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Hypothermia to reduce neurological damage following coronary artery bypass surgery (Review)

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[Intervention Review]

Hypothermia to reduce neurological damage following coronary artery bypass surgery

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ABSTRACT

Background

Coronary artery bypass surgery (CABG) may be life saving, but known side effects include neurological damage and cognitive impairment. The temperature used during cardiopulmonary bypass (CPB) may be important with regard to these adverse outcomes, where hypothermia is used as a means of neuroprotection.

Objectives

To assess the effectiveness of hypothermia during CABG in reducing neurological damage and subsequent cognitive deficits.

Search methods

The Cochrane Controlled Trials Register was searched for randomised controlled trials (RCT) and this was updated by searching MEDLINE and EMBASE to December 1999 using database specific RCT filters. Reference lists of retrieved articles were searched and experts in the field were contacted.

Selection criteria

Only RCTs were considered. All patients undergoing CABG, either first time or revisions, elective or emergency procedures, were included. Any hypothermia protocol was considered. Only trials reporting neurological outcomes were included.

Data collection and analysis

Studies were selected independently and data were extracted from the source papers independently by two reviewers. Authors were contacted for further information. Studies were combined with meta-analysis where appropriate, and meta-regression was used to explore heterogeneity.

Main results

There was a trend towards a reduction in the incidence of non fatal strokes in the hypothermic group (OR 0.68 (0.43, 1.05)). Conversely, there was a trend for the number of non stroke related perioperative deaths to be higher in the hypothermic group (OR 1.46 (0.9, 2.37)). There was no evidence to suggest that hypothermia had an effect on the incidence of non fatal myocardial infarction (OR 1.05

(0.81, 1.37)), but the incidence of another marker of myocardial damage, low output syndrome, was higher in the hypothermic group (OR 1.21 (0.99, 1.48). When pooling all "bad" outcomes (stroke, perioperative death, myocardial infarction, low output syndrome, intra aortic balloon pump use) there was no significant advantage of either hypothermia or normothermia (OR 1.07 (0.92, 1.24)). Only 4 of 17 trials reported neuropsychological function as an outcome.

Authors' conclusions

This review could find no definite advantage of hypothermia over normothermia in the incidence of clinical events. Hypothermia was associated with a reduced stroke rate, but this is off set by a trend towards an increase in non stroke related perioperative mortality and myocardial damage. There is insufficient data to date to draw any conclusions about the use of mild hypothermia. Similarly, there is insufficient data to date to comment on the effect of temperature during CPB on subtle neurological deficits, and further trials are needed in these areas.

PLAIN LANGUAGE SUMMARY

There is not enough evidence to show that lowering body temperature can reduce nerve damage during coronary artery bypass surgery.

For people with severe coronary artery (heart) disease, bypass surgery can be life saving. However, bypass surgery is sometimes associated with neurological complications, where very occasionally patients may suffer a stroke, or more commonly memory or personality may be affected. The temperature used during bypass surgery may influence these adverse effects. Reducing the temperature during surgery (hypothermia) may protect the brain and reduce the risk of complications. The review of trials found that there was not enough evidence to show the protective effects of hypothermia. More research is needed.

BACKGROUND

Coronary artery by-pass surgery or grafting (CABG) may be life-saving in patients with severe coronary artery disease, but may also result in neurological damage and cognitive impairment. Although the incidence of gross neurological events following CABG is fairly low, with the incidence of stroke between 0.5-2% (Javid 1969, Gilman 1990), more subtle neuropsychological impairment after CABG has been reported in between 15-80% patients and as high as 100% in the elderly (Hammeke 1988). Whilst survival is of obvious value, neurological damage and subsequent cognitive impairment may have devastating consequences on patients' emotional, occupational and social life. Relatively little attention has been paid to these sequelae, and the British Cardiac Patients Association have indicated that a review in this area is a priority.

Early reports suggested that clinical brain damage following CABG was relatively rare (Gersh 1983). Recently, more subtle neurological deficits have been reported following CABG, where measurable deficits are present in almost half of patients at one week, with a third of patients showing deficits at 2 months post surgery (Toner 1998). Most studies report an improvement in cognitive deficits with increasing time post surgery, possibly due to reversibility of injury, although the possibility of familiarization with the tests has been debated (Newman 1992, Robinson 1990). Although neurological deficits are often transient, affected individuals are more likely to show signs of early dementia at 5 years post surgery (Sotaniemi 1986). Small cerebral ischemic lesions have been detected by magnetic resonance imaging (MRI) following CABG, but the clinical significance of these is debated (Vanninen 1998).

Neurological damage associated with CABG may occur through a number of different mechanisms. First, many patients with coronary artery disease may also have cerebrovascular disease and CABG may trigger an acute cerebrovascular accident or stroke. Second, the method and duration of mechanical by-pass may cause micro-emboli to develop which may result in cerebral emboli, insufficient cerebral blood flow, focal ischemia and neurological damage sufficient to cause cognitive impairment. Third, cognitive impairment may be due to depressive illness associated with coronary artery disease, or following CABG. This review however is not concerned with the psychiatric sequelae of CABG.

Specific interventions to reduce the risk of neurological damage and cognitive impairment following CABG have been developed and fall into 4 major groups:

1) Degree of hypothermia and warming during CABG (Cook 1994; Craver 1995; Heyer 1997).

2) Mechanical interventions to reduce micro-emboli in by-pass machines (Hessel 1980; Henze 1990; Sellman 1991; Taggart 1997; Toner 1997).

3) Anaesthetic and pharmacological strategies to maintain cerebral perfusion and neuroprotection (Fish 1987; Bashein 1990; Zaidan 1991; Gold 1995).

4) Maintenance of physiological homeostasis during surgery through control of acid-base balance, substrate load and glucose management (Griffin 1992; Engelhardt 1996; Patel 1996).

This review will focus on the degree of hypothermia and warming during CABG on neurological outcome and cognitive function. Normothermia during coronary bypass surgery has been shown to be an important risk factor for stroke (Odds Ratio 4.85) (Rao 1995). Hypothermia may provide cerebral protection by reducing cerebral oxygen consumption, and decreasing the risk of cerebral ischaemia due to cerebral emboli as a result of lower cerebral blood flow requirements.

Whilst we are primarily interested in the effects of systemic temperature during cardiopulmonary bypass (CPB) on neurological protection, the mode of delivery of cardioplegia to the heart during surgery may also affect embolic load (Baker 1995). Several myocardial protection strategies have been developed using cardioplegia of different temperatures, composition, and different modes of delivery to the heart, either retrograde or antegrade, continuous or intermittent. We will also examine markers of myocardial damage, as there may be a trade off between myocardial protection and neurological protection.

A previous review of neurological outcomes and cardiopulmonary temperature has been conducted (Christakis 1995). The authors could not find any advantage of hypothermia versus normothermia during CABG in terms of both the incidence of strokes and deficits in neuropsychological function. However, this review was not formally systematic in its coverage, included some non-randomized studies, and several randomized controlled trials have been published since this time. Consequently, an up to date systematic review is indicated.

OBJECTIVES

To assess the effectiveness of hypothermia during CABG in reducing neurological damage and subsequent cognitive deficits.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials with parallel group design.

Types of participants

Adults of all ages (18 years plus) undergoing CABG for the first time or revisions. This includes emergency and elective procedures.

Types of interventions

Hypothermia during CABG. Any hypothermia protocol has been included. Protocols using mildly hypothermic or tepid temperatures have been analysed separately. Effects of the intervention on outcome variables have been examined over the short term (within one week of surgery) and longer term (up to 3 months post surgery) to assess short and longer term effects of neurological damage following CABG.

Types of outcome measures

Neurological outcomes:
Clinical evidence of cerebrovascular accident or stroke
Neuroradiological evidence of brain infarction
Neurological deficits identified by neurological examination
Neuropsychological testing for cognitive deficits
Trans-cranial Doppler estimates of micro-emboli
Biochemical markers for cerebral damage (e.g. S-100 protein, neurospecific endolase)
Subjective complaints of behaviour or memory change from patient or family
Quality of life measures.
Other clinical outcomes:
Perioperative death not caused by stroke
Perioperative non fatal myocardial infarction
Low output syndrome (LOS) and intra-aortic balloon pump use (IABP) as markers for myocardial damage

Search methods for identification of studies

The Cochrane Controlled Trials Register (CCTR) was searched using the strategy outlined below. This was updated by searching MEDLINE to December 1999 on Ovid using a standard RCT filter (Dickersin 1994) and EMBASE 1998 to December 1999 using an EMBASE RCT filter (Lefebvre 1996). In addition searches of reference lists of papers were made and expert advice was sought.
1 CORONARY-ARTERY-BYPASS*:ME
2 (CORONARY and BYPASS)
3 (AORTOCORONARY and BYPASS)
4 (AORTOCORONARY and SHUNT)

5 (AORTOCORONARY and ANASTOMOSIS)
6 (CORONARY and GRAFT)
7 (CORONARY and SURGERY)
8 (CARDIOPULMONARY and BYPASS)
9 EXTRACORPOREAL-CIRCULATION*:ME
10 EXTRACORPOREAL
11 HEART-ARREST-INDUCED*:ME
12 CARDIOPLEGI*
13 HYPOTHERMIA
14 HYPOTHERMIA-INDUCED*:ME
15 NORMOTHERMIA
16 TEPID
17 COGNITION-DISORDERS:ME
18 COGNITION
19 (COGNITIVE and FUNCTION*)
20 MENTAL-PROCESSES*:ME
21 (CEREBRAL and FUNCTION*)
22 (CEREBRAL and DYSFUNCTION)
23 (CEREBRAL and INJURY)
24 (NEUROPSYCHOLOGICAL and DEFICIT)
25 (NEUROLOGICAL and DEFICIT)
26 MENTAL
27 MEMORY
28 PERSONALITY*:ME
29 PERSONALITY
30 BRAIN-DAMAGE-CHRONIC:ME
31 BRAIN
32 PSYCHOLOGICAL-TESTS*:ME
33 PSYCHOLOGIC*
34 ELECTROENCEPHALOGRAPHY*:ME
35 ELECTROENCEPHALOGRAPH*
36 MAGNETIC-RESONANCE-IMAGING*:ME
37 MRI
38 (MAGNETIC and RESONANCE)
39 CEREBROVASCULAR-DISORDERS*:ME
40 CEREBROVASCULAR
41 EMBOLI*
42 (MICRO and EMBOLI*)
43 NEUROL*
44 ((((((#1 or #2) or #3) or #4) or #5) or #6) or #7)
45 (((((((#8 or #9) or #10) or #11) or #12) or #13) or #14) or #15) or #16)
46 ((((((((((#17 or #18) or #19) or #20) or #21) or #22) or #23) or #24) or #25) or #26) or #27)
47 ((((((((((((((#28 or #29) or #30) or #31) or #32) or #33) or #34) or #35) or #36) or #37) or #38) or #39) or #40) or #41) or #42) or #43)
48 (#46 or #47)
49 (#44 or #45)
50 (#48 and #49)
51 (#44 and #45)
52 (#50 or #51)

Data collection and analysis

From the searches, the title and abstract of each paper was reviewed by one reviewer and potentially relevant references retrieved. Following this initial screening, two reviewers independently selected trials to be included in this review using predetermined inclusion criteria. In all cases disagreements about any study inclusions were resolved by consensus. Study outcome data were extracted independently by two reviewers, and chief investigators of trials were contacted to provide additional relevant information where necessary. In addition to study outcome data, trial quality was assessed independently in terms of concealment of allocation, losses to follow up, blind assessment of outcomes, and adequacy of control. Data concerning patient characteristics; age, sex, urgent versus elective CABG, and details of the CABG procedure, the mode of cardioplegia delivery, and bypass time, were also collected as stated a priori to perform stratified analysis of the data using meta-regression.

Dichotomous outcomes for each study have been expressed as odds ratios and 95% confidence intervals (CI). Continuous variables have been expressed as the mean change from baseline to follow up, and the standard deviation difference from baseline to follow up for each comparison group. Where standard deviation differences have not been reported in the source papers, allowance has been made for within patient correlation from baseline to follow up measurements by using the correlation coefficient between the two (see Cochrane Heart Group web site for details and, Follmann 1992). A weighted mean difference (WMD) or standardised mean difference (SMD) and 95% CI have been calculated for each study. Data from each study were pooled as appropriate using a fixed effect model, except where substantial heterogeneity existed according to the Z statistic, and a random effects model was used (where a random effects model was used this is indicated in parentheses).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Details of the studies included in the review are shown in the table of characteristics of included studies.

Risk of bias in included studies

See also included studies table.

