

## Systematic Review

# Effect of remote ischemic preconditioning in patients with STEMI during primary percutaneous coronary intervention: a meta-analysis of randomized controlled trials

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Remote ischemic conditioning is usually associated with cardioprotective intervention against ischemia-reperfusion. However, the effect of remote ischemic preconditioning (RIC-pre) completed before myocardial reperfusion with intermittent limb ischemia-reperfusion in patients with STEMI undergoing primary percutaneous coronary intervention (PPCI) is unclear. PubMed, EMBASE, and the Cochrane Library were fully searched from the beginning of each database up to September 2019 to find seven RCTs, a total of 2796 patients with STEMI undergoing PPCI with RIC-pre and 2818 patients with STEMI undergoing PPCI alone. No significant discrepancy in cardiac death was observed between RIC-pre and control groups (RR 1.03, 95% CI [0.76–1.41],  $P = 0.83$ ,  $I^2 = 40\%$ ). The incidences of hospitalization for heart failure (RR 1.03, 95% CI [0.85–1.25],  $P = 0.77$ ,  $I^2 = 0\%$ ), myocardial infarction (RR 0.86, 95% CI [0.59–1.26],  $P = 0.44$ ,  $I^2 = 0\%$ ), and stroke (RR 1.04, 95% CI [0.62–1.77],  $P = 0.87$ ,  $I^2 = 0\%$ ) were not decreased in RIC-pre group when compared with control group. Subgroup analysis revealed similar risk in clinical adverse events at long- and short-term follow-up between two groups. However, peak of creatine kinase-myocardial band (CK-MB) was reduced in RIC-pre group (SWD -0.42, 95% CI [-0.77, -0.07],  $P = 0.02$ ,  $I^2 = 34\%$ ). RIC-pre tended to a low peak of CK-MB in patients with STEMI undergoing PPCI, but lacked significant beneficial effects on improving clinical outcomes at long- and short-term follow-up.

## Keywords

Meta-analysis; ST-segment elevation myocardial infarction; remote ischemic conditioning; primary percutaneous coronary intervention; ischemia-reperfusion

## 1. Introduction

Although timely and sufficient coronary reperfusion by primary percutaneous coronary intervention (PPCI) is well established in patients with STEMI (Ibanez et al., 2018), the mortality morbidity still remains high because of the ischemia-reperfusion

(I–R) injury (Hearse et al., 1975). Besides de novo myocardial cellular damage, I–R injury can lead to vasomotor dysfunction, contractile capacity deterioration, malignant arrhythmias, and even poor prognosis (Frohlich et al., 2013; Yellon and Hausenloy, 2007). Therefore, several adjunctive treatment strategies against effects of I–R injury have been developed and tested in clinical trials (Ibanez et al., 2015; Schmidt et al., 2014).

Remote ischemic conditioning (RIC) has been put forward as a promising cardioprotective strategy that involves induction of brief and intermittent cycles of ischemia and reperfusion in a distant organ (Pryds et al., 2019). Several clinical reports have revealed that RIC (prior, during, or following myocardial reperfusion) can reduce the myocardial infarction size, increase myocardial salvage, and prevent clinical adverse events happening in patients with STEMI undergoing PPCI (Bøtger et al., 2010; Crimi et al., 2013; Eitel et al., 2015; Gaspar et al., 2018; Prunier et al., 2014; Rentoukas et al., 2010; Sloth et al., 2014; Stiermaier et al., 2019; Verouhis et al., 2016; White et al., 2015). However, a recent CONDI-2/ERIC-PPCI trial found that RIC before reperfusion did not decrease the events of cardiac death and improve clinical outcomes (Hausenloy et al., 2019).

Several recent meta-analyses had been conducted to investigate the influence of RIC in patients with STEMI undergoing PPCI (Gong and Wu, 2019; Liu et al., 2018; Man et al., 2017; McLeod et al., 2017). Unfortunately, despite confirming the cardioprotective effect of RIC, these meta-analyses did not include the CONDI-2/ERIC-PPCI trial. Moreover, no uniform protocol for RIC exists in these meta-analyses, especially in combination with ischemic pre-, during, or post-conditioning. Hence, in the present work, we conducted a meta-analysis to determine the effect of RIC-pre completed before myocardial reperfusion with intermittent limb I–R in patients with STEMI undergoing PPCI on the basis of clinical events.

