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Effects of ischaemic postconditioning on outcomes of patients with ST-segment elevation myocardial infarction who underwent primary percutaneous coronary intervention: a meta-analysis

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ABSTRACT

Objective The aim of this meta-analysis was to evaluate the effects of ischaemic postconditioning (IPC) therapy on hard clinical endpoints in ST-segment elevation myocardial infarction (STEMI) patients who underwent primary percutaneous coronary intervention (PPCI).

Design Systematic review and meta-analysis to evaluate the effects of IPC on the outcomes of patients with STEMI.

Data sources PubMed, Embase and the Cochrane Library were systematically searched for relevant articles published prior to May 1, 2018.

Eligibility criteria for selecting studies Randomised trials comparing conventional PPCI to PPCI combined with IPC in STEMI patients were included. The primary endpoint was heart failure. Secondary endpoints were all-cause mortality and major adverse cardiac events (MACE), including cardiac death, heart failure and MI. The Cochrane Reviewer's Handbook 4.2 was used to assess the risk of bias.

Data extraction and synthesis Relevant data were extracted by two independent investigators. We derived pooled risk ratios (RRs) with random effects models. Sensitivity and subgroup analyses were performed.

Results Ten studies that had enrolled 3137 patients were included. PPCI combined with IPC failed to reduce heart failure (RR: 0.88, 95% CI: 0.61 to 1.26, p=0.47; absolute risk: 3.64% in the IPC group and 4.11% in the PPCI only group), all-cause mortality (RR: 0.94, 95% CI: 0.69 to 1.27, p=0.68; absolute risk: 5.07% in the IPC group and 5.27% in the PPCI onlygroup), MACE (RR: 1.05, 95% CI: 0.83 to 1.32, p=0.69; absolute risk: 9.37% in the IPC group and 8.93% in the PPCI only group), cardiac death (RR: 1.28, 95% CI: 0.85 to 1.93, p=0.24; absolute risk: 4.28% in the IPC group and 3.25% in the PPCI only group) and MI (RR: 1.08, 95% CI: 0.38 to 3.12, p=0.88; absolute risk: 3.61% in the IPC group and 3.44% in the PPCI only group).

Conclusions IPC combined with PPCI does not reduce heart failure, MACE and all-cause mortality compared with traditional PPCI in patients with STEMI.

Trial registration number CRD42017063959

Strengths and limitations of this study

- ► Unlike previous studies, we focused on clinical outcomes, such as heart failure or all-cause mortality.
- ► The recent DANAMI-3–iPOST study, which randomised 1234 patients with ST-segment elevation myocardial infarction (STEMI) to conventional primary percutaneous coronary intervention (PPCI) or PPCI with ischaemic postconditioning, was included, which may alter the conclusion regarding STEMI treatment.
- ► In order to give a solid conclusion, sensitivity and subgroup analyses were performed.
- ► A limitation of this meta-analysis is the inclusion of a relatively low number of patients.

BACKGROUND

Primary percutaneous coronary intervention (PPCI) has been proven to be effective in patients with ST-segment elevation myocardial infarction (STEMI) and has become a first-line therapy.[1] Although PPCI is effective in restoring blood flow, ischaemic reperfusion injury is not inevitable. Reperfusion injury can also induce deleterious effects with a subsequent increase in infarct size, which accounts for up to 50% of the final size of a myocardial infarct.[2] Both animal models of infarction and clinical proof-of-concept studies have shown that reopening of the infarct-related artery, followed by repetitive brief interruptions of blood flow before sustained reperfusion, may protect the myocardium against reperfusion injury, which is evaluated using cardiac biomarkers, single-photon emission CT (SPECT), echocardiography and contrast-enhanced cardiac magnetic resonance.[3–7] This strategy, known as ischaemic postconditioning (IPC), is safe and easy to perform without additional cost.[8] Related meta-analyses, using the above methods for evaluation, have also demonstrated that IPC can rescue cardiomyocytes.[9–11] However, whether improvements in these surrogate markers translate into

improved clinical outcomes, such as reduction in heart failure and/or all-cause mortality, remains controversial. The recent DANAMI-3–iPOST study, which randomised 1234 patients with STEMI to conventional PPCI or PPCI with IPC did not provide evidence indicating that PPCI with IPC leads to better clinical outcomes compared with traditional PPCI.[11]

Given the confusion surrounding the different results related to IPC combined with PPCI, a meta-analysis was done to evaluate whether IPC has a beneficial effect on hard endpoints, such as heart failure, all-cause mortality and MACE, compared with traditional PPCI.