A clear and adequate method of randomization was reported in 11/19 studies. Three of 19 studies reported inadequate randomization in that group allocation was alternate, or based on hospital

numbers. Sensitivity analyses have been performed excluding these studies and the results are presented below. Blinding of outcome assessors was considered to be important for those studies with neurological examination or psychometric testing as an outcome, rather than those just reporting clinical events. Four of 6 studies reported blinding of outcome assessors. Losses to follow up did not occur in most studies which report clinical events in the short term. One study (Heyer) reported very high losses to follow up for late psychometric testing at 6-9 weeks post surgery, and these data have not been included in the review.

Effects of interventions

From the searching, 19 studies reporting separate trials were identified which met our inclusion criteria. Of these, 13 studies reported hypothermia and normothermia as the primary comparison groups, 4 studies reported the effects of hypothermia, mild hypothermia or tepid temperature and normothermia, and 2 studies hypothermia and tepid temperature. Outcome variables were assessed for the comparison groups hypothermia and normothermia as per groupings in the individual trials, and separately for hypothermia and tepid temperature.

Individual trials recruited patients of very similar mean ages (mean 60.9 years, range across trials 57-65), and the majority of participants were men (84% men, range across trials 74-98%). Most trials excluded patients with neurological deficits. The case mix of patients across trials were relatively low risk patients with the exception of one trial that recruited only patients with left ventricular dysfunction (Rashid B). Most patients across trials underwent elective CABG (mean 14.3% urgent operations, range 0-59%), with the exception of one trial where the number of urgent cases exceeded the number of elective cases (Engleman cold).

Clinical outcome variables were assessed only over the short term within 30 days of the operation.

Clinical events

Hypothermia vs normothermia

The pooled effect estimate showed a reduction in the incidence of non fatal perioperative strokes in the hypothermic group (OR 0.68 (0.43, 1.05)), although this failed to reach statistical significance. Conversely, there was a non significant trend for the number of non stroke related perioperative deaths to be higher in the hypothermic group (OR 1.46 (0.9, 2.37)). Hypothermia had no effect on the incidence of perioperative non fatal myocardial infarction (OR 1.05 (0.81, 1.37)). Data were also collected on another more sensitive marker of myocardial damage, low output syndrome (LOS), which is described as the occurrence of persistent clinically threatening hypotension, and defined as a requirement for intra-aortic balloon pump support, or prolonged use of inotropes postoperatively to maintain systolic blood pressure and cardiac output. The incidence of low output syndrome in the hypothermic group was higher than in the normothermic group (OR 1.21 (0.99, 1.48). Paradoxically, the use of an intra-aortic balloon pump (IABP) was higher in the normothermic group (OR 0.67 (0.44, 1.03)). When pooling all "bad" outcomes (stroke, perioperative death, MI, LOS, IABP) there was no significant advantage of either hypothermia or normothermia (OR 1.07 (0.92, 1.24)).

Hypothermia vs tepid temperature

Only 5 studies reported non fatal stroke as an outcome. Moderate hypothermia had no effect on the incidence of perioperative non fatal stroke (OR 0.94 (0.33, 2.73)), perioperative death (OR 1.94 (0.39, 9.66)), or non fatal MI (OR 0.68 (0.26, 1.81)) compared to mild hypothermia or tepid temperature.

Psychometric testing to assess cognitive function

Hypothermia vs normothermia

Of the 17 studies in this comparison group, only 4 reported neuropsychological function as an outcome measure. Each trial used a number of different psychometric tests. Tests have been broadly divided into those measuring intellectual IQ function, memory, motor skill or dexterity, and executive function. Those trials which have used the same tests have been pooled to determine effect size. Subsets of tests have not been pooled as they often measure different things and respond differently across different age groups. This is particularly true for the Wechsler Memory Scale (WMS) (Lezak). A qualitative overview of all of the psychometric tests used in these trials are presented in Table 1 and Table 2. Results for both the quantitative and qualitative analysis have been divided into early tests (within 1 week of the operation) and late tests (1-3 months post operatively) as reported in the source papers.

For tests of intellectual IQ function and memory, higher scores indicate improved performance, so where mean changes from baseline to follow up are negative, this indicates a deterioration in performance. The opposite is true for all tests of motor skill/dexterity and executive function where higher scores show a deterioration in performance, therefore a mean change from baseline to follow up which is negative should be interpreted as an improvement in performance. For these reasons, the sign of the mean change in intellectual IQ function and memory has been changed for the pooled analysis so the direction of effect is in the appropriate direction.

No significant neuroprotective effects of hypothermia were seen for any of the early psychometric tests (within 1 week post op) in the quantitative analysis, although the numbers of trials in each comparison group were small. Similarly, no significant effects of hypothermia were seen for the late psychometric tests (1-3 months post op). The qualitative analysis shows variable responses to different tests for different trials (see Table 1 and Table 2 for early and late tests respectively). Most tests of cognitive function show deterioration immediately post operatively which is present in either group, or both groups to a similar extent. Conversely, for the late tests, most trials show an improvement in cognitive function from baseline to follow up, again individual trials showing variable responses of hypothermia and normothermia.

Neurological examination

Five trials in the hypothermia vs normothermia group reported

neurological examination outcomes using a number of different assessments. The results of these are presented qualitatively in Table 3. Deterioration in the Mathew score, and mini mental status score was seen to a similar extent post surgery in both comparison groups in the 2 trials that measured each of these as outcomes.

Psychometric testing and neurological examination in the hypothermia vs tepid temperature group

Two trials in this group reported psychometric testing, one for early tests within 1 week of surgery, and one for late tests at 6 weeks post surgery. Results are presented qualitatively in Table 4. Again, variable responses were seen between hypothermia and tepid temperature for each of the tests.

Neurological examination was reported in 3 trials in this group and results are presented qualitatively in Table 5. Deterioration in the Mathew score was seen 3-4 days post surgery in one trial to a similar extent in both groups. The mini mental status score was unchanged in either group in another trial from baseline to 6 days post surgery.

Health related quality of life

None of the trials reported health related quality of life as an outcome.

Sensitivity analysis

Sensitivity analyses excluding trials of low methodological quality, where randomisation was inadequately performed by allocation of patients on the basis of odd and even hospital numbers, or alternating patients to treatment group, had no effect on the pooled effect estimate for non fatal strokes (OR 0.65 (0.41, 1.05). Sensitivity analysis excluding studies where the systemic temperature is similar in both treatment groups has no effect on the pooled effect estimate for non-fatal strokes (OR 0.66 (0.42, 1.02)).

Stratified analysis

Subgroup analysis was performed to examine the effects of the method of cardioplegia delivery (either retrograde or antegrade) on the incidence of non fatal stroke. No significant advantage was seen with either method, although there were relatively few studies in each comparison group (retrograde cardioplegia, random effects model OR 0.68 (0.28, 1.62), antegrade cardioplegia OR 0.84 (0.44, 1.61)). This subgroup analysis was also carried out for the outcome perioperative deaths where similarly there was no significant advantage seen with either method (retrograde cardioplegia OR 1.31 (0.56, 3.11), antegrade cardioplegia OR 1.6 (0.87, 2.95)).

Heterogeneity was further explored with the use of meta regression. Co-variates defined a priori included retrograde or antegrade delivery of cardioplegia as a dichotomous variable, bypass time and percentage of patients undergoing urgent rather than elective surgery. The method of delivery of cardioplegia, or the percentage of urgent cases within each trial did not significantly affect the number of non-fatal strokes. The odds ratio for non-fatal strokes was however significantly affected by the mean time on bypass. The odds ratio for non-fatal stroke is multiplied by a factor of 1.03 per minute increase in bypass time (coefficient log OR 0.0297, (CI 0.00387, 0.0555), p=0.024), thus the number of non-fatal stokes increases with increasing time on bypass.

DISCUSSION

The findings from this systematic review using the current trial evidence cannot demonstrate any clear advantage of either hypothermic or normothermic CPB in the occurrence of clinical events. There is a non significant trend towards fewer strokes in the hypothermic group, but this is counterbalanced by a trend towards higher perioperative mortality and myocardial damage as shown by the data on low output syndrome. Conversely, there were no differences between the groups in the occurrence of MI, possibly because this is regarded as a relatively crude marker for myocardial damage. When we examine the pooled "bad" outcomes (including stroke, perioperative death, MI, LOS and IABP use) there is no difference in the summary effect estimate between hypothermia and normothermia.

Individual trials differ in both systemic and cardioplegic temperatures, and the mode of delivery of cardioplegia. These differences, particularly the mode of cardioplegia delivery, either retrograde or antegrade, continuous or intermittent, may affect the embolic load (Baker 1995). Cold cardioplegia was originally used to maintain cardiac arrest during surgery, and to minimise ischaemic damage. More recently "warm heart surgery" proposed to be more beneficial in myocardial protection has been introduced whereby the temperature of the cardioplegia is maintained at 37 degrees and cardiac arrest during surgery is maintained by the potassium concentration in the cardioplegia rather than by hypothermia. Systemic temperatures reflect those of the CPB perfusate, and patients may be actively warmed, actively cooled or allowed to drift towards mild hypothermia, depending on the protocol. Retrograde delivery of the cardioplegia via the coronary sinus prevents distal embolization of coronary or graft debris, and is recommended for redo CABG, and for tight coronary stenoses (Loop 1992). Cardioplegia can be distributed to the myocardium regardless of the state of the native vessels, and flooding of the operative field is reduced, allowing more continuous flow. Retrograde cardioplegia has also been reported to result in a higher incidence of emboli immediately after release of the aortic cross clamp compared with antegrade cardioplegia (Baker 1995). Antegrade delivery of cardioplegia is accomplished via the ascending aorta. Flow is necessarily limited in myocardial regions served by severely occluded coronary arteries.

In an attempt to determine the effects of retrograde or antegrade delivery of cardioplegia on the incidence of stroke, we have performed subgroup analyses, and meta regression. No significant advantage of either method was seen, although the number of trials in each group were small. Similarly, meta regression failed to show

a relationship between effect size and mode of cardioplegia delivery. The systemic temperature rather than cardioplegia temperature is more important in terms of neuroprotection. The group allocation to hypothermia or normothermia in all but 2 trials reflected the systemic temperature rather than cardioplegia temperature. Sensitivity analyses excluding these trials had little effect on the summary effect estimate for non fatal strokes.

The clinical event data contributing to the current meta-analysis is dominated by 2 multi centre RCTs, the study from Emory (Martin (Emory)) and the Warm Heart Investigators in Toronto (Warm Heart). To date, these are the only RCTs of warm versus cold surgery of sufficient power to detect possible differences in the stroke rate. The warm heart investigators found no difference in the rate of strokes or MI, less frequent low output syndrome, and a trend towards reduced perioperative mortality in the normothermic versus hypothermic groups. Conversely, the Emory series found no relative advantages of normothermia, but a significantly increased stroke rate which lead to early termination of the study. A number of factors may explain these opposing results, particularly the operative technique and the patient population. The Emory trial used continuous retrograde warm blood cardioplegia versus intermittent cold oxygenated crystalloid cardioplegia. Patients were actively warmed or cooled to maintain systemic normothermia or hypothermia respectively. The total number of adverse neurological events were 1.4% in the cold group, and 4.5% in the warm group. Multivariate analysis was used to determine predictors of stoke in this group of patients. Preoperative congestive heart failure, age, aortic cross clamp time and use of warm retrograde cardioplegia were all significantly associated with stroke. Differences in the stroke rate were non existent in patients under 60, twice as likely in the warm blood patients between the ages of 60-69, and five times as high in warm blood patients over the age of 70 (Guyton 1995).

In the warm heart investigators trial there were fewer women (16% vs 25%), fewer patients over the age of 70 (16% vs 30%), and fewer higher risk patients for re operations (14% vs 4%). Differences in the patient populations alone may explain the higher incidence of strokes in the Emory series. However, cardioplegia in both the warm and cold blood groups was primarily antegrade (94% of patients) in the warm heart investigators trial, whereas in the Emory trial patients received warm retrograde continuous cardioplegia. Warm patients in the warm heart investigators trial were not actively warmed to maintain systemic normothermia as in the Emory series, but rather allowed to drift to 33 degrees, so it is possible that a significant proportion of patients in this group were mildly hypothermic. Small differences in systemic temperature may affect the susceptibility of the brain to cerebral emboli due to differences in metabolic rate and cerebral blood flow.

In response to the different results found with normothermic CPB, tepid or mild hypothermic CPB has been proposed as a possible compromise. Only 5 trials totaling nearly 500 patients reported stroke as an outcome in this group, so there was insufficient power to detect differences between groups.

