The mortality of these patients is high, and there are no significant differences in relation to the age or sex of them. Conclusion: In patients who survive a cardiac arrest, the induction of moderate hypothermia is not recommended.

Keywords: Therapeutic Hypothermia, Cardiac Arrest, Mortality, Survival with Good Neurological Prognosis

1. Introduction

Cardiac arrest (CA) is defined as the cessation of heart beat of myocardial contraction [1]. In Europe, there are about 350,000-375,000 sudden CA a year outside the hospital, with estimated numbers of 17 – 53 patients with CA treated by the Emergency Medical Systems / 1000,000 habitants / year [2]; the one year-survival of patients suffering from CA varies between countries, being the average is 10% [3, 4]. Currently it is demonstrated that if a serie of successive actions, which can be performed by most people, called “Cardiopulmonary

Resuscitation (CPR) manuevres”, included into the “Chain of Survival”, could increase survival in 2-3 times; however, these manuevres are only carried out in 1 of every 5 people who suffer CA outside the hospital; hence, the importance of education to the general population [5].

In the first 48 hours after CA, a period of hyperthermia is frequent. A relationship between post-CA hyperthermia and poor prognosis has been demonstrated [6]. It is reasonable to treat hyperthermia in unconscious patients who survive a CA. Several studies done in animals and humans show that mild hypothermia is neuroprotective and improves prognosis after

a period of global cerebral ischemia [7]. The promising findings of 2 clinical trials of moderate hypothermia (MH) in survivors of a CA caused by ventricular fibrillation (VF) [8, 9] supported the recommendation of MH in the following CPR Guidelines of the European Resuscitation Council (ERC) [10], and even by analogy in CA situations of non-shockable rhythm. The inconclusive recent results of the Nielsen study [11] reduced the euphoria about the usefulness of this therapy, which became only a careful control of temperature and not of MH [12].

It is not clear if an intervention such as MH in CA is more or less useful depending on several factors: the observed cardiac rhythms in a CA situations; if the beginning of hypothermia at extra or intrahospital level, or even coinciding with cardiopulmonary resuscitations maneuvers; or the applied mechanism of hypothermia.

Hence the reason for this systematic review and meta-analysis: to collect all clinical trials conducted in recent years that evaluate the usefulness of MH to have a global view of its effectiveness, and perform subgroup analyzes to analyze whether this therapy may be more effective in some subgroups of patients.

2. Methods

2.1. Initial Objective

Our objective was to assess the efficacy of inducing MH in reducing mortality and/or increasing the survival of patients with good neurological prognosis. A board search in several dabatases was carried out, trying to find randomized controlled trials in which MH was compared with the absence of hypothermia. A comprehensive systematic review was carried out according to the recommendations concerning design quality of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement [13].

2.2. Included Population

Patients were adults who have had recovery of spontaneous circulation (ROSC) after CA. There are a lot of causes of CA. The study did not included patients in the context of severe trauma, a severe toxicological or metabolic disturb / drug overdose, severe hypothermia ($\leq 30^{\circ}\text{C}$) or being pregnant women.

2.3. Intervention

The evaluated intervention was the application of MH to survivors of CA. All types of hypothermia were assessed: external -applied on skin and mucous membranes- versus internal -infusion of cold fluid or cooling of blood in extracorporeal circuit-; extrahospital vs intrahospital, even intra-CA; etc.

2.4. Search of Clinical Trials

Several electronic databases were consulted:

- i. Pubmed, with a broad strategy and search syntax:

((“Cardiopulmonary Resuscitation”[Majr] OR “Heart arrest”[All Fields]) AND “Hypothermia, induced”[Majr]) AND (Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Review[ptyp]);

- ii. Clinicaltrials.gov, Trypdatabase, CENTRAL (Cochrane Central Register of Controlled Trials) and OVID, with a similar strategy -(cardiopulmonary resuscitation OR heart arrest) AND (hypothermia induced)-.

These databases were finally revised on May 6th, 2.018. All this information was supplemented with bibliographic references in several found systematic reviews and meta-analysis. We searched for the results of completed studies referred in ClinicalTrials.gov.

A priori there was no limits on language or date of publication.

2.5. Obtaining Results

Basic information (population, intervention, outcomes) and methodological quality (risk of bias) were obtained from the finally accepted studies in a peer review process; in aspects where there was no coincidence, an agreement was reached with the help of a third evaluator. Hypothermia was achieved with external and/or internal methods, and with adequate doses of sedation, analgesia and muscle relaxation.

2.5.1. Mathematical Analysis

Efficacy of MH was measured with reduction of global mortality and increased survival of patients with good neurological prognosis. This good neurological prognosis was measured with 2 scales: Pittsburgh Cerebral Performance Category (CPC) of 1 (good cerebral performance: conscious, alert, able to work, might have a mild neurological or psychological déficit) or 2 (moderate cerebral disability: conscious, sufficient cerebral function for independent activities in daily life, able to work in sheltered environment) [14]; and modified Rankin scale of 0 (no symptoms), 1 (no significant disability) or 2 (slight disability) [15]. These dichotomous variables were evaluated with a relative risk (RR) (probability of patients with the event in the moderate hypothermia group / probability of patients with the event in the control group). There would be a positive effect if the RR of mortality is <1 , and if the RR of patients with good neurological prognosis is >1 .

Since the heterogeneity between studies was probable, the random effects model was assumed and calculations were made using the Maentel-Haenszel model.

The quality of included studies was assessed with 2 methods: the 5 items included in the Bias Assessment Tool of the Rev Man programme: generation of randomisation sequence, concealment of randomisation sequence, patient and doctor blinding, blind assesment of outcomes and incomplete follow-up [16]; and Jadad scale, that evaluates randomisation sequence, blinding and incomplete follow-up [17].

The assessment of the publication bias was made with 2 methods: graphs (funnel-plot) and numerical, with the calculation of the number of unpublished studies with the

methods of Rosenthal and Glesser-Olkin.

2.5.2. Employed Software

Calculations were made using the Cochrane Collaboration Review Manager 5.3 program, the J Primo EXCEL spreadsheet posted on the CASPe website (www.redcaspe.org) and with STATA / IC v.14.2.

3. Results

The bibliographic search described above was carried out (figure 1). 38 clinical trials and 19 meta-analyzes were obtained. The abstract of a clinical trial of the year 2000 [18] was obtained; it was randomized, but with insufficient methodological data, so it was not included in the meta-analysis.



Figure 1. Flow chart of included and excluded studies in our meta-analysis.

Finally, 16 clinical trials were evaluated [8, 9, 11, 19, 32]. They are described in the Table of Characteristic of Included Studies (Appendix). The overall quality of the studies is shown in Fig. 2. Blinding of the patients and clinicians in this situation is impossible, so they can not be double blind; as an internal validity finding, in most studies blinding in the

evaluation of the functional prognosis of the patient is blind. Randomization is usually well done, with the exception of one of the initial pivotal work [19] that could clearly magnify its beneficial effect. The individual evaluation of each work is shown in Figure A1 (Appendix).

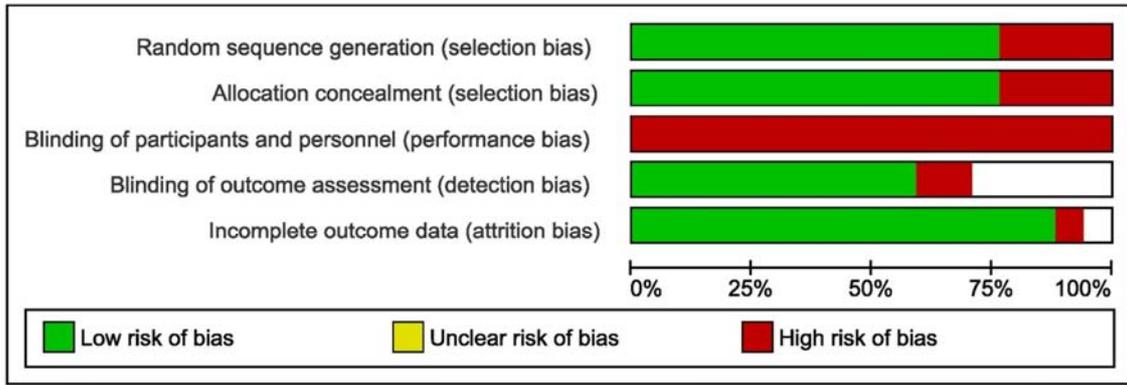


Figure 2. Global evaluation of the quality items of the Risk of Bias toolkit of the Cochrane Collaboration.