METHODS

Patient and public involvement

Qualitative patient data were the focus of this synthesis; however, patients and the public were not involved in the design of the study or analysis of the data.

Search strategy and selection criteria

This meta-analysis is reported in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[12] PubMed, Embase and Cochrane Library were systematically searched for relevant articles published before 1 May 2018. The terms 'IPC', 'PC', 'PCI', 'controlled trial (CT)', 'intervention study' and 'randomised CTs (RCTs)' were used to identify RCTs. MeSH, Emtree and keyword search terms were used in combination (online supplementary file). The results were limited to trials published in English. The reference lists of relevant studies and reviews, editorials and letters were manually searched to identify additional articles. Endnote (Thomson ISI ResearchSoft, Philadelphia, PA, USA) was used to manage relevant articles and remove duplicate articles.

Study criteria, quality assessment and data extraction

Studies were included in the meta-analysis when they met the following criteria: (1) the study design was a prospective randomised controlled clinical trial; (2) all patients with STEMI underwent PPCI treatment; (3) patients were randomly assigned to the PPCI in combination with the IPC group or the conventional PPCI group; (4) follow-up time was not less than 1 month and (5) relevant data were retrievable. When relevant data were missing, the authors were contacted by e-mail before excluding the references for inaccessibility of data.

The primary endpoint was heart failure. Secondary endpoints were all-cause mortality and major adverse cardiac events (MACE), including cardiac death, heart failure and MI. All clinical endpoints were evaluated according to per protocol definitions, at the longest available follow-up. Study quality was judged by evaluating trial procedures for random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias) and incomplete outcome data (attrition bias). The Cochrane Reviewer's Handbook 4.2 was used to assess the risk of bias.

Table 1 Detailed characteristics of included studies

Study	Patients (IPC/C)	Country	Age (years, IPC/C)	Male (%, IPC/C)	Symptom onset (hours)	Protocol (duration×cycles)	LAD (%, IPC/C)	DES (%, IPC/C)	Follow-up (months)
Lønborg *et al*, 2010[7]	59/59	Denmark	61/62	69/74	≤12	30″/30″×4	44/39	–	3
Garcia *et al*, 2010[15]	22/21	USA	61/55	86/76	≤12	30″/30″×4	36/24	–	41
Freixa *et al*, 2012[14]	39/40	Spain	59/60	84/72	≤12	60″/60″×4	51/39	–	6
Tarantini *et al*, 2012[19]	39/39	Italy	60/60	85/85	≤6	60″/60″×4	41/44	0/2.6	1
Dong *et al*, 2013[20]	32/30	China	70/68	63/73	≤12	30″/30″×3	57/43	–	1
Limalanathan *et al*, 2014[18]	136/136	Norway	61/60	84/80	≤6	60″/60″×4	46/51	29/29	4
Hahn *et al*, 2015[16]	350/350	South Korea	60/60	79/75	≤12	60″/60″×4	47/45	86/86	12
Eitel *et al*, 2015[13]	232/232	Germany	62/65	76/71	≤12	30″/30″×4	42/51	–	6
Luz *et al*, 2015[17]	43/44	Portugal	57/58	88/82	≤12	60″/60″×4	47/43	65/71	14
Engstrøm *et al*, 2017[8]	617/617	Denmark	63/62	80/79	≤12	30″/30″×4	43/40	93/93	38

C, control group (primary percutaneous coronary intervention only); DES, drug-eluted stent; IPC, ischaemic postconditioning group; LAD, left-descending anterior branch.