## 2. Methods

### 2.1 Search strategy

The protocol of this meta-analysis was carried out in accordance with PRISMA guidelines (Liberati et al., 2009). Systematic literature searches were performed in PubMed, EMBASE, and

the Cochrane Library from the beginning of each database up to September 2019. To retrieve all potential relevant unpublished and reported materials, conference proceedings referred to the topic, references of relevant clinical trials, and review articles were also searched. The search strategy was as follows: 1. "remote ischemic (Title/Abstract)" OR "remote ischemic (Title/Abstract)"; 2. "myocardial infarction (Title/Abstract)" OR "STEMI (Title/Abstract)" OR "percutaneous coronary intervention (Title/Abstract)"; 3. 1 and 2.

## 2.2 Study selection

RCTs comparing PPCI with RIC-pre completed before myocardial reperfusion and PPCI alone in patients with STEMI were eligible for inclusion. Studies were excluded if they featured: 1) non-completion of RIC before myocardial reperfusion (during or following balloon dilation); 2) local ischemic postconditioning with or without RIC-pre; and 3) deficiency of available data. Eligibility was determined by independently screening titles and abstracts and reviewing full-text articles. Discrepancies shall be solved by consensus or consultation with corresponding author.

## 2.3 Data extraction and outcome measures

Year of publication, region, time of follow-up, treatment allocation, RIC protocol, sex, age, smoking, diabetes, hypertension, hypercholesterolemia, infarct-related coronary artery, occluded vessel on arrival Thrombolysis in myocardial infarction study group grading of coronary flow (TIMI) and symptom-to-balloon time were extracted from the included RCTs.

The primary endpoint was cardiac death (CD) at long- and short-term follow-up. Long-term follow-up was defined as follow-up over 12 months after PPCI in patients with STEMI, short-term follow-up was considered as follow-up within 30 days. Secondary endpoints were hospitalization for heart failure (HHF), myocardial infarction (MI), and stroke (including transient ischemic attack, TIA). The peak of the creatine kinase-myocardial band (CK-MB) and ejection fraction (EF) at follow-up were also pooled into the analyses.

## 2.4 Quality assessment and statistical analysis

The Cochrane Collaboration Assessment Tool was used to evaluate the quality and risk of bias of included RCTs, and discrepancies in these assessments were resolved by consensus (Higgins et al., 2011).

Discontinuous variables were presented as numbers or percentages and relative risks (RR) at the 95% confidence interval (95% CI). Continuous variables were shown as means  $\pm$  SDs or medians (interquartile range) and standardized mean differences with 95% CIs for EF at follow-up and the peak of CK-MB. Heterogeneity was determined on the basis of  $I^2$  statistics and Cochrane Q chi-square statistics (Higgins et al., 2003). When Cochrane Q chi<sup>2</sup> test  $P \leq 0.1$  and  $I^2 \geq 50\%$ , high heterogeneity was considered, and the random-effects model would be selected (DerSimonian and Laird, 1986). The fixed-effects model was used when  $I^2 < 50\%$ . Endpoints were analyzed by using Forest plots with point estimates and 95% CIs.

Subgroup analyses (short-term vs. long-term follow-up) were also performed. Revman 5.3 was used for statistical analysis. A two-tailed  $P$  value  $< 0.05$  was considered statistically significant.

# 3. 3. Results

## 3.1 Study characteristics and quality assessment

A total of 1037 potential records were searched from the databases. After screening and reviewing, seven studies were included for further evaluation (Bøtker et al., 2010; Hausenloy et al., 2019; Liu et al., 2018; Munk et al., 2010; Prunier et al., 2014; Sloth et al., 2014; Yamanaka et al., 2015). These studies included a total of 2796 patients in RIC-pre group and 2818 patients in control group, as described in Fig. 1. Among these included studies, three were from the same clinical randomized trial (NCT00435266) with different reported endpoints (Bøtker et al., 2010; Munk et al., 2010; Sloth et al., 2017). Three studies revealed long-term clinical adverse events (Hausenloy et al., 2019; Liu et al., 2018; Sloth et al., 2014), and three studies reported short-term clinical outcomes (Bøtker et al., 2010; Hausenloy et al., 2019; Yamanaka et al., 2015). In contrast to other included RCTs, two RCTs by Yamanaka and Hausenloy were single-blinded (Hausenloy et al., 2019; Yamanaka et al., 2015), and RIC-pre protocols were performed by an automated continuous blood-pressure monitoring device. The characteristics of the included studies and demographic data were shown in Table 1 and 2. The quality of included RCTs was reported in Fig. 2.

