Renoprotection by Remote Ischemic Conditioning During Elective Coronary Revascularization: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Background Remote ischemic conditioning(RIC) has been recognized an emerging non-invasive approach for preventing acute kidney injury(AKI) in patients undergoing either elective coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI). On the other hand, accumulating evidence have indicated the involving role of pre-CABG contrast usage for coronary angiography in post-surgery AKI risk. Along with the shortening time delay of CABG after coronary angiography, and the prevalent hybrid coronary revascularization(HCR), the AKI prevention by RIC has faced challenges following coronary revascuralization.

Methods Randomized controlled trials (RCTs) were searched from *Pubmed*, *EMBase*, and *Cochrane library* (until May 2016). The primary outcome was postoperative AKI. The second outcomes included the requirement for renal replacement therapy(RRT), and in-hospital or 30-day mortality.

Results Twenty eligible RCTs (CABG, 3357 patients; PCI, 1501 patients) were selected. RIC significantly halved the incidence of AKI following PCI when compared with controls[n=1501; odds ratio(OR)= 0.51; 95% CI, 0.32 to 0.82; P=0.006; I2=29.6%]. However, RIC did not affect the incidence of AKI following CABG (n=1850; OR= 0.94; 95% CI, 0.73 to 1.19; P=0.586; I2=12.4%). The requirement for RRT and in-hospital mortality were not affected by RIC in CABG (n=2049,OR=1.04, P=0.87; n=1920, OR=0.89, P=0.7; respectively).

Conclusions Our meta-analysis suggests that RIC for preventing AKI following CABG has faced with challenges in terms of AKI, the requirement for RRT, and mortality. However, RIC shows a renoprotective benefit for PCI. Hence, our findings may infer the preserved renal effects of RIC in CABG with preconditioning before the coronary angiography, or in HCR.

Introduction

Acute kidney injury (AKI) following elective coronary artery bypass graft (CABG) surgery occurs up to 45% of patients and it is associated with increased medium- and long-term cardiovascular morbidity and mortality[1-5]. AKI after CABG has been attributed to reduced renal blood flow by cardiopulmonary bypass[6, 7] and hemodynamic instability. Contrast agent, regularly

used in percutaneous coronary intervention (PCI) [8-10], may also contribute to the risk of postoperative AKI in CABG patients undergoing pre-surgery coronary angiography[11-13]. This is an important issue given the shortening in the time interval between coronary angiography and CABG[11-13], and the increasing use of hybrid coronary revascularization(HCR) for multi-vessel coronary artery disease (CAD)[14, 15]. Therefore, novel strategies are needed to prevent AKI in patients undergoing CABG surgery.

In 1993, Przyklenk et al[16] first demonstrated that regional ischemic preconditioning protected remote virgin myocardium of dogs against subsequent sustained coronary artery occlusion and reflow, implying the release of protective factors which can be transported to other organs to increase ischemic tolerance. This phenomenon has been termed ‘remote ischemic preconditioning’ (RIPC), and it can be induced non-invasively by simply inflating and deflating a standard blood pressure cuff placed on the upper arm or thigh. Experimental studies have shown that RIC confers renoprotection against acute ischemia/reperfusion (I/R) injury in numerous animal models[17-20]. Whether perioperative RIC can reduce the incidence of AKI in patients undergoing elective CABG remain unclear.

Both single and multi-centre randomized controlled trials(RCT) have investigated the renal effect of RIC in the setting of CABG, but the results have been mixed[21-23] [24-26]. In contrast, evidence supporting the use of RIC as a renoprotective strategy in patients undergoing elective percutaneous coronary intervention (PCI) is increasing[27, 28], suggesting that RIPC may be beneficial in those patients undergoing pre-CABG coronary angiography or those undergoing PCI as a part of HCR strategy. Hence, we sought to comprehensively summarize the evidence for renoprotection of RIC both in CABG and PCI to highlight future opportunities for the use of RIC in the setting of CABG surgery.

Methods

Search strategy and study criteria

We searched English-published RCTs in *PubMed*, *EMBase*, and *Cochrane Library* (up to April 2016), and scientific sessions (2012~2015) of American Heart Association (AHA), American College of Cardiology(ACC), and European Society of Cardiology (ESC) using keywords "remote ischemic conditioning", "coronary artery bypass graft", "percutaneous coronary intervention", "coronary revascularization", "kidney", and "renal". Invasive procedures were defined as elective CABG or PCI. Exclusion criteria were: ① studies not reporting one of the following endpoints: AKI and renal replacement therapy (RRT), and ② primary PCI.

Literature review and data extraction

The literature review and data extraction were independently completed by two investigators (Y.L. and H.P). Discussion was conducted for consensus in case of discrepancies. Quality assessment was completed according to the Jadad score: randomization; blinding; withdrawals and dropouts (a possible score between 0 and 5). Trials with a score of more than 3 were considered to be high-quality[29]. Data extraction included baseline patient characteristics (age, male, diabetes, history of MI, dyslipidemia, hypertension, baseline left ventricular ejection fraction, target vessels≥2, β-blockers usage, statins usage) as well as information pertaining to the RIC protocol (number cycles, ischemic time, and which limb), and follow-up time.

