Clinical Trials and Regulatory Science in Cardiology 17 (2016) 1–8

Contents lists available at ScienceDirect

Clinical Trials and Regulatory Science in Cardiology

journal homepage: http://www.elsevier.com/locate/ctrsc

Remote ischaemic pre-conditioning does not affect clinical outcomes following coronary Artery bypass grafting. A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 11 January 2016
Received in revised form 25 January 2016
Accepted 10 March 2016
Available online xxxx

Keywords:
Remote ischaemic pre-conditioning
Coronary bypass grafting
Clinical outcomes
Troponins

ABSTRACT

Background: Trials of remote ischemic pre-conditioning (RIPC) have suggested this intervention reduces complications of angioplasty and coronary artery by-pass grafting (CABG). The aim of this work was to conduct a systematic review and meta-analysis of the effects of RIPC on mortality and myocardial damage in patients undertaking coronary artery bypass grafting with/without valve surgery.
Methods: A systematic review and subsequent meta-analysis of randomized controlled trials of RIPC versus usual care or sham RIPC was performed.
Results: Eighteen studies, totalling 4551 participants were analysed. RIPC reduced post troponin release as indicated by area under the curve at 72 h ($\mu g \cdot L^{-1}$) Mean Difference (MD) −3.72 (95% CI −3.92 to −3.53, $p < 0.00001$). However there was no significant difference between RIPC and control when mortality odds ratio (OR) 1.27 (95% CI 0.87 to 1.86, $p = 0.22$); the incidence of new onset atrial fibrillation OR 0.82 (95% CI 0.67 to 1.01, $p = 0.06$); inotropic support OR 1.27 (95% CI 0.84 to 1.91, $p = 0.25$); intensive care unit stay in days MD −0.02 (95% CI −0.12 to 0.07, $p = 0.61$); Hospital stay in days MD 0.18 (95% CI −0.30 to 0.66, $p = 0.47$) and serum creatinine MD −0.00 (95% CI −0.07 to 0.07, $p = 0.97$) were compared.
Conclusions: RIPC reduces does not confer any clinical benefit in patients undertaking CABG with/without valve surgery.

1. Introduction

Remote ischaemic pre-conditioning (RIPC) is a novel prophylactic treatment during which brief periods of ischaemia in a remote vascular bed provides protection against a subsequent longer bout of ischaemia in the heart. Initially demonstrated in a separate cardiovascular bed [1], it was later shown that protection could also be achieved by preconditioning in a remote organ [2] or in a remote limb [3]. Transfer of the signalling stimulus to the heart is thought to involve the somatosensory system, the spinal cord, the autonomous nervous system and humoral elements. Candidates for the humoral signal include nitric oxide, MicroRNA-144, and stromal derived factor-1α [4]. A further complex signal transduction occurs in the heart possibly involving the reperfusion injury salvage kinase (RISK) pathway [4]. Since the early animal studies [1–3], RIPC has been shown to reduce myocardial injury in patients undergoing both elective [5] and primary percutaneous interventions [6] as well as coronary artery bypass grafting (CABG) [7]. In addition to these cardioprotective effects, RIPC has also been used in the management of blood pressure [8], improvement of endothelial function and blood flow [9], and neuroprotection [10].

There have been a number of meta-analyses that have investigated the effects of remote ischaemic preconditioning during open heart surgery. An early study conducted in 2008 only managed to pool data from four studies [11]. Later studies conducted in 2012 predominately focussed on myocardial injury as indicated by troponin release [12–15] and there are many more clinical outcomes that were not assessed. To some extent this was addressed in a recent meta-analysis by Deng et al. [16] who compared aortic cross-clamping versus remote ischaemic preconditioning, however they did not investigate important clinical outcomes such as inotrope use and post-discharge mortality. Since then another six randomized trials have been published including 2 recent large scale multicentre trials [17–22], which also suggest another look is justified.

The aims of this work were to; (i) examine the effects of RIPC on a range of clinical outcomes and markers of myocardial and renal damage in patients undertaking coronary artery bypass grafting with/without valve surgery; (ii) relate these findings to established thresholds of clinical significance and provide an evidence based context for RIPC use.

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[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

http://dx.doi.org/10.1016/j.ctrsc.2016.03.001

Table 1
Characteristics of included studies.