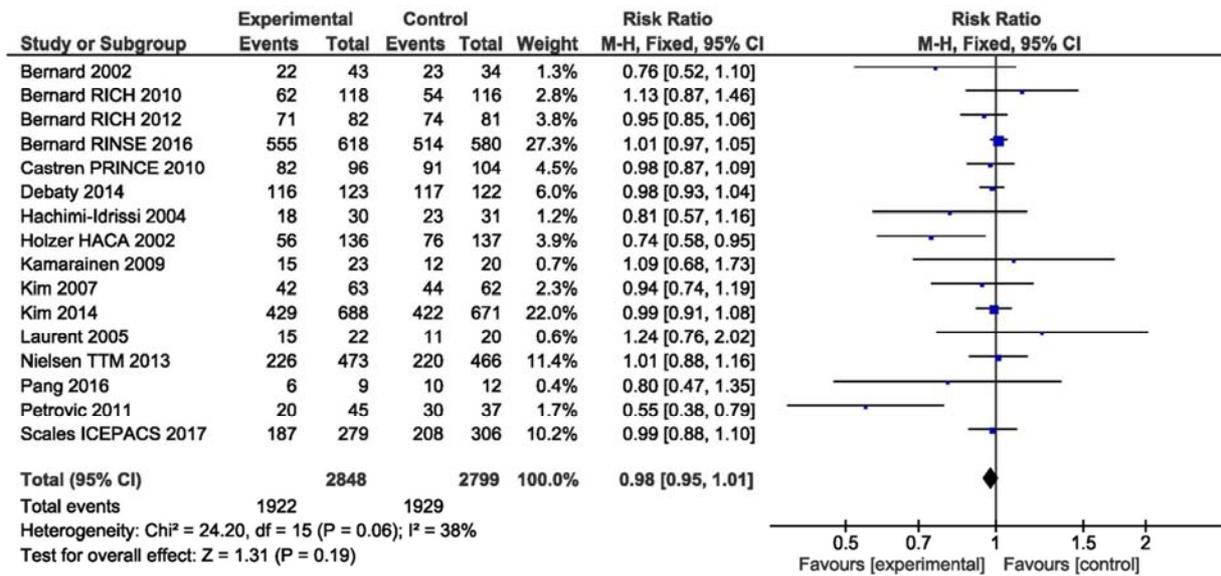


Figure 3. Global comparison of mortality of patients with hypothermia vs without hypothermia. A RR < 1 is an estimate in favor of hypothermia.

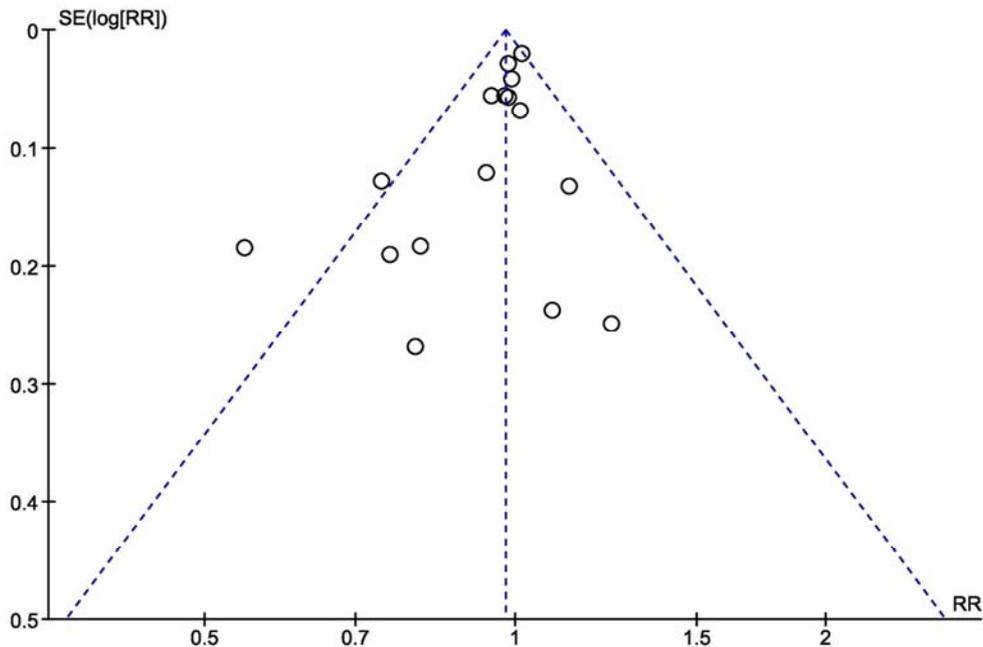


Figure 4. Funnel plot of included studies in the global evaluation of mortality.

The overall effectiveness of MH in terms of mortality variation is shown in Figure 3. Few studies show a significant reduction in mortality [8, 25]. The overall estimate shows no benefit with this intervention, with a RR of 0.97 and the estimation by confidence interval that exceeds the unit, and estimates of mortality in each branch of 67.7 and 68.9%. The funnel plot (fig 4) of these trials shows that there seems to be no publication bias; Neither the Rosenthal nor the Glesser-Olkin methods yield results that guide the presence of unpublished studies with non-significant results.

The separate assessment of the data of patients with CA by defibrillable and non-defibrillable rhythms shows analogous data. Figure 5 shows no benefit with MH in defibrillable rhythms, with risks of mortality in each branch of 50.6 and 50.4%. Figure 6 shows a similar result, with slightly better results, although without statistical significance non-significant ($p = 0.13$, RR 0.98, with 95% CI from 0.95 to 1.01), and with significantly higher mortality risks (87.3 and 89.1%).

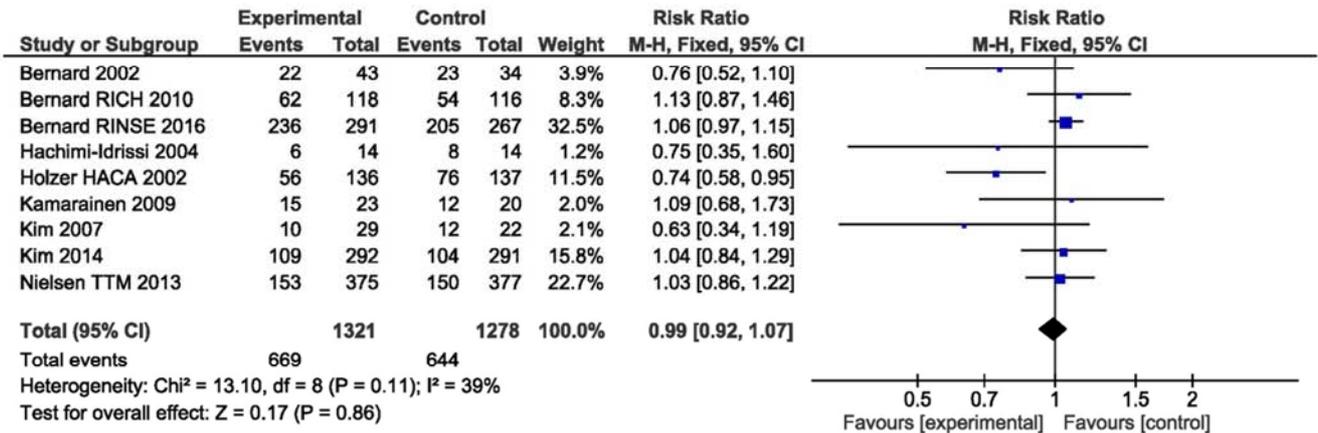


Figure 5. Comparison of mortality of patients with shockable rhythms. A RR < 1 is an estimate in favor of hypothermia.

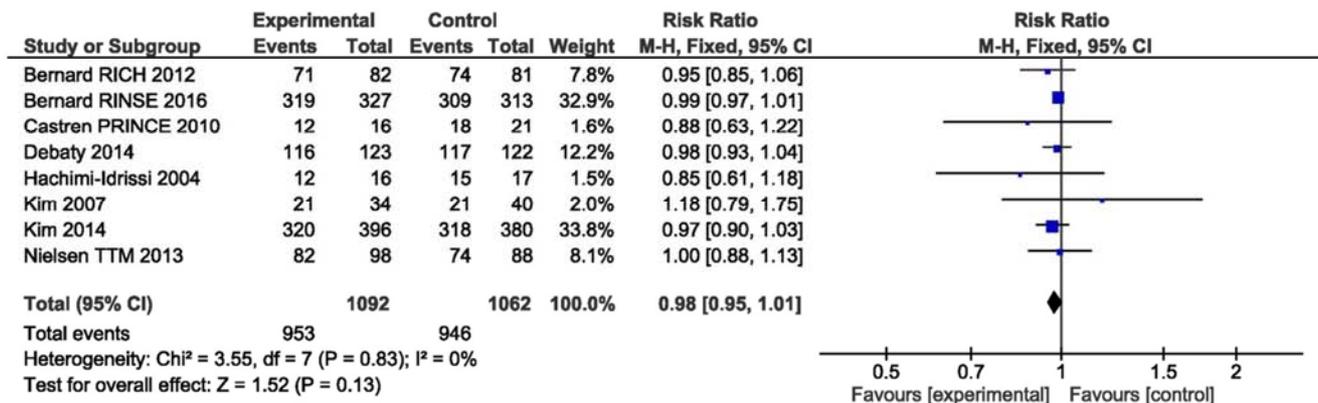


Figure 6. Comparison of mortality of patients with non-shockable rhythms.