Postoperative Outcomes and Definitions

The primary endpoints was incidence of AKI within 7 days after CABG or PCI, defined as follows: ① a relative increase of >50% or an absolute increase of >0.3 mg/dL in serum creatinine from baseline, ② a relative increase of ≥25% or an absolute increase of ≥0.5 mg/dL in serum creatinine from baseline, ③ a relative decrease in estimated glomerular filtration rate >25% from baseline, ④ urinary liver-type fatty acid-binding protein (L-FABP) levels >17.4 μg/g serum creatinine levels].

The secondary outcomes includes in-hospital RRT, and all-cause mortality(in-hospital or within 30 days).

Statistical analysis

For dichotomous ones (reported with incidence), we calculated odds ratio (OR) with 95% confidence interval (CI). Random-effect model was used for the pooled analysis in the consideration of potential clinical inconsistency. The study with no event occurred in either of the two (treated or untreated) groups was excluded from the pooled analysis. When only one group of the study contained no events, a fixed value(0.5) was added to each cell of the 2X2 table for the pooled analysis. Publication bias was assessed by Begg's test and Egger's test for AKI. Sensitivity analyses were used to evaluate the robustness of our results by removing each included study at one time to obtain and assess the remaining overall estimates of AKI. Meta-regression and subgroup analyses were performed to explore the potential sources of heterogeneity and a P value of less than 0.1 was accepted. $P<0.05$ (2-sided) was considered to be statistically significant for hypothesis testing. All statistical analyses were performed in Stata(version 11.0; Stata Corporation, College Station, TX).

Results

Study characteristics

After 2119 abstracts were excluded from initial search due to duplication, review, experimental design, and other irrelevant content, Seventy-four potential studies were selected for detailed evaluation. Fifty-four studies were further excluded for the following reasons: valve surgery (n=7), vascular surgery(n=6), pediatric surgery (n=11), primary PCI(n=9), irretrievable or unclear data (n=3), nonrenal endpoints (n=10), ongoing trial (n=2), and endothelial trials (n=6). Twenty trials[21-28, 30-36],[37-41] with a total of 4858 patients (n=2471 in RIC group) ultimately met our selection criteria, eleven[21-26, 30, 31, 34-36] of which were conducted for 3357 subjects in

elective CABG (Figure 1). The ischemic protocol (cycles×I/R) was 2~4×5min/5min in nineteen studies[21-26, 28, 30-36],[37-41], and 4×30s/30s in one[27]. The upper limb was used in fifteen studies[21-23, 25, 26, 28, 30-33],[37-41], the thigh in three[24, 34, 35], the combination of upper limb and thigh in one[36], and the heart in one[27]. The time interval between first cuff for remote conditioning to coronary reflow was 30~157 min in CABG, and several to 120 min in PCI. Perioperative AKI was reported in seventeen studies[21-25, 27, 28, 30-33, 36],[37-41], RRT in ten [21-23, 25, 26, 30, 31, 34-36], and mortality in eight[21-23, 25, 26, 30, 31, 35].Seventeen studies [21, 22, 24-28, 30-36],[37, 40, 41] had a Jadad score ≥3. Study design and patient characteristics are summarized in Table 1 and 2.

Effect of RIC on the incidence of AKI

The incidence of AKI following CABG was 31.4% (n=8 studies; RIC: 286/925;Control: 295/925) and 9.1% in PCI (n=9 studies; RIC: 51/814;Control: 96/796). RIC lowered the risk of AKI in patients undergoing PCI (OR= 0.51; 95% CI, 0.32 to 0.82; P=0.006; I2=29.6%) but not in CABG (OR= 0.96; 95% CI, 0.76 to 1.20; P=0.695; I2=6.8%) (Figure 2A and 2B).

The AKI stage I was reported in 1142 CABG patients with an overall incidence of 22.7%(n=6 studies; RIC:128/583; Control: 131/559). RIC did not reduce the incidence of AKI stage I (OR= 0.80; 95% CI, 0.49 to 1.31; P=0.377; I2=27.4%)(Figure 3A).

Effect of RIC on the Requirement for RRT and Mortality

The in-hospital RRT was reported in 2049 study subjects undergoing CABG, and the overall incidence was 3.1% (n=10 studies; RIC: 32/1033;Control: 31/1016). The requirement forpostoperative RRT was not reduced by RIC intervention(OR=1.04; 95% CI, 0.62 to 1.76; P=0.87; I2=0.0%)(Figure 3B).

Mortality was reported in 1920 study subjects for CABG cohort , and the overall incidence was 1.8% (n=8; RIC:17/972; Control:18/948). Mortality was nonsignificantly reduced with RIC

compared with control (OR=0.89, 95% CI: 0.45 to 1.76, P=0.74: I2=0.0%)(Figure 4) .

Potential Sources of Heterogeneity

Age, male (%), history of MI, diabetes (%), hypertension (%) , dyslipidaemia (%), contrast volume (ml), β -blockers(%), statins(%), and additive duration of ischemic conditioning(cycles time ischemic duration, min)were included in the random-effect univariate meta-regression analysis for AKI in PCI. As a result, the identified major sources of heterogeneity was additive duration of ischemic conditioning(min)(coefficient=-0.22; P=0.057; adjusted R2=1.00) for AKI. When compared with the 15-min subgroup, the 20-min subgroup demonstrated a significant reduction in the incidence of AKI levels [OR: 0.26 (P = 0.001) vs. 0.80 (P = 0.42); P = 0.02 for subgroup difference].