Study	RIPC protocol	Comparator	N RIPC (control)	Population	Age RIPC (control)	Male % RIPC (control)	All outcome measures
Ahmad et al., 2014 [17] Pakistan	Upper limb 3 × 5 min & 5 min reperfusion	Sham (Cuff deflated)	35 (32)	Triple vessel CABG	54.46 ± 8.83 (55.16 ± 10.95)	77 (78)	CK-MB Creatinine IABP Inotropic support Mortality
Ali et al., 2010 [23] Pakistan	Upper limb 3 × 5 min & 5 min reperfusion	Sham (Cuff deflated)	50 (50)	Double/triple vessel CABG	56.02 ± 8.24 (51.6 ± 9.58)	94 (84)	CK-MB IABP Inotropic support
Candilio et al., 2015 [7] UK	Upper and lower limb 3 × 5 min & 5 min reperfusion	Sham (Cuff deflated)	89 (89)	Single-quadruple vessel CABG and/or valve surgery	65 ± 10 (66 ± 10)	81 (75)	AF Creatinine hsTnT ICU stay Inotropic support MACE Mortality
Gedik et al., 2014 [18] Germany	Upper limb 3 × 5 min & 5 min reperfusion	Sham (Cuff deflated)	10 (10)	Double/triple vessel CABG	62.6 ± 3.4 (65.5 ± 4.2)	90 (80)	Autophagy markers cTnI Signalling markers
Hausenloy et al., 2007 [24] UK	Upper limb 3 × 5 min & 5 min reperfusion	Sham (Cuff deflated)	27 (30)	Single-quadruple vessel CABG	67 ± 11.8 (67 ± 9.4)	78 (80)	cTnT
Hausenloy et al., 2015 [21] UK	Upper limb 4 × 5 min & 5 min reperfusion	Sham (Cuff deflated)	801 (811)	CABG and valve surgery	76.1 ± 6.1 (76.3 ± 7)	70.4 (72.7)	Acute kidney injury cTnT Hospital stay ICU stay Inotropic support MACE
Holmberg et al., 2014 [19] Denmark	Upper limb 3 × 5 min & 5 min reperfusion	No RIPC	20 (21)	CABG and valve surgery	68 ± 11 (72 ± 9)	75 (67)	AF cTnT CK-MB Hospital stay ICU stay Inotropic support
Karuppasamy et al., 2011 [25] UK	Upper limb 3 × 5 min & 5 min reperfusion	Sham (Cuff deflated)	27 (27)	Double-quintuple vessel CABG	66.9 ± 11.2 (67.3 ± 10.3)	81 (85)	BNP cTnI CK-MB Cytokines Growth factors Hospital stay Inotropic support ICU stay
Kottenberg et al., 2012 [26] Isoflurane anaesthetic Propofol anaesthetic Germany	Upper limb 3 × 5 min & 5 min reperfusion	No RIPC	20 (19) 14 (19)	Triple vessel CABG	64 ± 9 (65 ± 9) 65 ± 15 (64 ± 12)	95 (84) 64 (84)	cTnI Creatinine
Lomivorotov et al., 2012 [27] Russia	Upper limb 3 × 5 min & 5 min reperfusion	Sham (Cuff deflated)	40 (40)	Mean 2.7 vessel CABG	56.5 ± 8.7 (58.1 ± 6.4)	90 (93)	cTnI CK-MB ICU stay Inotropic support Mortality
Lucchinetti et al., 2012 [28] Canada	Lower limb 4 × 5 min & 5 min reperfusion	Sham (Cuff deflated)	27 (28)	Mean 3.6 vessel CABG	59 ± 7 (62 ± 10)	96 (86)	AF Creatinine hsCRP hscTnT Mortality NT-proBNP S100
Meybohm et al., 2013 [29] Germany	Upper limb 4 × 5 min & 5 min reperfusion	Sham (Cuff inflated to 20 mm Hg)	90 (90)	CABG and valve surgery	70 (68)	77 (86)	AF cTnT Hospital stay Neurocognitive changes
Meybohm et al., 2015 [22] Germany	Upper limb 4 × 5 min & 5 min reperfusion	Sham (Dummy arm)	692 (693)	CABG and valve surgery	65.8 ± 10.7 (66 ± 10)	73.4 (75)	AF AKF Mortality MI Stroke
Rahman et al., 2010 [30]	Upper limb 3 × 5 min &	No RIPC	80 (82)	Triple to quadruple vessel CABG	63 (65)	89 (88)	AF cTnT