Overall results in terms of improvement in neurological prognosis also show no significant differences. Figure 7 shows a minimal non-significant trend towards improvement of the RR (1.07, with 95% CI between 0.94 and 1.21) with 27.5 and 26.6% of patients with good prognosis in each branch. In the funnel plot (fig 8) a striking asymmetry of studies is observed, which may be related to publication bias -not publication of some works without absence of neurological prognosis benefit-. However, as in the previous section on mortality, the

Rosenthal and Glesser-Olkin methods provide non-significant results. Figures A2 and A3 (Appendix) show analogous results to that described for the analysis of subgroups against mortality: absence of benefit in both defibrillable and non-defibrillable rhythms, and percentages of patients with good neurological results of 50.4 and 49.3% for the assumption of defibrillable rhythms, and 12.3 and 10.9% in rhythms that cannot be defibrillated.

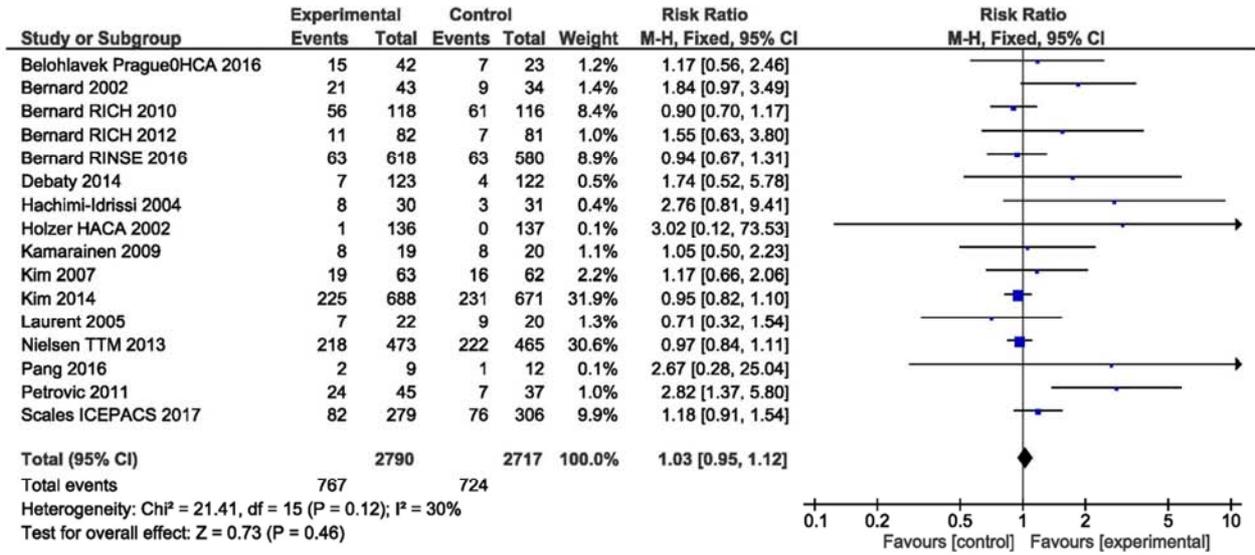


Figure 7. Global comparison of percentage of patients with good neurological prognosis with hypothermia vs without hypothermia. A RR > 1 is an estimate in favor of hypothermia.

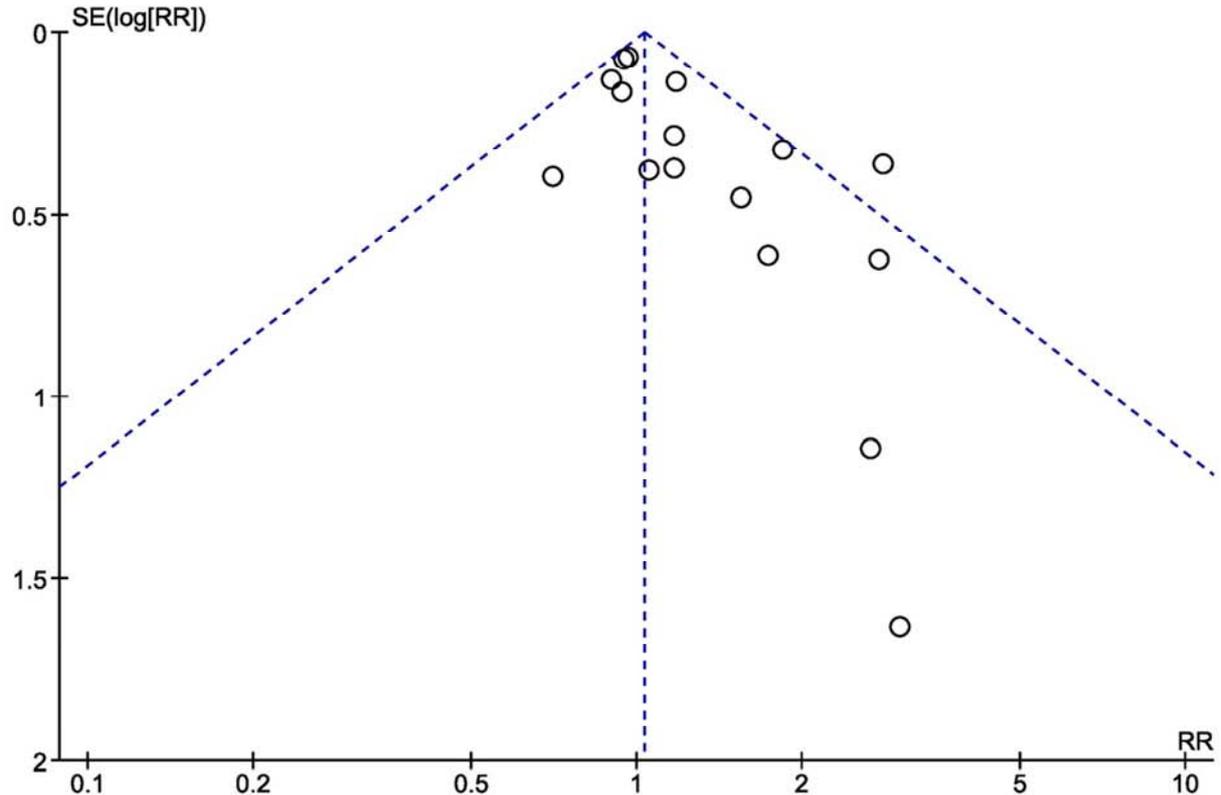


Figure 8. Funnel plot of included studies in the global evaluation of good neurological prognosis.

Assessing mortality, the cumulative meta-analysis of the 16 studies shows a striking curve (fig 9): initial benefit, with an estimate clearly below the unit in the first studies / years, with a trend towards no benefit from the year 2010, which is maintained from 2013.