Discussion

In the present meta-analysis of 20 randomized trials enrolling 4858 CAD patients undergoing elective coronary revascularization, we found that RIC may offer renoprotection by reducing in-hospital AKI, especially in PCI. Moreover, increase in the number of RIC cycles may improve the clinical benefit for renal function by RIC. However, the effect of RIC on the requirement for RRT and mortality merits further investigations.

Revascularization type. Up to now, CABG and PCI remain two key therapeutic options for treating patients with stable CAD, and both are associated with substantial risk of AKI. There has always been a concern whether renoprotective therapies established in PCI can be translated into the setting of CABG. Clinical studies investigating periprocedural use of statins[6, 42], N-acetylcysteine[43, 44], sodium bicarbonate[45, 46], and erythropoietin[47, 48] have produced neutral results. In our meta-analysis,a higher rate of AKI in CABG (35.1% vs 9.1% in PCI) was observed, and the absolute risk reduction of post-procedural AKI by RIC was 0.8% in CABG and 5.8% in PCI. This discrepancy may due to differences in the mechanisms of acute renal

injury(cardiopulmonary bypass and low CO in CABG versus contrast in PCI) [8-10], potential interference of volatile anesthetics[49], and higher rate of blood product transfusion during CABG[50]. Future studies should help elucidate the differential effects of RIC on renal injury.

Optimal conditioning protocol. In the meta-analysis, the most widely used RIC protocol was 2~4 cycles of 5-min ischemia and reperfusion intervals of one unilateral limb achieved using a blood pressure cuff(inflated to ≥200mmHg or 50 mmHg> SBP). However, whether optimization in RIC protocol algorithm could confer renoprotective benefits remains unknown-for example combined conditioning in two remote organs[36], increase in the number of cycles, or a prolonged ischemic interval. In our investigation, the additive duration for ischemic conditioning in PCI is 15min in six studies and 20 min in three one. Further regression analysis showed that additive duration was negatively correlated with risk of AKI(Ln-transformation), reducing by 0.22 per 1 min increase. This first intriguing indication for renal protection may provide some suggestion in the clinical setting of RIC.

Optimal timing, new concept and clinical implication. It is also unknown how long RIC should be initiated before coronary revascularization to achieve renal benefit. RIC has been shown to elicit the protective effect in 2 different phases: early phase (<4 hours) and delayed phase (24~72hours)[51]. The time window in our analysis is quite wide-ranging (CABG, 30 ~157 min; PCI , several ~120 min). In our subgroup analysis, a dramatic difference in the effect of RIC on postprocedural AKI between CABG and PCI was obtained. How to improve the renal effect of RIC in patients undergoing CABG is an interesting issue. Recently, the pivotal role of time interval between coronary angiography and CABG surgery in postoperative AKI has been proposed in several large retrospective adjusted analyses[11-13]. The risk of AKI was highest in whom CABG was performed ⩽1 day after cardiac catheterization, indicating that the underlying mechanisms of postprocedural AKI may be complicated with pre-existed contrast-induced injury. Based on these

evidence, the optimal timing for the reduction in CABG-associated AKI is a question that needs comprehensive consideration. The initiation of RIC before coronary angiography in patients waiting for CABG may be a new concept for preventing AKI in clinical practice.

HCR has become a popular choice for its potential clinical benefit in selected patient with multivessel CAD. Although the off-pump technique itself has shown to provide better preservation of renal function than on-pump CABG[52, 53], AKI may be aggravated by simultaneous coronary angiography. Wang et al[54] using a propensity-matched analysis found a higher incidence of AKI in the hybrid group than that in the off-pump CABG(25.2% vs 17.6%). Our pooled analysis could add the potential renal evidence of translation for RIC in HCR in the future.

Strengths and Limitations. The strengths of this meta analysis include the main concern for renal outcomes, clinical sufficient consistency(restricted type of invasive procedures), and its ability in garnering a new large study population. On the other hand, several limitations should be pointed out for this study. Firstly, the potential influences of other co-morbidities (such as age, diabetes, and contrast volume)[27] and cardiovascular medications (such as β-blocker[55]) may be underestimated. Secondly, the definitions for AKI varied trial from trial. Thirdly, AKI has been used as a surrogate endpoint to assess efficacy of RIC. However, there was no trend towards benefit with RIC in the hard renal outcomes such as hemodialysis or death. Lastly, the effect of RIC on long-term cardiovascular morbidity and mortality in elective coronary revascularization still need further evidence in future clinical trials.

Conclusions

Our meta-analysis suggests that RIC does not offer renoprotection during CABG surgery in terms of preventing AKI, reducing the requirement for RRT, and mortality. However, our study does show the renoprotective effect of RIPC in preventing AKI in patients undergoing elective PCI. Hence, our findings may infer the preserved renal effects of RIC in CABG with preconditioning

before the coronary angiography, or in HCR

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Figure legends:

Figure 1. Searching process for the eligible studies. RCT, randomized controlled trial; CABG, coronary artery

bypass graft; PCI, percutaneous coronary intervention.