## 3.2 Outcomes

Clinical endpoints were assessed in trials with available data. No significant discrepancy in CD between two groups was observed (RR 1.03, 95% CI [0.76--1.41],  $P = 0.83$ ,  $I^2 = 40\%$ ), as shown in Fig. 3A. The incidences of HHF, MI, and stroke were not reduced in the RIC-pre group (RR 1.03, 95% CI [0.85--1.25],  $P = 0.77$ ,  $I^2 = 0\%$ ; RR 0.86, 95% CI [0.59--1.26],  $P = 0.44$ ,  $I^2 = 0\%$ ; RR 1.04, 95% CI [0.62--1.77],  $P = 0.87$ ,  $I^2 = 0\%$ ) when compared with control group, as revealed in Fig. 3B, C and D. Subgroup analysis according to the time of follow-up (long-term vs. short-term) were illustrated in Fig. 4; no significant difference in the long-term and short-term benefits of RIC-pre for CD, HHF, MI, and stroke were detected.

No statistically significant difference in EF at follow-up was indicated between two groups, as presented in Fig. 5A (SWD 0.16, 95% CI [-0.03, 0.35],  $P = 0.11$ ,  $I^2 = 2\%$ ). However, peak of CK-MB in the RIC-pre group was reduced compared with that in control group, as illustrated in Fig. 5B (SWD -0.42, 95% CI [-0.77, -0.07],  $P = 0.02$ ,  $I^2 = 34\%$ ).

# 4. Discussion

The meta-analysis focused on definite protocol of RIC in patients with STEMI undergoing PPCI accomplished before myocardial reperfusion by intermittent limb I--R. The results revealed no demonstrable benefits for CD, HHF, MI, and stroke at long- and short-term follow-up in RIC-pre group. Despite the positive effect of RIC-pre on peak of CK-MB, RIC-pre failed to improve left ventricular function or show discrepancies in EF.

Besides to patients with STEMI undergoing PPCI, RIC is involved in elective PCI, cardiac surgery, contrast-induced nephropathy, vascular surgery and ischemic stroke (Bahr Hosseini et al., 2019; Pieri et al., 2019; Stather et al., 2019; Wang et al., 2017; Zhan et al., 2019). However, no standard protocol for RIC (prior to intervention, during ischemia, or after reperfusion) exists. Moreover, the site and timing of RIC remain nonuniform. These

