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Keywords:	Ischemic postconditioning therapy, percutaneous coronary intervention, all-cause mortality, major adverse cardiac events, meta-analysis

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

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Objective: the aim of this meta-analysis is to evaluate the effects of ischemic postconditioning therapy (IPC) on clinical hard endpoiont.

Setting: treatment for STEMI

Intervention: IPC

Eligible studies: we included randomized trials comparing PPCI in combination with IPC with conventional PPCI in patients with STEMI.

The primary and secondary endpoint: The primary end point was all-cause mortality, major adverse cardiac events (MACE) including cardiac death, heart failure, nonfatal MI and revascularization. Secondary end point included each individual component of MACE (cardiac death, heart failure, nonfatal MI and revascularization).

Results: Nine studies enrolling 3088 patients were included. PPCI in combination with IPC failed to reduce all-cause mortality (RR:0.94, 95% CI: 0.69–1.27, P= 0.68), MACE (RR: 1.14, 95%CI: 0.88-1.46, p=0.32), cardiac death (RR: 1.28, 95%CI: 0.85-1.93, p=0.24), MI (RR: 1.08, 95%CI: 0.38-3.21, p=0.88), heart failure (RR: 1.05, 95%CI: 0.62-1.75, p=0.87), and revascularization (RR: 1.35, 95%CI:0.81-2.26, p=0.25)..

Conclusion: This meta-analysis suggested that the use of IPC in STEMI patients undergoing PPCI did not reduce all-cause mortality, MACE compared with traditional PPCI.

Strengths and limitations of this study

1. This meta-analysis included the recent relevant studies and provided the latest RCTs about treatment of STEMI.
2. In order to give a solid conclusion, trial sequential analysis was performed to evaluate

the simple size.

3. We include the recent DANAMI-3–iPOST study, which randomized 1234 patients with STEMI to conventional PPCI or PPCI with IPC, and may change our opinion on treatment of STEMI.
4. A limitation of this meta-analysis is the reduced number of trials included.
5. Bias between studies may exist. However, subgroup analysis was performed to evaluate catheter-directed thrombolysis.

Key words: Ischemic postconditioning therapy (IPC); percutaneous coronary intervention (PCI); all-cause mortality; major adverse cardiac events (MACE); meta-analysis

Abbreviation

IPC	Ischemic postconditioning therapy
PCI	percutaneous coronary intervention
MACE	major adverse cardiac events
SPECT	single-photon emission computed tomography
ce-CMR	contrast-enhanced cardiac magnetic resonance
RCT	controlled clinical trial

Background

Primary percutaneous coronary intervention(PPCI) has proved effective in patients

with ST-segment elevation myocardial infarction (STEMI) and has become the first-line therapy[1]. Although PPCI is effective in restoring blood flow, ischemic reperfusion injury is not inevitable. Reperfusion injury can also induce deleterious effects with a subsequent increase of infarct size, which accounts for up to 50% of the final size of a myocardial infarct[2]. Furthermore, both animal models of infarction and clinical proof-of-concept studies have shown IPC can effectively protect myocardium from reperfusion injury evaluated by cardiac biomarkers, single-photon emission computed tomography(SPECT), echocardiography, and contrast-enhanced cardiac magnetic resonance(ce-CMR) [3-7]. Related meta-analysis also demonstrated that IPC could rescue cardiomyocytes evaluated by above methods[8-10]. However, whether improvements in these surrogate makers translate into improved clinical outcomes evaluated by hard end points such as all-cause mortality remains controversial. the recent DANAMI-3–iPOST study, which randomized 1234 patients with STEMI to conventional PPCI or PPCI with IPC, did not provide evidences in favor of PPCI with IPC compared with traditional PPCI[10].

Given the confusing situations of IPC in PPCI, we performed this meta-analysis. The aim of this meta-analysis was to evaluate whether IPC has a beneficial effect on hard end points such as all-cause mortality and MACE compared with traditional PPCI.

Methods

Search strategy and selection criteria

This meta-analysis is reported in accordance of the Preferred Reporting Items for

System Reviews and Meta-Analyses(PRISMA) Statement and was registered at International Prospective Register of Systematic Reviews(CRD42017063959)[11].we systemically searched PubMed, Embase, and Cochrane Library for relevant articles published before April 1, 2017. We used the terms: ischemic postconditioning, postconditioning, percutaneous coronary intervention(PCI), controlled trial, intervention study, and randomized controlled trials(RCTs) to identify randomized controlled trials. MeSH, Emtree, and keyword search terms were used in combination. Results were limited to trials published in English. We manually searched the reference lists of relevant studies and reviews, editorials, and letters to identify further articles.

We used Endnote (Thompson ISI ResearchSoft, Philadelphia, USA) to manage relevant articles and remove duplicated articles.

Study criteria, quality assessment, and data extraction

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

The primary end point was all-cause mortality and major adverse cardiac events (MACE) including cardiac death, heart failure, myocardial infarction(MI), and revascularization. Secondary end point included each individual component of MACE

(cardiac death, heart failure, MI, and revascularization). All clinical endpoints were evaluated according to per protocol definitions, at the longest available follow-up. We judge study quality 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 risk of bias.

Relevant data were extracted by 2 independent investigators (ZW Zhu and JB Huang). Disagreements were resolved by consensus or a third investigator (XQ Hu). We abstracted the following data from the selected articles: first author, publication date, study design, onset of symptoms, characteristics of included participants, total number of IPC group and conventional group, events of postconditioning group and conventional group, stent type, follow-up time.

Data analysis

Meta-analysis was performed to calculate the Risk Ratio (RR) and 95% confidence interval (CI) of all-cause mortality , MACE , and each component of MACE. Pooled RRs were computed as the Mantel-Haenszel-weighted average of the RRs for all included studies. Since the true treatment effect of various postconditioning 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 statistical significant. Data analysis will be

done on an intention-to-treat basis. All analysis was performed using Review Manger Software (Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.) and Stata (Stata12.0 (StataCorp LP, College Station, Texas).)

Outcomes

Search results and Bias assessment

As reported in Supplementary Fig 1, the combined search strategy identified 273 potential relevant manuscripts, 22 studies were finally retrieved for more detailed assessment. Finally, 9 RCTs were included in this meta-analysis, involving 3088 patients[7.13.14.15.16.17.18.19.20]. We used the Cochrane Reviewer's Handbook 4.2 to assess risk of bias (Supplementary Fig 2).

The main features of the 9 included RCTs and baseline clinical characteristics of patients have been presented in Table 1. In the 9 trails, 1544 patients (50%) were randomly assigned to postconditioning therapy. The mean age of the trial patients was 61 years, 78% of these patients were male. The IPC protocol (cycles*ischemia/reperfusion in seconds) varied between studies, being 30″/30″ × 4 in 4 studies, 60″/60″ × 4 in 5 studies. The follow-up in the trials varied from 1 month to 41 months. The time of symptoms onset varied between studies, being 6 hours in 2 studies, 12 hours in 7 studies.

Table 1: detailed characteristics of included studies.

Study	Patients(P	Country	Age(y)	Male	Symptom	Protocol(duratio	LAD (%)	DES	Follow-u

	C/C)			(%)	onset(h)	n*cycles)		(%)	p(m)
Lønborg 2010[7]	59/59	Denmark	61/62	69/74	≤12 h	30″/30″ × 4	44/39	-	3
Garcia 2010[20]	22/21	USA	61/55	86/76	≤12 h	30″/30″ × 4	36/24	-	41
Freixa 2012[19]	39/40	Spain	59/60	84/72	≤12 h	60″/60″ × 4	51/39	-	6
Tarantini 2012[16]	37/38	Italy	60/60	85/85	≤6 h	60″/60″ × 4	41/44	0/2.6	1
Limalanathan 2014[15]	136/136	Norway	61/60	84/80	≤6 h	60″/60″ × 4	46/51	29/29	4
Hahn 2015[14]	350/350	South Korea	60/60	79/75	≤12 h	60″/60″ × 4	47/45	86/86	12
Eitel 2015[18]	232/232	Germany	62/65	76/71	≤12 h	30″/30″ × 4	42/51	NA	6
Luz 2015[17]	43/43	Portugal	57/58	88/82	≤12 h	60″/60″ × 4	47/43	65/71	14
Engstrøm 2017[13]	617/617	Denmark	63/62	80/79	≤12 h	30″/30″ × 4	43/40	93/93	38

134 PC : postconditioning group ; C; control group; LAD: left descending anterior branch; DES:

135 drug eluted stent

136

All-cause mortality and MACE

When we pooled the data, the RR for all-cause mortality was 0.94 (95% CI: 0.69–1.27, P= 0.68) in random-effects model (Fig 1). No evident statistical heterogeneity was present among studies (I^2=0, p=0.76). IPC during PPCI did not reduce all-cause mortality compared with traditional PPCI.

Based on the pooled results, we did not find that IPC could reduce cardiac death (RR: 1.28, 95%CI: 0.85-1.93, p=0.24), MI (RR: 1.08, 95%CI: 0.38-3.21, p=0.88), heart failure (RR: 1.05, 95%CI: 0.62-1.75, p=0.87), and revascularization (RR: 1.35, 95%CI:0.81-2.26, p=0.25). When all these events (MACE) were considered, the net benefit did not favor IPC during PPCI (RR: 1.14, 95%CI: 0.88-1.46, p=0.32, Fig 2).

Sensitivity analysis and potential sources of heterogeneity

We performed sensitivity by excluding each included study at one time and recalculating the overall effects. Each excluded study did not influence the direction of the overall effects of all-cause mortality (Supplementary Table 1).

There were no heterogeneities between studies with regards the observed effects in all-cause mortality (I^2=0, p=0.63), cardiac death (I^2=0, p=0.91), and revascularization (I^2=0, p=0.49). However, moderate between-study heterogeneity was identified in case of heart failure (I^2=57%, p=0.02) and MI (I^2=53%, p=0.09). The heterogeneity of heart failure was generated by the Eital 2015 study, excluding these studies from the analysis restored the homogeneity of heart failure dataset(I^2=19%, p=0.28). The heterogeneity of MI was mainly caused by the Limalanathan 2014 study. When we excluded this study, No heterogeneity

was observed (I^2=0%, p=0.40). The conclusions were still consistent with previous analysis. Meta-regression did not find any baseline risk factor, such as age, diabetes, hypertension et al, was a modifier of the relationship between IPC and all-cause mortality, MACE. Sensitivity and subgroup analysis did not identify any patient-level or study-level covariate as a significant source of heterogeneity except for this subgroup analysis (Table 2).