Figure 2. Forest plot for in-hospital acute kidney injury(AKI) in elective CABG (A) or PCI (B).RIC, remote ischemic conditioning. Ctrl, control.

Figure 3. Forest plot for in-hospital AKI stage I (A) and requirement of renal replacement therapy(B) in elective CABG.. RIC, remote ischemic conditioning. Ctrl, control.

Figure 4. Forest plot for mortality in elective CABG.. RIC, remote ischemic conditioning. Ctrl, control.

Figure 1

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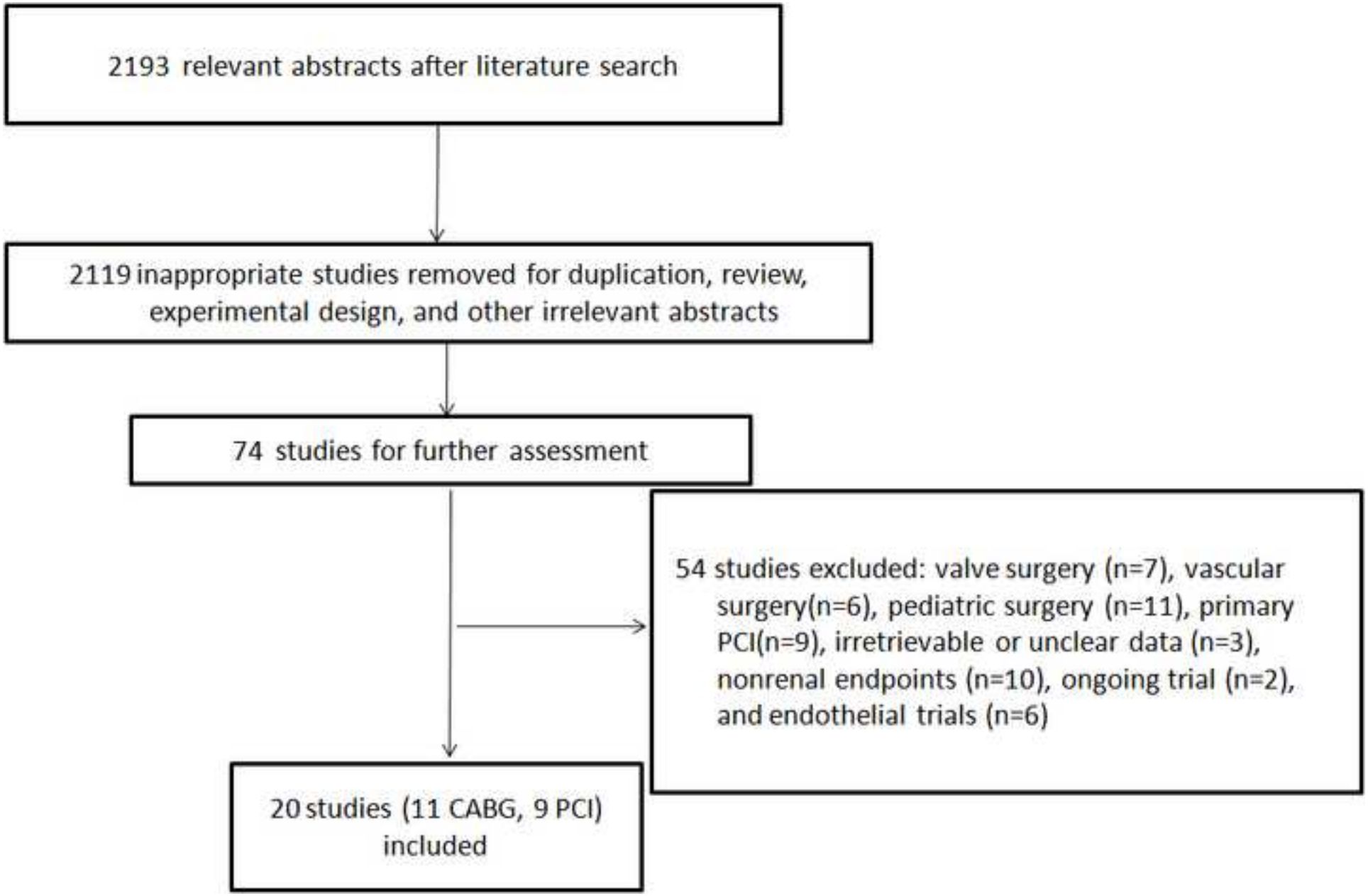