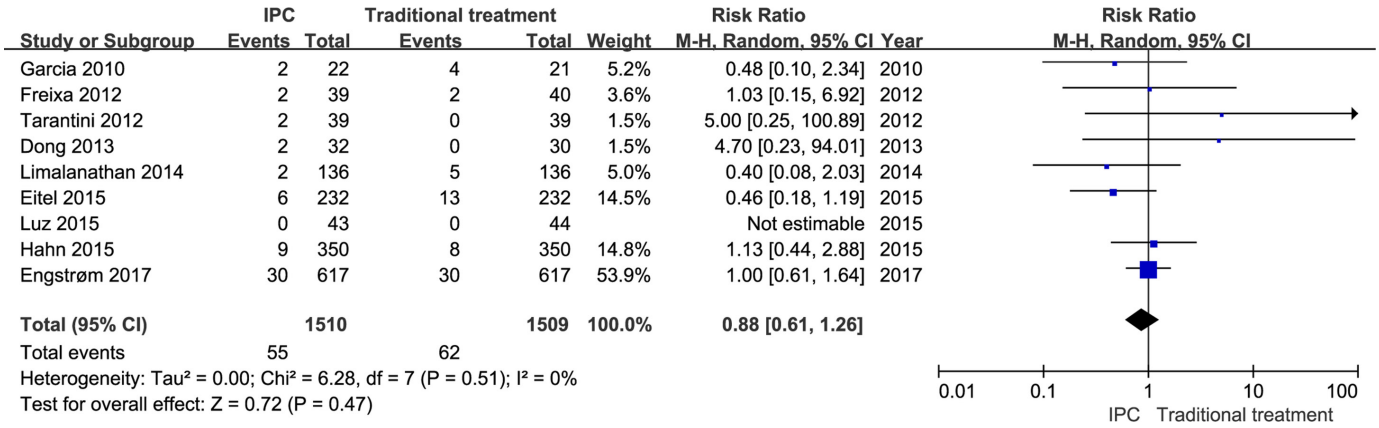

Figure 1 Effect of PPCI with IPC versus PPCI only on heart failure in STEMI patients undergoing PPCI. IPC, ischaemic postconditioning group; PPCI, primary percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Relevant data were extracted by two independent investigators (XP and JH). Disagreements were resolved by consensus or a third investigator (XH). The following data were abstracted from the selected articles: first author, publication date, study design, onset of symptoms, characteristics of included participants, total number of IPC and conventional groups, events of the IPC and conventional groups, stent type and follow-up time.

Data analysis

Meta-analysis was performed to calculate the risk ratio (RR) and 95% CI. Pooled RRs were computed as the Mantel-Haenszel-weighted average of the RRs for all included studies. Because the true treatment effect of various IPC protocols may have varied among the included trials, the random effects model was used in the analysis. Statistical heterogeneity among the trial-specific RRs was checked and quantified by the I^2 statistic, and a p value≤0.05 was considered statistically significant. We performed sensitivity analysis to assess the contribution of each study to the pooled estimation by excluding one trial at a time and recalculating the pooled RR estimation for the remaining studies. Subgroup analyses were conducted in terms of time of symptom onset, IPC protocols and antiplatelet therapies. Data analysis was performed on an intention-to-treat basis. All analyses were performed using Review Manager Software (Review Manager [RevMan] [Computer program]. V.5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.).

Outcomes

Search results and bias assessment

Online supplementary figure 1 shows that the combined search strategy identified 273 potential relevant manuscripts, from which 33 studies were retrieved for more detailed assessment (detailed search strategies for PubMed is shown in the complementary file). A total of 10 RCTs, involving 3137 patients, are included in this meta-analysis.[7 8 13–20] The Cochrane Reviewer's Handbook 4.2 was used to assess the risk of bias (online supplementary figure 2). No high-risk studies were identified and six studies had a low risk of bias.