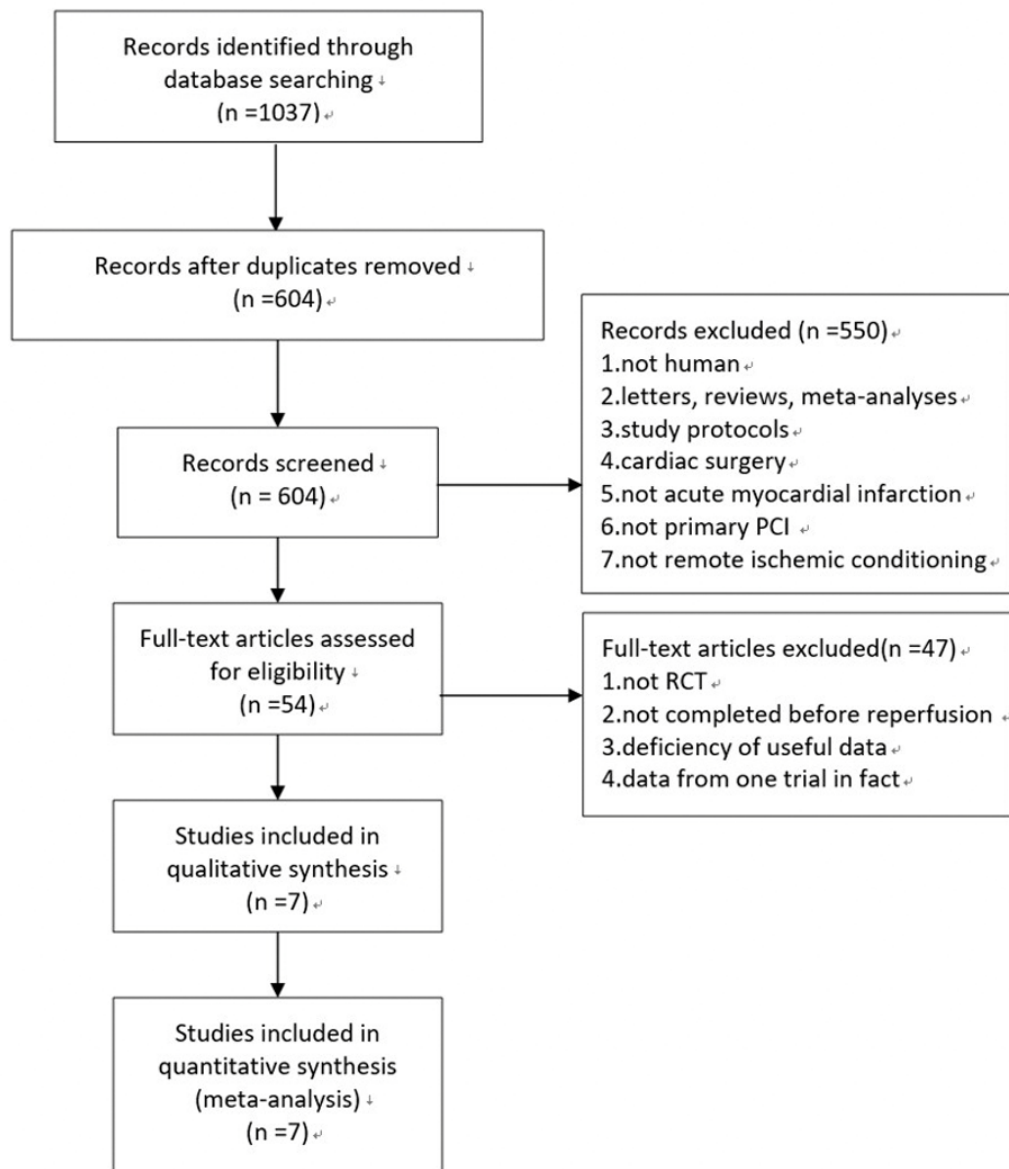
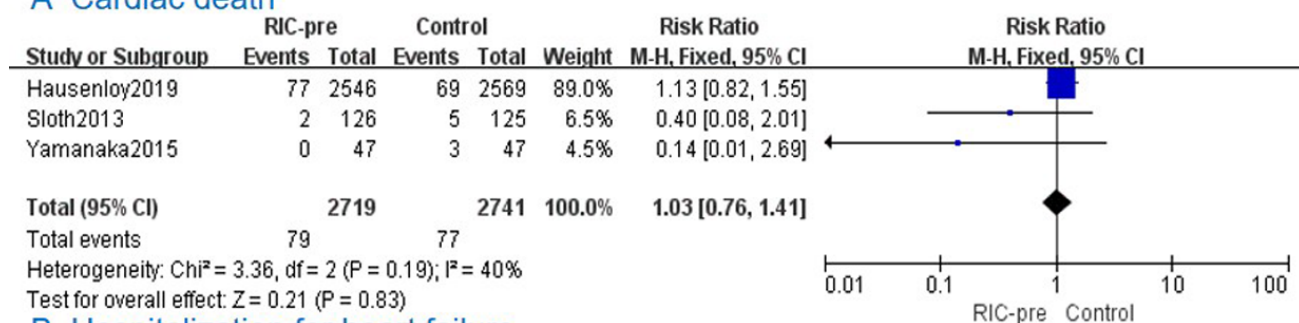


Figure 1. Flow diagram showing the process of study selection including eligibility against the inclusion and exclusion criteria set out in the methods section of this meta-analysis. The number of studies at the bottom of the flowchart was the selected studies that were considered eligible for inclusion in this meta-analysis.

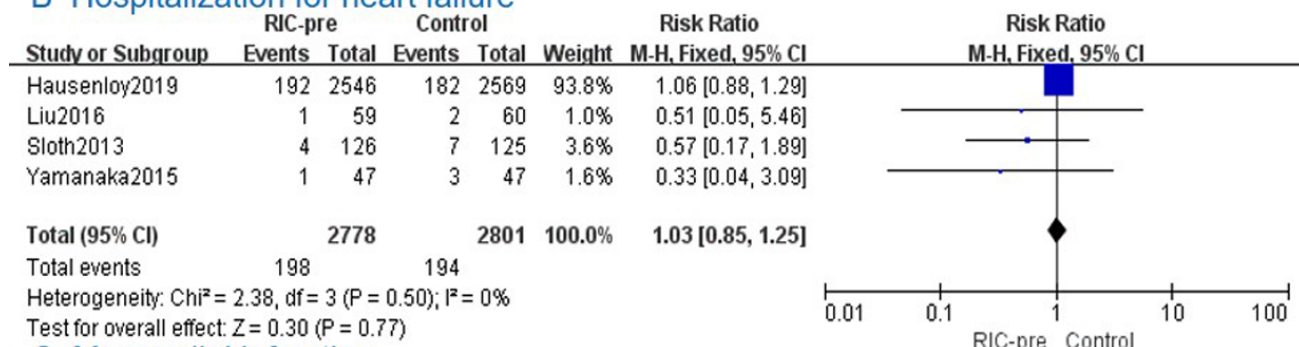
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bøtker2010	+	+	-	-	+	+	+
Hausenloy2019	+	+	-	+	+	+	+
Liu2016	+	+	-	-	+	+	+
Munk2010	+	+	-	-	+	+	+
Prunier2014	+	+	-	-	+	+	+
Sloth2013	+	+	-	-	+	+	+
Yamanaka2015	+	+	+	+	+	+	+

Figure 2. The quality of included randomized controlled trials shows the risks of bias, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias.