Figure 2

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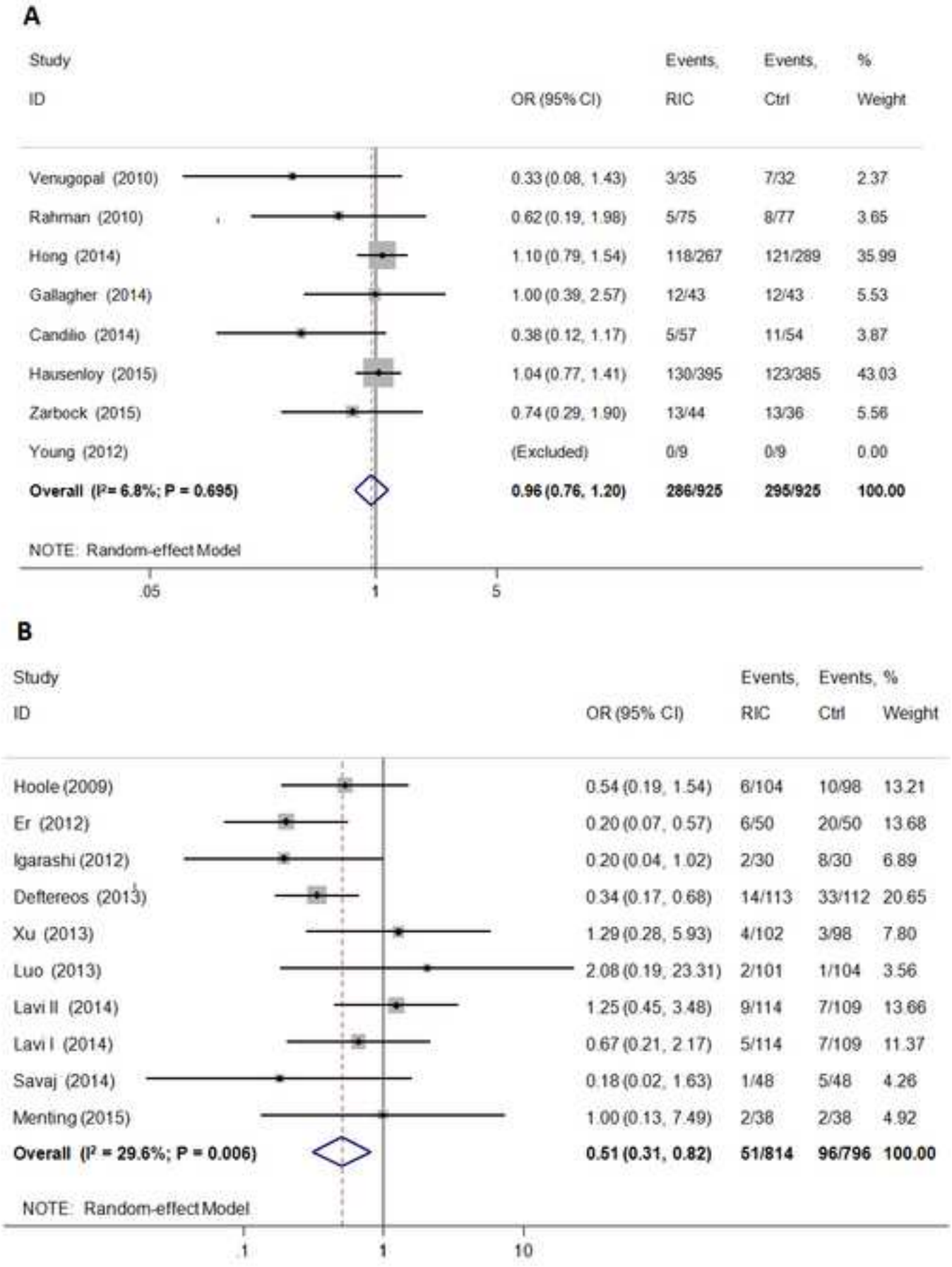

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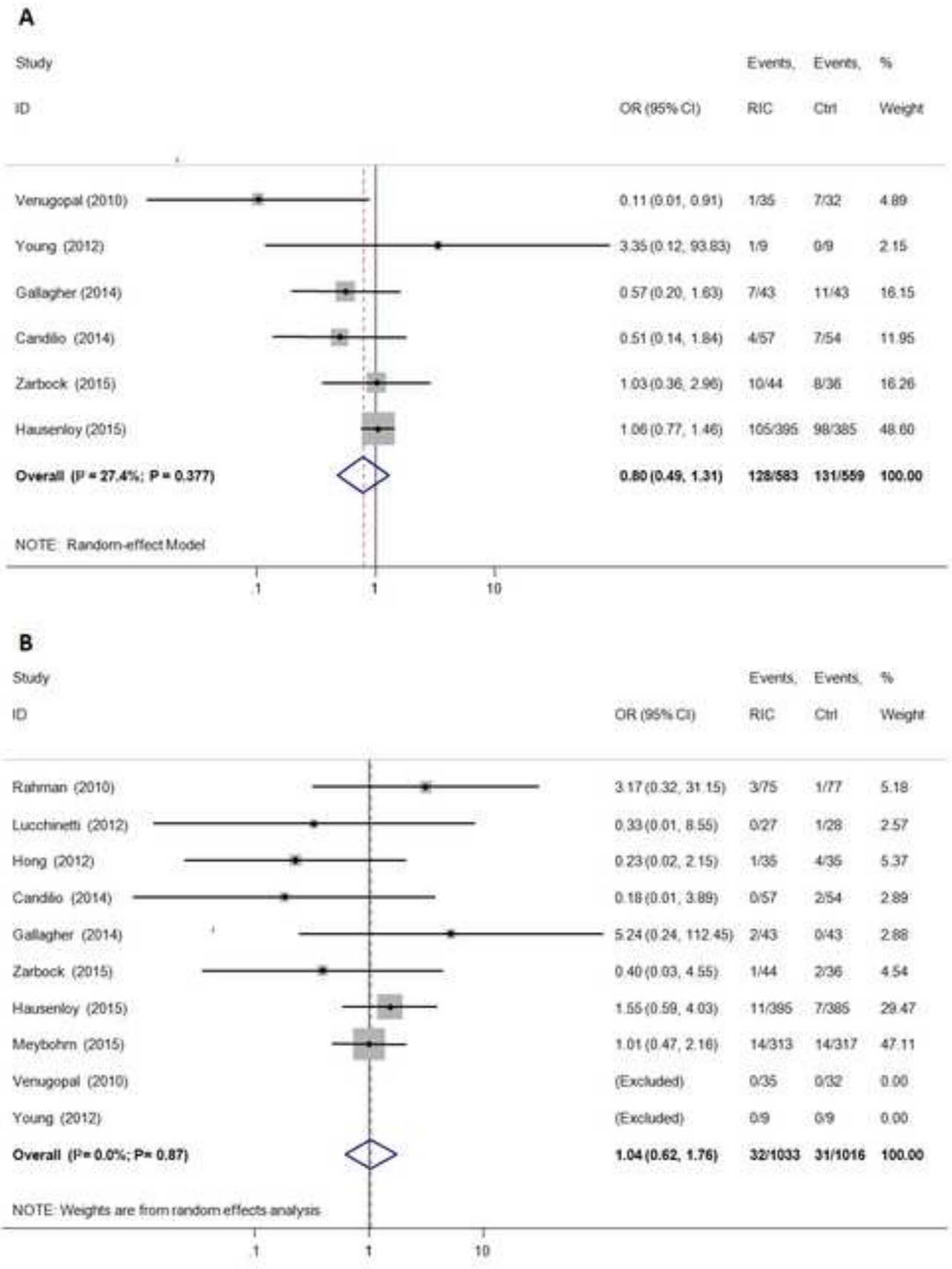