The main features of the 10 included RCTs and the baseline clinical characteristics of the patients are presented in table 1. In the 10 trials, 1569 patients (50%) were randomly assigned to PPCI with IPC. The mean age of the trial patients was 61 years and 78% of the patients were male. The IPC protocols (cycles×ischaemia/reperfusion in seconds) varied between studies and were as follows: 30″/30″×4 in four studies, 60″/60″×4 in five studies and

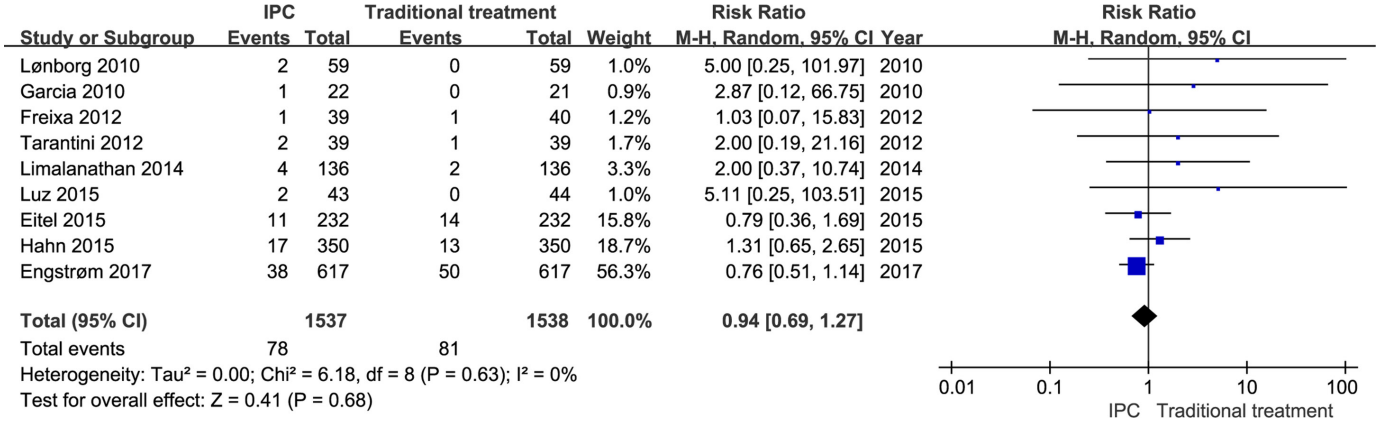

Figure 2 Effect of PPCI with IPC versus PPCI only on all-cause mortality in STEMI patients undergoing PPCI. IPC, ischaemic postconditioning group; PPCI, primary percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