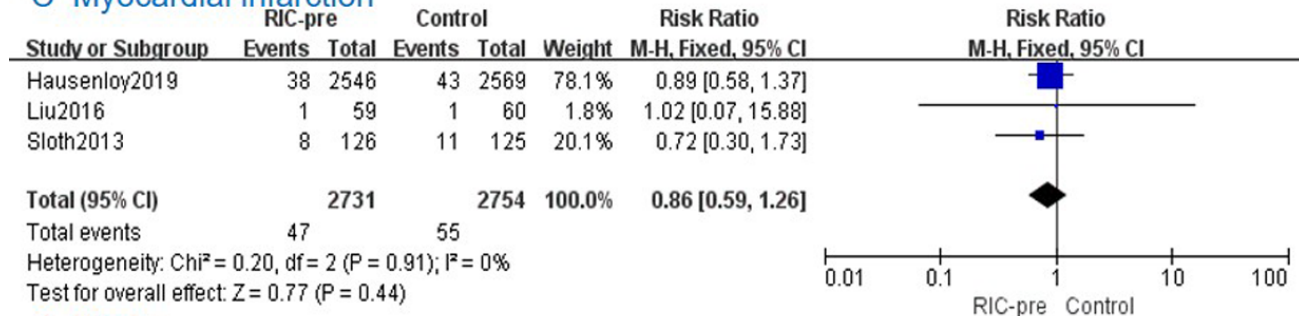
## A Cardiac death



## B Hospitalization for heart failure



## C Myocardial infarction



## D Stroke

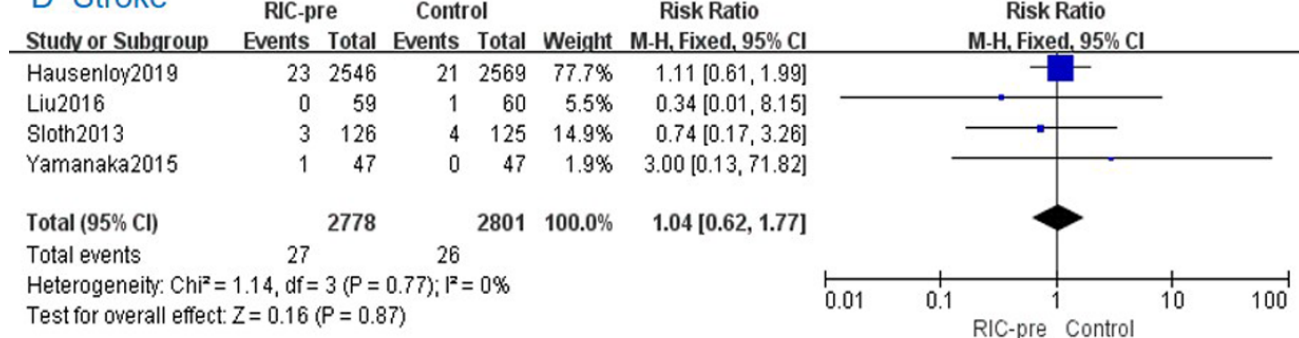


Figure 3. A forest plots represents the statistical effect of clinical outcomes in the follow up time between the RIC-pre and the control group, including cardiac death, hospitalization for heart failure, myocardial infarction and stroke.