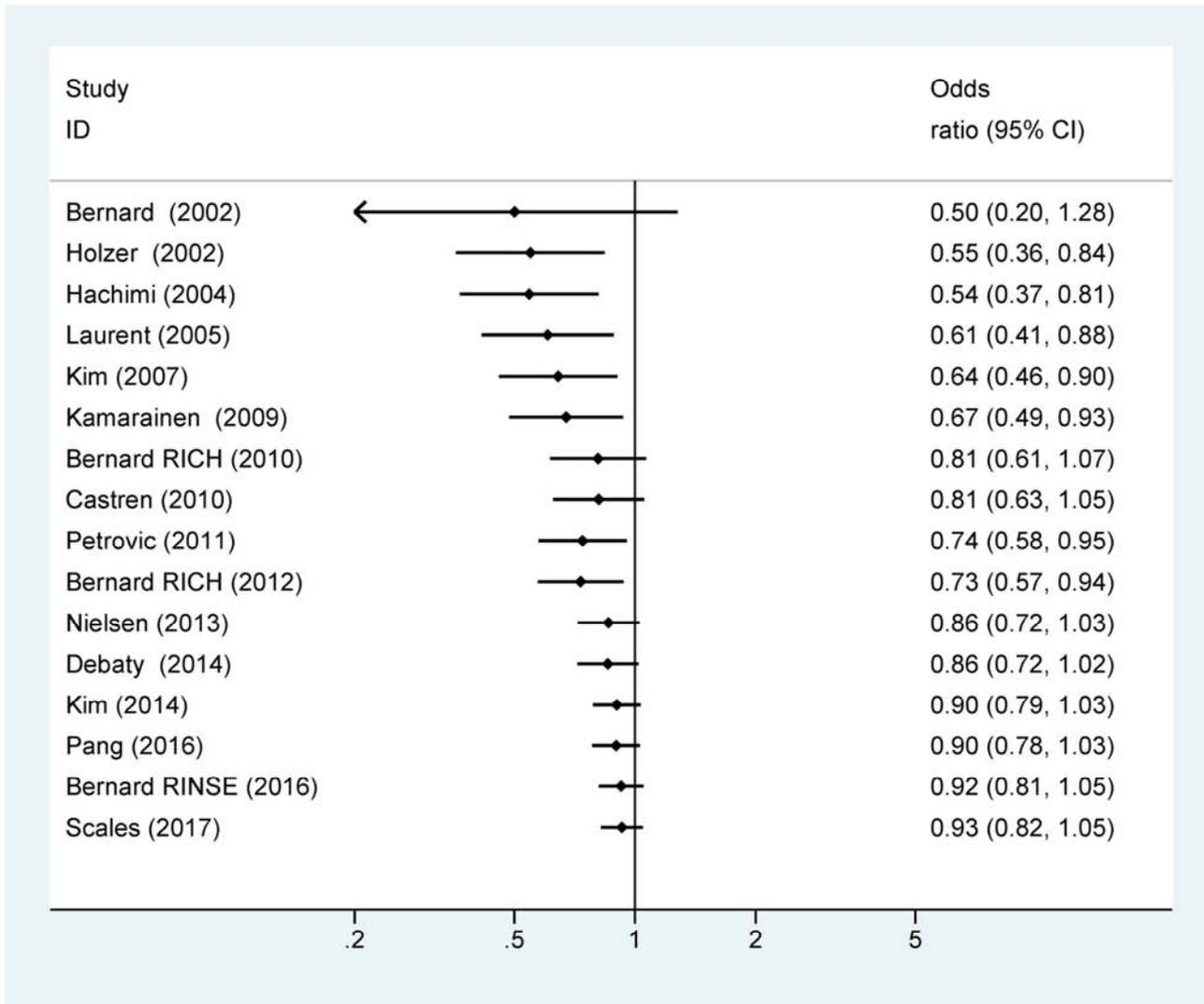


Figure 9. Cumulated meta-analysis with an estimate of odds ratio (OR) of mortality. An OR < 1 is an estimate in favor of hypothermia.

The type of cooling is an element that can influence the final outcome of the patient. Figure 10 shows the subgroup analysis of the studies according to the type of used cooling method. The internal methods (mostly obtained by infusion of cold saline, at 4°C) and the mixed, combination of internal and external methods, do not provide mortality benefit, while the aggregated estimation of the works with external cooling seems to show certain benefit (RR 0.85, with CI 95% from 0.76 to 0.95); however, this estimate is made on a small group of patients (only 10.87% of the total number of patients

included in the meta-analysis). In recent years there is a greater use of intranasal cooling, although mostly in combination with other methods: the only found studies in which this method is used alone are Castren [24] (without significant difference in mortality) and Belohlavek [31] (without significant differences in neurological prognosis). No significant differences were found either in mortality - RR 1.01 (0.97 - 1.04) - nor in neurological prognosis - RR 1.01 (0.75 - 1.35) - in the studies that perform intra-CA cooling [30, 33, 34].

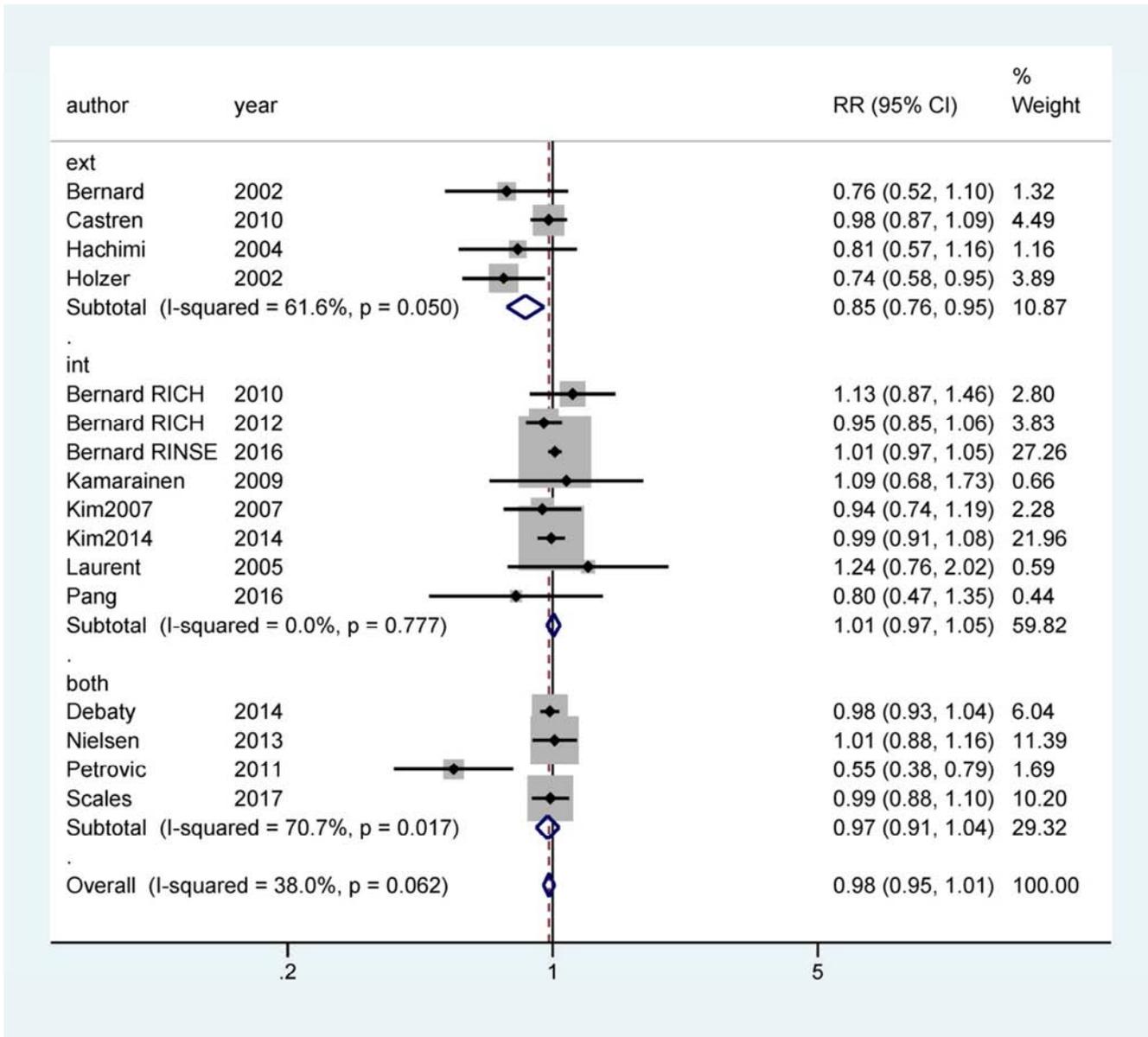


Figure 10. Analysis of subgroups of the different types of cooling used.

The evaluation of the methodological quality of the studies provides surprising data. We can use the Jadad scale, and describe the low quality studies with a score <3 points, and high quality with ≥ 3 points. Subgroup analysis (Figure 11) shows no benefit in high quality studies (RR = 1) and a trend to statistical significance in studies with lower quality (RR = 0.8). The result is analogous for the assessment of neurological prognosis (figure A4). If the quality is managed as a continuous numerical variable, and a meta-regression is

made, the result does not become statistically significant, but a greater slope of a line between a higher quality and an absence of effect (RR next to 1). In other words, at a lower methodological quality of the works, a greater reduction in mortality is observed (Figure A5). There are also no notable differences if the studies are published in Core Clinical Journals (journals of greater impact and quality) than in other journals (figure A6).