Table 2: Subgroup analysis

	All-cause mortality	Cardiac death	Heart failure	MI	Revascularization
Symptom onset					
≤6 h	2.00(0.51-7.86)	5.00(0.25-101)	1..02(0.09-11.5)	0.22(0.05-1.01)	5.0 (0.25-101)
≤12h	0.90(0.66-1.23)	1.23(0.81-1.87)	1.08 (0.62-1.87)	1.26 (0.79-2.00))	1.30 (0.77-2.19)
Protocol					
30″/30″ × 4	0.80(0.56-1.14)	1.21(0.73-1.99)	0.99 (0.51-1.91)	1.19(0.74-1.91)	0.96 (0.17-5.37)
60″/60″ × 4	1.38(0.76-2.52)	1.44(0.70-2.94)	1.21 (0.43-3.39)	0.84(0.05-14.2)	1.16(0.44-3 ,05)
Follow-up					
≤ 12 m	1.16(0.73-1.87)	1.49(0.74-2.99)	1.20 (0.55-2.62)	1.20(0.16-8.81)	0.89 (0.29-2.77)
> 12 m	0.78(0.52-1.16)	1.18(0.71-1.96)	0.94 (0.58-1.50)	1.14(0.70-1.85)	1.60 (0.87-2.93)
Analysis model					
Fixed effect model	0.96(0.71-1.30)	1.30(0.87-1.96)	1.08(0.82, 1.41)	1.05 (0.69,-1.60)	1.34 (0.82-2.20)

Random effects	0.94(0.69-1.27)	1..28(0.85-1.93)	1.05(0.62-1.75)	1.08(0.38-3.12)	1.35 (0.81-2.26)

Discussion

The current meta-analysis of 9 RCTs including 3088 patients with STEMI treated with PPCI did not show benefits of IPC in reducing all-cause mortality , MACE and individual component of MACE compared with traditional PPCI with a mean follow-up of 20 months. Subgroup analysis concerning different IPC protocols and different time of symptoms onset did not show improved clinical outcomes as well.

IPC was first introduced by Zhao et al. in 2003[12]. Subsequent clinical trials and meta-analysis found that salutary effect of IPC on infarct size evaluated by CK, CK-MB, troponin, SPECT, and cardiac function evaluated by left ventricular ejection fraction(LVEF)[11-17]. However , opposite results also existed[13-17]. The DANAMI-3-iPOST trial, which is the largest study to date, did not show that IPC could reduce infarct size, microvascular obstruction[13]. Furthermore, whether the surrogate end points of infarct size, myocardial salvage, and resolution of ST-segment elevation can translate into hard endpoints such as all-cause mortality is really a problem. Unlike these surrogate end points, all-cause mortality and MACE are, what clinics and patients, really considering.

Unlike previous meta-analysis mainly focusing on cardiac biomarkers, cardiac imaging, cardiac function, clinical outcomes should be put more importance. However, our meta-analysis did not show that IPC could improve clinical outcomes. Several factors may

play a role in the results of these RCTs. That routine IPC failed in the present study, may on the other hand suggest that some patients may respond to the therapy. A meta-analysis of 19 RCTs concluded that cardioprotection with regard to cardiac enzymes leakage, infarct size and left ventricular function is more prone in patients with LAD artery involvement because of a greater myocardial area being at risk [7]. Zhou et al. performed a meta-analysis consisting of 10 RCTs and found that effects of cardiac protection are more pronounced among young and male patients, and those in whom direct-stenting techniques were used [8]. IPC protocol is also an important factor in determining the results. IPC may cause myocardial ischemia and expand the infarct area. Many trials chose 4 cycles of 1 minute of reperfusion followed by 1 minute of reocclusion. On the contrary, other trials chose 4 cycles of 30-second reperfusion followed by 30-second low-pressure balloon occlusion. However, our subgroup analysis did not find the difference. Time of symptoms onset, which is the independent predictor of MACE in patients with STEMI undergoing PPCI, might play a role in the results of these trials. Subgroup analysis did not detect the difference as well.

Neutral subgroup analysis can result from many reasons. The key reason is that IPC might have no effect on cardioprotection. As a result, our subgroup analysis was neutral. The other reason could not be neglected as well. the sample size of the studies may have been small to detect minor beneficial effects. Many confounding factors such as patient's baseline characteristics, coexisting diseases, medications, IPC strategies used may partly affect the cardioprotective benefits of IPC. With the use of new antiplatelet and lipid-lowering agents and timely PPCI, the outcome of STEMI improves greatly. The

declining rate of death makes it harder to demonstrate a minor benefit of additional therapy with regard to overall mortality.

Limitations

It should be noted that our conclusion should be viewed in the context of its limitation. First, although there was not apparent heterogeneity in statistics, the heterogeneity in clinical and methodology were inevitable including different risk profiles of the included patients, IPC strategies, follow-up time et al. However, we performed meta-regression and subgroup analysis and did not find that these heterogeneities could affect our conclusion. In addition, we based our conclusion on the random effects model, which can account for certain degree of heterogeneity. Second, although we performed an extensive search strategy, some studies might not be included in this meta-analysis. But, this meta-analysis is the largest population-based analysis of IPC. Third, Further RCTs are necessary to evaluate the long-term clinical outcomes.

Conclusions

This system review and meta-analysis suggested that the use of IPC in STEMI patients undergoing PPCI did not reduce the incidence of all-cause mortality, MACE compared with traditional PPCI.

Additional Information

The authors declare that they have no conflict of interest.

Contributors ship statement: Xinqun Hu and Zhenhua Xing designed the study and provided methodological expertise in systematic reviews and searching strategies. Jiabing Huang and Xiaofan Peng searched the databases and performed tables. Zhenhua Xing drafted the manuscript. All authors read, provided critical feedback and approved the final manuscript.

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Competing interests: none

Data sharing statement: No additional data available.

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Figure legend

Fig 1: ischemic postconditioning versus traditional PPCI on all-cause mortality in patients with STEMI.

Fig 2: ischemic postconditioning versus traditional PPCI on MACE in patients with STEMI.

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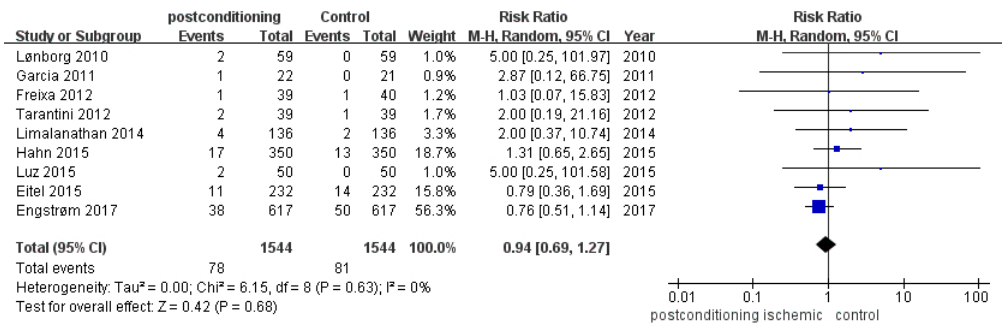

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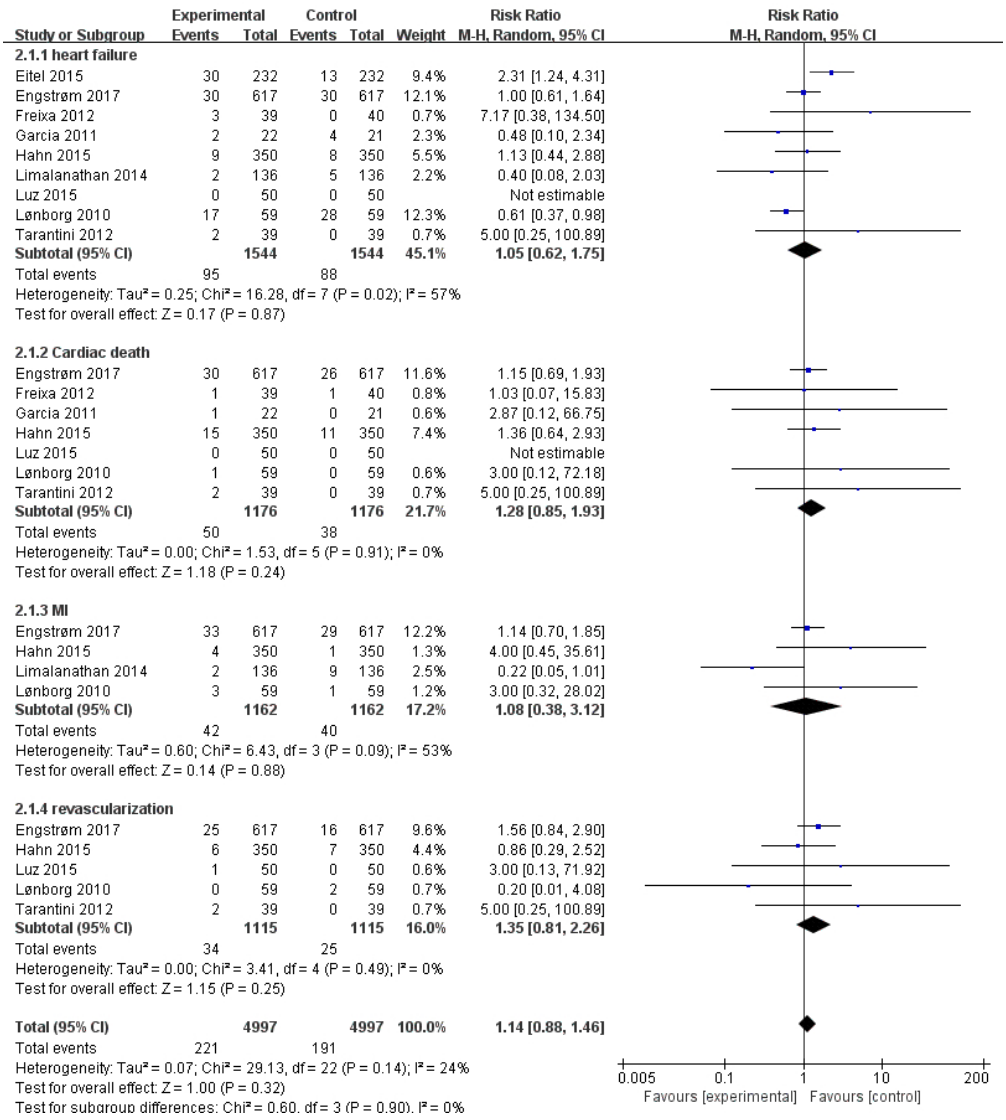