Across all trials, meta regression was used to examine the effects of cardioplegia delivery as mentioned previously, but also the number of urgent rather than elective procedures, and bypass time on the incidence of strokes. The effect size was unrelated to the mode of cardioplegia delivery, or the number of urgent procedures. Mean bypass time was however associated with the incidence of strokes, where the number of strokes increases with increasing time on bypass. This finding is however based on mean trial data rather than individual patient data and should be interpreted with caution. Other potentially important co-variates include variability in co-interventions and operative techniques, volumes and flow rates of cardioplegia, individual patient systemic temperatures, and surgeon specific outcomes.

Subtle neurological deficits detected by neurological examination or psychometric testing, and quality of life measures, have been considered important outcomes of CABG with the reduction in stroke rates over the years. Unfortunately very few trials reported these as outcomes, and in those that did, several different measures/scales were used which makes interpretation of findings between trials difficult. None of the trials included in this review reported quality of life as an outcome.

AUTHORS' CONCLUSIONS

Implications for practice

This review could find no definite advantage of hypothermia over normothermia in the incidence of clinical events. Hypothermia was associated with a reduced stroke rate, but this is off set by a trend towards an increase in perioperative mortality and myocardial damage. There is insufficient trial evidence to date to draw any conclusions about the use of tepid CPB. Similarly, no conclusions can be made concerning the effect of temperature on more subtle neurological deficits due to lack of data.

Implications for research

To date only 2 trials included within this review are of sufficient power to detect differences in the stroke rate between hypothermia and normothermia. Differences in operative techniques and patient population may explain the contradictions found between these 2 trials. Further trials are required of standard format to resolve some of these discrepancies, perhaps with the use of tepid CPB given the high stroke rate reported in the Emory series. There is insufficient data to date to comment on the effect of temperature during CPB on subtle neurological deficits and further trials are needed in this area. Similarly, health related quality of life which is an important outcome has not been reported in any trial to date, and future trials should address this.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Birdi cold

Methods	Randomisation by card allocation to one of three groups.
Participants	300 patients (35 women) randomised to cold, tepid or warm CPB. Mean age 60 years. 88% patients for elective CABG
Interventions	CPB perfusate temperature maintained to give a target nasopharyngeal temperature of 28 degrees, 32 degrees, or 37 degrees for the cold, tepid and warm groups respectively. Myocardial protection achieved by cold antegrade crystalloid cardioplegia and topical cooling
Outcomes	Stroke (defined by neurologic examination), perioperative death, MI, IABP
Notes	Excluded patients with previous stroke or TIA

Birdi tepid

Methods	Same study as Birdi cold. Comparison groups cold vs tepid.
Participants	Same study as Birdi cold. Comparison groups cold vs tepid.
Interventions	Same study as Birdi cold. Comparison groups cold vs tepid.
Outcomes	Same study as Birdi cold. Comparison groups cold vs tepid.
Notes	Same study as Birdi cold. Comparison groups cold vs tepid.

Cook

Methods	Method of randomisation unclear.
Participants	60 patients randomised to cold or warm CPB. No details regarding age and sex. All patients elective first time CABG
Interventions	CPB perfusate temperature maintained to give a target nasopharyngeal temperature of 28 degrees and 37 degrees repectively for the cold and warm group
Outcomes	Stroke (defined as a focal neurologic deficit), MI
Notes	Excluded patients with prior CVD or diabetes.

Engleman cold

Methods	Patients randomised to 3 CPB temperatures, cold, tepid and warm using a random number table and sealed envelopes. Outcome assessors of neurological tests were blind to group allocation. Comparison group cold vs warm
Participants	291 patients randomised (24% women). Mean age 62.8 years. 41% patients for elective surgery
Interventions	3 perfusate temperatures, cold (20 degrees), tepid (32 degrees) and warm (37 degrees) for CPB in association with 3 myocardial preservation temps, cold (8-12 degrees), tepid (32 degrees) and warm (37 degrees) cardioplegia. 3/4 surgeons administered antegrade-retrograde cardioplegia, one surgeon used only retrograde cardioplegia
Outcomes	Stroke (defined by neurological examination and CT scan), perioperative death, MI, Matthew score - neurological assessment including cognitive function, elemental examination and degree of disability. Matthew score measured at 3-4 days postop and 1 month post op
Notes	Excluded patients >76 years, patients with any history of neurological dysfunction, and patients with LVEF <30%

Engleman tepid

Methods	Same study as Engleman cold. Comparison groups cold vs tepid
Participants	Same study as Engleman cold. Comparison groups cold vs tepid
Interventions	Same study as Engleman cold. Comparison groups cold vs tepid
Outcomes	Same study as Engleman cold. Comparison groups cold vs tepid
Notes	Same study as Engleman cold. Comparison groups cold vs tepid

Fiore

Methods	Method of randomisation unclear.
Participants	52 patients randomised (12 women). Mean age 64.7 years. All for elective CABG
Interventions	Intermittant antegrade cold blood cardioplegia (4 degrees) vs intermittent antegrade tepid blood cardioplegia (29 degrees). Systemic temperature was allowed to drift to 32 degrees in both groups
Outcomes	Stroke (defined as transcient neurologic deficit).
Notes	

Hayashida cold A

Methods	Patients randomised by means of a computer generated randomisation table. Comparison group cold antegrade vs warm antegrade.
Participants	72 patients (7 women) randomised to 6 groups: cold, tepid and warm, antegrade and retrograde cardioplegia. Mean age 60.3 years (range 35-79). 32% of patients for urgent CABG
Interventions	6 cardioplegic strategies: Cold antegrade cardioplegia (8 degrees), cold retrograde caridioplegia (8 degrees), warm antegrade cardioplegia (37 degrees), warm retrograde cardioplegia (37 degrees), tepid antegrade cardioplegia (allowed to drift to 29 degrees), tepid retrograde cardioplegia (allowed to drift to 29 degrees). Systemic temperatures for all groups were allowed to drift to 33 degrees
Outcomes	Stroke (defined as transcient neurologic deficit), perioperative death, MI, LOS (defined as requirement for inotrophic medication or balloon pump support), IABP
Notes	

Hayashida cold R

Methods	Same study as Hayashida cold A. Comparison group cold retrograde vs warm retrograde.
Participants	Same study as Hayashida cold A. Comparison group cold retrograde vs warm retrograde.
Interventions	Same study as Hayashida cold A. Comparison group cold retrograde vs warm retrograde
Outcomes	Same study as Hayashida cold A. Comparison group cold retrograde vs warm retrograde.
Notes	Same study as Hayashida cold A. Comparison group cold retrograde vs warm retrograde

Hayashida tepid A

Methods	Same study as Hayashida cold A. Comparison group cold antegrade vs tepid antegrade
Participants	Same study as Hayashida cold A. Comparison group cold antegrade vs tepid antegrade
Interventions	Same study as Hayashida cold A. Comparison group cold antegrade vs tepid antegrade
Outcomes	Same study as Hayashida cold A. Comparison group cold antegrade vs tepid antegrade
Notes	Same study as Hayashida cold A. Comparison group cold antegrade vs tepid antegrade

Hayashida tepid R

Methods	Same study as Hayashida cold A. Comparison group cold retrograde vs tepid retrograde
Participants	Hayashida cold A. Comparison group cold retrograde vs tepid retrograde
Interventions	Hayashida cold A. Comparison group cold retrograde vs tepid retrograde
Outcomes	Hayashida cold A. Comparison group cold retrograde vs tepid retrograde
Notes	Hayashida cold A. Comparison group cold retrograde vs tepid retrograde

Heyer

Methods	Consecutive patients randomised to moderate or mild hypothermia. Stratified randomisation according to age. Not stated whether outcome assessors were blind to group allocation
Participants	99 patients randomised (18 women). Mean age 64 years. All patients for elective surgery undergoing first procedures
Interventions	Moderate hypothermic (target nasopharyngeal temp 28 degrees) vs mild hypothermic CPB (target nasopharyngeal temp 34 degrees). Antegrade and retrograde cold blood cardioplegia used in both groups
Outcomes	Neurologic and neuropsychometric exam pre and post op. Neuropsychometric tests included trails A and B, repetitive tapping, grooved pegboard and Busche memory tests. Data has been analysed for early tests at 6 days post op, but not late tests (6-9 weeks post hospital discharge) due to high loss to follow up
Notes	Excluded patients prior to randomisation with evidence of neurologic or psychiatric disease

Kadoi

Methods	Consecutive patients randomised to either hypothermic or normothermic CPB, method of randomisation unclear
Participants	30 patients randomised. Mean age 64 years. All for elective CABG
Interventions	Hypothermic (target nasopharyngeal temp 30 degrees) vs normothermic (target nasopharyngeal temp >35 degrees) CPB. Intermittant antegrade blood cardioplegia (37 degrees warm group, 5 degrees cold group)
Outcomes	Mini mental status tests done preoperatively and 7 days post operatively (unpublished data kindly provided by the authors)
Notes	No pre-existing CVD

Lajos

Methods	Method of randomisation unclear "patients were alternated..."
Participants	108 (28 women) patients randomised to cold blood or warm blood cardioplegia. Mean age 64 years
Interventions	Cold blood retrograde and antegrade cardioplegia vs warm retrograde and antegrade cardioplegia (temp 37 degrees). Systemic temperature lowered to 30 degrees in the cold group, and maintained at 36-37 degrees in the warm group
Outcomes	Stroke (not defined), perioperative death, MI, IABP.
Notes	55 further patients randomised to cold crystalloid cardioplegia. These have not been included in this analysis due to the lack of an appropriate comparison group

Landymore

Methods	Patients randomised to either warm or cold blood cardioplegia by a computer generated series of random numbers
Participants	40 patients randomised. Mean age 57.5 years. All elective surgery
Interventions	Antegrade warm (37 degrees) or antegrade cold blood (8 degrees) cardioplegia. Systemic temperature maintained at 37 degrees (nasopharyngeal temp) during CPB in both groups
Outcomes	Stroke, MI, perioperative death, LOS and IABP as defined by use of inotropes and IABP use
Notes	Patients included if they had 3 vessel CAD and had LVEF>25%. Excluded patients who had undergone prior cardiac operations, or who required concomitant surgery

Martin (Emory)

Methods	2 center RCT (Emory). Patients randomised by computer generated random number assignment
Participants	1001 patients randomised (24.5% women). Mean age 63.3. All elective surgery. 14.4% patients had prior CABG
Interventions	Continuous warm retrograde blood cardioplegia (>35 degrees, with systemic normothermia - >35 degrees) vs intermittant antegrade cold crystalloid cardioplegia (<8 degrees, with systemic hypothermia - <28 degrees)
Outcomes	Stroke (defined as a persistent central neurologic deficit), perioperative death, MI, LOS (inferred from inotrophic drug use), IABP use. Substudy re: Mora examined neuropsychometric data at 1 week and 4-6 weeks post op in a subgroup of 138 patients
Notes	

McLean (Warm Heart)

Methods	As for Warm Heart Investigators. Outcome assessors of psychometric tests were blind to group allocation
Participants	201 patients. Mean age 58.7.
Interventions	As for Warm Heart Investigators.
Outcomes	Neuropsychometric tests at 4-5 days post op, and 3 months post op. Tests included Trails A and B, WAIS revised digit symbol, WMS revised visual reproduction, Buschke total recall test and long term retrieval and grooved pegboard
Notes	Substudy of Warm Heart Investigators RCT.