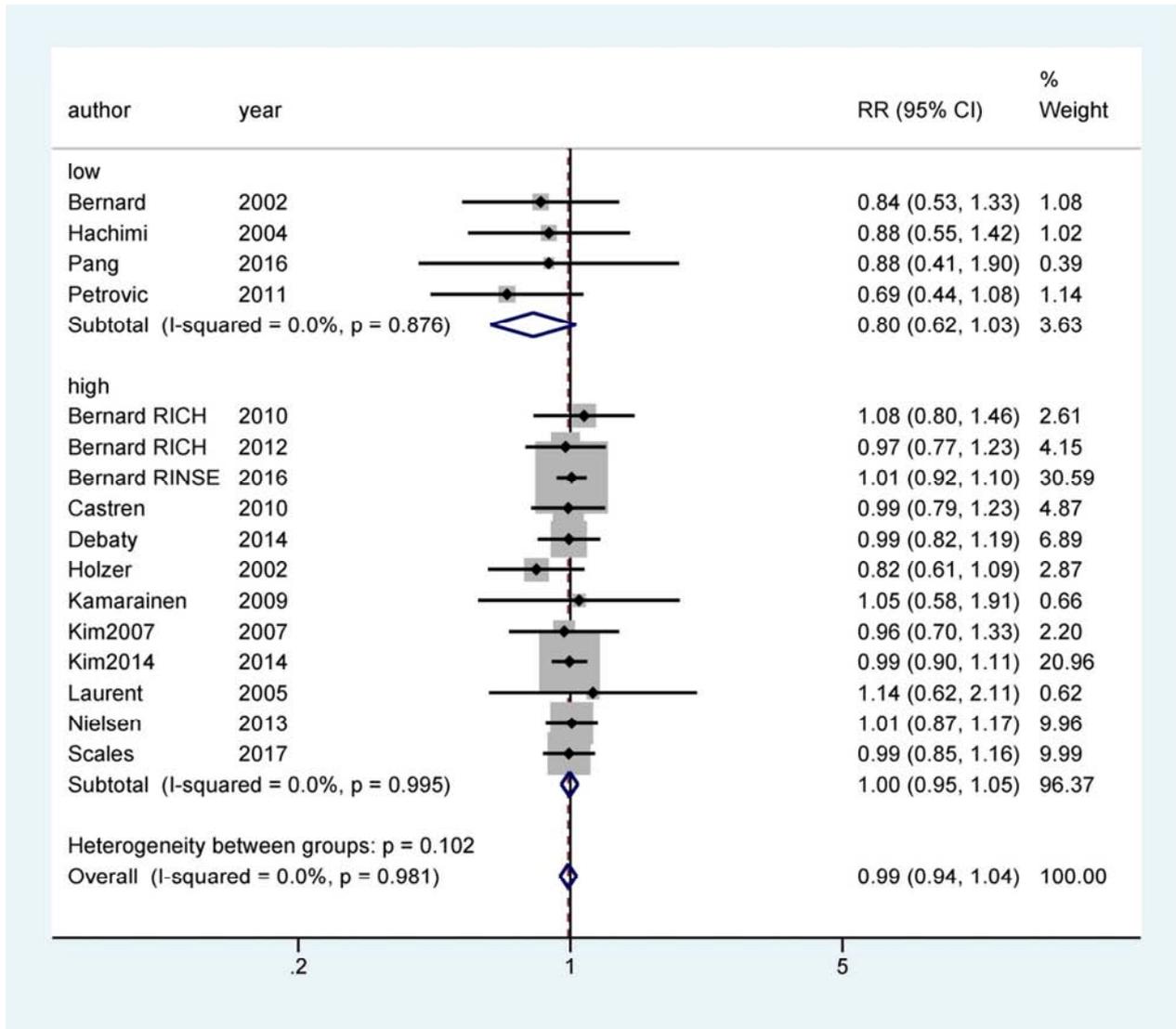


Figure 11. Analysis of subgroups of mortality with the methodological quality with Jadad scale. Low indicates Jadad < 3. High indicates Jadad >=3.

The influence that the sex or age of the patients can have is evaluated in figures A7 and A8 of the Appendix. Meta-regression (in which are assessed the average / median age of the patients included in each study, their effect and sample size, in relation to the RR of mortality) does not yield statistically significant data. A higher percentage of men and older populations are related with a greater mortality (RR > 1), with a slope of the line slightly higher for a higher age than for a higher percentage of men, although in both cases this slope seems minimally positive.

Finally, the assessment of the degree of efficiency of the technique as a function of the mortality rate in each study is assessed with the L'Abbé chart (Figure A9 Appendix). We can see most of the effect estimates on the bisector of the graph, which means that the RR of death is 1; in some studies with a risk of death of 0.4-0.7 the RR seems to be <1 (there are several circles plotted below that bisector); but the number and area of trials with RR of 1 is much higher, so the overall effect must be close to unity.

4. Discussion

The result of our work is conclusive. There is no benefit in survival or favorable neurological prognosis of the application of MH measures. And this finding is independent of the heart rhythm present at the CA, the cooling method used, the age or sex of the patients treated, or the mortality rate of the patients included in the studies. It should be noted that heterogeneity in terms of the methods used for cooling, the temperature sought and achieved with cooling, and the time of hypothermia (see Table of Characteristic of Included Studies, Appendix); these factors can contribute to an absence of significant results. Perhaps, one specific mode of moderate hypothermia can achieve benefits, but with this study we can't probe this assumption and it seems very unlikely. In recent years, the tendency is starting hypothermia at the beginning of CA. The current global result is the lack of benefit of this intervention. Without being conclusive, it is striking that the degree of benefit shown by the intervention is inversely proportional to

the quality of the study.

The cumulative meta-analysis curve is surprising. In other published cumulative meta-analyses that evaluate effective therapeutic interventions [33, 34], the initial estimates are close to the absence of effect, and with the accumulation of data from successive studies the effect is outlined as significant (RR or OR apart from 1). In our graph it seems to be the opposite, with initial significant effect and final estimation without effect (RR or OR = 1). The revision of the cardiopulmonary resuscitations recommendations is carried out every 5 years, the last one in 2015. Perhaps the change in the words and in the intention of the hypothermia in the CA (we remember, not as MH, but as "careful handling of the temperature", more in the sense of avoiding hyperthermia) could have been ahead of time.

Up to now, 19 meta-analyses have been published with the aim of evaluating MH in CA (citations A to S in Appendix). Of them, 10 (#A - J) are favorable to the application of this therapy, most of them prior to 2013, although the most representative one, which is the last revision of this topic by the Cochrane Collaboration, has been made in 2016. 3 of these works (#C, D and E) give favorable results, but cast doubts (limited data, low level of evidence). The remaining 9 (#K - S), with unfavorable result to MH, are all dated 2013 or later. The results of our work are concordant with these last meta-analyses. As it has happened a lot of times in the history of Medicine, an intervention recommended at one time was not recommended a few years later. It gives the impression that the moment of MH in CA has passed.

The most recent studies, aimed at the use of intranasal cooling devices, or with the initiation of intra-CA cooling, also show no reduction in mortality or improvement in neurological prognosis. Soon the results of several works developed in recent years will be published [35, 36]; with the absence of previously demonstrated benefit, it is unlikely that these data reverse the trend of no benefit. Perhaps the future of MH in the management of CA survivors is that reflected in the latest CPR Guidelines (2015) [11] as "temperature control" only in the sense of avoiding hyperthermia.

5. Conclusion

In patients who survive a CA, the induction of MH doesn't get improvement in survival or neurological prognosis, therefore it isn't recommended in these patients.

Acknowledgements

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in general, to all the staff of the Intensive Care Unit of the Hospital de Sagunto, for their encouragement to carry out this work.

Contributors

All authors have contributed to the development of the work. MAGG and MARA have made the bibliographic search and collected the studies to be reviewed; MAGG, AMC, LPLL, MARA and DAL have reviewed the finally included studies in the revision; MAGG y LPLL have performed the mathematical analysis; and MAGG, AMC and MARA have drawn the final conclusions and translated the manuscript into English.

Competing Interest

The authors declare no conflict of interests.

Funding

There is no source of funding of this study.

Bioethics Note

This study is a systematic review and meta-analysis of clinical trials. According to the declaration of Helsinki, it is not necessary for its development to be approved by the Bioethics Committee of the Hospital de Sagunto.

Note

All web links have been visited for the last time on August 20, 2018.

Key Messages

What is already known about this subject?

1. Hyperthermia in survivors of PC seems to worsen the prognosis.
2. It is advisable the careful handling of the temperature of the patients that survive a PC

What does this study add?

1. Moderate hypothermia does not seem to provide a benefit in reducing mortality or improving neurological prognosis.
2. There is no benefit in any cardiac arrest situation: rhythms defibrillable or not, different hypothermia devices, etc

How might this impact on clinical practice?

1. The induction of moderate hypothermia in survivors of CA should not be mandatory.
2. It seems advisable to avoid post-cardiac arrest hyperthermia.

Appendix

Appendix A. Table of Characteristics of Included Studies

Table A1. Characteristics of included studies.