Table 1 (*continued*)

Study	RIPC protocol	Comparator	N RIPC (control)	Population	Age RIPC (control)	Male % RIPC (control)	All outcome measures
	5 min reperfusion						Creatinine ECG Echocardiography Haemodynamics IABP Inotropic support Mortality
UK							
Slagsvold et al., 2014 [20] Norway	Upper limb 3 × 5 min & 5 min reperfusion	Sham (Cuff deflated)	30 (30)	Double to quadruple vessel CABG	64.2 ± 9.0 (68.1 ± 8.2)	90 (77)	AF cTnT CK-MB miRs Mitochondrial respiration NT-proBNP
Thielmann et al., 2010 [31] Germany	Upper limb 3 × 5 min & 5 min reperfusion	Sham (Cuff deflated)	27 (26)	Double to triple vessel CABG	63.4 ± 11.3 (64.1 ± 12.3)	85 (85)	AF cTnT CK-MB Creatinine CRP ECG Hospital stay ICU stay MACE Mortality
Thielmann et al., 2013 [32] Germany	Upper limb 3 × 5 min & 5 min reperfusion	Sham (Cuff deflated)	162 (167)	Triple vessel CABG	68.2 ± 10.3 (69.1 ± 9.2)	83 (80)	cTnI Creatinine ECG Hospital stay ICU stay MACE Mortality
Venugopal et al., 2009 [33] UK	Upper limb 3 × 5 min & 5 min reperfusion	Sham (Cuff deflated)	23 (22)	Single to quadruple vessel and valve surgery	62 ± 9.7 (64 ± 9.0)	83 (86)	cTnT

Legend: AF, atrial fibrillation; AKF, acute kidney failure; BNP, B-type natriuretic peptide; CABG, coronary artery bypass grafting; CK-MB, creatine kinase muscle brain band; cTnI, cardiac troponin I; cTnT, cardiac troponin T; ECG, electrocardiography; hsCRP, high sensitivity C-reactive protein; hscTnT, high sensitivity troponin T; IABP, intra-aortic balloon pump; ICU, intensive care unit; I/R, ischaemia reperfusion; MACE, major adverse coronary events; MI, myocardial infarction; miRs, microRNAs; NT-proBNP, N-terminal probrain natriuretic peptide.

2. Methods

2.1. Search strategy

To identify potential studies systematic searches were carried out using the following databases: EMBASE, PubMed, Web of Science and the Cochrane Central Registry of Controlled Trials (CENTRAL). The search was supplemented by scanning the reference lists of eligible studies. The search strategy included the key concepts of "remote ischaemic preconditioning" and "coronary artery bypass grafting". All identified papers were assessed independently by two reviewers. A third reviewer was consulted to resolve disputes. Searches of published papers were conducted up until November 1st, 2015.

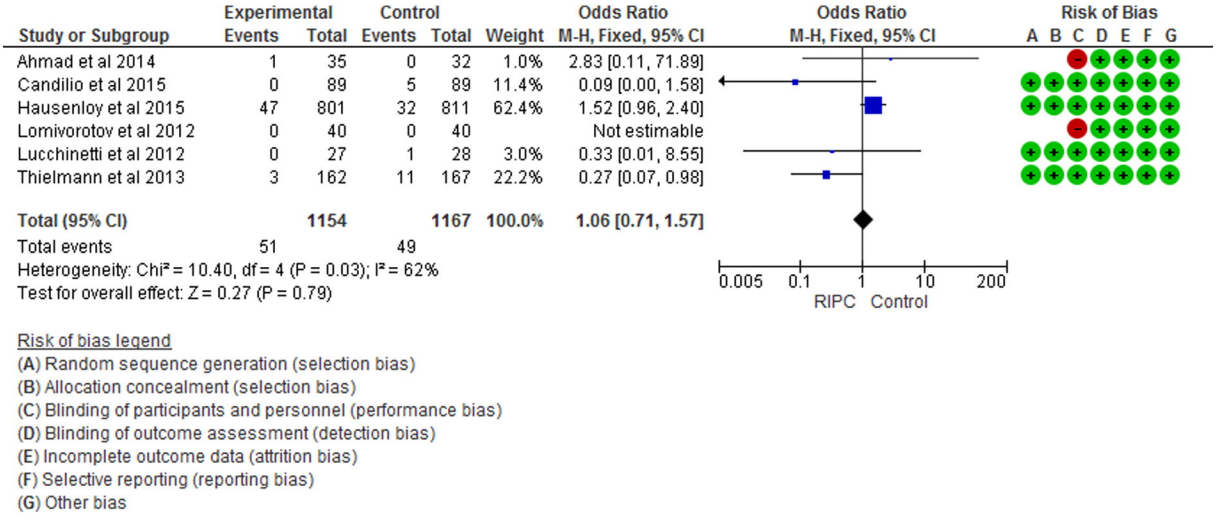

Fig. 1. Post discharge mortality.