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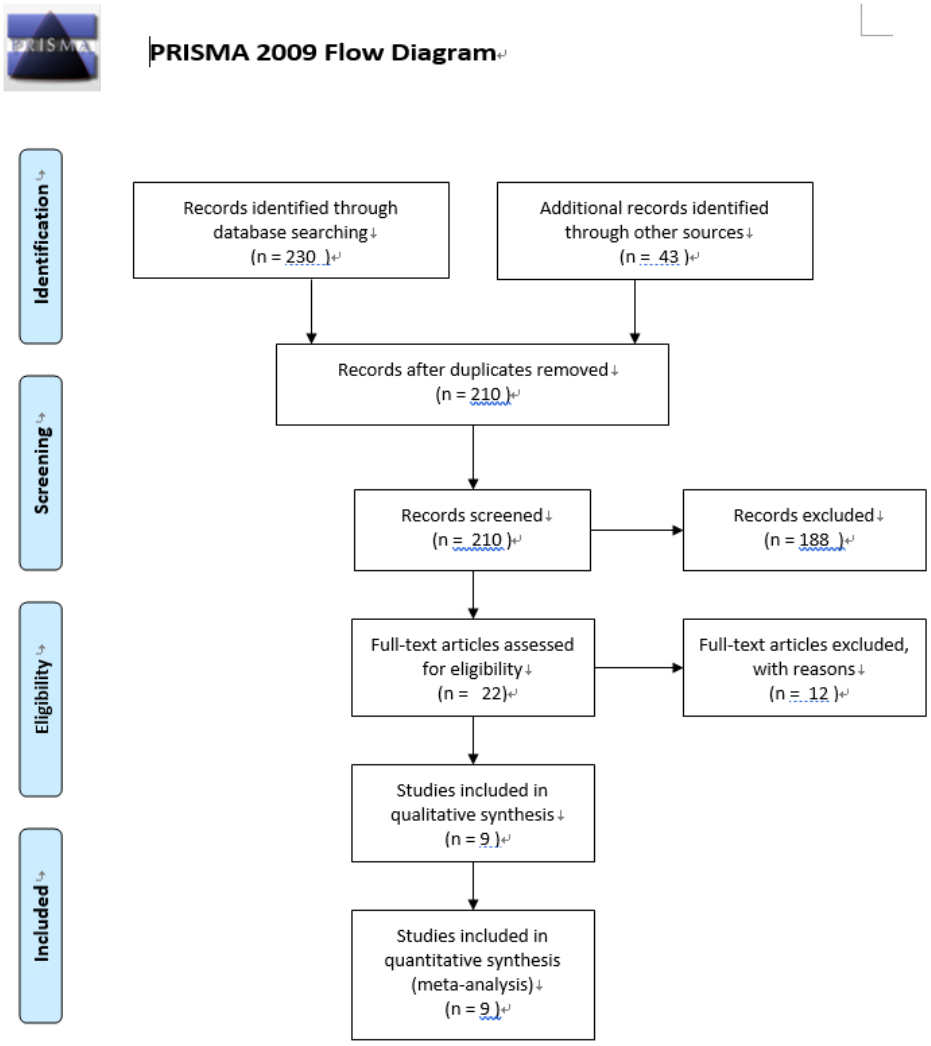

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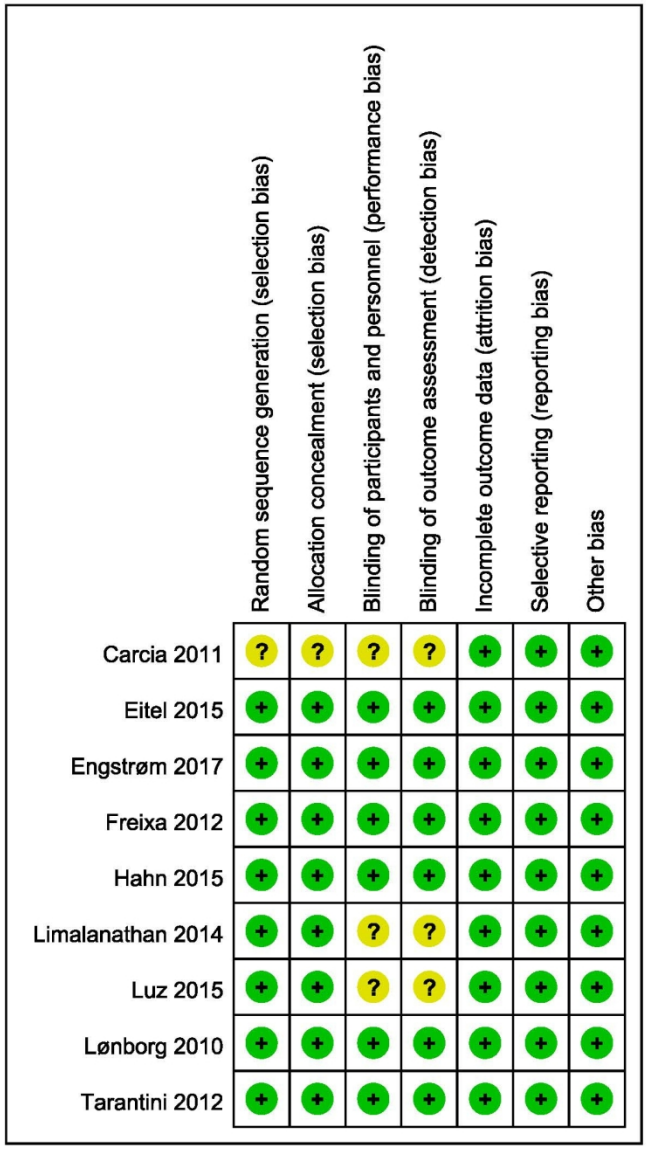

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Supplementary table 1: Sensitivity analysis of randomized primary prevention trials

Excluded study	RR	95%CI	Heterogeneity (p-value)	benefit (p-value)
Carcia 2010	0.95	0.70-1.29	0.58	0.75
Freixa 2012	0.96	0.71-1.30	0.52	0.80
Tarantini 2012	0.95	0.70-1.29	0.57	0.74
Limalanathan 2014	0.94	0.69-1.27	0.62	0.68
Hahn 2015	0.90	0.65-1.25	0.65	0.53
Eitel 2015	1.00	0.72-1.38	0.55	1.00
Luz 2015	0.94	0.69-1.27	0.67	0.68
Engstrøm 2017	1.28	0.81-2.00	0.80	0.29

PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5
Synthesis of results	21	Present the main results of the review. If meta-analyses done, include for each, confidence intervals and measures of consistency.	5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	5
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	6
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	9

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

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

Methods: We included randomized trials comparing PPCI in combination with IPC with conventional PPCI in STEMI patients. We systemically searched PubMed, Embase, and the Cochrane Library for relevant articles published before May 1, 2018. The primary endpoint was heart failure. Secondary endpoints were all-cause mortality and major adverse cardiac events (MACE), including cardiac death, heart failure, and myocardial infarction (MI). The Cochrane Reviewer's Handbook 4.2 was used to assess the risk of bias.

Results: Ten studies enrolling 3,137 patients were included. PPCI in combination with IPC failed to reduce heart failure (RR: 0.88, 95% CI: 0.61,1.26, P = 0.47),all-cause mortality (RR: 0.94, 95% CI: 0.69,1.27, P = 0.68),MACE (RR: 1.05, 95% CI: 0.83,1.32, P = 0.69), cardiac death (RR: 1.28, 95% CI: 0.85,1.93, P = 0.24), and MI (RR: 1.08, 95% CI: 0.38,3.21, P = 0.88).

Conclusions: IPC during PPCI does not reduce heart failure, MACE, and all-cause mortality in patients with STEMI compared to traditional PPCI. (CRD42017063959)

Strengths and limitations of this study

1. This meta-analysis included recent relevant studies and provided the latest RCTs on STEMI.
2. To generate a solid conclusion, sensitivity analysis and subgroup analyses were

performed to evaluate the sample size.

3. We included the recent DANAMI-3–iPOST study, which randomized 1,234 patients with STEMI to conventional PPCI or PPCI with IPC, which may change our opinion on treatment of STEMI.

4. A limitation of this meta-analysis is the inclusion of a relatively low number of trials.

5. Bias between studies may exist. However, subgroup analysis was performed to evaluate catheter-directed thrombolysis.

Key words: Ischemic postconditioning therapy (IPC); percutaneous coronary intervention (PCI); all-cause mortality; major adverse cardiac events (MACE); meta-analysis

Abbreviations

IPC	Ischemic postconditioning therapy
PCI	Percutaneous coronary intervention
STEMI	ST-segment elevation myocardial infarction
MACE	Major adverse cardiac events
SPECT	Single-photon emission computed tomography
ce-CMR	Contrast-enhanced cardiac magnetic resonance
RCT	Randomized controlled trial

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, ischemic 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 (IRA) 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 computed tomography (SPECT), echocardiography, and contrast-enhanced cardiac magnetic resonance (ce-CMR)[3-7]. This strategy, known as ischemic postconditioning (IPC), is safe and easy to perform without additional cost[8]. Related meta-analyses also demonstrated that IPC could rescue cardiomyocytes evaluated by the above methods[9-11]. However, whether improvements in these surrogate markers can translate into improved clinical outcomes evaluated by hard endpoints, such as heart failure, or all-cause mortality remains controversial. The recent DANAMI-3–iPOST study, which randomized 1,234 patients with STEMI to conventional PPCI or PPCI with IPC did not provide evidence in favor of PPCI with IPC compared to traditional PPCI[11].

Given the confusing situations of IPC during PPCI, we performed this meta-analysis to evaluate whether IPC has a beneficial effect on hard endpoints, such as heart failure, all-cause mortality, and MACE, compared to traditional PPCI.

Methods

Patients and public involvement

No patients and/or the public were involved in this study.

Search strategy and selection criteria

This meta-analysis is reported in accordance to the Preferred Reporting Items for System Reviews and Meta-Analyses (PRISMA) Statement and was registered at International Prospective Register of Systematic Reviews (CRD42017063959)[12]. We systemically searched PubMed, Embase, and Cochrane Library for relevant articles published before May 1, 2018. We used the terms ischemic postconditioning, postconditioning, percutaneous coronary intervention (PCI), controlled trial, intervention study, and randomized controlled trials (RCTs) to identify randomized controlled trials. MeSH, Emtree, and keyword search terms were used in combination (Supplementary file). The results were limited to trials published in English. We manually searched the reference lists of relevant studies and reviews, editorials, and letters to identify additional articles.

We used Endnote (Thompson ISI ResearchSoft, Philadelphia, PA, USA) to manage relevant articles and remove duplicate articles.

Study criteria, quality assessment, and data extraction

Studies were included in our meta-analysis when these met the following criteria: (1)

the study design was a prospective randomized controlled clinical trial (RCT); (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 one month; and (5) relevant data should be retrievable. When relevant data were missing, 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 myocardial infarction (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 risk of bias.