Mora (Emory)

Methods	As for Martin. Outcome assessors of psychometric tests were blind to group allocation
Participants	138 patients (22% women). Mean age 63 years.
Interventions	As for Martin.
Outcomes	Neurological assessment and neuropsychometric assessment. Tests included WAIS digit span and digit symbol, WMS associate learning and mental control, and grooved pegboard. Tests were carried out at 1 week and 4-6 weeks post op
Notes	Substudy of Emory RCT. 12% patients had a previous stroke in the cold group, 3% in the warm group

Pelletier

Methods	Patients randomised in blocks of 4 for equal sample size in the 2 groups
Participants	200 patients randomised (42 women). Mean age 61 years (40-80 years)
Interventions	Intermittant antegrade warm blood cardioplegia vs intermittant antegrade cold blood cardioplegia. Systemic temperature during CPB allowed to drift to 33-34 degrees in both groups
Outcomes	Stroke (defined as clinical presentation of the individual patient), perioperative death, MI, LOS (defined as inotrophic drug use) and IABP
Notes	Excluded patients having ops within 7 days acute MI, urgent ops, reops, and coronary ops associated with any other surgical procedure

Plourde

Methods	Randomisation by sequentially numbered sealed envelopes. Outcome assessors of psychometric tests were blind to group allocation
Participants	62 patients (4 women) randomised to cold or warm CPB . Mean age 57 years. All for elective surgery
Interventions	CPB perfusate temperature maintained to give a target nasopharyngeal temperature of 28 degrees and 34-35 degrees in the cold and warm groups respectively. Intermittant antegrade cold blood cardioplegia (4 degrees) used for all patients, except for 6 in the warm group who recieved continuous warm blood cardioplegia
Outcomes	Stroke (not defined), perioperative death, MI. Psychometric testing 1 week post op. Tests included WAIS information subset, picture and completion subset, and digit span subset, COWAT, Trailmaking B
Notes	Excluded patients who had had prior cardiac surgery, CVD, or LVEF<0.4. Further data available for subsets of the WMS, but different versions of the tests were used pre and post operatively so data have not been collected

Rashid A

Methods	Consecutive patients randomised according to hospital numbers
Participants	281 patients (70 women). Mean age 60.2. 63% patients for elective surgery
Interventions	Moderate systemic hypothermia (nasopharyngeal temp 28 degrees, cardioplegic temp 4-6 degrees) vs normothermia (nasopharyngeal temp 37 degrees). Retrograde continuous warm and intermittant cold blood cardioplegia
Outcomes	Stroke (not defined), MI, perioperative death. LOS (inferred with inotrope use) and IABP use
Notes	

Rashid B

Methods	Consecutive patients randomised according to hospital numbers
Participants	108 patients (20 women). Median age 59 years. 72% patients for elective surgery
Interventions	Moderate systemic hypothermia (nasopharyngeal temp 28 degrees, cardioplegic temp 8 degrees) vs normothermia (nasopharyngeal temp 37 degrees). Retrograde continuous warm and intermittant cold blood cardioplegia
Outcomes	Stroke (defined as CVA - stroke and confusion), MI, perioperative death. LOS and IABP use
Notes	Patients selected prior to randomisation for moderate to severe left ventricular dysfunction (CASS score 14-15)

Regragui cold

Methods	Patients randomised by using a random number table. Comparison group cold vs warm CPB
Participants	96 patients (12 women) randomised to one of 3 groups, cold, tepid or warm CPB. Mean age 59 years. 24% patients for urgent CABG
Interventions	CPB perfusate temperature maintained to give a target nasopharyngeal temperature of 28 degrees, 32 degrees, or 37 degrees for the cold, tepid and warm groups respectively. Myocardial protection achieved by cold antegrade crystalloid cardioplegia and topical cooling
Outcomes	Perioperative death, neurological examination and psychometric testing at 6 weeks post surgery. Psychometric tests included WAIS digit span, picture arrangement, block design, object assembly and digit symbol, and WMS verbal and visual paired associates
Notes	Excluded patients with previous neurologic disease or psychiatric illness

Regragui tepid

Methods	Same study as Regragui cold. Comparison group cold vs tepid CPB
Participants	Same study as Regragui cold. Comparison group cold vs tepid CPB
Interventions	Same study as Regragui cold. Comparison group cold vs tepid CPB
Outcomes	Same study as Regragui cold. Comparison group cold vs tepid CPB
Notes	Same study as Regragui cold. Comparison group cold vs tepid CPB

Tonz

Methods	Consecutive patients randomised, no method stated.
Participants	30 patients (2 women). Mean age 61.5 years. All for elective surgery, all first procedures
Interventions	Moderate systemic hypothermia (blood temperature 26-28 degrees) vs normothermia (36-37 degrees). Management of myocardial protection was identical in both groups - cold intermittant blood cardioplegia administered either retrogradely, antegradely or both
Outcomes	Stroke (defined as cerebrovascular insult), perioperative death
Notes	Excluded patients >65 years, and ejection fraction <0.35, and any previous cardiac procedure

Warm Heart

Methods	3 center RCT (Toronto). Treatment allocation by sealed envelope, stratified by surgeon and urgent vs elective cases
Participants	1732 patients (285 women). Mean age 61 years (40-80 years). 74% elective cases
Interventions	Warm antegrade cardioplegia (37 degrees) vs cold antegrade cardioplegia (5-8 degrees). 6.3% of patients recieved at least some retrograde cardioplegia. Target systemic temperature in the warm group kept between 33-37 degrees). Target systemic temperature in the cold group reduced to 25-28 degrees by active cooling
Outcomes	Stroke (defined as persistent central neurologic deficit), perioperative death, MI, LOS (use of inotropic medication or IABP for 60 mins + to sustain SBP>90mmHg), IABP use. Substudy re: McLean looked at neurological and neuropsychological function at 5 days and 3 months post op in 201 patients
Notes	5.5% patients had had a previous TIA or stroke. Excluded patients scheduled for concomitant cardiac surgical or vascular procedures

Yau A cold A

Methods	Patients randomised using computer generated randomisation table
Participants	107 (8 women) patients randomised to 5 groups: cold antegrade, cold retrograde, warm antegrade, warm retrograde and intermittant cold cardioplegia. Mean age 59 years. 89% patients underwent elective surgery
Interventions	5 cardioplegic strategies: Warm antegrade cardioplegia (37 degrees), warm retrograde cardioplegia (37 degrees), cold antegrade cardioplegia (5 degrees), cold intermittant antegrade cardioplegia (5 degrees) and cold retrograde cardioplegia (5 degrees). In patients recieving warm cardioplegia systemic temps were allowed to drift to 30 degrees, patients recieving cold cardioplegia were actively cooled to 28 degrees
Outcomes	Stroke (not defined), perioperative death, MI, LOS (defined as IABP use), IABP
Notes	

Yau A cold int. A

Methods	As for Yau cold A. Comparison group intermittant cold antegrade cardioplegia vs warm antegrade cardioplegia
Participants	As for Yau cold A. Comparison group intermittant cold antegrade cardioplegia vs warm antegrade cardioplegia
Interventions	As for Yau cold A. Comparison group intermittant cold antegrade cardioplegia vs warm antegrade cardioplegia
Outcomes	As for Yau cold A. Comparison group intermittant cold antegrade cardioplegia vs warm antegrade cardioplegia
Notes	As for Yau cold A. Comparison group intermittant cold antegrade cardioplegia vs warm antegrade cardioplegia

Yau A cold R

Methods	As for Yau cold A. Comparison group cold retrograde cardioplegia vs warm retrograde cardioplegia
Participants	As for Yau cold A. Comparison group cold retrograde cardioplegia vs warm retrograde cardioplegia
Interventions	As for Yau cold A. Comparison group cold retrograde cardioplegia vs warm retrograde cardioplegia
Outcomes	As for Yau cold A. Comparison group cold retrograde cardioplegia vs warm retrograde cardioplegia
Notes	As for Yau cold A. Comparison group cold retrograde cardioplegia vs warm retrograde cardioplegia

Yau B

Methods	Patients randomised using computer generated randomisation table
Participants	53 (1 female) patients randomised. Mean age 58.5 years. All elective CABG, with stable exertional angina
Interventions	Warm continuous antegrade blood cardioplegia vs antegrade intermittant cold blood cardioplegia. Systemic temperature in the warm group allowed to drift to 30-32 degrees, patients in the cold group were actively cooled to 25-28 degrees
Outcomes	Stroke (not defined), perioperative death, MI, LOS (defined as inotropic drug use or IABP use), IABP
Notes	

CABG - coronary artery bypass graft
CASS - coronary artery surgery study
CVD - cerebrovascular disease
CPB - cardiopulmonary bypass
IABP - intra-aortic balloon pump use
LOS - low output syndrome
LVEF - left ventricular ejection fraction
MI - myocardial infarction
TIA - transcient ischaemic attack
Psychometric tests:
COWART - control oral word association test
WAIS - Wechsler Adult Intelligence Scale
WMS - Wechsler Memory Scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Arom	Tepid vs warm temperature protocol.
Birdi	No neurological outcomes measured.
Chello	No neurological outcomes measured.
Christakis	No neurological outcomes measured.
Christakis 2	No neurological outcomes measured.
Craver	Not a randomised controlled trial.
Elwatidy	No neurological outcomes measured.
Frank	No neurological outcomes measured.
Gozal	No neurological outcomes measured.
Grech	No neurological outcomes measured.
Guiraudon	No neurological outcomes measured. Both comparison groups used hypothermia, mode of cardioplegia delivery, either antegrade or retrograde was the focus of this study
Hayashida	No neurological outcomes measured.
Kaukoranta	Tepid vs warm temperature protocol.
Nathan	No neurological outcomes measured.
Regragui	No neurological outcomes measured.
Yau	No neurological outcomes measured.

DATA AND ANALYSES

Comparison 1. Hypothermia versus normothermia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Non fatal stroke	18	4249	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.68 [0.44, 1.05]
2 Perioperative deaths (not strokes)	16	4201	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.46 [0.90, 2.37]
3 Non fatal MI	17	4219	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.05 [0.81, 1.37]
4 Low output syndrome (LOS)	13	3711	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.21 [0.99, 1.48]
5 Intra-aortic balloon pump use (IABP)	13	3949	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.67 [0.44, 1.03]
6 Pooled "bad" outcomes (perioperative death, stroke, MI, LOS, IABP)	19	4311	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.07 [0.92, 1.24]
7 Early cognitive function tests	4	1546	Mean Difference (IV, Fixed, 95% CI)	-0.43 [-1.49, 0.63]
7.1 Intellectual IQ function - WAIS RDS	3	297	Mean Difference (IV, Fixed, 95% CI)	-0.94 [-3.38, 1.50]
7.2 Intellectual IQ function - digit span	2	146	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-1.98, 0.58]
7.3 Memory - Buschke consistent longterm retrieval	2	241	Mean Difference (IV, Fixed, 95% CI)	-0.72 [-8.53, 7.08]
7.4 Motor skill / dexterity - Trails A	2	241	Mean Difference (IV, Fixed, 95% CI)	2.29 [-1.58, 6.17]
7.5 Motor skill / dexterity - Grooved Pegboard	3	326	Mean Difference (IV, Fixed, 95% CI)	3.49 [-5.33, 12.31]
7.6 Executive function - Trails B	3	295	Mean Difference (IV, Fixed, 95% CI)	2.27 [-8.43, 12.98]
8 Late cognitive function tests	3	811	Mean Difference (IV, Fixed, 95% CI)	-0.23 [1.00, 0.55]
8.1 Intellectual IQ function - WAIS RDS	3	297	Mean Difference (IV, Fixed, 95% CI)	-0.32 [-2.20, 1.57]
8.2 Intellectual IQ function - digit span	2	144	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-1.21, 1.05]
8.3 Memory - WMS verbal paired associates / associated learning	2	133	Mean Difference (IV, Fixed, 95% CI)	-0.35 [-1.64, 0.94]
8.4 Motor skill / dexterity - Grooved Pegboard	2	237	Mean Difference (IV, Fixed, 95% CI)	-1.28 [-10.01, 7.45]

Comparison 2. Hypothermia versus tepid temperature or mild hypothermia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Non fatal stroke	5	493	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.33, 2.73]
2 Perioperative deaths (not strokes)	3	460	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.94 [0.39, 9.66]
3 Non fatal MI	4	441	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.68 [0.26, 1.81]

Comparison 3. Hypothermia versus normothermia, retrograde delivery of cardioplegia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Non fatal stroke	6	1720	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.55 [0.32, 0.97]
2 Perioperative deaths (not strokes)	4	1588	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.31 [0.56, 3.11]

Comparison 4. Hypothermia versus normothermia, antegrade delivery of cardioplegia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Non fatal stroke	5	2237	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.93 [0.47, 1.85]
2 Perioperative deaths (not strokes)	5	2237	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.82 [0.97, 3.40]

Analysis 1.1. Comparison 1 Hypothermia versus normothermia, Outcome 1 Non fatal stroke.