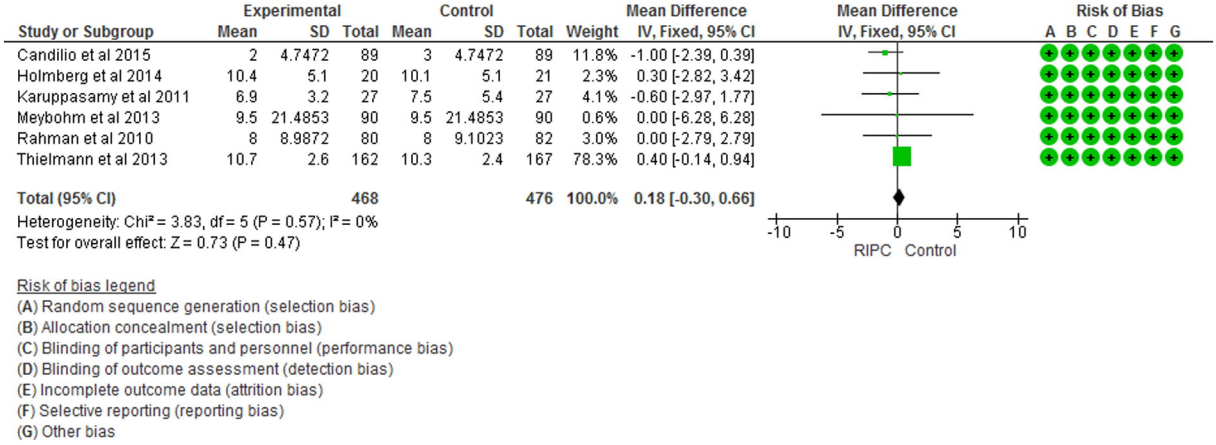

Fig. 2. Length of hospital stay (days).

2.2. Types of studies to be included

Only randomized controlled trials (RCTs) of RIPC in patients undergoing coronary artery bypass grafting with/without valve surgery were included. There were no language restrictions. Animal studies, review papers and non-randomized controlled trials were excluded. Studies that do not have any of the desired outcome measures or participants who were treated by other modalities such as percutaneous coronary intervention were excluded. Authors were contacted to provide missing data or to clarify if data was duplicated in multiple publications. Incomplete data, or data from an already included study, were excluded. Studies that included interventions other than RIPC were excluded.

2.3. Participants/population

This meta-analysis analysed RCTs of both male and female adult (≥18 years) patients with coronary artery disease who were undergoing coronary artery bypass grafting with/without valve surgery. Other treatment modalities and interventions for coronary artery disease such as RIPC in percutaneous coronary intervention were excluded.

2.4. Intervention(s), exposure(s)

This meta-analysis considered all RCTs where patients with stable angina or acute coronary syndrome being treated with coronary artery bypass grafting with/without valve surgery were exposed to RIPC. More specifically, all RCTs where the intervention of expanding a blood pressure cuff or applying a medical tourniquet in a remote limb was carried out before coronary artery bypass grafting.

2.5. Comparator(s)/control

The meta-analysis utilised RCT's that compare RIPC during coronary artery bypass grafting with/without valve surgery with a usual care control group receiving sham or no RIPC during coronary artery bypass grafting with/without valve surgery.

2.6. Search results

Our initial search found 74 articles. Of these 7 studies were excluded on the basis of title and abstract. Forty two studies were excluded as they were not RCTs. Of these RCTs we excluded 7 studies: 2 studies included post-conditioning; 2 studies concentrated on STAT5; 1 study each concentrated on kinin receptor expression in neutrophils, on glycolysis, or on nitric oxide synthetase respectively (see supplementary Table S1). Eighteen studies were included in our analysis [7,17–33].