Relevant data were extracted by two independent investigators (ZW Zhu and JB Huang). Disagreements were resolved by consensus or a third investigator (XQ Hu). 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% confidence interval (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 postconditioning 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. If one study have no events, we did not include this study in the calculation of RR. 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.To determine the impact of baseline characteristics (symptom onset, different IPC protocol,duration of follow-up et. al.) on the observed clinical benefit, subgroup analyses were performed. All analysis was performed using Review Manager Software (Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.).

Outcomes

Search results and bias assessment

Supplementary Figure 1 shows that the combined search strategy identified 273 potential relevant manuscripts, from which 33 studies were finally retrieved for more detailed assessment. Finally, 10 RCTs were included in this meta-analysis, involving

3,137 patients[7, 8, 13-20]. We used the Cochrane Reviewer's Handbook 4.2 to assess risk of bias (Supplementary Fig 2). No high-risk studies existed. Six of them had a low risk of bias.

The main features of the 10 included RCTs and baseline clinical characteristics of the patients are presented in Table 1. In the 10 trials, 1,569 patients (50%) were randomly assigned to postconditioning therapy. The mean age of the trial patients was 61 years, and 78% of these patients were male. The IPC protocol (ischemia/reperfusion×cycles in seconds) varied between studies, being 30″/30″ × 4 in four studies, 60″/60″ × 4 in five studies, and 30″/30″ × 3 in one study. The follow-up in the trials varied from 1 month to 41 months. The time of symptoms onset varied between studies, being 6 hours in 2 studies, 12 hours in 8 studies.

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 2010	59/59	Denmark	61/62	69/74	≤12 h	30″/30″ × 4	44/39	-	3
Garcia 2010	22/21	USA	61/55	86/76	≤12 h	30″/30″ × 4	36/24	-	41
Freixa	39/40	Spain	59/60	84/72	≤12 h	60″/60″ × 4	51/39	-	6

2012									
Tarantini 2012	39/39	Italy	60/60	85/85	≤6 h	60″/60″ × 4	41/44	0/2.6	1
Dong 2013	32/30	China	70/68	63/73	≤12 h	30″/30″ × 3	57/43	-	1
Limalanathan 2014	136/136	Norway	61/60	84/80	≤6 h	60″/60″ × 4	46/51	29/29	4
Hahn 2015	350/350	South Korea	60/60	79/75	≤12 h	60″/60″ × 4	47/45	86/86	12
Eitel 2015	232/232	Germany	62/65	76/71	≤12 h	30″/30″ × 4	42/51	-	6
Luz 2015	43/44	Portugal	57/58	88/82	≤12 h	60″/60″ × 4	47/43	65/71	14
Engstrøm 2017	617/617	Denmark	63/62	80/79	≤12 h	30″/30″ × 4	43/40	93/93	38

IPC: Ischemic postconditioning group; C; control group; LAD: left descending anterior branch; DES: drug-eluted stent;

Primary endpoint: heart failure

When we pooled the data, the RR for heart failure was 0.88 (95% CI: 0.61–1.26, P= 0.47) in the random-effects model (Fig 1). No evident statistical heterogeneity among studies was observed (I^2 = 0, P = 0.51). IPC during PPCI did not reduce heart failure compared to traditional PPCI.

Second endpoints: all-cause mortality and MACE

Our pooled data showed that IPC does not reduce all-cause mortality compared to traditional PPCI (RR: 0.94, 95%CI: 0.69,1.27, P=0.68, Fig 2). No evident statistical heterogeneity among studies was observed (I^2=0, P =0.63). Furthermore, IPC does not reduce cardiac death (RR: 1.28, 95% CI: 0.85,1.93, P = 0.24), MI (RR: 1.08, 95% CI: 0.38,3.21, P = 0.88) and heart failure (RR: 0.85, 95% CI: 0.59,1.23, P = 0.40). When all these events (MACE) were considered, the net benefit did not favor IPC during PPCI (RR: 1.05, 95% CI: 0.83,1.32, P = 0.69, Fig 3).

Sensitivity analysis and potential sources of heterogeneity

Sensitivity analysis was performed by omitting each study in turn to assess the stability and consistency of the results. Each excluded study did not influence the pooled RRs of the overall effects of heart failure, MI, cardiac death, and all-cause mortality (Supplementary Table 1).

There were no heterogeneities with regards to the observed effects on all-cause mortality (I^2=0, p=0.63) and cardiac death (I^2=0, p=0.91) between studies. 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 we excluded this study, no obvious heterogeneity was observed (I^2 = 0%, P = 0.40). The conclusions were still consistent with previous analysis. Subgroup analysis did not find any baseline risk factor, such as symptom onset, duration of follow-up, and antiplatelet therapies as a modifier of the relationship between IPC and clinical endpoints (Table 2).

Sensitivity and subgroup analysis did not identify any patient- or study-level covariate as a significant source of heterogeneity, except for this subgroup analysis.

Table 2: Subgroup analysis.

	Cardiac death	Heart failure	MI	All-cause mortality
Symptom onset				
≤6 h	5.00 (0.25,101)	1.02 (0.09,11.5)	0.22 (0.05,1.01)	2.00 (0.51,7.86)
≤12 h	1.25 (0.83,1.89)	0.89 (0.61,1.29)	1.26 (0.79,2.00)	0.90 (0.66,1.23)
IPC Protocol				
30″/30″ × 4	1.21 (0.73,1.99)	0.76 (0.45,1.29)	1.19 (0.74,1.91)	0.80 (0.56,1.14)
60″/60″ × 4	1.44 (0.70,2.94)	0.98 (0.48,2.04)	0.84 (0.05,14.2)	1.38 (0.76,2.52)
Duration of follow-up				
≤ 12 m	1.49 (0.74,2.99)	0.81 (0.44,1.47)	1.20 (0.16,8.81)	1.16 (0.73,1.87)
>12 m	1.18 (0.71,1.96)	0.94 (0.58,1.50)	1.14 (0.70,1.85)	0.88 (0.45,1.71)
Analysis model				
Fixed-effect model	1.30 (0.87,1.96)	0.89 (0.62, 1.26)	1.05 (0.69, 1.60)	0.96 (0.71,1.30)
Random effects	1..28 (0.85,1.93)	0.88 (0.61,1.26)	1.08 (0.38,3.12)	0.94 (0.69,1.27)
Antiplatelet or anticoagulation therapies				
Clopidogrel	1..28 (0.85,1.93)	0.98 (0.66,1.45)	1.08 (0.38,3.12)	0.97 (0.69,1.35)
GPIIb/IIIa inhibitors	1.23 (0.81,1.88)	0.84 (0.56,1.27)	1.08 (0.38,3.12)	0.93 (0.67,1.30)
Bivalirudin	1.44 (0.70,2.94)	0.98 (0.47,2.03)	0.84 (0.77,14.24)	1.48 (0.81,2.69)

MI: myocardial infarction; IPC: Ischemic postconditioning group

Discussion

The current meta-analysis of 10 RCTs, including 3,137 patients with STEMI undergoing PPCI, did not show the benefits of IPC in reducing heart failure, all-cause mortality, and MACE compared to traditional PPCI. Subgroup analysis did not show improved clinical outcomes either.

IPC was first introduced by Zhao et al. in 2003[21]. Subsequent clinical trials and meta-analyses found the 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 (LVEF)[3-5]. However, the opposite results have also been reported[8, 16-19]. The DANAMI-3-iPOST trial, which is the largest study to date, did not show that IPC could reduce infarct size[8]. Furthermore, whether the surrogate endpoints, such as infarct size, myocardial salvage, and resolution of ST-segment elevation, can translate into hard endpoints, such as heart failure, all-cause mortality, or MACE, remains a point of debate. Unlike these surrogate endpoints, heart failure, all-cause mortality, and MACE are what clinics and patients really consider.

Unlike previous meta-analyses that were mainly focused on cardiac biomarkers, cardiac imaging, and cardiac function, clinical outcomes should be given more importance. However, our meta-analysis did not show that IPC could improve clinical outcomes, and several factors may affect its effectiveness. A meta-analysis of 19 RCTs concluded that cardioprotection evaluated by cardiac enzymes leakage, infarct size, and left ventricular function is more prone in patients with LAD artery involvement because of a greater

myocardial area being at risk.[9] Zhou et al. performed a meta-analysis of 10 RCTs and found that the effects of cardiac protection are 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 effectiveness of IPC. IPC may cause myocardial ischemia 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, our subgroup analyses did not find the effectiveness of IPC.any differences.

Time of symptoms onset, which is an independent predictor of MACE in patients with STEMI undergoing PPCI, may have influenced the results of these trials. Subgroup analysis did not detect the effectiveness of IPC either.

The result of subgroup analyses did not support IPC. The key reason is that IPC might have no effect on cardioprotection. Furthermore, the sample size of the studies may have been too small to detect minor beneficial effects. Several confounding factors, such as patient's baseline characteristics, coexisting diseases, medications, and IPC strategies used, may influence 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 the minor benefits of using additional therapy.

Limitations

This study has a number of 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 time, were inevitable. However, we performed subgroup analysis and did not find that these heterogeneities affected our conclusion. In addition, we based our conclusion on the random effects model, which can account for a certain degree of heterogeneity. Second, although we performed an extensive search strategy, some studies might not be included in this meta-analysis. However, this meta-analysis is the largest population-based analysis of IPC. Third, 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 to traditional PPCI.

Additional Information

The authors have no conflicts of interest to declare.

No patients and/or the public were involved in this study.

We thank the staff and patient advisers who participated in these studies.

Author contribution statement: Xinqun Hu and Zhenhua Xing designed the study and provided methodological expertise in systematic reviews and searching strategies. Jiabing

Huang and Xiaofan Peng searched the databases and constructed the tables. Zhenhua Xing drafted the manuscript. All authors have read, provided critical feedback, and approved the final manuscript.

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Figure legends

Fig 1: Ischemic postconditioning versus traditional PPCI on heart failure in STEMI patients undergoing PPCI

Fig 2: Ischemic postconditioning versus traditional PPCI on all-cause mortality in STEMI patients undergoing PPCI.

Fig 3: Ischemic postconditioning versus traditional PPCI on MACE in STEMI patients undergoing PPCI.