	Patients	Interventions	Outcomes	Others
Bernard 2002 NEJM	Australia, SEPTEMBER 1996 – JUNE 1999. Patients with initial cardiac rhythm of ventricular fibrillation (VF), persistent coma after the return of spontaneous circulation (ROSC).	PREHOSPITAL HYPOTHERMIA (HT). Paramedics began measures in the field to initiate HT by removing clothing and applying EXTERNAL cold packs to the patient's head and torso with a temperature target of 33°C; this temperature was maintained until 12 hours; beginning at 18 hours, patients were actively rewarmed for the next 6 hours. The treatment of patients assigned to normothermia (NT) followed usual prehospital treatment protocols. 12 hours after admission: 32.7°C (HT) vs 37.1°C (NT); 18 after admission, 36 vs 37.4°C.	Discharge from the hospital. Discharge to home, or to a rehabilitation facility (good outcome), or also to a long-term nursing facility (poor outcome).	There's no clear information about funding.
Holzer 2002 NEJM	Europe (Austria, Italy, Belgium, Finland). MARCH 1996 – JANUARY 2001. Witnessed cardiac arrest (CA), VF or nonperfusing ventricular tachycardia (VT) as the initial cardiac rhythm, a presumed origin of CA, age of 18 – 75 years, interval of 5-15 minutes from collapse to 1st attempt at resuscitation by emergency medical personnel.	PREHOSPITAL HT. Patients in the HT group were cooled to a target temperature of 32-34°C with an EXTERNAL cooling device (matress that delivers cold air over the entire body. Goal was to reach this target within 4 hours after ROSC, and was maintained for 24 hours, followed by passive rewarming. Patients assigned to NT group were placed on conventional hospital beds and NT was maintained.	1 ^{ary} outcome: Favorable neurological outcome within 6 months, defined as Cerebral Performance Category (CPC) of 1 (good recovery) or 2 (moderate disability). 2 ^{ary} outcomes: mortality at 6 months, rate of complications during first 7 days after CA.	This study was supported by grants from the Biomedicine and Health Programme (BIOMED2) of the European Union, the Ministry of Science and the Austrian Science Foundation.
Hachimi-Idrissi 2004 Resuscitation	Europe (Belgium). OCTOBER 1999 – JUNE 2002. Adults with CA and cardiopulmonary resuscitation (CPR) after non-traumatic CA with ROSC who were admitted to Department of Emergency.	PREHOSPITAL and INTRAHOSPITAL HT. Patients with asystole or pulseless electrical activity assigned to HT a helmet device to induce mild HT (33°C) was placed on the head of the patients at the scene. When a body temperature of 33°C was reached, within 4 hours, helmet was removed and patients were allowed to regain NT passively and slowly during the next 18 hours. Patients with VF or non perfusing VT were cooled as soon as they were admitted to Emergency room with a cooling device (matress that delivers cool air), and aiming to reach a body temperature of 33°C, maintaining this for 24 hours. Patients randomised to NT were allowed to rewarm-up passively to NT and kept at NT.	Peripheral blood sample of S-100β. Neurological outcome from the first week up to 6 months.	There's no clear information about funding.
Laurent 2005 JACC	Europe (France), MAY 2000 – MARCH 2002. Patients consecutively admitted to Intensive Care Unit (ICU) with CA of apparently related to heart disease. Initial VF or asystole.	INTRAHOSPITAL HT. 3 strategies: isovolumic high-volume hemofiltration (HF) (200 ml/kg/hour over 8 hours) with a temperature of the fluid at 37°C; HF + HT, with a temperature of the fluid set at 30°C, INTERNAL COOLING, and was decreased to 15°C with ice packs around the infusion line; at the end of HF, mild HT (32-33°C) was maintained by EXTERNAL cooling for 16 hours. And control group with standard supportive care. We compared data from HF vs HF+HT groups.	Survival with a follow-up time of 6 months. Survival with a favorable neurological outcome (CPC 1-2)	There's no clear information about funding.
Kim 2007 Circulation	USA. NOVEMBER 2004 – FEBRUARY 2006. Patients admitted to acute care hospitals and resuscitated by paramedics after out-of-hospital CA.	EXTRAHOSPITAL HT. Infusion of 500-2000 ml of 4°C normal saline without adjusted to body weight (INTERNAL COOLING) before hospital arrival, vs standard care. Mean temperature decrease -1.24 °C, hospital arrival 34.7°C vs -0.1°C, hospital arrival 35.7°C. there was much variability in the subsequent management of temperature, with HT and NT.	Esophageal temperature. Deaths before hospital admission. In-hospital deaths. Discharged alive. Discharged with severe neurological deficits. Safety data from first 12 hours.	Supported by a grant from the Medic Ine Foundation and National Institutes of Health.
Kamarainen 2009 Acta Anaesthesiol Scand	Finland. MAY 2005 – DECEMBER 2008. All patients >= 18 years, regardless of the initial cardiac	PREHOSPITAL HT. Rapid infusion of 4°C Ringer's acetate at a rate of 100 ml/min (INTERNAL COOLING). The target naso-pharyngeal temperature was set at 33°C. In the conventional group,	Naso-pharyngeal temperature at arrival to the emergency department. Patients	There's no clear information about funding.

	Patients	Interventions	Outcomes	Others
	rhythm, with ROSC > 9 minutes and consciousness remained lowered.	naso-pharyngeal temperature monitoring. Temperature in hospital 34.1°C (HT) vs 35.2°C (control).	characteristic, resuscitation details and outcome data to discharge.	
Bernard RICH 2010 Circulation	Australia. OCTOBER 2005 – NOVEMBER 2007. Out-of-hospital CA with an initial rhythm of VF. CA time > 10 minutes.	PREHOSPITAL HT. Infusion by paramedics of up to 2000 ml of ice-cold lactated Ringer's solution during transport to hospital (INTERNAL COOLING); standard measures in control group. Posterior intra-hospital maintenance of HT at a target temperature of 33°C for 24 hours.	Proportion of patients with a favorable outcome at discharge. Temperatures at hospital arrival, prehospital pulmonary edema, and recurrent prehospital CA.	Grants from the Australian National Health and Medical Research Council, and the National Heart Foundation of Australia.
Castren 2010 Circulation	Europe (Sweden, Belgium, Germany, Italy and Czech Republic). NOVEMBER 2008 – JUNE 2009. Witnessed CA patients with a treatment interval (delay of the start of CPR manoeuvres) ≤ 20 minutes.	INTRA-ARREST, EXTRA-HOSPITAL COOLING (RhinoChill, trans-nasal device, EXTERNAL COOLING), vs standard care. All patients received standard post-RCP treatment on hospital arrival. Mean tympanic temperature 34.2°C (HT) vs 35.5°C (NT).	All adverse events through 24 hours to day 7. Time in the ICU. Cooling rates, ROSC rate, survival to discharge, survival with good neurological outcome at hospital discharge.	This work was supported by BeneChill, Inc, San Diego, USA
Petrovic 2011 Vojnosanit Pregl	Europe (Serbia). FEBRUARY 2005 – MAY 2009. Consecutive comatose patients admitted to a clinic after CA an ROSC.	INTERNAL + EXTERNAL COOLING (cooling pads) during 24 hours, in the first 240 minutes after ROSC, after which spontaneous rewarming started. EXTRAHOSPITAL COOLING. Posterior cooling according to ILCOR protocol, with lowering temperature to 32-34°C over a 12-24 hours period, when the initial rhythm is VF.	Neurological outcome (CPC), and mortality rate after 30 days	There's no clear information about funding
Bernard RICH 2012 Crit Care Med	Australia. OCTOBER 2005 – NOVEMBER 2007. Out-of-hospital CA with an initial rhythm of asystole or pulseless electrical activity. CA time > 10 minutes.	PREHOSPITAL HT. Infusion by paramedics of up to 2000 ml of ice-cold lactated Ringer's solution during transport to hospital (INTERNAL COOLING); standard measures in control group. Posterior intra-hospital maintenance of HT at a target temperature of 33°C for 24 hours.	Proportion of patients with a favorable outcome at discharge. Temperatures at hospital arrival, prehospital pulmonary edema, and recurrent prehospital CA.	Grants from the Australian National Health and Medical Research Council, and the National Heart Foundation of Australia.
Belohlavek 2012 J Translational Med (abstract Resuscitation 2016)	Europe (Czech Republic). Witnessed refractory out-of-hospital CA of cardiac origin.	PREHOSPITAL INTRA-ARREST HT. Hiperinvasive arm with mechanical compression device (LUCAS) with intranasal evaporative cooling Benechill (EXTERNAL COOLING) vs standard arm. Mild HT (33-34°C) will be started as soon as possible after ROSC.	6 months survival with good neurological prognosis (CPC 1-2)	Economical support by Puroklima, a company distributor for Benechill.
Nielsen 2013 NEJM	36 ICUs in Europe and Australia. NOVEMBER 2010 – JANUARY 2013. Out-of-hospital CA of presumed cardiac cause, unconscious survivors. > 20 minutes of ROSC.	Target management temperature (TTM) at 33 vs 36°C. EXTRAHOSPITAL INTERNAL + EXTERNAL COOLING. Achieve the assigned temperature as rapidly as possible with ice-cold fluids, ice-packs; intravascular or surface temperature management devices at the discretion of the sites. After 28 hours, gradual rewarming. EXTRAHOSPITAL INTRA-ARREST COOLING.	All-cause mortality through the end of the trial. Neurological function (CPC and modified Rankin scale) and death after 180 days. Serum concentration of neuron-specific enolase (NSE) at baseline, 3, 6, 12, 24, 48 and 72 hours. Neurological outcome at hospital discharge and 30 days, using the Pittsburgh CPC categories.	Supported by independent grant for the Swedish Heart-Lung Foundation.
Debaty 2014 Intensive Care Med	France (Europe). SEPTEMBER 2009-JULY 2012. Out-of-hospital CA eligible for advanced life support irrespective of rhythm.	Infusion of up to 2000 ml of ice-cold 0.9% saline solution at 100 ml/min during CA. Also surface cooling was also induced using gel pads (INTERNAL + EXTERNAL COOLING) vs control group. Following hospital admission, HT was maintained or induced, with a target temperature of 32-34°C during 24 hours, and controlled rewarming later phase. Standard care with/without PREHOSPITAL COOLING. Infusing 2 l of 4°C of normal saline as soon as possible following ROSC		Grant from the French Society of Emergency Medicine.
Kim 2014 JAMA	USA. DECEMBER 2007 – DECEMBER 2012. Adults with pre-hospital CA, with VF and non-VF rhythms.	(INTRAVASCULAR COOLING). Patients with VF, at hospital arrival, cooling during the next 24 hours. Patients with non VF, there's no clear information.	Survival and neurological status at discharge.	This study was funded by grants from the National Heart, Lung and Blood Institute.