2.7. Outcome(s)

The primary outcomes analysed were:

1. Mortality.
2. Hospital stay.

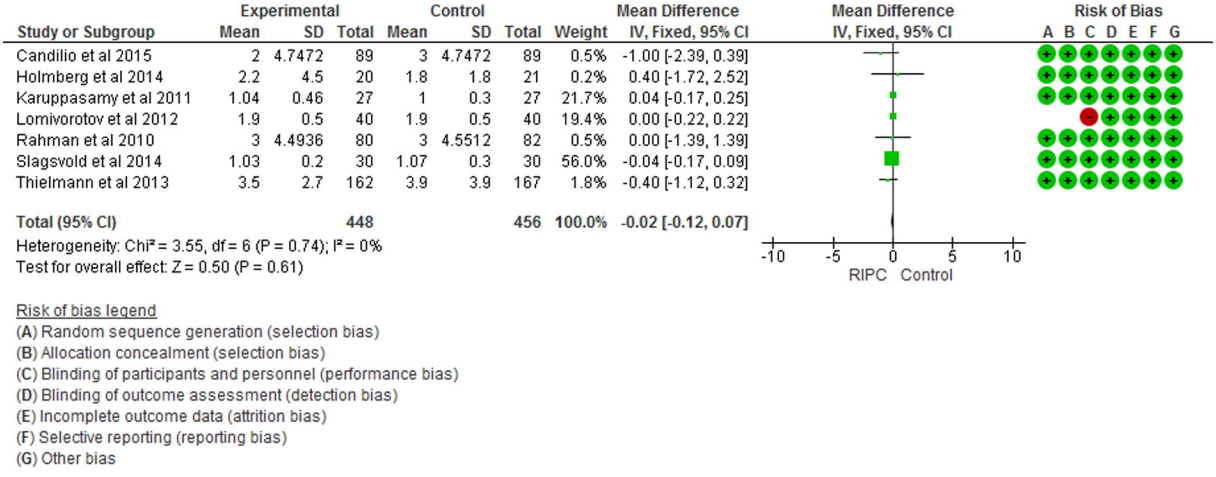

Fig. 3. Length of ICU stay (days).

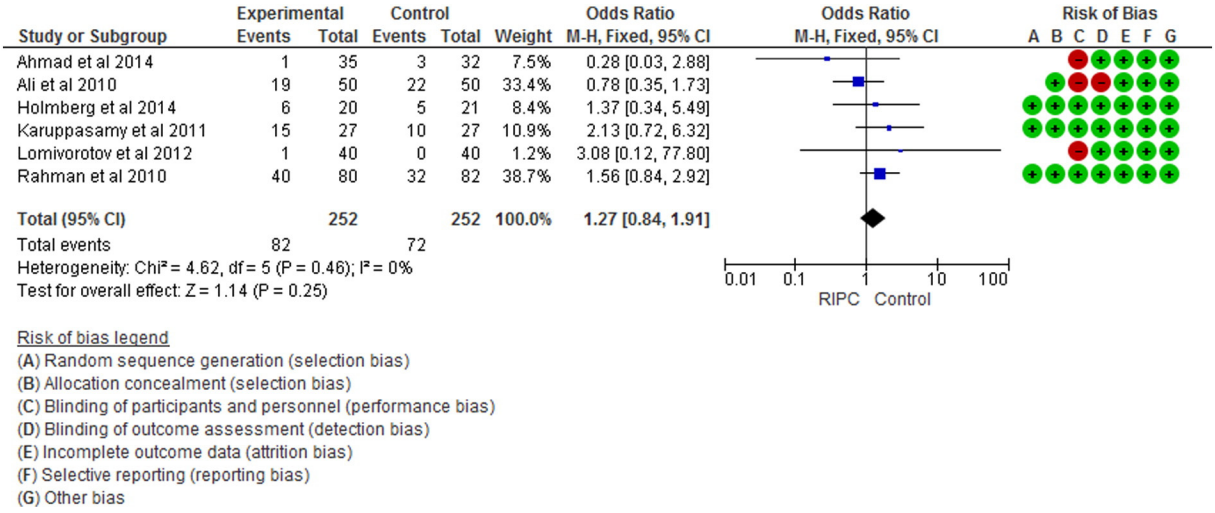

Fig. 4. Inotrope usage events post surgery.

3. ICU stay.
4. Inotrope usage.
5. New onset atrial fibrillation.
6. Cardiac troponins (cTnT and cTnI. Area under the curve).
7. Serum creatinine.