Review: Hypothermia to reduce neurological damage following coronary artery bypass surgery

Comparison: 1 Hypothermia versus normothermia

Outcome: 1 Non fatal stroke

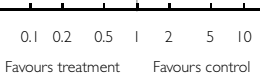
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Birdi cold	0/100	1/100		1.2 %	0.14 [0.00, 6.82]
Cook	0/30	0/30			Not estimable
Engleman cold	6/100	4/98		11.8 %	1.49 [0.42, 5.30]
Hayashida cold A	0/12	0/12			Not estimable
Hayashida cold R	0/12	1/12		1.2 %	0.14 [0.00, 6.82]
Lajos	0/54	3/54		3.6 %	0.13 [0.01, 1.28]
Landymore	0/20	0/20			Not estimable
Martin (Emory)	6/508	20/493		31.2 %	0.32 [0.15, 0.70]
Pelletier	2/100	1/100		3.7 %	1.96 [0.20, 19.07]
Plourde	0/29	1/33		1.2 %	0.15 [0.00, 7.76]
Rashid A	4/144	2/137		7.3 %	1.87 [0.37, 9.43]
Rashid B	2/50	2/58		4.8 %	1.17 [0.16, 8.56]
Tonz	0/16	0/14			Not estimable
Warm Heart	13/872	14/860		32.8 %	0.91 [0.43, 1.96]
Yau A cold A	0/20	0/21			Not estimable
Yau A cold int. A	1/22	0/21		1.2 %	7.06 [0.14, 356.21]
Yau A cold R	0/22	0/22			Not estimable
Yau B	0/26	0/27			Not estimable
Total (95% CI)	**2137**	**2112**		**100.0 %**	**0.68 [0.44, 1.05]**

Total events: 34 (Treatment), 49 (Control)

Heterogeneity: Chi^2 = 13.48, df = 10 (P = 0.20); I^2 =26%

Test for overall effect: Z = 1.72 (P = 0.086)

Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 Hypothermia versus normothermia, Outcome 2 Perioperative deaths (not strokes).

Review: Hypothermia to reduce neurological damage following coronary artery bypass surgery

Comparison: 1 Hypothermia versus normothermia

Outcome: 2 Perioperative deaths (not strokes)

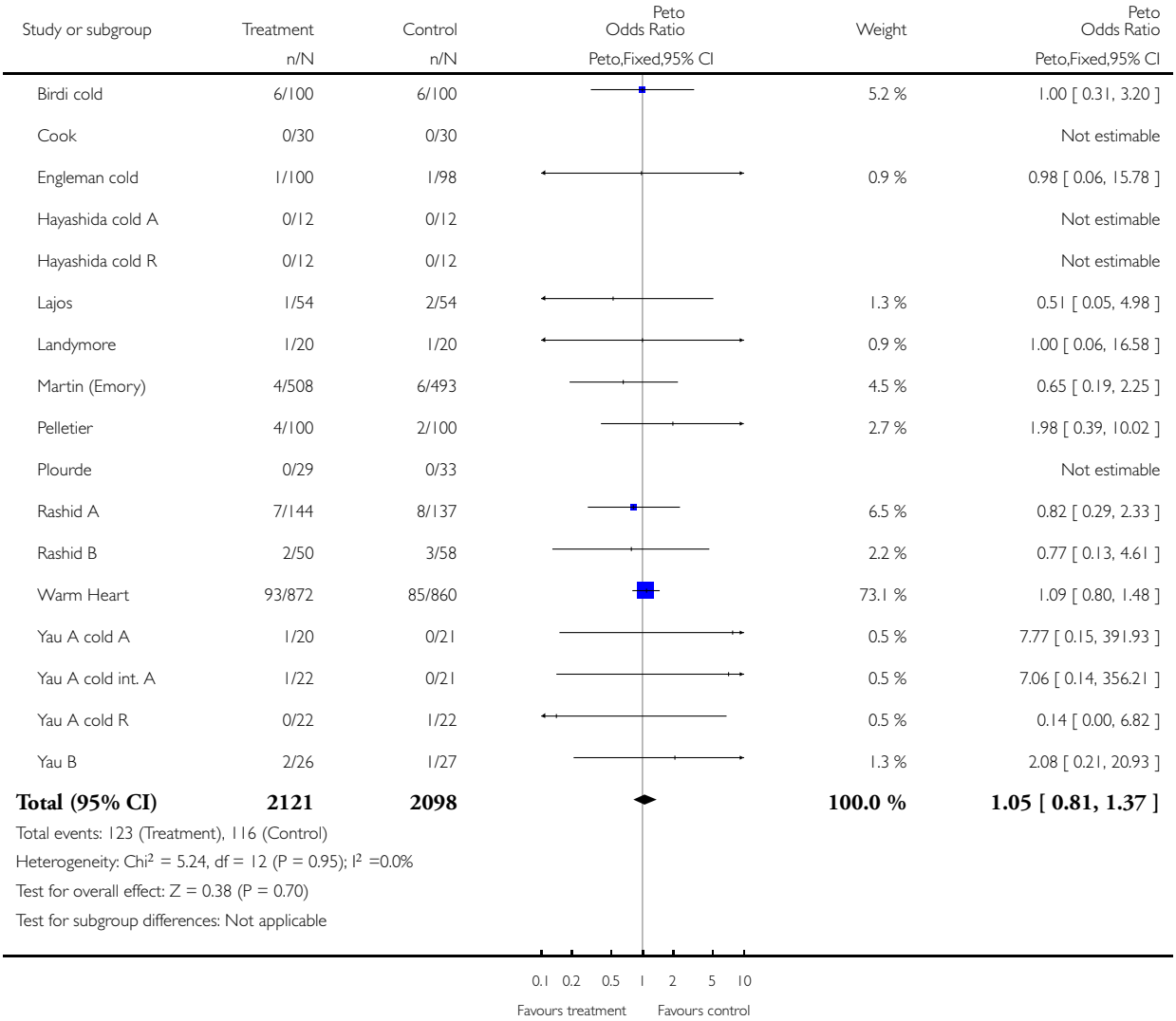
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Birdi cold	2/100	1/100		4.5 %	1.96 [0.20, 19.07]
Engleman cold	1/100	1/98		3.0 %	0.98 [0.06, 15.78]
Lajos	0/54	2/54		3.0 %	0.13 [0.01, 2.15]
Landymore	0/20	1/20		1.5 %	0.14 [0.00, 6.82]
Martin (Emory)	8/508	5/493		19.4 %	1.55 [0.52, 4.62]
Pelletier	1/100	1/100		3.0 %	1.00 [0.06, 16.10]
Plourde	0/29	0/33			Not estimable
Rashid A	3/144	1/137		6.0 %	2.61 [0.36, 18.77]
Rashid B	0/50	2/58		3.0 %	0.15 [0.01, 2.49]
Regragui cold	1/31	0/29		1.5 %	6.93 [0.14, 349.88]
Tonz	0/16	0/14			Not estimable
Warm Heart	22/872	12/860		50.5 %	1.80 [0.91, 3.54]
Yau A cold A	0/20	0/21			Not estimable
Yau A cold int. A	1/22	0/21		1.5 %	7.06 [0.14, 356.21]
Yau A cold R	0/22	1/22		1.5 %	0.14 [0.00, 6.82]
Yau B	1/26	0/27		1.5 %	7.68 [0.15, 387.26]
Total (95% CI)	**2114**	**2087**		**100.0 %**	**1.46 [0.90, 2.37]**
Total events: 40 (Treatment), 27 (Control)					
Heterogeneity: Chi^2 = 11.02, df = 12 (P = 0.53); I^2 =0.0%					
Test for overall effect: Z = 1.55 (P = 0.12)					
Test for subgroup differences: Not applicable					

Analysis 1.3. Comparison 1 Hypothermia versus normothermia, Outcome 3 Non fatal MI.

Review: Hypothermia to reduce neurological damage following coronary artery bypass surgery

Comparison: 1 Hypothermia versus normothermia

Outcome: 3 Non fatal MI

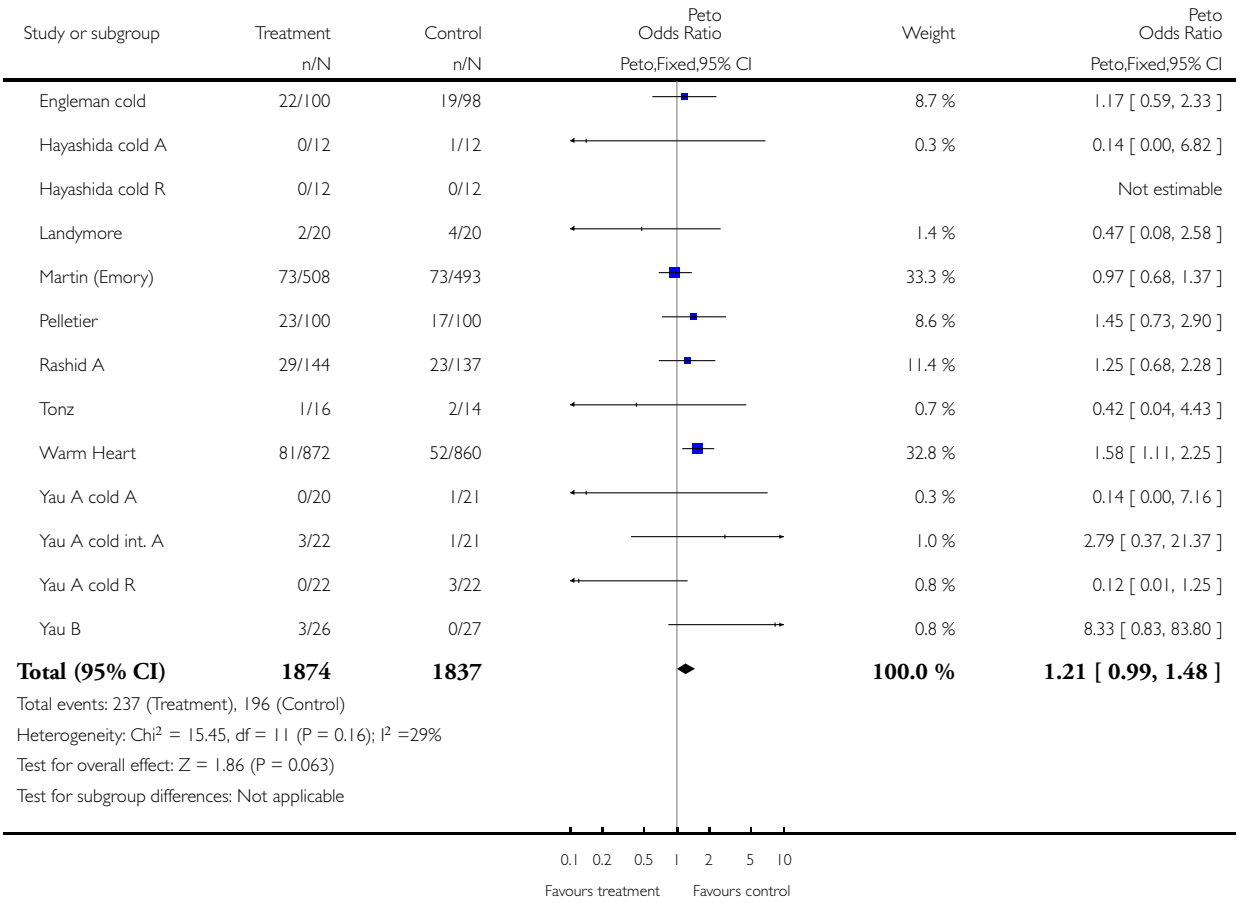


Analysis 1.4. Comparison 1 Hypothermia versus normothermia, Outcome 4 Low output syndrome (LOS).

Review: Hypothermia to reduce neurological damage following coronary artery bypass surgery

Comparison: 1 Hypothermia versus normothermia

Outcome: 4 Low output syndrome (LOS)



Analysis 1.5. Comparison 1 Hypothermia versus normothermia, Outcome 5 Intra-aortic balloon pump use (IABP).

Review: Hypothermia to reduce neurological damage following coronary artery bypass surgery

Comparison: 1 Hypothermia versus normothermia

Outcome: 5 Intra-aortic balloon pump use (IABP)

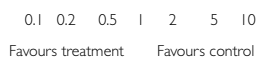
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Birdi cold	3/100	4/100		8.1 %	0.74 [0.17, 3.35]
Engleman cold	1/100	3/98		4.7 %	0.35 [0.05, 2.56]
Hayashida cold A	0/12	1/12		1.2 %	0.14 [0.00, 6.82]
Hayashida cold R	0/12	0/12			Not estimable
Lajos	1/54	1/54		2.4 %	1.00 [0.06, 16.20]
Martin (Emory)	10/508	7/493		19.9 %	1.39 [0.53, 3.62]
Pelletier	3/100	5/100		9.2 %	0.60 [0.15, 2.44]
Rashid A	3/144	4/137		8.1 %	0.71 [0.16, 3.17]
Warm Heart	14/872	21/860		40.8 %	0.66 [0.34, 1.28]
Yau A cold A	0/20	1/21		1.2 %	0.14 [0.00, 7.16]
Yau A cold int. A	0/22	1/21		1.2 %	0.13 [0.00, 6.51]
Yau A cold R	0/22	3/22		3.4 %	0.12 [0.01, 1.25]
Yau B	0/26	0/27			Not estimable
Total (95% CI)	**1992**	**1957**		**100.0 %**	**0.67 [0.44, 1.03]**

Total events: 35 (Treatment), 51 (Control)

Heterogeneity: $Chi^2 = 6.73$, df = 10 (P = 0.75); $I^2 = 0.0\%$

Test for overall effect: Z = 1.82 (P = 0.069)

Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1 Hypothermia versus normothermia, Outcome 6 Pooled "bad" outcomes (perioperative death, stroke, MI, LOS, IABP).