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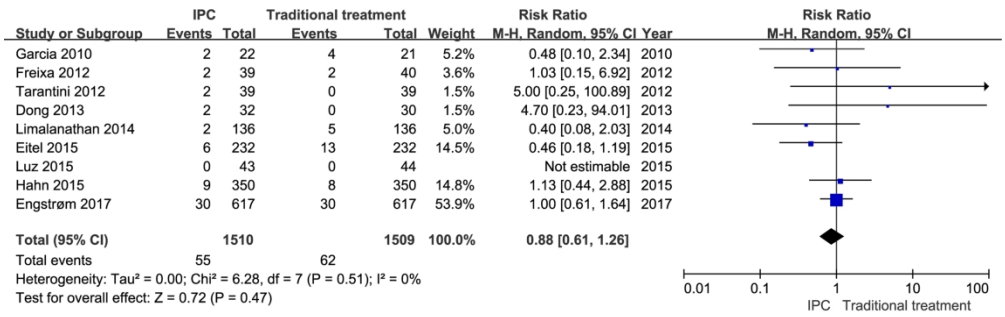

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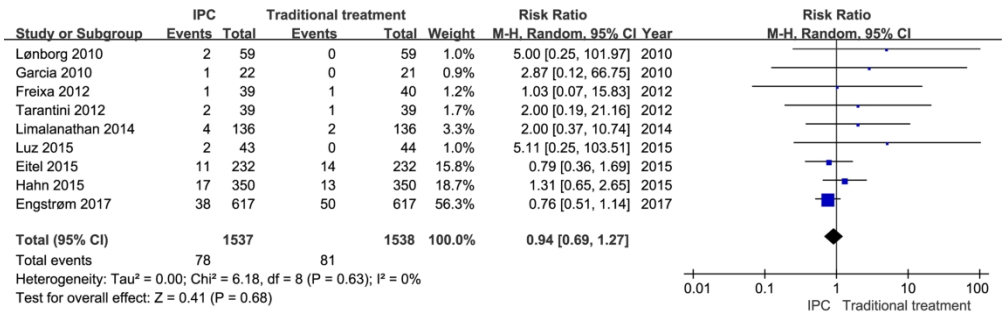

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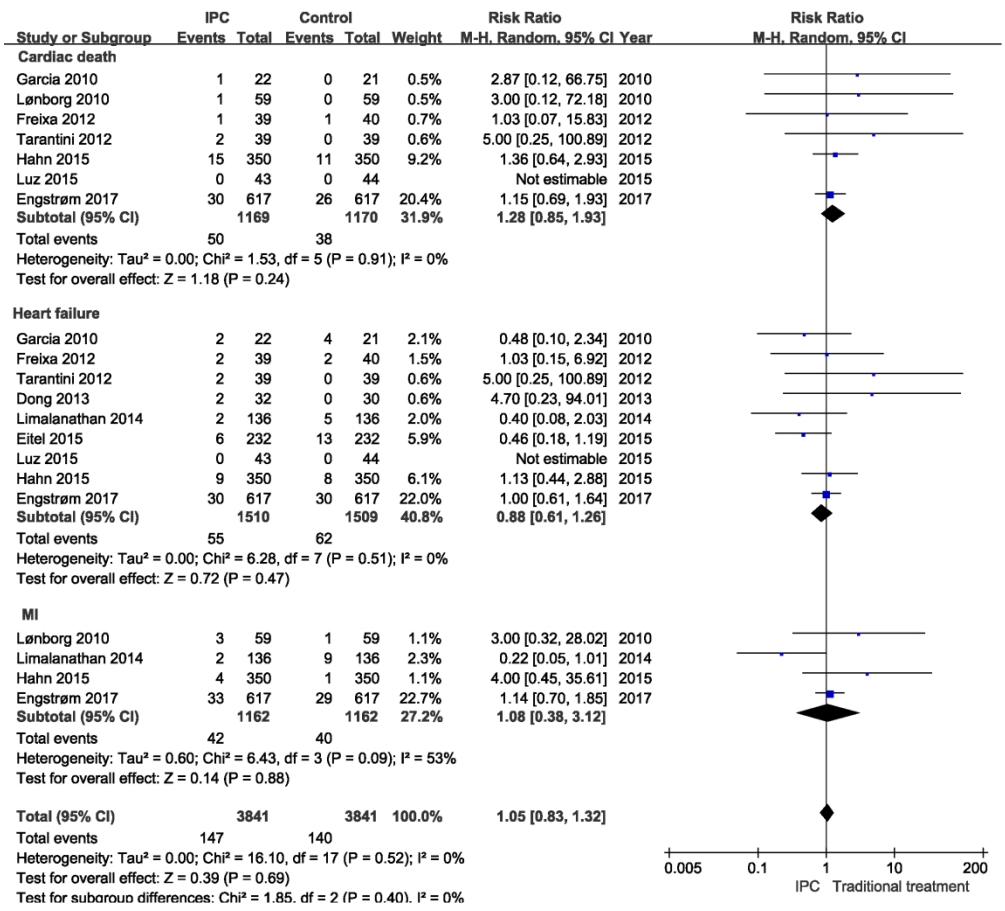

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Effects of ischemic postconditioning on outcomes of patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: a meta-analysis

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#2 Search conditioning[Title/Abstract] 55132

#3 Search percutaneous coronary intervention[MeSH Terms] 46594

#4 Search PCI[Title/Abstract] 21330

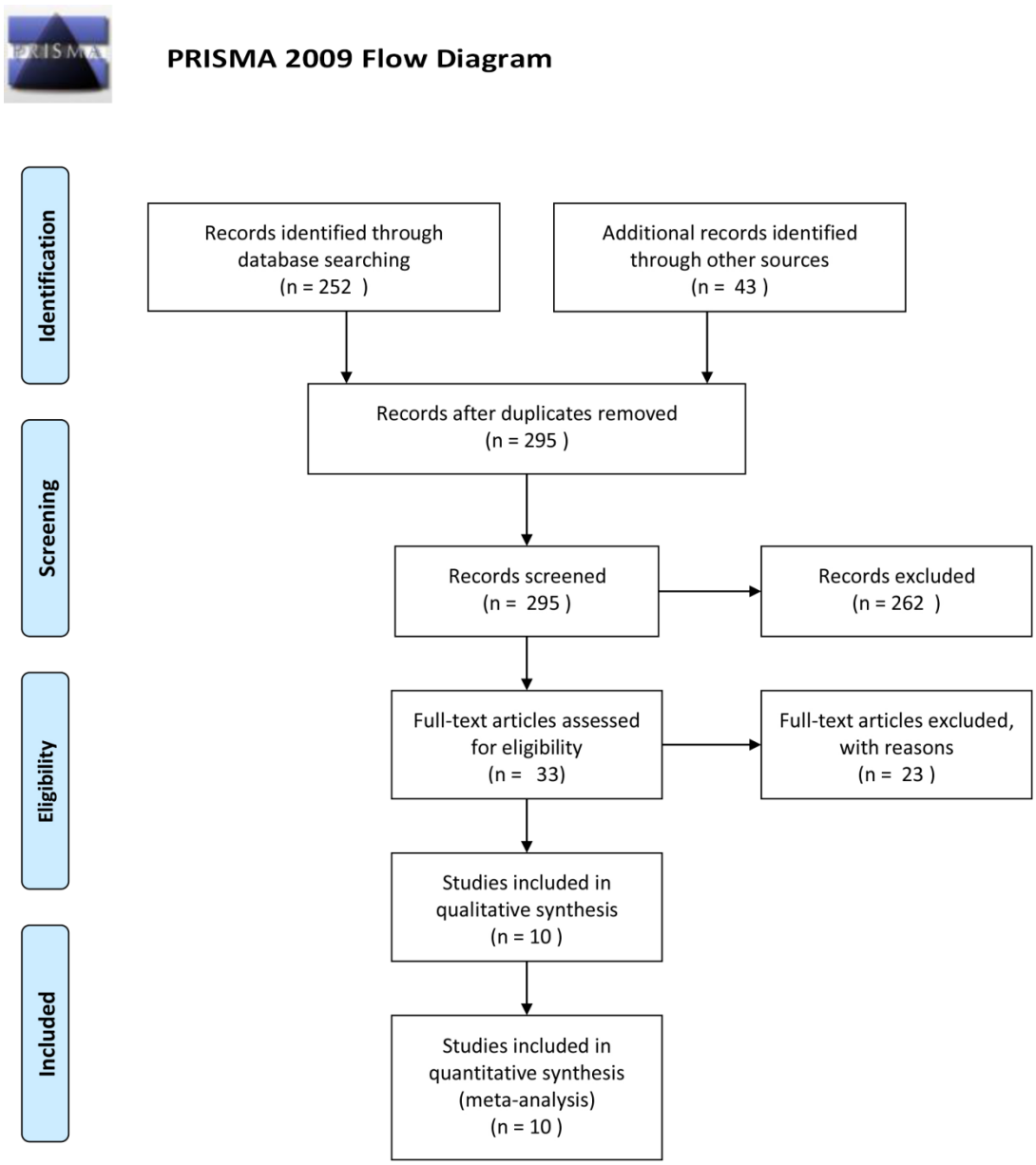
#5 Search (PCI[Title/Abstract]) OR percutaneous coronary intervention[MeSH Terms] 55884

#6 Search (conditioning[Title/Abstract]) OR ischemic postconditioning[MeSH Terms] 55763