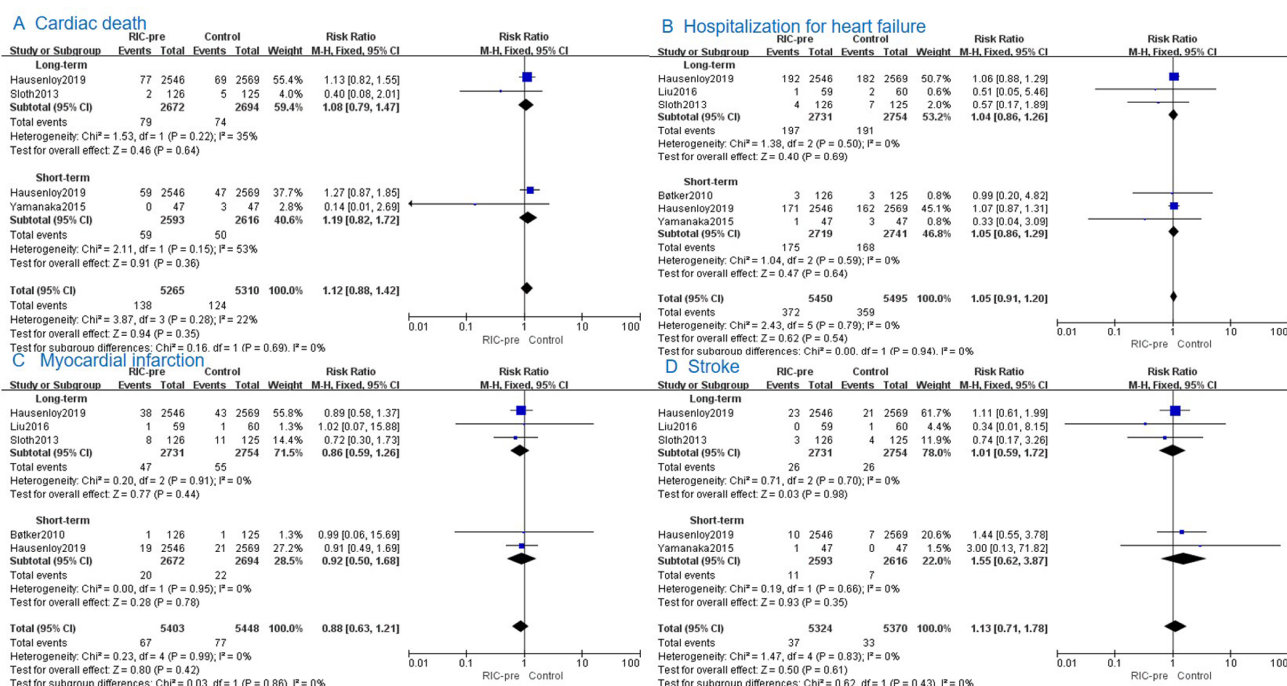


Figure 4. Subgroup analysis according to the time of follow-up (long-term vs. short-term) on cardiac death, hospitalization for heart failure, myocardial infarction and stroke between the RIC-pre and the control groups.

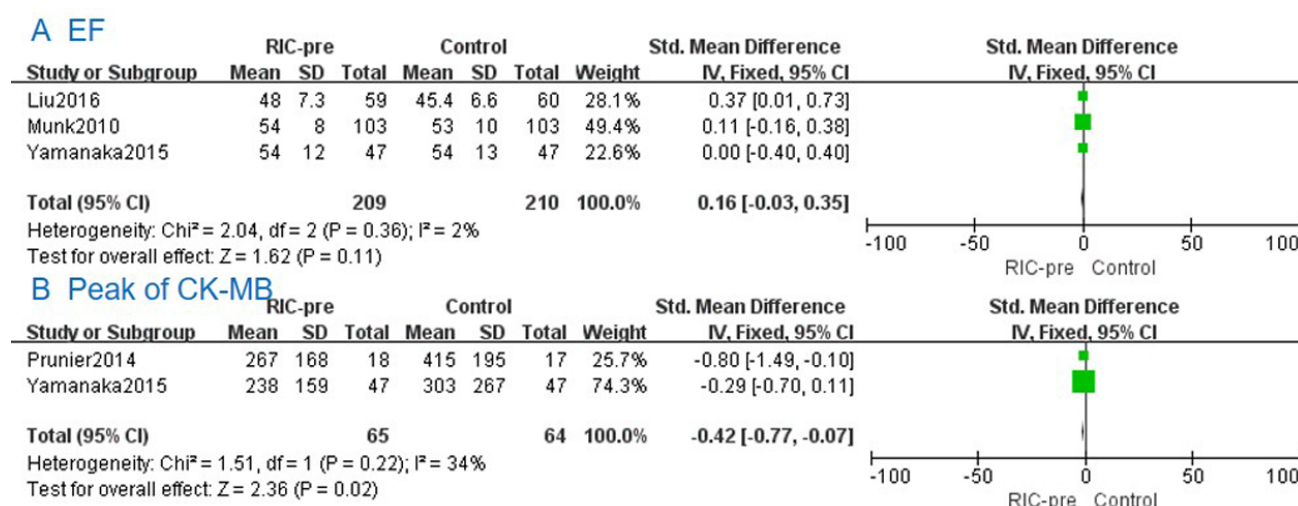


Figure 5. A forest plots represents the statistical effect of EF after procedure and the peak of CK-MB between the RIC-pre and the control groups. Abbreviation: CK-MB: creatine kinase-myocardial band; EF: ejection fraction

Table 1. Characteristics of the 7 included studies.