Review: Hypothermia to reduce neurological damage following coronary artery bypass surgery

Comparison: 1 Hypothermia versus normothermia

Outcome: 6 Pooled "bad" outcomes (perioperative death, stroke, MI, LOS, IABP)

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Birdi cold	8/100	8/100		2.2 %	1.00 [0.36, 2.77]
Cook	0/30	0/30			Not estimable
Engleman cold	31/100	28/100		6.1 %	1.15 [0.63, 2.12]
Hayashida cold A	0/12	2/12		0.3 %	0.12 [0.01, 2.10]
Hayashida cold R	0/12	1/12		0.1 %	0.14 [0.00, 6.82]
Lajos	1/54	7/54		1.1 %	0.20 [0.05, 0.84]
Landymore	3/20	6/20		1.0 %	0.43 [0.10, 1.87]
Martin (Emory)	101/508	111/493		24.3 %	0.85 [0.63, 1.16]
Pelletier	33/100	26/100		6.1 %	1.40 [0.76, 2.56]
Plourde	0/29	1/33		0.1 %	0.15 [0.00, 7.76]
Rashid A	46/144	38/137		8.6 %	1.22 [0.73, 2.03]
Rashid B	4/50	7/58		1.4 %	0.64 [0.19, 2.23]
Regragui cold	1/31	0/29		0.1 %	6.93 [0.14, 349.88]
Tonz	1/16	2/14		0.4 %	0.42 [0.04, 4.43]
Warm Heart	223/872	184/860		45.3 %	1.26 [1.01, 1.58]
Yau A cold A	1/20	2/21		0.4 %	0.52 [0.05, 5.32]
Yau A cold int. A	6/22	2/21		1.0 %	3.14 [0.69, 14.34]
Yau A cold R	0/22	6/22		0.8 %	0.10 [0.02, 0.57]
Yau B	4/26	1/27		0.7 %	3.82 [0.62, 23.72]
Total (95% CI)	**2168**	**2143**		**100.0 %**	**1.07 [0.92, 1.24]**

Total events: 463 (Treatment), 432 (Control)

Heterogeneity: Chi^2 = 29.74, df = 17 (P = 0.03); I^2 =43%

Test for overall effect: Z = 0.90 (P = 0.37)

Test for subgroup differences: Not applicable

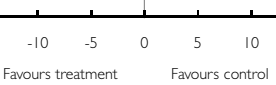
Analysis 1.7. Comparison 1 Hypothermia versus normothermia, Outcome 7 Early cognitive function tests.

Review: Hypothermia to reduce neurological damage following coronary artery bypass surgery

Comparison: 1 Hypothermia versus normothermia

Outcome: 7 Early cognitive function tests

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Intellectual IQ function - WAIS RDS							
McLean (Warm Heart)	77	5.7 (9.5)	78	6.6 (11.1)		10.7 %	-0.90 [-4.15, 2.35]
Mora (Emory)	43	6 (12)	45	6 (12.9)		4.2 %	0.0 [-5.20, 5.20]
Plourde	24	1.2 (8.3)	30	3.2 (11.4)		4.1 %	-2.00 [-7.26, 3.26]
Subtotal (95% CI)	**144**		**153**			**19.0 %**	**-0.94 [-3.38, 1.50]**
Heterogeneity: Chi^2 = 0.28, df = 2 (P = 0.87); I^2 =0.0%							
Test for overall effect: Z = 0.75 (P = 0.45)							
2 Intellectual IQ function - digit span							
Mora (Emory)	47	0 (3.9)	45	1 (3.32)		51.8 %	-1.00 [-2.48, 0.48]
Plourde	24	0 (4.67)	30	-0.2 (4.85)		17.4 %	0.20 [-2.35, 2.75]
Subtotal (95% CI)	**71**		**75**			**69.2 %**	**-0.70 [-1.98, 0.58]**
Heterogeneity: Chi^2 = 0.64, df = 1 (P = 0.42); I^2 =0.0%							
Test for overall effect: Z = 1.07 (P = 0.28)							
3 Memory - Buschke consistent longterm retrieval							
Heyer	40	13.9 (23.8)	46	14.2 (27)		1.0 %	-0.30 [-11.04, 10.44]
McLean (Warm Heart)	77	-9.1 (34.6)	78	-7.9 (37.6)		0.9 %	-1.20 [-12.57, 10.17]
Subtotal (95% CI)	**117**		**124**			**1.9 %**	**-0.72 [-8.53, 7.08]**
Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.91); I^2 =0.0%							
Test for overall effect: Z = 0.18 (P = 0.86)							
4 Motor skill / dexterity - Trails A							
Heyer	40	0 (18.8)	46	-1.3 (14.6)		2.2 %	1.30 [-5.89, 8.49]
McLean (Warm Heart)	77	4.1 (15.5)	78	1.4 (13.65)		5.3 %	2.70 [-1.90, 7.30]
Subtotal (95% CI)	**117**		**124**			**7.5 %**	**2.29 [-1.58, 6.17]**
Heterogeneity: Chi^2 = 0.10, df = 1 (P = 0.75); I^2 =0.0%							
Test for overall effect: Z = 1.16 (P = 0.25)							
5 Motor skill / dexterity - Grooved Pegboard							
Heyer	40	10 (39.4)	46	4.7 (29.2)		0.5 %	5.30 [-9.54, 20.14]
McLean (Warm Heart)	77	30.3 (45.05)	78	23.3 (35.5)		0.7 %	7.00 [-5.78, 19.78]
Mora (Emory)	41	14 (44.6)	44	24 (55.4)		0.2 %	-10.00 [-31.31, 11.31]
Subtotal (95% CI)	**158**		**168**			**1.5 %**	**3.49 [-5.33, 12.31]**



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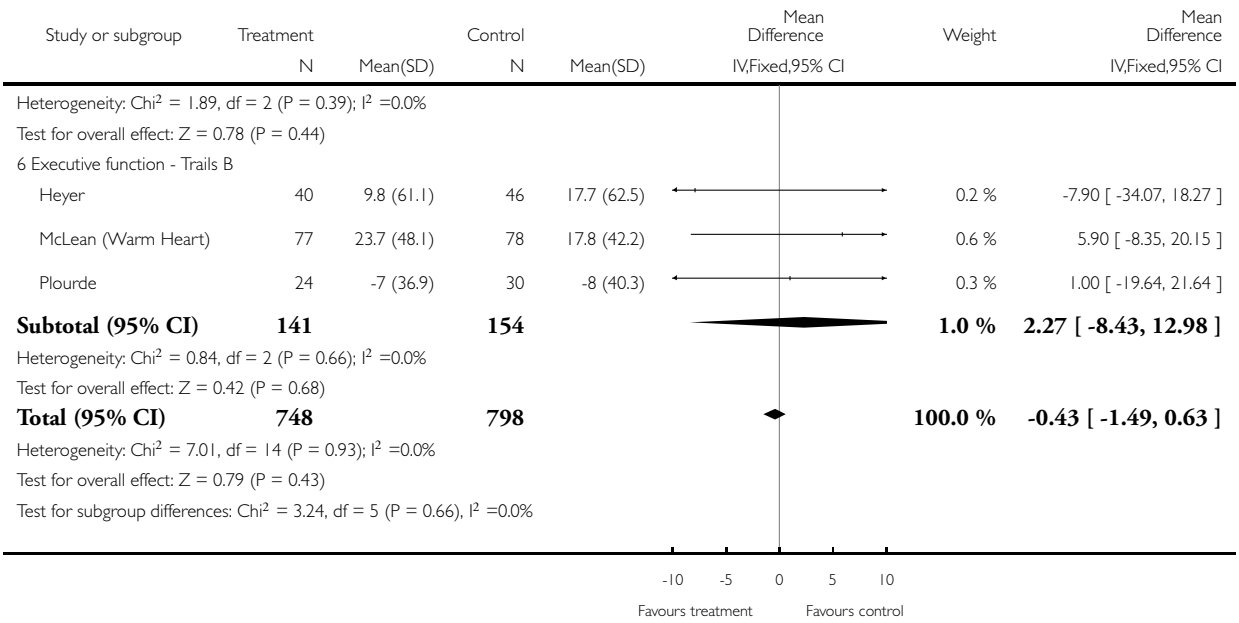
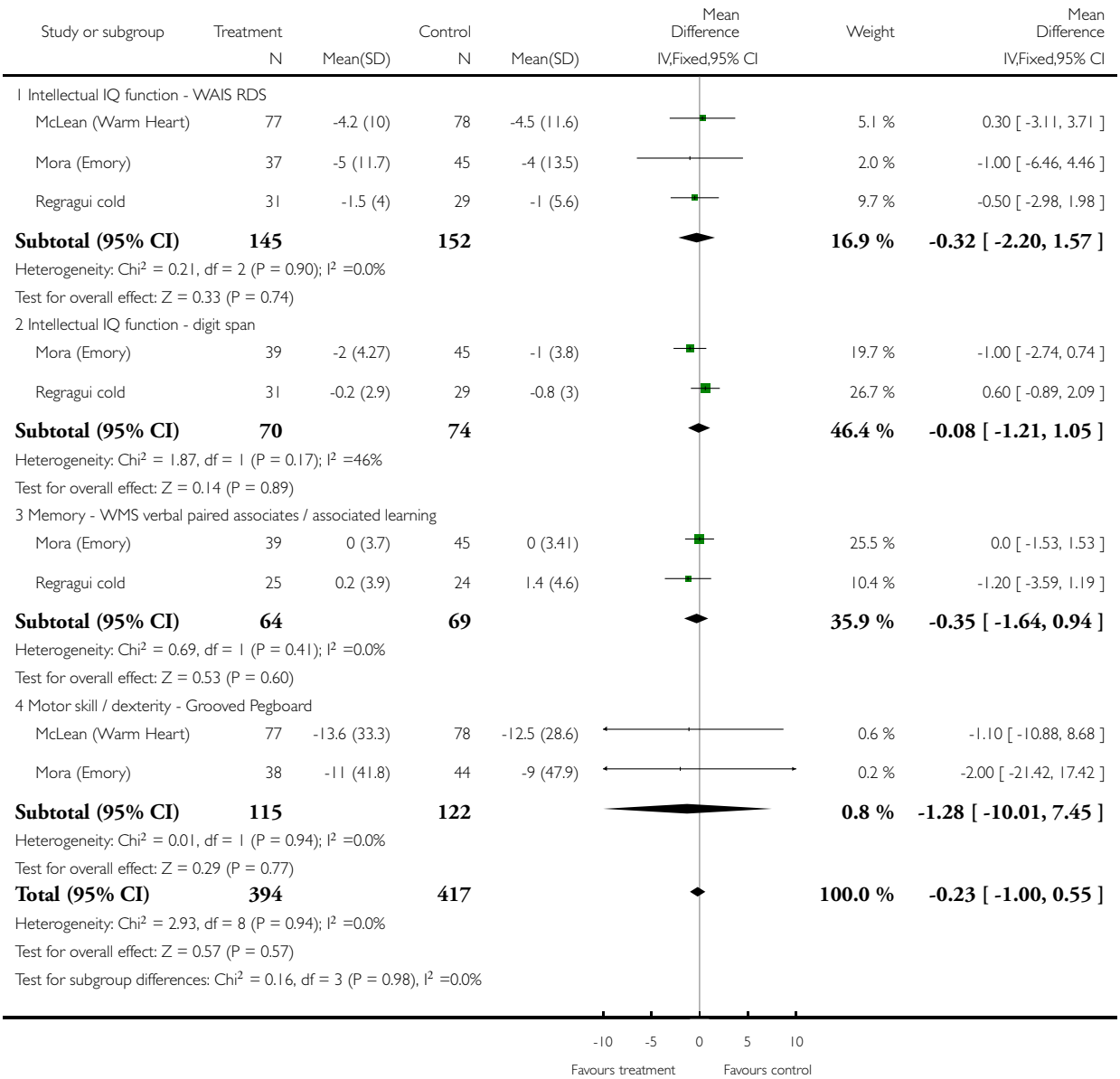


Analysis 1.8. Comparison 1 Hypothermia versus normothermia, Outcome 8 Late cognitive function tests.