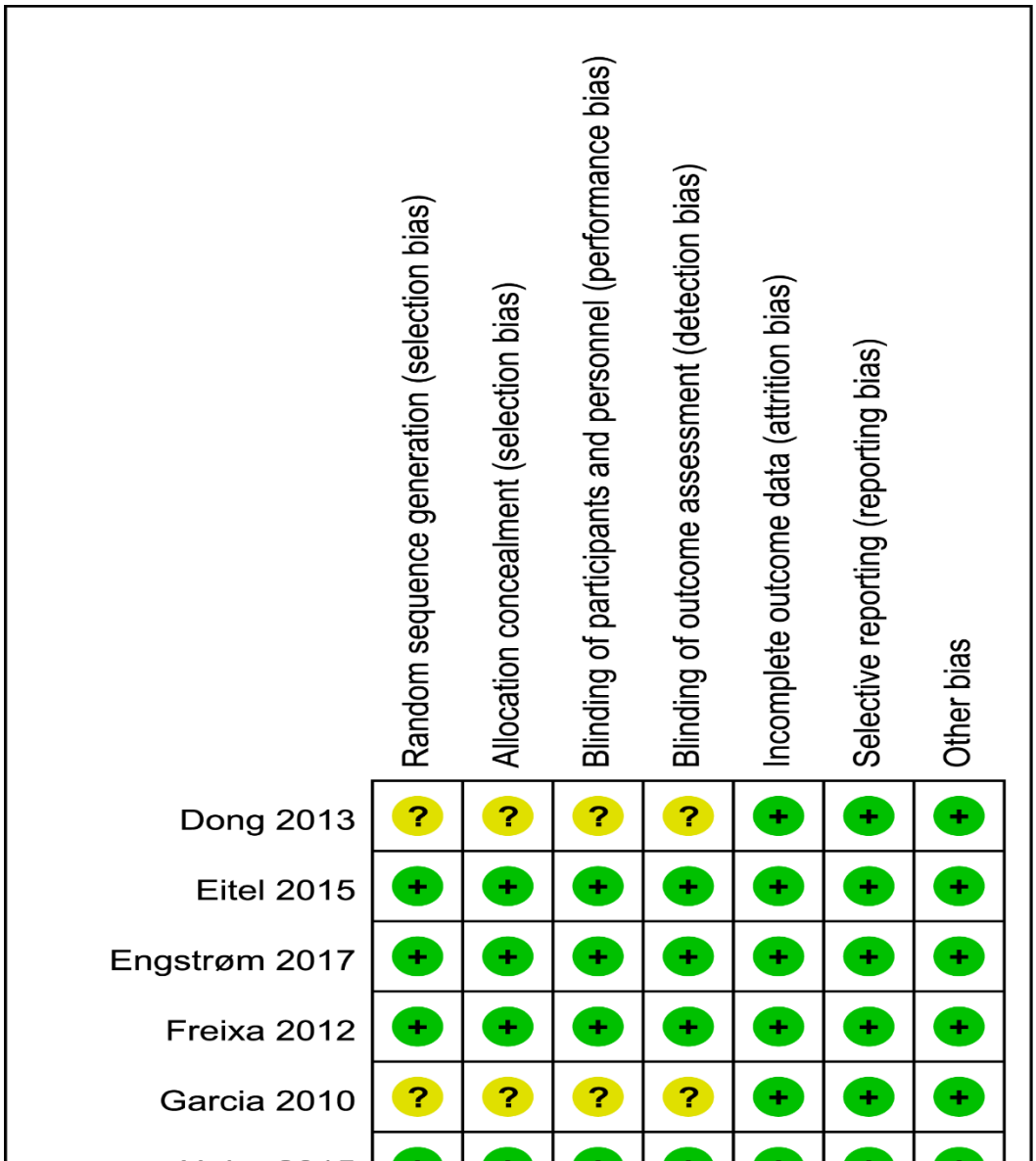
#7 Search (((conditioning[Title/Abstract]) OR ischemic postconditioning[MeSH Terms])) AND ((PCI[Title/Abstract]) OR percutaneous coronary intervention[MeSH Terms]) 153

Supplementary table 1: Sensitivity analysis of randomized primary prevention trials

Excluded study	Heart failure	MI	Cardiac death	All-cause mortality
Lønborg 2010	-	0.90(0.25,3.24)	1.49(0.74,2.99)	0.90(0.69,1.27)
Garcia 2010	0.91(0.62,1.31)	-	1.26(0.84,1.91)	0.95(0.70,1.29)
Freixa 2012	0.86(0.58,1.28)	-	1.29(0.85,1.95)	0.96(0.70,1.30)
Tarantini 2012	0.85(0.59,1.22)	-	1.25(0.83,1.89)	0.95(0.70,1.29)
Limalanathan 2014	0.91(0.63,1.32)	1.26(0.79,2.00)	-	0.94(0.69,1.27)
Hahn 2015	-	0.84(0.25,2.84)	1.23(0.77,2.03)	0.90(0.65,1.25)
Eitel 2015	0.98(0.66,1.45)	-	-	1.00(0.72,1.38)
Luz 2015	0.88(0.61,1.26)	-	1.28(0.85,1.93)	0.94(0.69,1.27)
Engstrøm 2017	0.75(0.44,1.28)	1.20(0.78,1.32)	1.54(0.78,3.04)	1.28(0.81,2.00)
Dong 2013	0.85(0.59,1.23)	-	-	-



Supplementary Figure 1: Flow diagram of literature searched for meta-analysis.



Supplementary Fig2. Bias assessment using Cochrane Reviewer's Handbook 4.2

PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5
Synthesis of results	21	Present the main results of the review. If meta-analyses done, include for each, confidence intervals and measures of consistency.	5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	5
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	6
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	9

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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

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Keywords:	Ischemic postconditioning therapy, percutaneous coronary intervention, all-cause mortality, major adverse cardiac events, meta-analysis

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

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

Methods: Randomized trials comparing conventional PPCI to PPCI combined with IPC in STEMI patients were included. PubMed, Embase, and the Cochrane Library were systematically searched for relevant articles published prior to May 1, 2018. The primary endpoint was heart failure. Secondary endpoints were all-cause mortality and major adverse cardiac events (MACE), including cardiac death, heart failure, and myocardial infarction (MI). The Cochrane Reviewer's Handbook 4.2 was used to assess the risk of bias.

Results: Ten studies that had enrolled 3,137patients were included. PPCI combined with IPC failed to reduce heart failure (RR: 0.88, 95% CI: 0.61,1.26, P = 0.47), all-cause mortality (RR: 0.94, 95% CI: 0.69,1.27, P = 0.68), MACE (RR: 1.05, 95% CI: 0.83,1.32, P = 0.69), cardiac death (RR: 1.28, 95% CI: 0.85,1.93, P = 0.24), and MI (RR: 1.08, 95% CI: 0.38,3.12, P = 0.88).

Conclusions: IPC combined with PPCI does not reduce heart failure, MACE, and all-cause mortality compared to traditional PPCI in patients with STEMI. (CRD42017063959)

Strengths and limitations of this study

1. Unlike previous studies, we focused on clinical outcomes such as heart failure, or all-cause mortality.

2. The recent DANAMI-3–iPOST study, which randomized 1,234 patients with STEMI to conventional PPCI or PPCI with IPC, was included, which may alter the conclusion regarding STEMI treatment.

3. In order to give a solid conclusion, sensitivity and subgroup analyses were performed.

4. A limitation of this meta-analysis is the inclusion of a relatively low number of patients.

Key words: Ischemic postconditioning therapy (IPC); percutaneous coronary intervention (PCI); all-cause mortality; major adverse cardiac events (MACE); meta-analysis

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, ischemic 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 (IRA), 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 computed tomography (SPECT), echocardiography, and contrast-enhanced cardiac magnetic resonance (ce-CMR)[3-7]. This strategy, known as ischemic 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 randomized 1,234 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 to 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 to 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 System Reviews and Meta-Analyses (PRISMA) Statement and was registered at International Prospective Register of Systematic Reviews (CRD42017063959)[12]. PubMed, Embase, and Cochrane Library were systematically searched for relevant articles published before May 1, 2018. The terms “ischemic postconditioning”, “postconditioning”, “percutaneous coronary intervention (PCI)”, “controlled trial”, “intervention study”, and “randomized controlled trials (RCTs)” were used to identify randomized controlled trials. MeSH, Emtree, and keyword search terms were used in combination (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 (Thompson 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 randomized controlled clinical trial (RCT); (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 one 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 myocardial infarction (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 risk of bias.

Relevant data were extracted by two independent investigators (ZW Zhu and JB Huang). Disagreements were resolved by consensus or a third investigator (XQ Hu). 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% confidence interval (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, antiplatelet therapies. Data analysis was performed on an intention-to-treat basis. All analysis was performed using Review Manager Software (Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.).

Outcomes

Search results and bias assessment

Supplementary Figure 1 shows that the combined search strategy identified 273 potential relevant manuscripts, from which 33 studies were retrieved for more detailed assessment. 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 risk of bias (Supplementary Fig 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, 1,569 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 protocol (cycles × ischemia/reperfusion in seconds) varied between studies and were as follows: 30″/30″ × 4 in four studies, 60″/60″ × 4 in five studies, and 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 2 studies to 12 hours in 8 studies.

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 2010	59/59	Denmark	61/62	69/74	≤12	30″/30″ × 4	44/39	-	3
Garcia 2010	22/21	USA	61/55	86/76	≤12	30″/30″ × 4	36/24	-	41
Freixa 2012	39/40	Spain	59/60	84/72	≤12	60″/60″ × 4	51/39	-	6
Tarantin	39/39	Italy	60/60	85/85	≤6	60″/60″ × 4	41/44	0/2.6	1

i 2012									
Dong 2013	32/30	China	70/68	63/73	≤12	30″/30″ × 3	57/43	-	1
Limalanathan 2014	136/136	Norway	61/60	84/80	≤6	60″/60″ × 4	46/51	29/29	4
Hahn 2015	350/350	South Korea	60/60	79/75	≤12	60″/60″ × 4	47/45	86/86	12
Eitel 2015	232/232	Germany	62/65	76/71	≤12	30″/30″ × 4	42/51	-	6
Luz 2015	43/44	Portugal	57/58	88/82	≤12	60″/60″ × 4	47/43	65/71	14
Engstrøm 2017	617/617	Denmark	63/62	80/79	≤12	30″/30″ × 4	43/40	93/93	38

IPC: Ischemic postconditioning group; C; control group(PPCI only); LAD: left descending anterior branch; DES: drug-eluted stent

Primary endpoint: heart failure

When the data was pooled, the RR for heart failure was 0.88 (95% CI: 0.61,1.26, P=

0.47) in the random-effects model (Fig 1). No evident statistical heterogeneity among studies was observed (I^2 = 0, P = 0.51). IPC during PPCI did not reduce heart failure compared to traditional PPCI.

Secondary endpoints: all-cause mortality and MACE

The pooled data showed that IPC did not reduce all-cause mortality compared to traditional PPCI (RR: 0.94, 95% CI: 0.69,1.27, P = 0.68, Fig 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: 0.85,1.93, P = 0.24), MI (RR: 1.08, 95% CI: 0.38,3.12, P = 0.88) and heart failure (RR: 0.85, 95% CI: 0.59,1.23, P = 0.40). When all events (MACE) were considered, IPC during PPCI provided no net benefit of IPC during PPCI (RR: 1.05, 95% CI: 0.83,1.32, P = 0.69, Fig 3).

Sensitivity analysis and potential sources of heterogeneity

Sensitivity analysis 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 (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). Sensitivity and subgroup analysis did not identify any patient- or study-level covariate as a significant source of heterogeneity, except for this subgroup analysis.

Table 2: Subgroup analysis.