Figure 4

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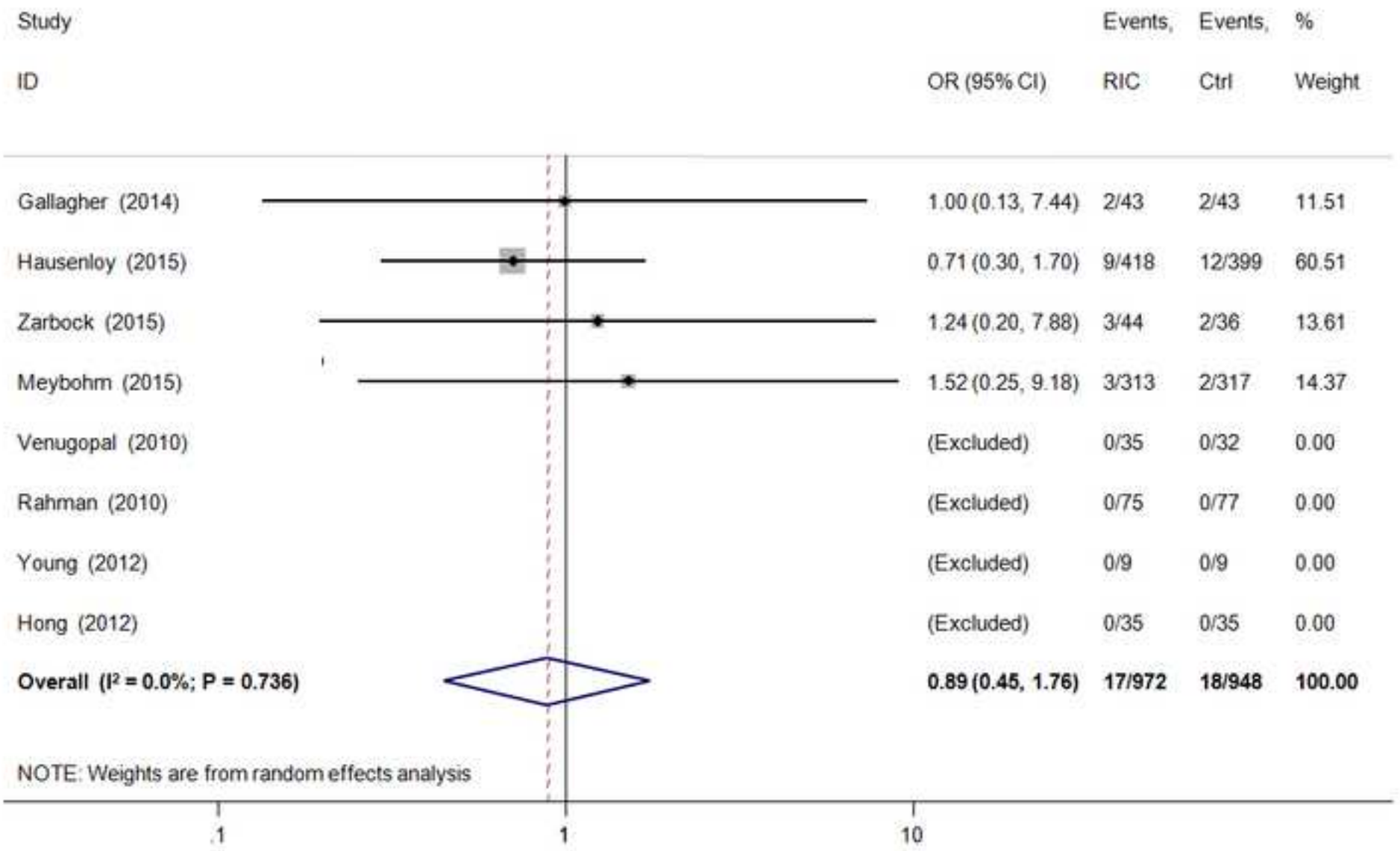