Review: Hypothermia to reduce neurological damage following coronary artery bypass surgery

Comparison: 1 Hypothermia versus normothermia

Outcome: 8 Late cognitive function tests



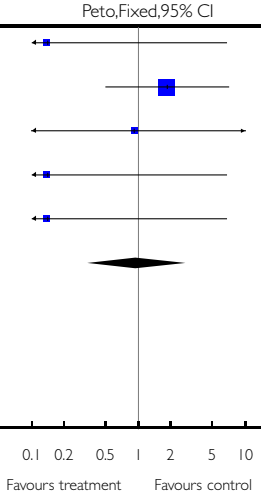
Analysis 2.1. Comparison 2 Hypothermia versus tepid temperature or mild hypothermia, Outcome 1 Non fatal stroke.

Review: Hypothermia to reduce neurological damage following coronary artery bypass surgery

Comparison: 2 Hypothermia versus tepid temperature or mild hypothermia

Outcome: 1 Non fatal stroke

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Birdi tepid	0/100	1/100		7.4 %	0.14 [0.00, 6.82]
Engleman tepid	6/100	3/93		63.5 %	1.86 [0.49, 7.07]
Fiore	1/27	1/25		14.4 %	0.92 [0.06, 15.22]
Hayashida tepid A	0/12	1/12		7.4 %	0.14 [0.00, 6.82]
Hayashida tepid R	0/12	1/12		7.4 %	0.14 [0.00, 6.82]
Total (95% CI)	**251**	**242**		**100.0 %**	**0.94 [0.33, 2.73]**
Total events: 7 (Treatment), 7 (Control)					
Heterogeneity: Chi^2 = 3.82, df = 4 (P = 0.43); I^2 =0.0%					
Test for overall effect: Z = 0.11 (P = 0.91)					
Test for subgroup differences: Not applicable					

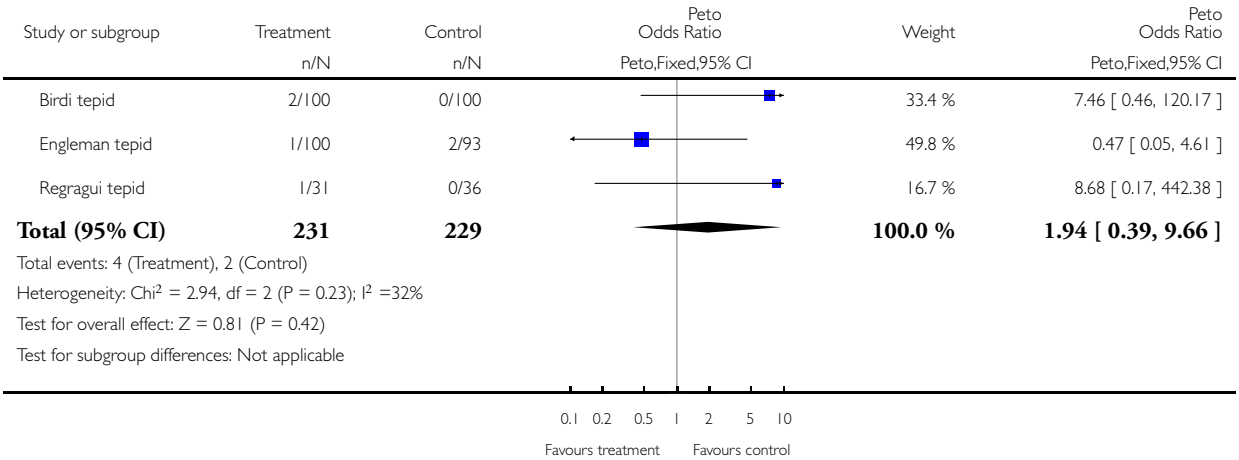


Analysis 2.2. Comparison 2 Hypothermia versus tepid temperature or mild hypothermia, Outcome 2 Perioperative deaths (not strokes).

Review: Hypothermia to reduce neurological damage following coronary artery bypass surgery

Comparison: 2 Hypothermia versus tepid temperature or mild hypothermia

Outcome: 2 Perioperative deaths (not strokes)



Analysis 2.3. Comparison 2 Hypothermia versus tepid temperature or mild hypothermia, Outcome 3 Non fatal MI.

Review: Hypothermia to reduce neurological damage following coronary artery bypass surgery

Comparison: 2 Hypothermia versus tepid temperature or mild hypothermia

Outcome: 3 Non fatal MI

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Birdi tepid	6/100	8/100		81.4 %	0.74 [0.25, 2.18]
Engleman tepid	1/100	1/93		12.4 %	0.93 [0.06, 15.00]
Hayashida tepid A	0/12	0/12			Not estimable
Hayashida tepid R	0/12	1/12		6.2 %	0.14 [0.00, 6.82]
Total (95% CI)	**224**	**217**		**100.0 %**	**0.68 [0.26, 1.81]**

Total events: 7 (Treatment), 10 (Control)

Heterogeneity: $Chi^2 = 0.72$, df = 2 (P = 0.70); $I^2 = 0.0\%$

Test for overall effect: Z = 0.77 (P = 0.44)

Test for subgroup differences: Not applicable

Analysis 3.1. Comparison 3 Hypothermia versus normothermia, retrograde delivery of cardioplegia, Outcome 1 Non fatal stroke.

Review: Hypothermia to reduce neurological damage following coronary artery bypass surgery

Comparison: 3 Hypothermia versus normothermia, retrograde delivery of cardioplegia

Outcome: 1 Non fatal stroke

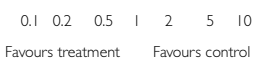
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Engleman cold	6/100	4/98		19.6 %	1.49 [0.42, 5.30]
Hayashida cold R	0/12	1/12		2.1 %	0.14 [0.00, 6.82]
Lajos	0/54	3/54		6.1 %	0.13 [0.01, 1.28]
Martin (Emory)	6/508	20/493		52.2 %	0.32 [0.15, 0.70]
Rashid A	4/144	2/137		12.1 %	1.87 [0.37, 9.43]
Rashid B	2/50	2/58		8.0 %	1.17 [0.16, 8.56]
Total (95% CI)	**868**	**852**		**100.0 %**	**0.55 [0.32, 0.97]**

Total events: 18 (Treatment), 32 (Control)

Heterogeneity: $Chi^2 = 8.97$, df = 5 (P = 0.11); $I^2 = 44\%$

Test for overall effect: Z = 2.06 (P = 0.040)

Test for subgroup differences: Not applicable

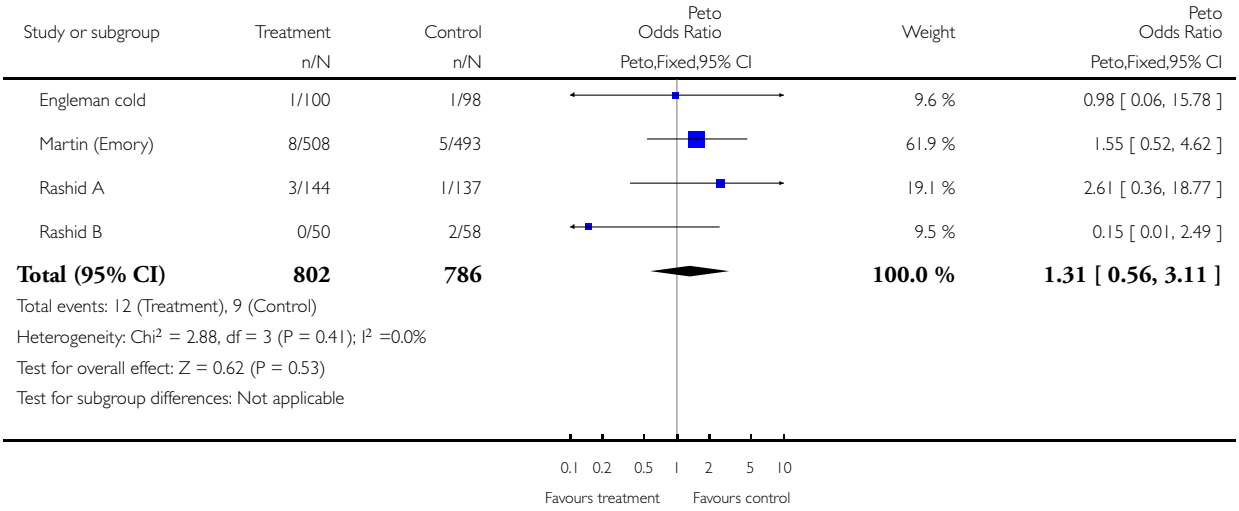


Analysis 3.2. Comparison 3 Hypothermia versus normothermia, retrograde delivery of cardioplegia, Outcome 2 Perioperative deaths (not strokes).

Review: Hypothermia to reduce neurological damage following coronary artery bypass surgery

Comparison: 3 Hypothermia versus normothermia, retrograde delivery of cardioplegia

Outcome: 2 Perioperative deaths (not strokes)



Analysis 4.1. Comparison 4 Hypothermia versus normothermia, antegrade delivery of cardioplegia, Outcome 1 Non fatal stroke.

Review: Hypothermia to reduce neurological damage following coronary artery bypass surgery

Comparison: 4 Hypothermia versus normothermia, antegrade delivery of cardioplegia

Outcome: 1 Non fatal stroke

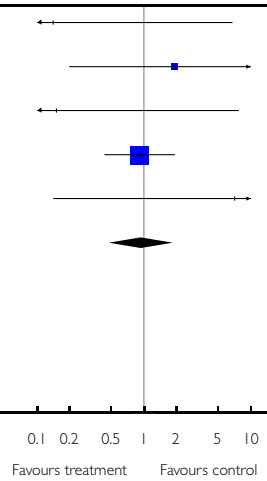
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Birdi cold	0/100	1/100		3.1 %	0.14 [0.00, 6.82]
Pelletier	2/100	1/100		9.1 %	1.96 [0.20, 19.07]
Plourde	0/29	1/33		3.1 %	0.15 [0.00, 7.76]
Warm Heart	13/872	14/860		81.7 %	0.91 [0.43, 1.96]
Yau A cold int. A	1/22	0/21		3.1 %	7.06 [0.14, 356.21]
Total (95% CI)	**1123**	**1114**		**100.0 %**	**0.93 [0.47, 1.85]**

Total events: 16 (Treatment), 17 (Control)

Heterogeneity: $Chi^2 = 3.18$, df = 4 (P = 0.53); $I^2 = 0.0\%$

Test for overall effect: Z = 0.20 (P = 0.84)

Test for subgroup differences: Not applicable

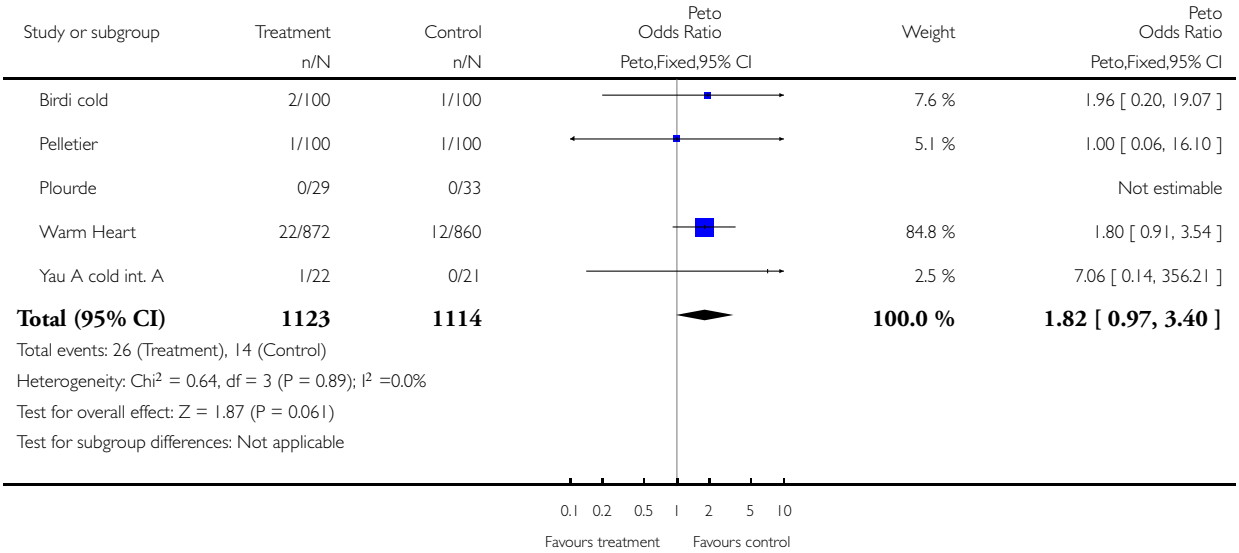


Analysis 4.2. Comparison 4 Hypothermia versus normothermia, antegrade delivery of cardioplegia, Outcome 2 Perioperative deaths (not strokes).