	Cardiac death	Heart failure	MI	Al-cause mortality
Symptom onset				
≤6 hous	5.00 (0.25,101)	1.02 (0.09,11.5)	0.22 (0.05,1.01)	2.00 (0.51,7.86)
≤12 hours	1.25 (0.83,1.89)	0.89 (0.61,1.29)	1.26 (0.79,2.00)	0.90 (0.66,1.23)
Protocol				
30″/30″ × 4	1.21 (0.73,1.99)	0.76 (0.45,1.29)	1.19 (0.74,1.91)	0.80 (0.56,1.14)
60″/60″ × 4	1.44 (0.70,2.94)	0.98 (0.48,2.04)	0.84 (0.05,14.2)	1.38 (0.76,2.52)
Follow,up				
≤ 12 months	1.49 (0.74,2.99)	0.81 (0.44,1.47)	1.20 (0.16,8.81)	1.16 (0.73,1.87)
>12 months	1.18 (0.71,1.96)	0.94 (0.58,1.50)	1.14 (0.70,1.85)	0.88 (0.45,1.71)

Analysis model				
Fixed-effect model	1.30 (0.87,1.96)	0.89 (0.62, 1.26)	1.05 (0.69, 1.60)	0.96 (0.71,1.30)
Random effects	1.28 (0.85,1.93)	0.88 (0.61,1.26)	1.08 (0.38,3.12)	0.94 (0.69,1.27)
Antiplatelet or anticoagulation therapies				
Clopidogrel	1.28 (0.85,1.93)	0.98 (0.66,1.45)	1.08 (0.38,3.12)	0.97 (0.69,1.35)
GPIIb/IIIa inhibitors	1.23 (0.81,1.88)	0.84 (0.56,1.27)	1.08 (0.38,3.12)	0.93 (0.67,1.30)
Bivalirudin	1.44 (0.70,2.94)	0.98 (0.47,2.03)	0.84 (0.77,14.24)	1.48 (0.81,2.69)

MI: myocardial infarction; GPIIb/IIIa:glycoprotein IIb/IIIa

Discussion

The current meta-analysis of 10 RCTs, including 3,137 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

(LVEF)[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 ischemia 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 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 a number of 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 envents, such as heart failure, the simple 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 suggest that the use of IPC in STEMI patients undergoing PPCI does not reduce the incidence of heart failure, MACE, and all-cause mortality compared to traditional PPCI.

Additional Information

The authors have no conflicts of interest to declare.

Patients consent: No patients, patient advises, and/or the public were involved in this study.

Author contribution statement: Xinqun Hu and Zhenhua Xing designed the study and provided methodological expertise in systematic reviews and searching strategies. Jiabing Huang and Xiaofan Peng searched the databases and constructed the tables. Zhenhua Xing drafted the manuscript. All authors have read, provided critical feedback, and approved the final manuscript.

Funding: None

Competing interests: None

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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Figure legends

Fig 1: Effect of PPCI with IPC versus PPCI only on heart failure in STEMI patients undergoing PPCI

PPCI:primary percutaneous coronary intervention;IPC: Ischemic postconditioning group;STEMI:ST-segment elevation myocardial infarction

Fig 2: Effect of PPCI with IPC versus PPCI only on all-cause mortality in STEMI patients undergoing PPCI.

PPCI:primary percutaneous coronary intervention;IPC: Ischemic postconditioning group;STEMI:ST-segment elevation myocardial infarction

Fig 3: Effect of PPCI with IPC versus PPCI only on MACE in STEMI patients undergoing PPCI.

PPCI:primary percutaneous coronary intervention;IPC: Ischemic postconditioning group;STEMI:ST-segment elevation myocardial infarction; MACE:major adverse cardiac events

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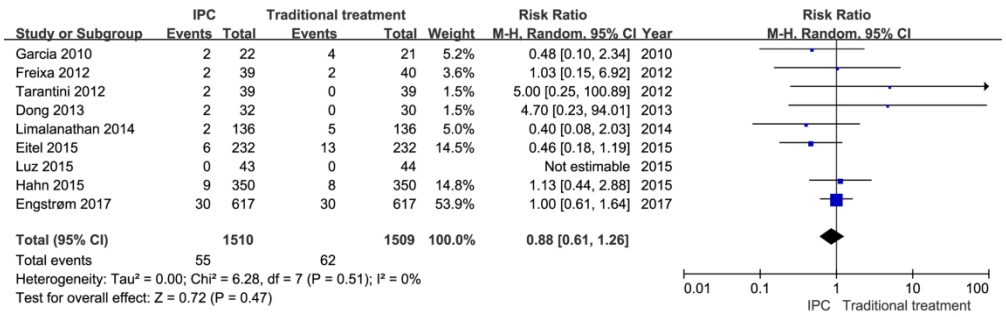

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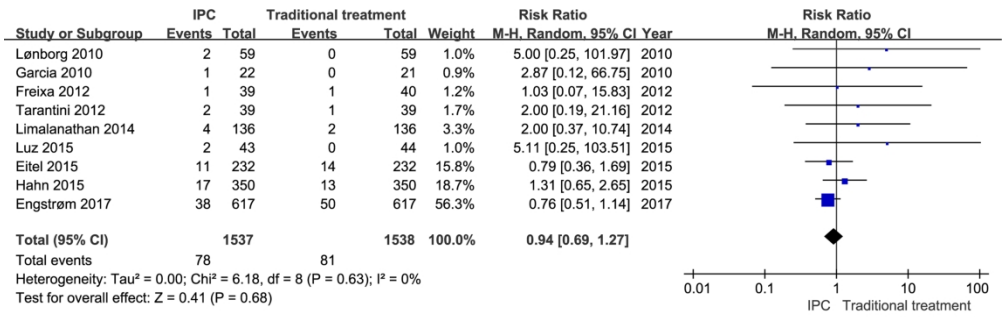

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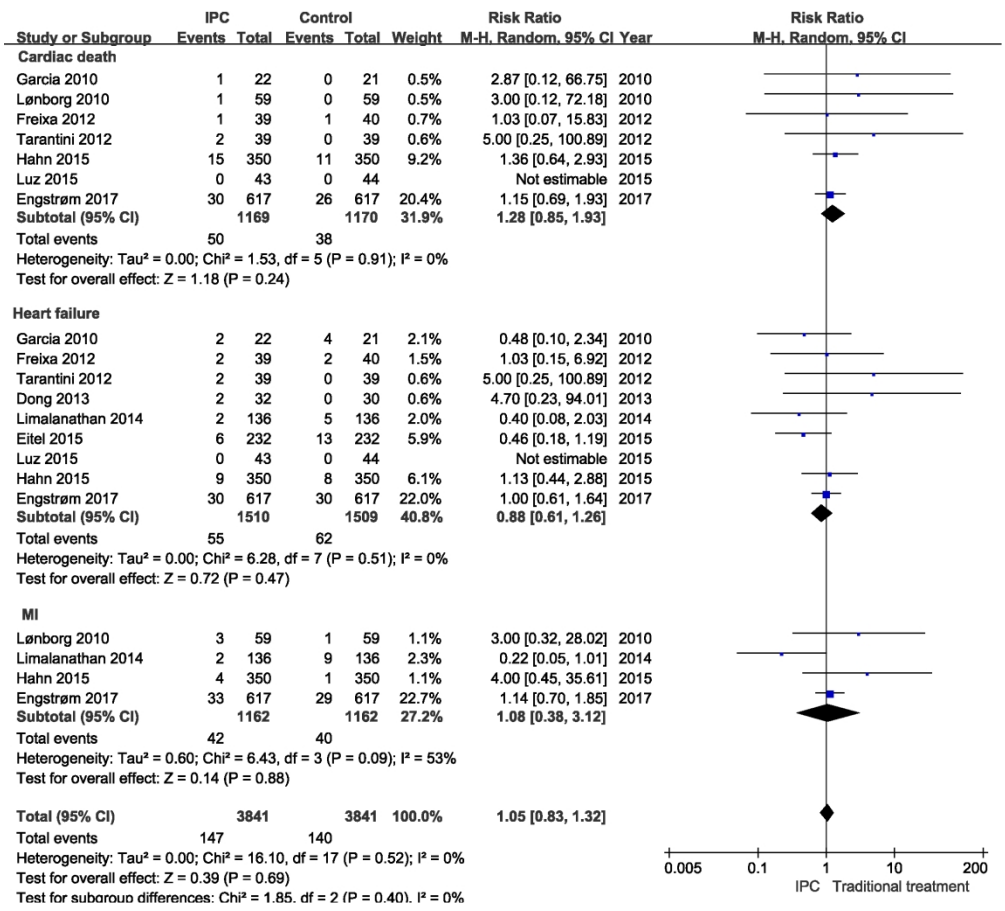

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Effects of ischemic postconditioning on outcomes of patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: a meta-analysis

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Search Query Items found

#1 Search ischemic postconditioning[MeSH Terms] 849

#2 Search conditioning[Title/Abstract] 55132

#3 Search percutaneous coronary intervention[MeSH Terms] 46594

#4 Search PCI[Title/Abstract] 21330

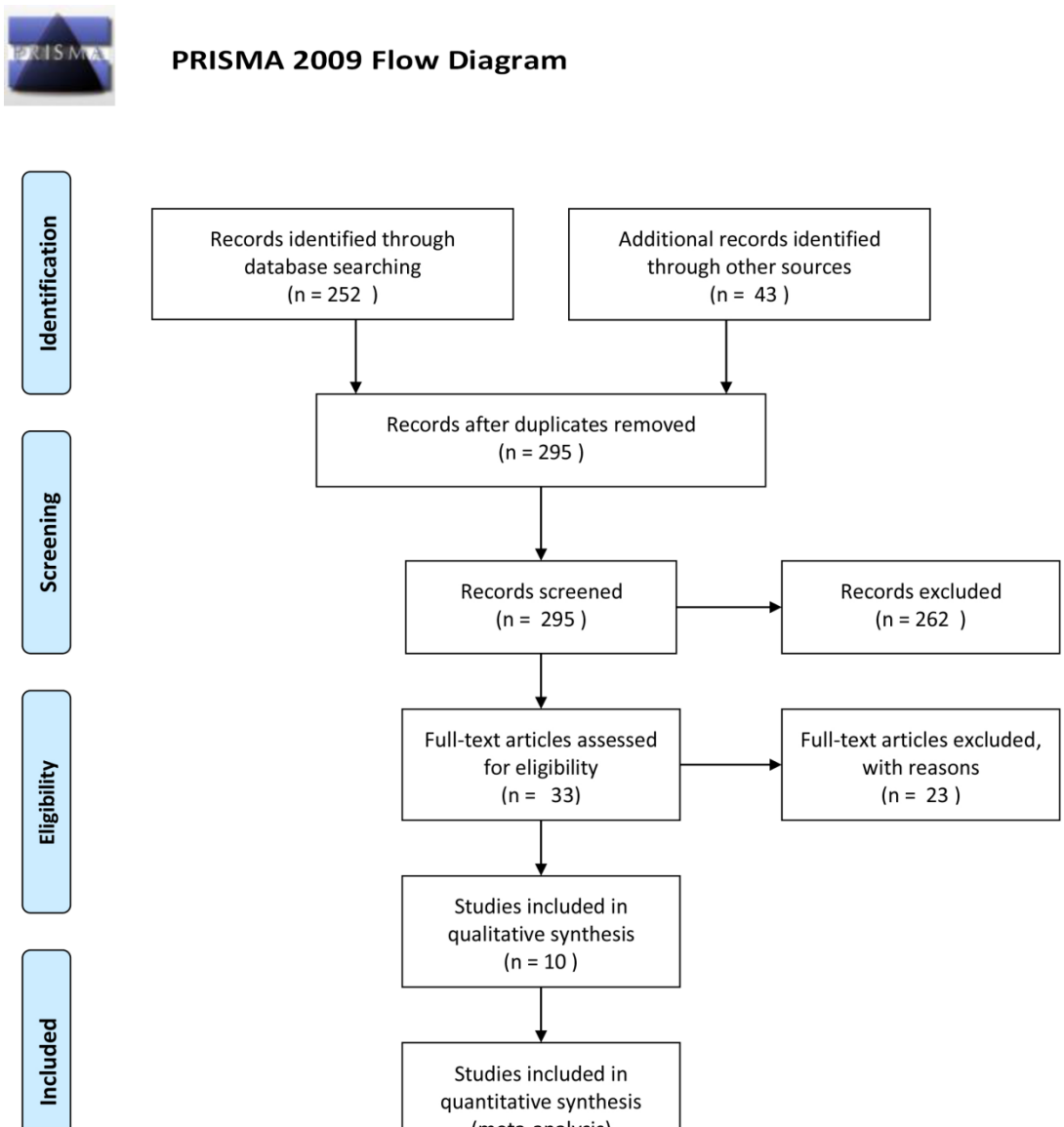
#5 Search (PCI[Title/Abstract]) OR percutaneous coronary intervention[MeSH Terms] 55884