2.8. Risk of bias (quality) assessment

The JADAD scale was used to assess study quality and reporting [34].

2.9. Strategy for data synthesis

Odds ratios were calculated for dichotomous data. Mean differences were calculated for continuous data. Meta-analyses were completed for continuous data by calculating the mean difference between intervention and control groups from post-intervention data only. It is an accepted practice to only use post-intervention data for meta-analysis, but this method assumes that random allocation of participants always creates intervention groups matched at baseline for age, disease severity. All analyses were conducted using Revman 5.0 (Nordic Cochrane Centre Denmark). A fixed effects inverse variance model was used unless heterogeneity was >75%, then a random effects model was used. Heterogeneity was quantified using the Cochrane Q test [33]. We used a 5% level of significance and 95% confidence intervals; figures were produced using Revman 5.3.

3. Results

The eighteen studies included in the analyses had an aggregate of 4551 participants, 2267 of which received RIPC and 2283 were control/sham group participants. Table 1 summarizes the characteristics of the included studies. Supplementary Table S1 lists the excluded RCTs and reasons for exclusion. Fifteen studies used a sham control group, as opposed to usual care. Only two studies utilized the lower limb for RIPC. The RIPC protocols were very similar in terms of periods of cuff occlusion and periods of reperfusion.

3.1. Long term postoperative outcomes

Eight studies reported post discharge mortality. The odds ratio (OR) for the pooled analysis was 1.27 (95% confidence interval [CI] 0.87 to 1.86, p = 0.22), see Fig. 1.

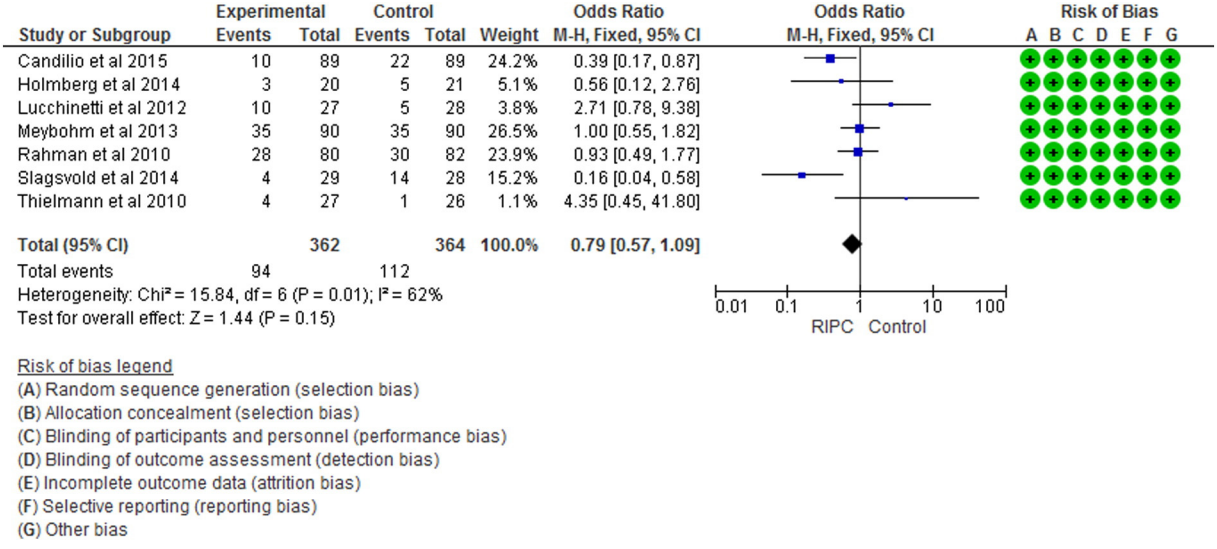

Fig. 5. Incidence of new onset atrial fibrillation.

3.2. Short term postoperative outcomes — length of hospital and ICU stay (days)

Six studies reported the length of hospital stay in days. The MD for the pooled analysis was 0.18 (95% CI −0.30 to 0.66, p = 0.47) (see Fig. 2). Seven studies reported the length of ICU stay in days. The MD for the pooled analysis was −0.02 (95% CI −0.12 to 0.07, p = 0.61) (see Fig. 3).