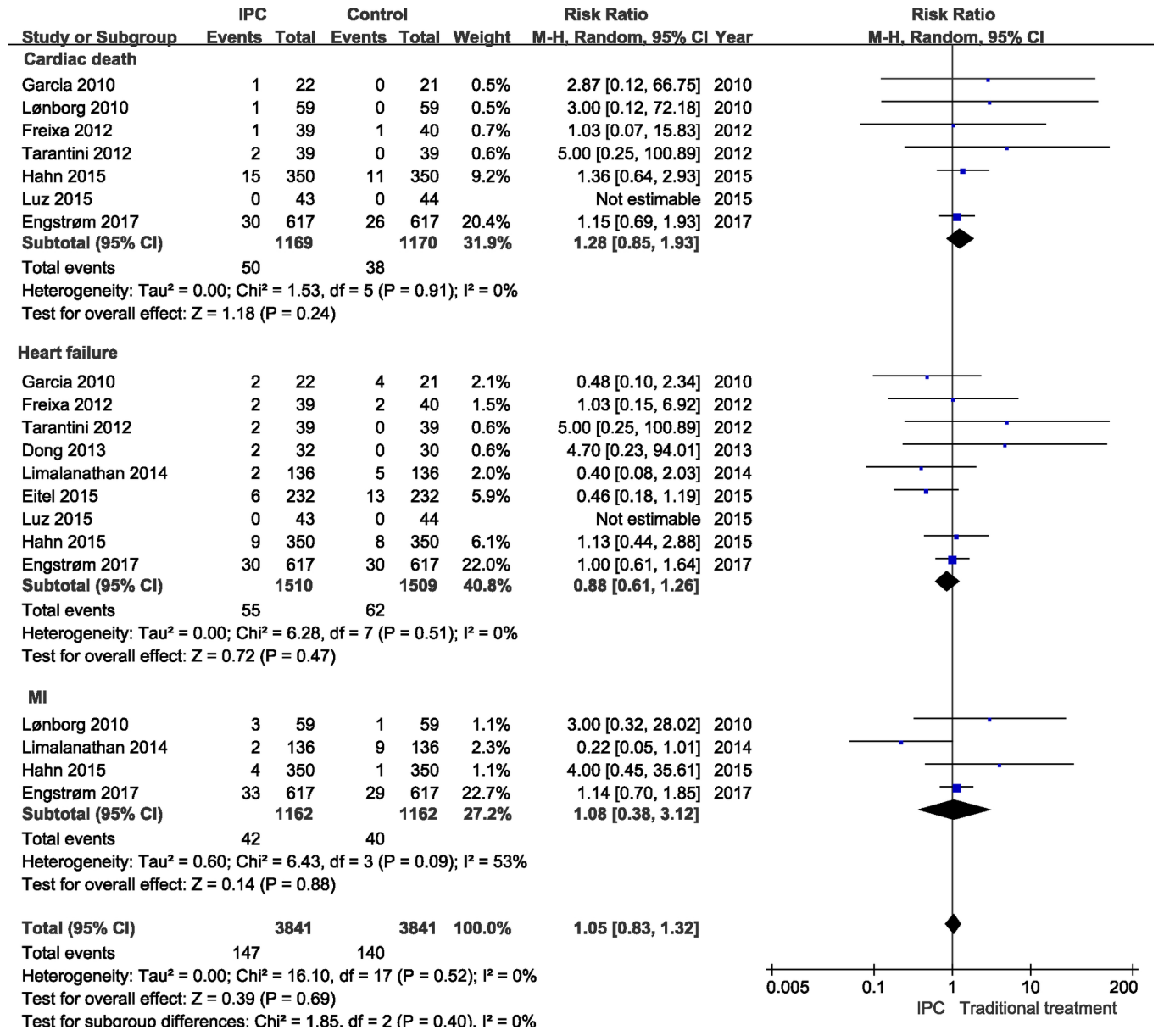

Figure 3 Effect of PPCI with IPC versus PPCI only on MACE in STEMI patients undergoing PPCI. IPC, ischaemic postconditioning group; MACE, major adverse cardiac events; PPCI, primary percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

30″/30″×3 in one study. Follow-up among trials varied from 1 month to 41 months. The time of symptom onset varied between studies from 6 hours in two studies to 12 hours in eight studies.

Primary endpoint: heart failure

When the data were pooled, the RR for heart failure was 0.88 (95% CI: 0.61 to 1.26, p=0.47; absolute risk: 3.64% in the IPC group and 4.11% in the PPCI only group) in the random effects model (figure 1). No evident statistical heterogeneity among studies was observed (I^2=0, p=0.51). IPC during PPCI did not reduce heart failure compared with traditional PPCI.