Study	Year of publication	Region	Follow-up	RIC-pre	Control	RIC protocol	Main findings( RIC-pre group vs. Control group)
Bøtker	2010	Denmark	30 days	126	125	Intermittent arm ischemia through four cycles of 5-min inflation and 5-min deflation of a blood-pressure cuff	Myocardial salvage index: 0.75 (0.50-0.93) vs. 0.55 (0.35-0.88), $P = 0.0333$ ; Final infarction size (% of left ventricle): 4% (1-14) vs. 7% (1-21), $P = 0.10$
Hausenloy	2019	UK, Denmark, Spain, Serbia	12 months	2546	2569	Applying to the arm through four alternating cycles of cuff inflation for 5 min to 200 mm Hg and deflation for 5 min	Cardiac death 3.1% vs. 2.7%, $P = 0.46$ ; Hospitalization for heart failure 7.6% vs 7.1%, $P = 0.55$
Liu	2016	China	12 months	59	60	Four cycles inflating a pneumatic cuff above the upper arm to 200 mm Hg for 5 min and then followed by a 5-min deflation	Myocardial infarction size (% left ventricle): $14.2 \pm 6.1$ vs. $16.6 \pm 6.7$ , $P = 0.042$ ; MACCE: 5.1% vs. 13.3%, $P = 0.116$
Munk	2010	Denmark	30 days	123	119	Intermittent arm ischemia through four cycles of 5-min inflation and 5-min deflation of a blood-pressure cuff	Myocardial area at risk % left ventricle: $26 \pm 14\%$ vs. $27 \pm 16\%$ , $P = 0.9$ ; EF: $54 \pm 8\%$ vs. $53 \pm 10\%$ , $P = 0.42$
Prunier	2014	France	3 days	18	17	Three cycles of 5-min inflation to 200 mmHg and 5-min deflation of an upper arm blood-pressure cuff inflation to 200 mmHg and 5-min deflation of an upper arm	Peak of CK-MB (U/L): $267 \pm 168$ vs. $415 \pm 195$ , $P = 0.016$
Sloth	2013	Denmark	5 years	126	125	Intermittent arm ischemia through four cycles of 5-min inflation and 5-min deflation of a blood-pressure cuff	MACCE: 13.5% vs. 25.6%, $P = 0.018$ ; All-cause mortality:4% vs. 12%, $P = 0.027$
Yamanaka	2015	Japan	30 days	47	47	Three cycles of the upper arm achieved by 5 min cuff inflation at 200 mm Hg followed by 5 min of complete cuff deflation	MACCE:4% vs. 14%, $P = 0.07$ ; Peak of CK-MB(IU/L): $238 \pm 159$ vs. $303 \pm 267$ , $P = 0.15$

MACCE: major adverse cardiac and cerebrovascular events.

Table 2. Clinical baseline characteristics of 7 included studies (RIC-pre/Control).

Study	Year of publication	Age	Male(%)	Diabetes (%)	Hypertension (%)	Smoker (%)	Hypercholeste rolemia (%)	Symptom to balloon time, min	Infarct-related coronary artery (non-LAD,%)	Occluded vessel on arrival TIMI 0-1,(%)
Bøtker	2010	$62 \pm 12/63 \pm 11$	76.0/75.0	9.0/9.0	38.0/24.0	56.0/57.0	15.0/19.0	190 (134-305)/188 (134-309)	61.0/57.0	56.0/61.0
Hausenloy	2019	$63.9 \pm 12.1/63.1 \pm 12.2$	76.0/77.6	11.9/10.4	43.7/40.1	40.5/40.9	28.0/27.2	178 (130-278)/177 (128-279)	59.1/56.9	73.7/74.8
Liu	2016	$62.1 \pm 12.1/62.6 \pm 11.9$	76.3/81.7	20.3/20.0	45.8/40.0	39.0/46.7	32.2/28.3	$420 \pm 174/402 \pm 156$	52.5/58.3	66.1/75.0
Munk	2010	$62 \pm 11/62 \pm 11$	77.0/78.0	9.0/8.0	38.0/24.0	56.0/57.0	15.0/18.0	190 (134-304)/185 (129-299)	62.0/58.0	58.0/61.0
Prunier	2014	$66.1 \pm 16.2/61.7 \pm 14.0$	78.0/76.0	11.0/12.0	50.0/41.0	22.0/47.0	33.0/35.0	$227 \pm 103/241 \pm 75$	61.0/59.0	NA/NA
Sloth	2013	$62 \pm 12/63 \pm 11$	76.0/75.0	9.0/9.0	38.0/24.0	56.0/57.0	15.0/19.0	190 (134-305)/188 (134-309)	61.0/57.0	56.0/61.0
Yamanaka	2015	$67 \pm 12/67 \pm 15$	76.0/76.0	31.0/37.0	61.0/65.0	59.0/51.0	51.0/53.0	$326 \pm 278/360 \pm 274$	60.0/56.0	NA/NA