3.3. Immediate postoperative outcomes — inotrope usage and dysrhythmia

Six studies reported the use of inotropes to support patients, the OR for the pooled analysis was 1.27 (95% CI 0.84 to 1.91, p = 0.25) (see Fig. 4). Eight studies reported the incidence of new onset atrial fibrillation. The OR for the pooled analysis was 0.82 (95% CI 0.67 to 1.01, p = 0.06), see Fig. 5.

3.4. Biomarkers — troponin release and serum creatinine

Nine studies reported the area under the curve for troponin release after surgery. The MD for the pooled analysis was −3.72 (95% CI −3.92 to −3.53, p < 0.00001) (see Fig. 6). Five studies (six intervention groups) reported the serum creatinine concentration, the MD for the pooled analysis was 0.00 (95% CI −0.07 to 0.07, p = 0.97) (see Fig. 7).

4. Discussion

Our meta-analysis is the first to include the results of two large scale multi-centre trials investigating the role of RPIC in CABG with/without valve surgery. It is also the first to investigate longer term outcomes such as post discharge mortality. The results showed that troponin release is significantly reduced by RPIC, which is in agreement with other meta-analyses in this field [12–15]. Perhaps more pertinently, indicators of clinical outcome such as mortality, ICU and hospital stay, inotropic usage and new onset atrial fibrillation were unaltered by RPIC. This suggests that whilst RPIC does no harm it does not offer additional cardioprotective effects above and beyond that already provided by cardioplegia and volatile anaesthetics.

Our results showed that RIPC reduced troponin release as indicated by the area under the curve. Earlier studies that only concentrated on biomarker release also showed that RIPC reduced biomarker release [11,13–15]. Like the current study, when data from several studies was pooled in these earlier works, high heterogeneity was present [11,15]. In spite of this we considered this to be justified as repeated troponins may be a more accurate method than evaluating biomarkers at a single time point. Our work is also consistent with that of Deng et al. [16].

Our results also show that the incidence of postoperative atrial fibrillation was not reduced with RIPC. Femi et al. [36] investigated the risk of 1 year mortality, myocardial infarction (MI) and stroke in patients receiving CABG at The Cleveland Clinic. They found that there was a 3.7% increased risk of death (Hazard Ratio [HR] 1.89, 95% CI 1.42–2.53, p < 0.001) following postoperative atrial fibrillation [36]. Risk of MI and stroke were unaffected. One of the studies investigated here determined death at one year [32]. In that study RIPC reduced the incidence of one year mortality from 6.9% in control to 1.9% (HR 0.27, 95% CI 0.08–0.98, p = 0.046) [30].

Our work expands on that of Deng et al. [16]. We have also investigated the important clinical outcome of inotrope use, although there was no significant difference between the control and RIPC groups. Where our work is consistent with Deng et al. [16], is the findings that neither ICU nor hospital stay were shortened by RIPC.

Acute kidney injury is a known complication of revascularisation, with a recent study reporting a 2–3 times higher odds ratio for CABG compared to percutaneous coronary intervention [35]. We however found no differences in the serum creatinine between the control and RIPC groups. Unfortunately parameters such as urine volume and glomerular filtration rate were not measured in the studies. This prevented us from calculating the important parameter of creatinine clearance. Notwithstanding this, our work does support the meta-analysis by Deng et al. [16] who also found the incidence of acute kidney injury to be no different between control and RIPC groups.

4.1. Study limitations

RIPC did not affect post discharge mortality. However one limitation of the current study was the different reporting periods used. In one study where mortality was measured at 30 days, there was no difference [31]. However as the reporting time increased so did the mortality of the patients in the control group. Thus when mortality was measured at 6 weeks, five control patients had died compared to none in the RIPC group [7]. Then when mortality was measured at one year 3 patients in the RIPC group had died compared to 11 patients in the control group [32]. This suggests that more studies using a uniform reporting period are required.

5. Conclusions

Remote ischaemic preconditioning prior to CABG with/without valve surgery causes no harm but does not improve clinical outcomes.