Review: Hypothermia to reduce neurological damage following coronary artery bypass surgery

Comparison: 4 Hypothermia versus normothermia, antegrade delivery of cardioplegia

Outcome: 2 Perioperative deaths (not strokes)



ADDITIONAL TABLES

Table 1. Early psychometric test results (within 1 week post op)

Study ID	Type of test	Specific test	N Intervention	Mean change	SD Difference	N Control	Mean change	SD Difference	Interpretation
Mora (Emory) 1996	Intellectual IQ function	WAIS revised digit symbol	43	-6	12	45	-6	12.9	Deterioration in both groups to same extent
Plourde 1997		WAIS revised digit symbol	24	-1.2	8.3	30	-3.2	11.4	Deterioration greater in control group

Table 1. Early psychometric test results (within 1 week post op) (*Continued*)

McLean (Warm Heart) 1994		WAIS revised digit symbol	77	-5.7	9.5	78	-6.6	11.1	Deterioration greater in control group
Mora (Emory) 1996		WAIS digit span	47	0	3.9	45	-1.0	3.3	Deterioration in control group
Plourde 1997		WAIS digit span	24	0	4.7	30	0.2	4.85	No deterioration in either group
Plourde 1997		WAIS information	24	1.4	5.34	30	1.3	6.05	No deterioration in either group
Plourde 1997		WAIS picture completion	24	1.1	2.88	30	0.9	3.15	No deterioration in either group
McLean (Warm Heart) 1994	Memory	WMS visual reproduction	77	0.8	5.9	78	1.5	5.5	No deterioration in either group
Mora (Emory) 1996		WMS associated learning	43	-4.0	3.3	43	-3.0	2.83	Deterioration greater in intervention group
Mora (Emory) 1996		WMS mental control	47	0	1.93	45	-1.0	1.9	Deterioration in control group
McLean (Warm Heart) 1994		Buschke total recall test	77	8	20.3	78	9.2	20.1	No deterioration in either group

Table 1. Early psychometric test results (within 1 week post op) (*Continued*)

McLean (Warm Heart) 1994		Buschke CLTR	77	9.1	34.6	78	7.9	37.6	No deterioration in either group
McLean (Warm Heart) 1994	Motor skill / dexterity	Trails A	77	4.1	15.5	78	1.4	13.65	Deterioration greater in intervention group
Mora (Emory) 1996		Grooved pegboard	41	14.0	44.6	44	24.0	55.4	Deterioration greater in control group
McLean (Warm Heart) 1994		Grooved pegboard	77	30.3	45.1	78	23.3	35.5	Deterioration greater in intervention group
Plourde 1997	Executive function	Trails B	24	-7.0	36.9	30	-8.0	40.3	Improvement in both groups
McLean (Warm Heart) 1994		Trails B	77	23.7	48.1	78	17.8	42.2	Deterioration greater in intervention group
Plourde 1997		COWAT	24	2.7	9.2	30	1.5	10.8	Deterioration in both groups

Table 2. Late psychometric test results (1-3 months post op)

Study ID	Type of test	Specific test	N Intervention	Mean change	SD Difference	N Control	Mean Change	SD Difference	Interpretation
Mora (Emory) 1996	Intellectual IQ function	WAIS revised digit symbol	37	5	11.7	45	4	13.5	Improvement in

Table 2. Late psychometric test results (1-3 months post op) (*Continued*)

									both groups
Regragui - cold 1996		WAIS revised digit symbol	31	1.5	4	29	1	5.6	Improvement in both groups
McLean (Warm Heart) 1994		WAIS revised digit symbol	77	4.2	10	78	4.5	11.6	Improvement in both groups
Mora (Emory) 1996		WAIS digit span	39	2	4.3	45	1	3.8	Improvement in both groups
Regragui - cold 1996		WAIS digit span	31	0.2	2.9	29	0.8	3	Slight improvement both groups
Regragui - cold 1996		WAIS picture arrangement	31	0.2	5.6	28	-1.4	5.2	Deterioration in control group
Regragui - cold 1996		WAIS block design	31	-0.5	5.7	29	-1.0	7.1	Deterioration greater in control group
Regragui - cold 1996		WAIS object assembly	31	0.5	3.9	29	-0.2	5.6	No real change in either group
McLean (Warm Heart) 1994	Memory	WMS visual reproduction	77	2.2	5.45	78	1.8	5.5	Improvement in both groups
Regragui - cold 1996		WMS visual paired associates	23	1.5	4.7	21	-0.1	3.8	Slight improvement in intervention

Table 2. Late psychometric test results (1-3 months post op) (*Continued*)

									group
Regragui - cold 1996		WMS verbal paired associates	25	-0.2	3.9	24	-1.4	4.6	Deterioration greater in control group
Mora (Emory) 1996		WMS associated learning (same test as verbal paired associates)	39	0	3.7	45	0	3.4	No change in either group
Mora (Emory) 1996		WMS mental control	39	1	1.85	45	0	1.9	Slight improvement intervention group
McLean (Warm Heart) 1994		Buschke total recall test	77	8.4	17.7	78	8.2	19.5	Improvement in both groups
McLean (Warm Heart) 1994		Buschke CLTR	77	10.3	33.9	78	11.6	35.3	Improvement in both groups
McLean (Warm Heart) 1994	Motor skill / dexterity	Trails A	77	-1.6	11.7	78	-1.8	13.2	Improvement in both groups
Mora (Emory) 1996		Grooved pegboard	38	-11	41.8	44	-9.0	47.9	Improvement in both groups
McLean (Warm Heart) 1994		Grooved pegboard	77	-13.6	33.3	78	-12.5	28.6	Improvement in both groups
McLean (Warm Heart)	Executive function	Trails B	77	-10.2	32.9	78	-8.8	33.8	Improvement in

Table 2. Late psychometric test results (1-3 months post op) (*Continued*)

1994									both groups

Table 3. Neurological examination results in hypothermia vs normothermia

Study ID	Investigation(s)	Results
Engleman cold	Mathew Scale measured at baseline, 3-4 days post op, and I month post op	Deterioration seen in both groups to a similar extent 3-4 days post op (mean change -4.9 and 4.6 respectively for I and C groups), which is improved but not resolved at 1 month (mean change from baseline -1.3 for both groups)
Kadoi 1999 (unpublished data)	Mini Mental Status score measured at baseline and 7 days post op	Deterioration as shown by a decrease in score was seen in both groups post operatively, with greater deficit seen in the intervention group (mean change in score -6 and -4 respectively for I and C groups)
Martin 1994 (EMORY)	Neurological examination 3 days or less post op. Looked for global confusion or incoherence suggestive of diffuse encephalopathy	Diffuse encephalopathy seen in 0.2% of patients in the hypothermic group, and 0.4% of patients in the normothermic group
Mora 1996 (substudy of EMORY)	Neurologic assessment included an evaluation of mental status, motor and sensory function, hand coordination, deep tendon and primitive reflexes, at baseline and post operatively before discharge. Perioperative neurological deficits were diagnosed by any of the following: altered level of consciousness or confusion, impaired speech, visual disturbances, new or worsened motor or sensory deficits	Perioperative central neurologic deficits were found in 6/68 patients in the normothermic group, none in the hypothermic group
Regragui 1996	Full neurologic examination on day 4 post op	A positive grasp reflex, and positive Babinski reflex were elicited in 4/60 patients post operatively (2 in each comparison group)

Table 4. Early and late psychometric test results - moderate vs mild hypothermia

Study ID	Type of test	Specific test	N Intervention	Mean Change	SD Difference	N Control	Mean Change	SD Difference	Interpretation
EARLY TESTS (1 week post op)									

Table 4. Early and late psychometric test results - moderate vs mild hypothermia (*Continued*)

Heyer 1997	Memory	Buschke CLTR	40	-13.9	23.8	46	-14.2	27	Deterioration in both groups to similar extent
Heyer 1997		Buschke LTR	40	-21.3	24	46	-21.5	28.5	Deterioration in both groups to similar extent
Heyer 1997	Motor skill / dexterity	Trails A	40	0	18.8	46	-1.3	14.6	Slight improvement in control group
Heyer 1997 (dominant hand)		Grooved pegboard	40	10.0	39.4	46	4.7	29.2	Deterioration greater in intervention group
Heyer 1997 (non-dominant hand)		Grooved pegboard	40	17.1	62.7	46	10.1	34.1	Deterioration greater in intervention group
Heyer 1997 (dominant hand)		Repetitive tapping	40	-1.2	9.6	46	-2.9	10.3	Improvement in both groups
Heyer 1997 (non-dominant hand)		Repetitive tapping	40	-2.2	7.7	46	-0.9	9.9	Improvement in both groups
Heyer 1997	Executive function	Trails B	40	9.8	61.1	46	17.7	62.5	Deterioration greater in control group

Table 4. Early and late psychometric test results - moderate vs mild hypothermia (*Continued*)

LATE TESTS (6 weeks post op)									
Regragui - tepid 1996	Intellectual IQ function	WAIS revised digit symbol	31	1.5	4	36	3.4	5.1	Improvement in both groups
Regragui - tepid 1996		WAIS digit span	31	0.2	2.9	35	0.11	2.7	Very slight improvement both groups
Regragui - tepid 1996		WAIS picture arrangement	31	0.2	5.6	35	-1.2	4.0	Deterioration in control group
Regragui - tepid 1996		WAIS block design	31	-0.5	5.7	35	1.6	5.9	Slight deterioration in the intervention group.
Regragui - tepid 1996		WAIS object assembly	31	0.5	3.9	36	1.5	4.6	Slight improvement greater in control group
Regragui - tepid 1996	Memory	WMS visual paired associates	23	1.5	4.7	28	-0.9	4.6	Slight improvement in intervention group
Regragui - tepid 1996		WMS verbal paired associates	25	-0.2	3.9	31	-0.4	3.7	Very slight deterioration in both groups

Table 5. Neurological examination results in moderate vs mild hypothermia

Study ID	Investigation(s)	Results
Engleman tepid	Mathew Scale measured at baseline, 3-4 days post op, and I month post op	Deterioration in scores to a similar extent in both groups (mean change in score -4.9 in the hypothermic group, -4.6 in the tepid group), this is improved but not resolved at 1 month (mean change from baseline -1.3 and -1.8 respectively in the I and C groups)
Regragui 1996 tepid	Full neurologic examination on day 4 post op	A positive grasp reflex elicited in 3/67 patients (2 in the hypothermic group, 1 in the tepid group), and a positive Babinski reflex elicited in 6/67 patients (2 in the hypothermic group, and 4 in the tepid group)
Heyer 1997	Mini Mental Status score measured at baseline and 6 days post op	No significant change in score in either group.
Heyer 1997	Neurological examination including evaluation of cranial nerves and motor, sensory and cerebellar systems, gait, station, deep tendon and primitive reflexes, measured at baseline and post operatively before hospital discharge	Subtle deficits were detected by neurologic examination in 35% of patients in the hypothermic group, and 27% of patients in the normothermic group

WHAT'S NEW

Last assessed as up-to-date: 23 October 2000.

Date	Event	Description
11 December 2012	Review declared as stable	This review is of historical interest as hypothermia has been superseded in many countries by alternative method. We consider it worth keeping on the library

HISTORY

Protocol first published: Issue 4, 2000

Review first published: Issue 1, 2001

Date	Event	Description
27 October 2008	Amended	Converted to new review format.
23 October 2000	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

All co-reviewers were involved in the design of the review and in providing critical comments about the manuscript. Karen Rees and Morven Beranek-Stanley independently assessed studies for inclusion or exclusion, and independently extracted data from the source papers. Margaret Burke searched the literature for relevant trials. Karen Rees performed statistical analyses. Shah Ebrahim was the primary advisor. Karen Rees was primarily responsible for carrying out and writing the review and was principal author.

We gratefully acknowledge the contribution made by Professor David Naylor who provided us with data and valuable advice.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Department of Social Medicine, University of Bristol, UK.

External sources

- British Heart Foundation, UK.
- Research and Development, Department of Health, UK.

NOTES

This review is of historical interest as hypothermia has been superseded in many countries by alternative method. We consider it worth keeping on the library.

INDEX TERMS

Medical Subject Headings (MeSH)

*Hypothermia, Induced [adverse effects; mortality]; Cardiac Output, Low [etiology]; Cognition Disorders [prevention & control]; Coronary Artery Bypass [*adverse effects; mortality]; Meta-Analysis as Topic; Myocardial Infarction [etiology]; Randomized Controlled Trials as Topic; Stroke [mortality; *prevention & control]

MeSH check words

Humans