LAD: left anterior descending coronary (LAD); TIMI: thrombolysis in myocardial infarction study group grading of coronary flow; NA: not available.

confounding factors would influence the efficacy of RIC in the target organ (e.g., brain, kidney, and heart) (Johnsen et al., 2016; Loukogeorgakis et al., 2007). In our meta-analysis, we only included RCTs involving patients with STEMI undergoing PPCI with the condition that RIC-pre must be completed prior to balloon dilation during the procedure. After screening the included RCTs, RIC stimulation was applied to the arm in all cases, and at least three cycles of five min of ischemia and five min of reperfusion (Table 1) were performed. These approaches indicate that the protocols of RIC-pre in the included studies were comparable.

RIC was previously associated with reduced acute myocardial infarction size and improved clinical outcomes in clinical and experimental animal studies (Donato et al., 2017; Pryds et al., 2019). However, in our meta-analysis, no clinically meaningful beneficial effects of RIC-pre on various clinical outcomes (CD, HHF, MI, and stroke) in patients with STEMI undergoing PPCI was found. To investigate time to RIC-pre effect, we performed subgroup analysis based on time of follow-up. RIC-pre failed to show positive effects at the short- and long-term endpoints. Most of the included studies had a 12-month follow-up (only one accomplished a follow-up duration of 5 year) post-STEMI. This follow-up duration may be short so that no positive effect of RIC on clinical outcomes had been detected.

A certain degree of heterogeneity in the short-term subgroup of CD ( $I^2 = 53$ ) was observed because of the discrepancy of cardiovascular risk related factors in patients with STEMI, including diabetes, hypertension, hypercholesterolemia, and smoking could influence the effect of RIC-pre (Ferdinandy et al., 2014). As shown in Table 2, the proportion of patients with these cardiovascular risk related factors reported by Yamanaka et al. was higher than that reported by Hausenloy.

Interestingly, our meta-analysis revealed that RIC-pre reduced peak of CK-MB. However, the positive effect of RIC-pre did not translate to improved clinical outcomes. As reported by a previous trial, the association between reductions in myocardial infarction size by RIC applied as an adjunctive strategy to PPCI and improvements in clinical outcomes remain unclear (Bøtker et al., 2010; Gaspar et al., 2018). Gaspar et al. found that RIC could reduce the incidence of CD and HHF at a 2.1-year median follow-up but failed to limit myocardial infarction size as determined by cardiac biomarkers. In a RIC-STEMI trial, Gaspar et al. similarly indicated that the primary benefit of RIC in patients with STEMI undergoing PPCI was on left ventricular function, with 10% absolute enhancement in median EF. Therefore, we pooled the EF data at follow-up into the analysis and found no beneficial effect in the RIC-pre group.

According to the results of our meta-analysis and in direct contrast to the results of animal studies, RIC-pre did not show a positive effect on patients with STEMI undergoing PPCI (Heusch, 2017, 2018). The translation of cardioprotective effects to clinical practice from successful animal studies is often weak and even inconsistent (Hausenloy et al., 2017). Sean et al. hypothesized that targeting only one mechanism could not be able to produce a robust and strong effect in clinical studies, especially when numerous uncontrolled variables are combined (Davidson et al., 2019). Multitarget cardioprotective therapy is necessary to obtain effective cardioprotection in clinical practice. Additive benefits must

first be tested in animal models. Cardiac remodeling and arrhythmias should be further considered into multitarget cardioprotective therapy for patients with STEMI.

Our meta-analysis had several limitations. First, the included trials in our meta-analysis was limited and short of individual patient data, so that we were unable to excluded the potential impact of individual patient. Second, besides the peak of CK-MB, which indirectly reflects myocardial infarct size, no other indicators, such as those from cardiac images or other cardiac biomarkers, were reported to assess myocardial infarct size because of the limited data. Finally, we did not evaluate publication bias because of small-study effects. Given these limitations, the findings of our meta-analysis should be interpreted with caution.

## 5. Conclusion

RIC-pre tended to a low peak of CK-MB in patients with STEMI undergoing PPCI, but lacked significant beneficial effects on improving clinical outcomes at long- and short-term follow-up.

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## Conflicts of interest

The authors have no any conflicts of interest to declare.

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