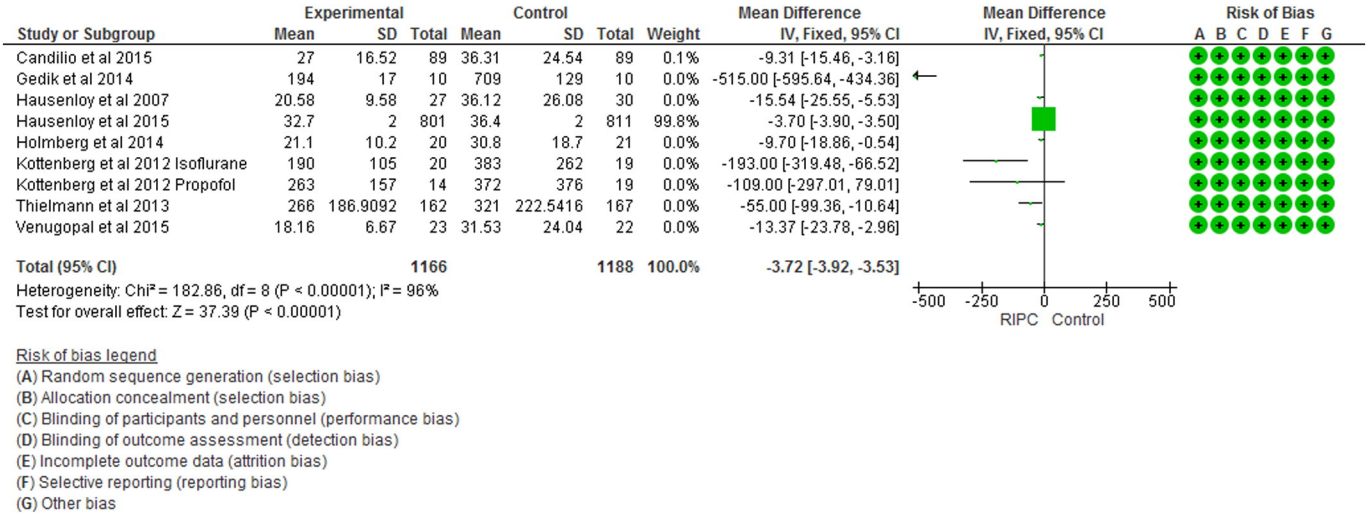

Fig. 6. Troponins (area under the curve, $\mu g \cdot L^{-1}$) 72 hpost-surgery.

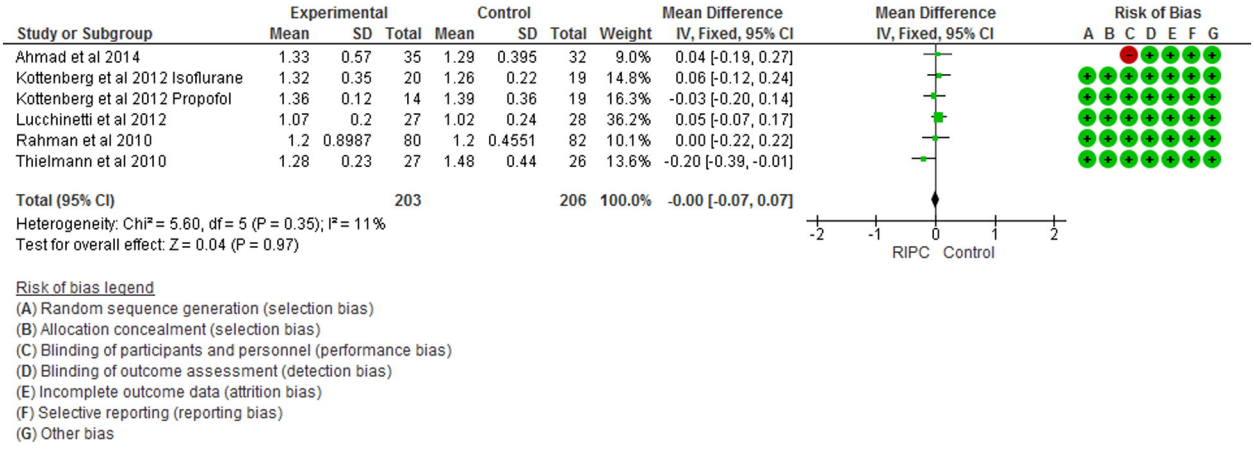

Fig. 7. Peak post-surgery creatinine.

Funding

None.

Conflicts of interest

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ctrsc.2016.03.001.

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Glossary

CABG: coronary artery bypass grafting
CI: confidence interval
HR: hazard ratio
ICU: intensive care unit
MD: mean difference
MI: myocardial infraction
MRI: magnetic resonance imaging
OR: odds ratio
RCT: randomised controlled trial
RIPC: remote ischaemic pre-conditioning