	Patients	Interventions	Outcomes	Others
Pang 2016 J Cardiothoracic Surg	Singapore (Asia). AUGUST 2013 – JANUARY 2015. Patients receiving extracorporeal life support (ECLS) for CA	INTRAHOSPITAL and INTRAVASCULAR COOLING. Cooling to a target temperature of 34°C by modulating the heat exchanger component of the ECLS circuit, and maintained at 34°C for 24 hours in the ICU.	Neurological status (CPC 1-2) and survival to hospital discharge and 6 months.	This study was supported by a SingHealth Foundation Grant. This study was funded by the National Health and Medical Research Council. Was closed early due to changes in temperature management at major receiving hospitals.
Bernard RINSE 2016 Circulation	Australia. DECEMBER 2010 – DECEMBER 2014. Adults in CA on arrival of paramedics.	EXTRAHOSPITAL AND INTRAVASCULAR COOLING. Rapid intravenous infusion of up to 2 l / 30 ml/kg of cold saline DURING CARDIOPULMONARY RESUSCITATION vs standard care. After arrival at the emergency department, all patients receive standard care that may include cooling to 33°C for 24 hours.	Survival at hospital discharge. % ROSC of patients with shockable / non-shockable rhythms.	This study was funden by a grant from the Canadian Institute of Health Research.
Scales 2017 Resuscitation	Canada (America. JULY 2012 – JANUARY 2016. Emergency medical system – treated out-of-hospital CA with sustained ROSC >= 5 minutes.	EXTRAHOSPITAL COOLING, INTERNAL + EXTERNAL COOLING (surface ice packs, cold saline infusion) initiated 5 minutes after ROSC, vs no-prehospital cooling. All in-hospital procedures, including application of TTM, were left at the discretion of the treating clinical team.	Achieving a target temperature of 32-34°C within 6 hours of emergency department arrival. Survival with good neurological outcome (CPC 1-2) at hospital discharge.	

Appendix B. Additional Figures

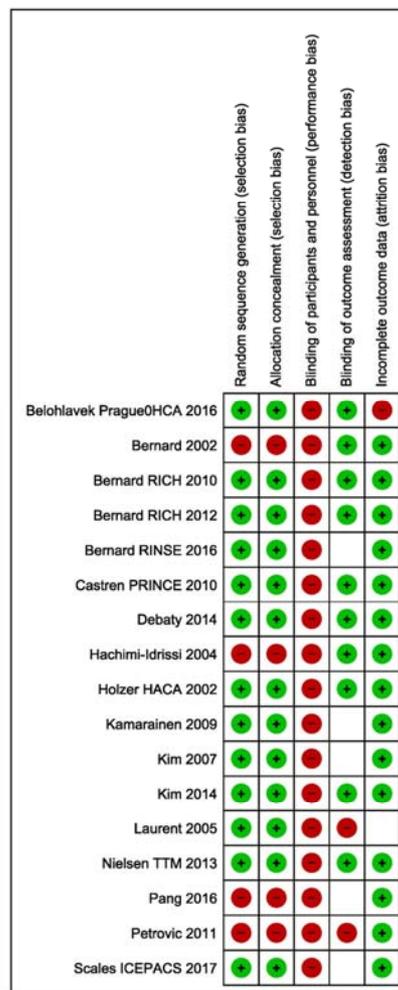


Figure A1. Quality description of each study included in the meta-analysis.

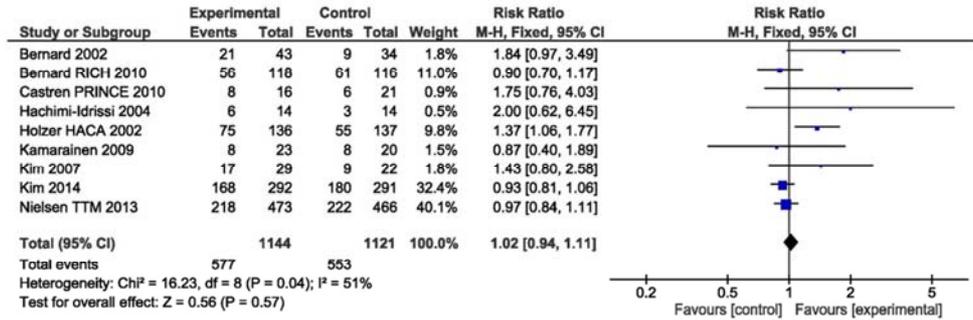


Figure A2. Comparison of percentages of patients with good neurological prognosis mortality in shockable rhythms. A RR > 1 is an estimate in favor of hypothermia.

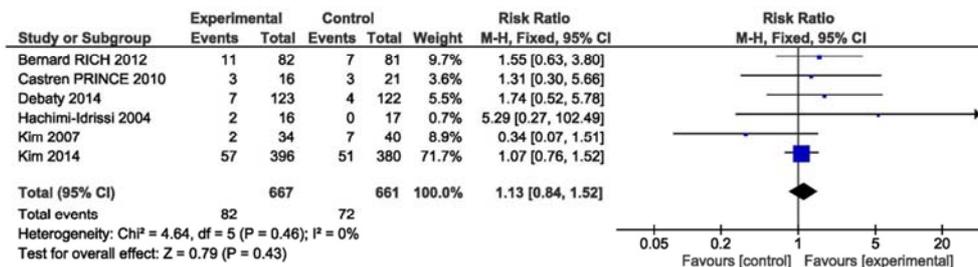


Figure A3. Comparison of percentages of patients with good neurological prognosis mortality in non-shockable rhythms. A RR > 1 is an estimate in favor of hypothermia.

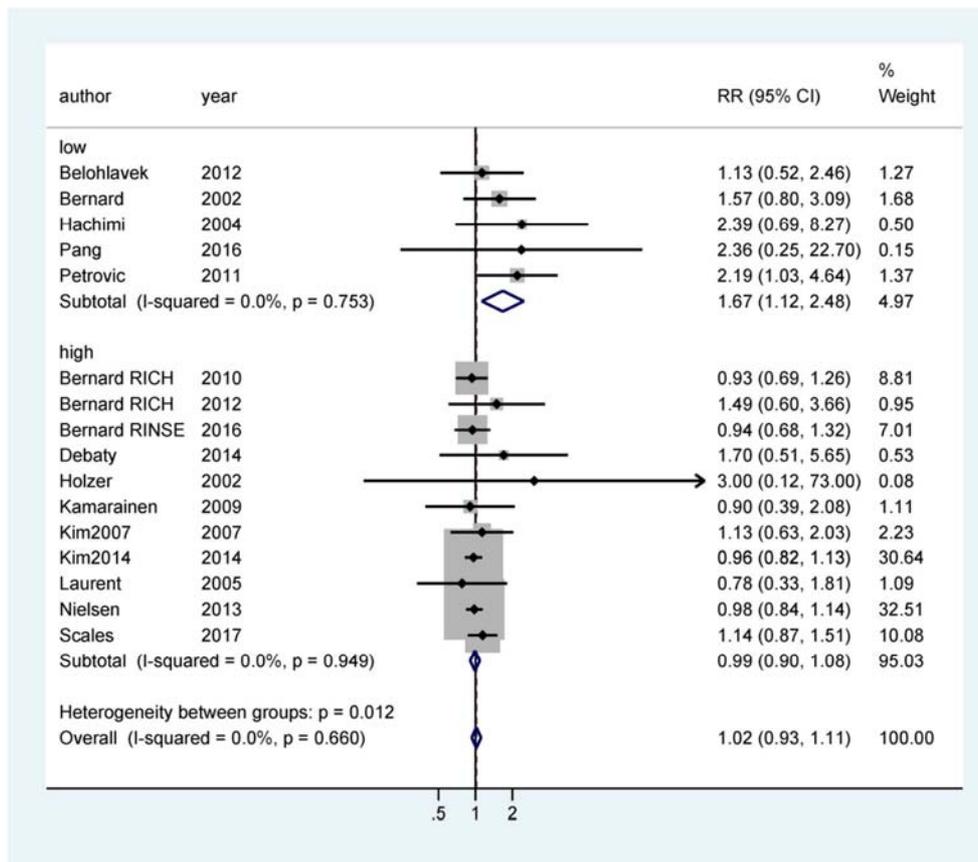


Figure A4. Analysis of subgroups of good neurological prognosis with the methodological quality with Jadad scale. Low indicates Jadad < 3. High indicates Jadad >=3.