Table 1

Table 1 Study design in all included randomized trials

Study	Country	Surgery	Pts. No. RIC vs Ctrl	RIC protocol		RIC initiation to invasive procedure	Placebo Control	Renal Endpoints	Baseline Creatinine level(mg/dl)	AKI Definition	F-up	Jadad score
				Cycles×I/R	Cuff pressure							
Rahman 2010[21]	UK	CABG(On)	42 vs 38	3×5min/5min at upper limb	200mmHg	74 mins	Yes	AKI, RRT, Mortality	1.10	SCr ↑ >0.5 mg/dl	30 d	5
Venugopal 2010[22]	UK	CABG(On)	35 vs 32	3×5min/5min at upper limb	200mmHg	<45~60mins	Yes	AKI,RRT,Mortality	0.95	SCr ↑ ⩾50% or ⩾0.3 mg/dl	30 d	4
Young 2012[31]	New Zealand	CABG(On) (Substudy)	9 vs 9	3×5min/5min at upper limb	200mmHg	N.A	Yes	AKI, RRT, Mortaltiy	1.10	SCr ↑ ⩾50% or eGFR ↓ ⩾25%	30 d	5
Lucchinetti 2012[34]	Canada	CABG (On)	27 vs 28	4×5min/5min at thigh	300mmHg	N.A	Yes	RRT	1.01	RRT	6 mon	5
Hong 2012[35]	Korea	CABG(Off)	35 va 35	4×5min/5min at thigh	200mmHg	18 mins	Yes	RRT, Mortality	1.10	RRT	30 d	3
Hong 2014[24]	Korea	CABG(Off) (Substudy)	267 vs 289	4×5min/5min at thigh	200mmHg	N.A	Yes	AKI	N.A	SCr ↑ ⩾50% or ⩾0.3 mg/dl	In-hospital	5
Gallagher 2014[23]	UK	CABG	43 vs 43	3×5min/5min at upper limb	50mmHg > SBP	N.A	Yes	AKI, RRT, Mortality	1.37	SCr ↑ ⩾50% or ⩾0.3 mg/dl	30 d	2
Candilio 2014[36]	UK	CABG(On) (Substudy)	57 vs 54	2×5min/5min at upper limb and thigh	200mmHg	<45mins	Yes	AKI, RRT	N.A	SCr ↑ ⩾50% or ⩾0.3 mg/dl	In-hospital	5
Hausenloy 2015[25]	UK	CABG(On) (Substudy)	395 vs 385	4×5min/5min at upper limb	200mmHg	105 min	Yes	AKI, RRT, Mortality	N.A	SCr ↑ ⩾50% or ⩾0.3 mg/dl	In-hospital	5
Zarbock 2015[30]	German	CABG(On) (Substudy)	44 vs 36	3×5min/5min at upper limb	200mmHg or 50mmHg > SBP	N.A	Yes	AKI, RRT, Mortality	1.15	SCr ↑ ⩾50% or ⩾0.3 mg/dl	In-hospital	5
Meybohm 2015[26]	German	CABG(On) (Substudy)	313 vs 317	4×5min/5min at upper limb	⩾200mmHg or 15mmHg > SBP	N.A	Yes	RRT, Mortality	N.A	SCr ↑ ⩾50% or ⩾0.3 mg/dl	In-hospital	5
Hoole 2009[32]	UK	PCI	104 vs 98	3×5min/5min at upper limb	200mmHg	96.0 mins	Yes	AKI	N.A	SCr ↑ > 25%	24h	4
Er 2012[41]	Germany	PCI	50 vs 50	4×5min/5min at upper limb	50mmHg > SBP	40.0 to 85.0 mins	Yes	AKI	1.63	SCr ↑ ⩾25% or ⩾0.5 mg/dl	48h	5
Igarashi 2013[33]	Japan	PCI	30 vs30	4×5min/5min at upper limb	200mmHg	120min	No	AKI	1.13	Urinary L-FABP ↑ >25% or >17.4 μg/g SCr	48h	3
Luo 2013[40]	China	PCI	101 vs 104	3×5min/5min at upper limb	200mmHg	<120.0 mins	Yes	AKI	N.A	SCr ↑ > 25%	16 h	3
Deftereos 2013[27]	Greece	PCI	113 vs 112	4×30s/30s at heart	<3 atm	Immediately	Yes	AKI	1.0	SCr ↑ ⩾ 25% or ⩾0.5 mg/dl	96h	3
Xu 2013[37]	China	PCI	102 vs 98	3×5min/5min at upper limb	200mmHg	30.0 to 120.0 mins	No	AKI	0.86	SCr ↑ > 25%	16 h	5
Savaj 2014[38]	Iran	PCI	48 vs 48	3×5min/5min at upper limb	200mmHg	15 mins	No	AKI	1.19	SCr ↑ ⩾ 30% or ⩾0.3mg/dl	24h	1
Lavi 2014 I[28]	Canada	PCI	120 vs 120	3×5min/5min at upper limb	200mmHg or 50mmHg > SBP	Several mins after PCI	Yes	AKI	N.A	SCr ↑ > 25% or >0.5 mg/dl	24 h	5
Lavi 2014 II[28]	Canada	PCI	120 vs 120	3×5min/5min at thigh	200mmHg or 50mmHg > SBP	Several mins after PCI	Yes	AKI	N.A	SCr ↑ > 25% or >0.5 mg/dl	24 h	5
Menting 2015[39]	Netherland	PCI	38 vs 38	4×5min/5min at upper limb	50mmHg > SBP	<45.0 mins	Yes	AKI	1.32	SCr ↑ ⩾25% or ⩾0.5 mg/dl	72h	2