Secondary endpoints: all-cause mortality and MACE

The pooled data showed that IPC did not reduce all-cause mortality compared with traditional PPCI (RR: 0.94, 95% CI: 0.69 to 1.27, p=0.68; absolute risk: 5.07% in the IPC group and 5.27% in the PPCI only group, figure 2). No evident statistical heterogeneity among studies was observed (I^2=0, p=0.63). Furthermore, IPC did not reduce cardiac death (RR: 1.28, 95% CI: 0.85 to 1.93, p=0.24; absolute risk: 4.28% in the IPC group and 3.25% in the PPCI only group), MI (RR: 1.08, 95% CI: 0.38 to 3.12, p=0.88; absolute risk: 3.61% in the IPC group and 3.44% in the PPCI only group) and heart failure (RR: 0.85, 95% CI: 0.59 to 1.23, p=0.40; absolute risk: 3.64% in the IPC group and 4.11% in the PPCI only group). When all events (MACE) were considered, IPC during PPCI provided no net benefit of IPC during PPCI (RR: 1.05, 95% CI: 0.83 to 1.32, p=0.69; absolute risk: 9.37% in the IPC group and 8.93% in the PPCI only group, figure 3).

Table 2 Subgroup analysis

	Cardiac death	Heart failure	MI	All-cause mortality
Symptom onset				
≤6 hours	5.00 (0.25 to 101)	1.02 (0.09 to 11.5)	0.22 (0.05 to 1.01)	2.00 (0.51 to 7.86)
≤12 hours	1.25 (0.83 to 1.89)	0.89 (0.61 to 1.29)	1.26 (0.79 to 2.00)	0.90 (0.66 to 1.23)
Protocol				
30″/30″×4	1.21 (0.73 to 1.99)	0.76 (0.45 to 1.29)	1.19 (0.74 to 1.91)	0.80 (0.56 to 1.14)
60″/60″×4	1.44 (0.70 to 2.94)	0.98 (0.48 to 2.04)	0.84 (0.05 to 14.2)	1.38 (0.76 to 2.52)
Follow-up				
≤12 months	1.49 (0.74 to 2.99)	0.81 (0.44 to 1.47)	1.20 (0.16 to 8.81)	1.16 (0.73 to 1.87)
>12 months	1.18 (0.71 to 1.96)	0.94 (0.58 to 1.50)	1.14 (0.70 to 1.85)	0.88 (0.45 to 1.71)
Analysis model				
Fixed effects	1.30 (0.87 to 1.96)	0.89 (0.62 to 1.26)	1.05 (0.69 to 1.60)	0.96 (0.71 to 1.30)
Random effects	1.28 (0.85 to 1.93)	0.88 (0.61 to 1.26)	1.08 (0.38 to 3.12)	0.94 (0.69 to 1.27)
Antiplatelet or anticoagulation therapies				
Clopidogrel	1.28 (0.85 to 1.93)	0.98 (0.66 to 1.45)	1.08 (0.38 to 3.12)	0.97 (0.69 to 1.35)
GPIIb/IIIa inhibitors	1.23 (0.81 to 1.88)	0.84 (0.56 to 1.27)	1.08 (0.38 to 3.12)	0.93 (0.67 to 1.30)
Bivalirudin	1.44 (0.70 to 2.94)	0.98 (0.47 to 2.03)	0.84 (0.77 to 14.24)	1.48 (0.81 to 2.69)

MI, myocardial infarction.

Sensitivity analysis and potential sources of heterogeneity

Sensitivity testing was performed by excluding each included study, one at a time, and recalculating the overall effects. The direction of the overall effects, in terms of heart failure, MI, cardiac death and all-cause mortality, were not influenced no matter which study was excluded (online supplementary table 1).

There were very little heterogeneities between studies with regard to the observed effects on all-cause mortality (I^2=0, p=0.63) and cardiac death (I^2=0, p=0.91). However, moderate between-study heterogeneity was identified in the case of MI (I^2=53%, p=0.09). MI heterogeneity was mainly caused by the Limalanathan 2014 study. When this study was excluded, no heterogeneity was observed (I^2=0%, p=0.40) and the conclusions were still consistent with the previous analysis. Subgroup analysis did not identify any baseline risk factor, such as symptom onset, duration of follow-up or antiplatelet therapies, as a modifier of the relationship between IPC and clinical endpoints (table 2).