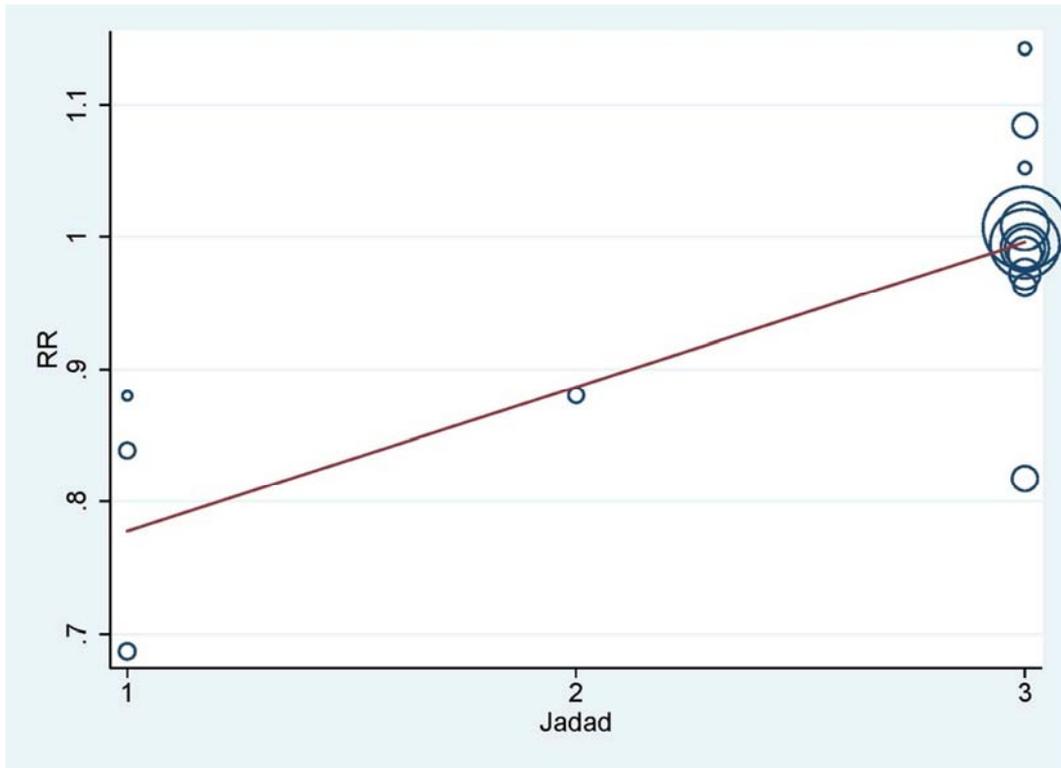


Figure A5. Metaregression that assesses the risk of mortality according to the quality measured by the Jadad scale.

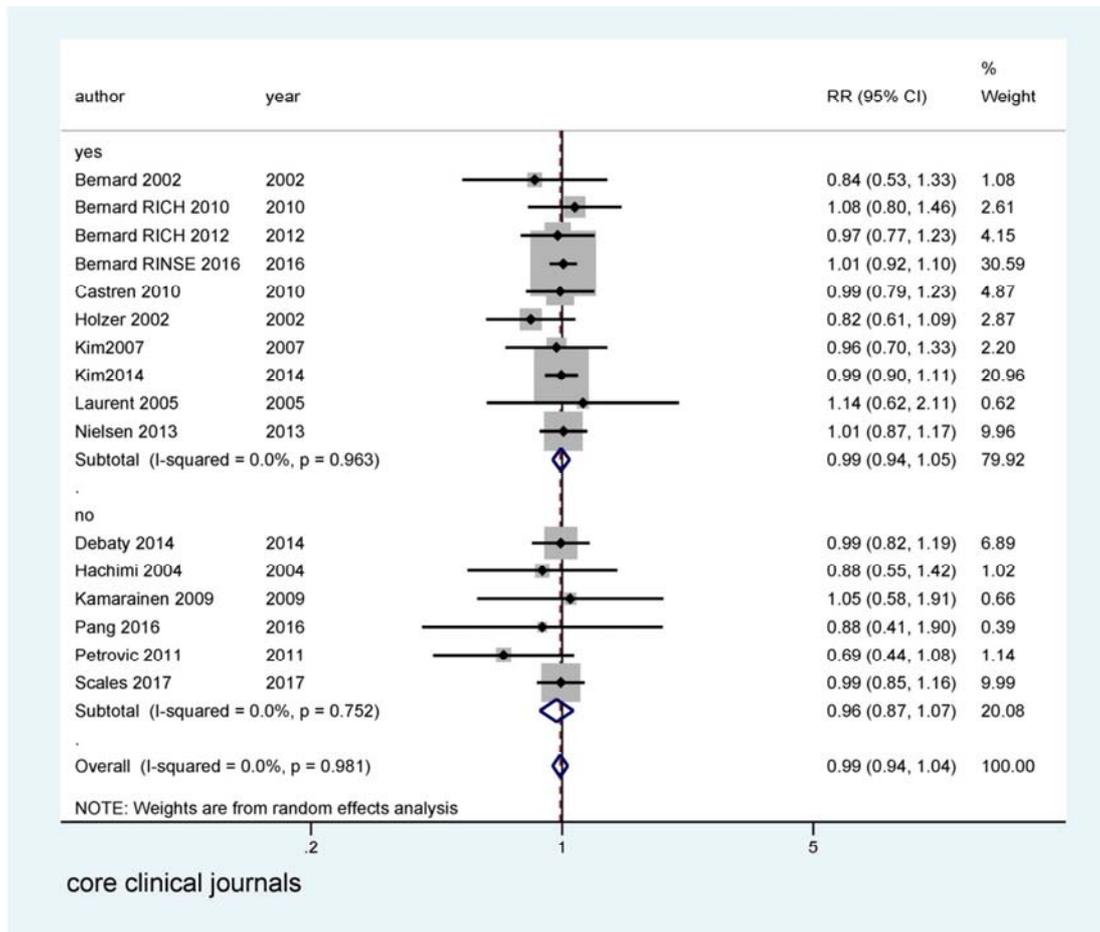


Figure A6. Analysis of mortality with the publication in a Core Clinical Journal.

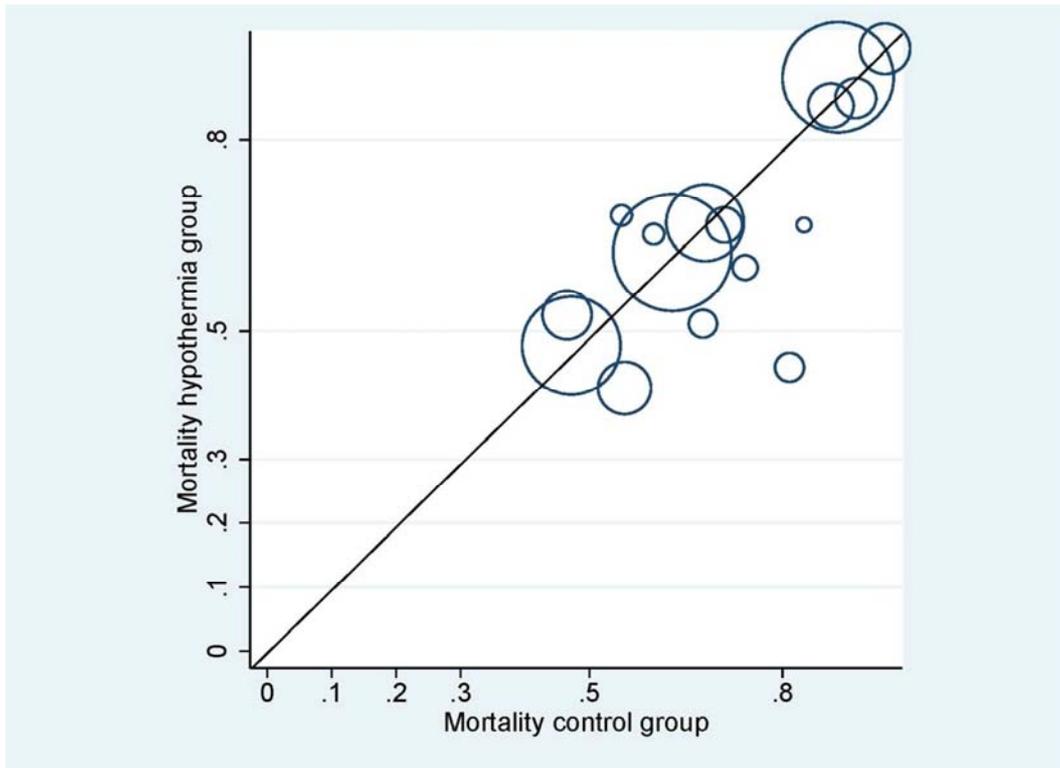


Figure A9. L'Abbé graph. Graphic comparison of mortality risk in each treatment arm of each study included in the meta-analysis. The absence of benefit of hypothermia is present in studies with lower and higher mortality risk.

Appendix C. Reference List Meta-Analysis

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Appendix D. Clinical Trials Excluded from the Meta-Analysis (Flow-Chart)

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