Note: CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; I/R, ischemia/reperfusion; SBP, systolic blood pressure; atm, atmosphere; AKI, acute kidney injury; RRT, renal replacement treatment; SCr, serum creatinine; eGFR, estimated glomerular filtration rate; L-FABP, liver-type fatty acid-binding protein; N.A, not available; RIC, remote ischemic conditioning; Ctrl, control.

Table 2

Table 2 Patient characteristics in all included randomized trials

Substudy	Age	Male(%)	Pre-MI (%)	DM (%)	HT (%)	Dyslipidemia (%)	Renal dysfunction (%)	CPB duration (min)	Contrast Dose(ml)	Baseline LVEF(%)	Target Vessels≥2 (%)	β -blockers (%)	Statins (%)
Rahman 2010[21]	64.0	88.5	0.0	0.0	59.3	74.1	N.A	98	/	60.1	100.0	81.0	88.0
Venugopal 2010[22]	65.0	82.0	23.0	0.0	65.4	75.6	N.A	86	/	N.A	96	55	79.5
Young 2012[31]	66.4	62.5	27.8	N.A	N.A	60.4	N.A	111.1	/	N.A	57.3	66.7	60.4
Lucchinetti 2012[34]	60.5	91.0	41.8	0.0	70.9	85.5	N.A	101	/	52.0	100.0	91.0	96.0
Hong 2012[35]	64.7	72.9	N.R	35.7	68.6	17.1	0	54	/	≥30.0	100.0	64.3	72.9
Hong 2014[24]	60.8	61.3	7.3	30.2	48.6	53.8	3.1	159.7	/	57	N.A	42.7	N.A
Gallagher 2014[23]	70.8	80.2	52.3	64.0	82.6	77.9	N.A	94	/	52	96.5	35	91.9
Candilio 2014[36]	65.5	78.1	28.7	29.2	78.8	74.2	0	93.2	/	N.A	93.1	74.2	80.9
Hausenloy 2015[25]	76.2	70.8	39.5	25.7	74.5	69.8	0	70.0	/	N.A	N.A	N.A	N.A
Zarbock 2015[30]	70.4	62.9	0	37.5	96.7	N.A	30.9	118	/	N.A	N.A	73.0	82.5
Meybohm 2015[26]	66.0	74.2	28.9	24.8	N.A	N.A	11.2	N.A	/	N.A	N.A	63.2	65.5
Hoole 2009[32]	62.5	78.2	55.4	21.8	51.5	N.A	N.A	/	192.2	50.2	16.8	79.2	95.0
Er 2012[41]	71.1	71.7	N.A	33.3	N.A	N.A	eGFR:30~60 (48.2)	/	92.4	N.A	N.A	43.3	75.0
Igarashi 2013[33]	73.0	71.0	41.0	64.0	91	75.0	eGFR< 60(38.3)	/	113.5	59.6	N.A	82.0	N.A
Luo 2013[40]	59.3	76.1	21.5	27.8	65.9	N.A	eGFR=100	/	149.4	64.0	27.8	82.4	N.A
Deftereos 2013[27]	68	64.0	N.A	36	65	59	eGFR>60(75)	/	270	56	55.1	17	36
Xu 2013[37]	69.0	68.0	23.0	100.0	63.5	N.A	eGFR=99.9	/	167.6	63.7	N.A	80.0	100.0
Savaj 2014[38]	62	32.3	16.7	100	70.9	N.A	eGFR>50(86.5)	/	125.2	N.A	N.A	N.A	N.A
Lavi 2014 I[28]	63.7	72.9	43.0	32.5	70.0	67.0	eGFR>30	/	187.5	N.A	18.8	N.A	N.A
Lavi 2014 II[28]	64.3	74.2	42.0	29.5	70.0	65.0	eGFR>30	/	187.5	N.A	21.67	N.A	N.A
Menting 2015[39]	72	48.5	40	25	72.5	N.A	eGFR=51	/	98.5	N.A	N.A	65.5	N.A

Note: Pre-MI, previous myocardial infarction; DM, diabetes mellitus; HT, hypertension; CPB, cardiopulmonary bypass; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; N.A, not available.