DISCUSSION

The current meta-analysis of 10 RCTs, including 3137 patients with STEMI undergoing PPCI, showed that no reduction in heart failure, all-cause mortality or MACE when comparing PPCI in combination with IPC to traditional PPCI over a mean follow-up of 20 months. Similarly, no improvement in clinical outcomes was shown in the subgroup analysis.

IPC was first introduced by Zhao *et al* in 2003.[21] Subsequent clinical trials and meta-analyses found a salutary effect of IPC on infarct size as evaluated by CK, CK-MB, troponin, SPECT and cardiac function based on the left ventricular ejection fraction.[3–5] However, opposite results have also been reported.[8 16–19] The DANAMI-3–iPOST trial, which is the largest study to date, showed that IPC did not reduce infarct size.[8] Furthermore, whether surrogate endpoints, such as infarct size, myocardial salvage and resolution of ST-segment elevation, translate into hard endpoints, such as heart failure, all-cause mortality or MACE, remains a point of debate. Unlike the above surrogate endpoints, heart failure, all-cause mortality and MACE are what are generally considered to be most important by both clinics and patients.

Previous meta-analyses mainly focused on cardiac biomarkers, cardiac imaging and cardiac function; however, clinical outcomes are also very consequential. In the current meta-analysis, IPC was not shown to improve clinical outcomes, though several factors may influence its effectiveness. A meta-analysis of 19 RCTs concluded that cardioprotection, as evaluated by cardiac enzyme leakage, infarct size and left ventricular function, is more likely in patients with LAD artery involvement because of a greater myocardial area is at risk.[9] Zhou *et al* performed a meta-analysis of 10 RCTs and found that the effects of cardiac protection were more pronounced among young and male patients and those who received direct stenting.[10] The IPC protocol is also an important factor in determining the IPC efficacy. IPC may cause myocardial ischaemia and expand the infarct area. Several trials chose four cycles of 1 min of reperfusion followed by 1 min of reocclusion. However, other trials selected four cycles of 30 s reperfusion followed by 30 s low-pressure balloon occlusion. However, the subgroup analyses in the

current study found no differences in the effectiveness of IPC when comparing different protocols.

Time of symptom onset, which is an independent predictor of MACE in patients with STEMI undergoing PPCI, may have influenced the results of these trials. However, subgroup analysis in this study did not detect differences between trials related to the time of symptom onset. The key reason is that IPC might have no effect on cardioprotection; thus, the results of the subgroup analysis in this study were neutral. Furthermore, the sample size of the studies may have been too small to detect minor beneficial effects. Several confounding factors, such as baseline characteristics of patients, coexisting diseases, medications and IPC strategies used, may have influenced the cardioprotective benefits of IPC. With the use of novel antiplatelet and lipid-lowering agents and timely PPCI, the outcome of STEMI has significantly improved. The decreasing mortality rate also makes it harder to demonstrate minor benefits of using additional therapy.

LIMITATIONS

This study has several limitations. First, although no apparent heterogeneity in statistical analysis was observed, variations in the methodology among studies, such as different risk profiles of the included patients, IPC strategies and follow-up times, were observed. However, according to the meta-regression and subgroup analyses performed in this study, the above heterogeneities should not have affected the conclusion. In addition, the conclusion was based on the random effects model, which accounts for a certain degree of heterogeneity. Second, because of low incidence of adverse events, such as heart failure, the sample size is relatively small. Nonetheless, this meta-analysis is the largest population-based analysis of IPC. Additional RCTs are necessary to evaluate long-term clinical outcomes.

CONCLUSIONS

This meta-analysis suggests that the use of IPC in STEMI patients undergoing PPCI does not reduce the incidence of heart failure, MACE and all-cause mortality compared with traditional PPCI.

Contributors XH and ZX designed the study and provided methodological expertise in systematic reviews and searching strategies. ZX and LT drafted the manuscript. JH and XP searched the databases and constructed the tables. All authors have read, provided critical feedback and approved the final manuscript.

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Data sharing statement All data generated and research materials used during this systematic review and meta-analysis are available from the corresponding author on reasonable request.

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