#6 Search (conditioning[Title/Abstract]) OR ischemic postconditioning[MeSH Terms] 55763

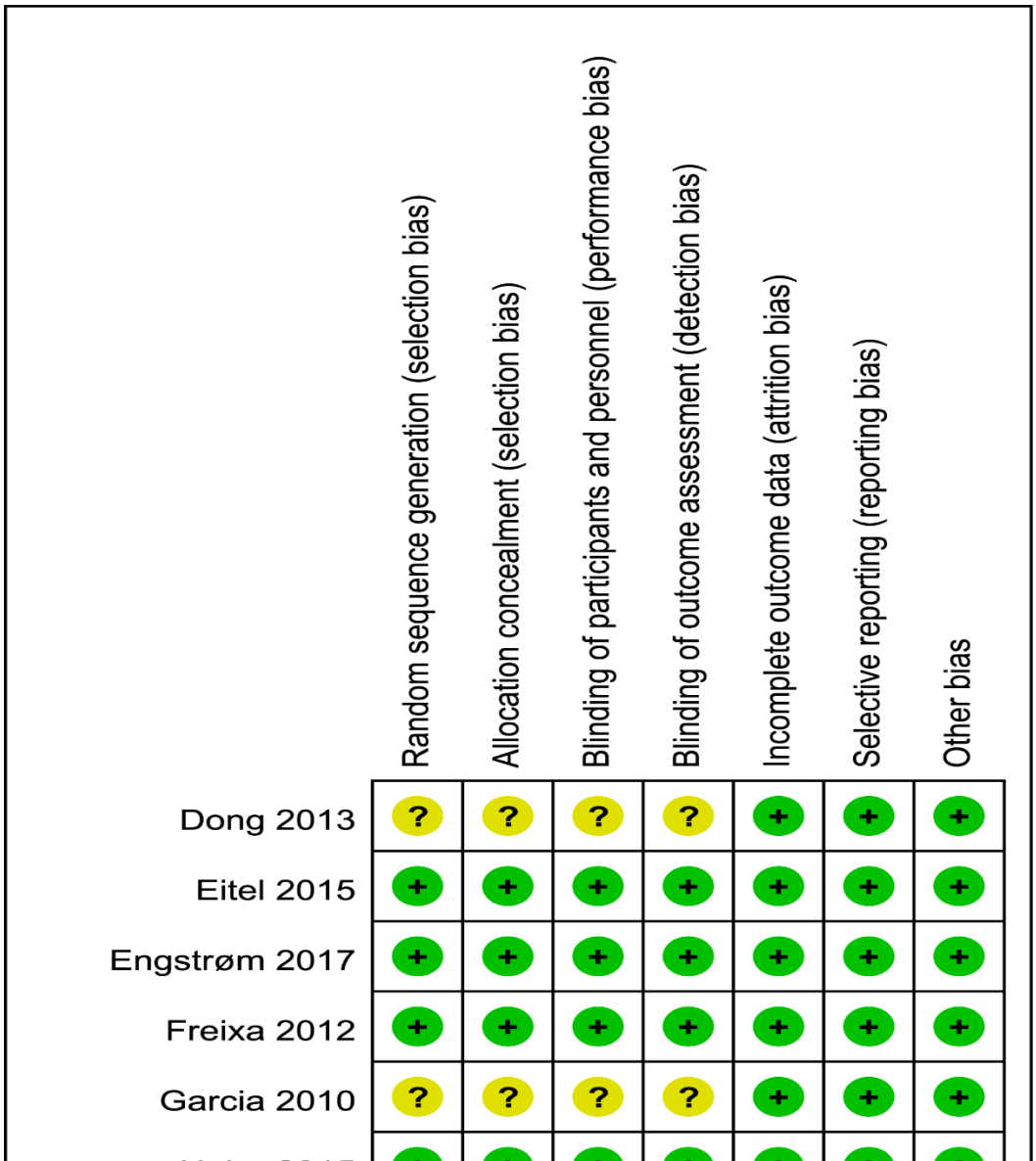
#7 Search (((conditioning[Title/Abstract]) OR ischemic postconditioning[MeSH Terms])) AND ((PCI[Title/Abstract]) OR percutaneous coronary intervention[MeSH Terms]) 153

Supplementary table 1: Sensitivity analysis of randomized primary prevention trials

Excluded study	Heart failure	MI	Cardiac death	All-cause mortality
Lønborg 2010	-	0.90(0.25,3.24)	1.49(0.74,2.99)	0.90(0.69,1.27)
Garcia 2010	0.91(0.62,1.31)	-	1.26(0.84,1.91)	0.95(0.70,1.29)
Freixa 2012	0.86(0.58,1.28)	-	1.29(0.85,1.95)	0.96(0.70,1.30)
Tarantini 2012	0.85(0.59,1.22)	-	1.25(0.83,1.89)	0.95(0.70,1.29)
Limalanathan 2014	0.91(0.63,1.32)	1.26(0.79,2.00)	-	0.94(0.69,1.27)
Hahn 2015	-	0.84(0.25,2.84)	1.23(0.77,2.03)	0.90(0.65,1.25)
Eitel 2015	0.98(0.66,1.45)	-	-	1.00(0.72,1.38)
Luz 2015	0.88(0.61,1.26)	-	1.28(0.85,1.93)	0.94(0.69,1.27)
Engstrøm 2017	0.75(0.44,1.28)	1.20(0.78,1.32)	1.54(0.78,3.04)	1.28(0.81,2.00)
Dong 2013	0.85(0.59,1.23)	-	-	-



Supplementary Figure 1: Flow diagram of literature searched for meta-analysis.



Supplementary Fig2. Bias assessment using Cochrane Reviewer's Handbook 4.2

PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5
Synthesis of results	21	Present the main results of the review. If meta-analyses done, include for each, confidence intervals and measures of consistency.	5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	5
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	6
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	9

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Ischemic postconditioning therapy, percutaneous coronary intervention, all-cause mortality, major adverse cardiac events, meta-analysis

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

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Objective: The aim of this meta-analysis was to evaluate the effects of ischemic postconditioning therapy (IPC) 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: Randomized 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 myocardial infarction (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 3,137patients were included. PPCI combined with IPC failed to reduce heart failure (RR: 0.88, 95% CI: 0.61,1.26, P = 0.47), all-cause mortality (RR: 0.94, 95% CI: 0.69,1.27, P = 0.68), MACE (RR: 1.05, 95% CI: 0.83,1.32, P = 0.69), cardiac death (RR: 1.28, 95% CI: 0.85,1.93, P = 0.24), and MI (RR: 1.08, 95% CI: 0.38,3.12, P = 0.88).

Conclusions: IPC combined with PPCI does not reduce heart failure, MACE, and all-

cause mortality compared to traditional PPCI in patients with STEMI. (CRD42017063959)

Key words: Ischemic postconditioning therapy (IPC); percutaneous coronary intervention (PCI); all-cause mortality; major adverse cardiac events (MACE); meta-analysis

Strengths and limitations of this study

1. Unlike previous studies, we focused on clinical outcomes such as heart failure, or all-cause mortality.
2. The recent DANAMI-3–iPOST study, which randomized 1,234 patients with STEMI to conventional PPCI or PPCI with IPC, was included, which may alter the conclusion regarding STEMI treatment.
3. In order to give a solid conclusion, sensitivity and subgroup analyses were performed.
4. 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, ischemic 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 (IRA), 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 computed tomography (SPECT), echocardiography, and contrast-enhanced cardiac magnetic resonance (ce-CMR)[3-7]. This strategy, known as ischemic 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 randomized 1,234 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 to 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 to 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 System Reviews and Meta-Analyses (PRISMA) Statement and was registered at International Prospective Register of Systematic Reviews (CRD42017063959)[12]. PubMed, Embase, and Cochrane Library were systematically searched for relevant articles published before May 1, 2018. The terms “ischemic postconditioning”, “postconditioning”, “percutaneous coronary intervention (PCI)”, “controlled trial”, “intervention study”, and “randomized controlled trials (RCTs)” were used to identify randomized controlled trials. MeSH, Emtree, and keyword search terms were used in combination (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 (Thompson 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 randomized controlled clinical trial (RCT); (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 one 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 myocardial infarction (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 risk of bias.

Relevant data were extracted by two independent investigators (XF Peng and JB Huang). Disagreements were resolved by consensus or a third investigator (XQ Hu). 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% confidence interval (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, antiplatelet therapies. Data analysis was performed on an intention-to-treat basis. All analysis was performed using Review Manager Software (Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.).

Outcomes

Search results and bias assessment

Supplementary Figure 1 shows that the combined search strategy identified 273 potential relevant manuscripts, from which 33 studies were retrieved for more detailed assessment. 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 risk of bias

(Supplementary Fig 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, 1,569 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 protocol (cycles*ischemia/reperfusion in seconds) varied between studies and were as follows: 30″/30″ × 4 in four studies, 60″/60″ × 4 in five studies, and 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 2 studies to 12 hours in 8 studies.

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 2010	59/59	Denmark	61/62	69/74	≤12	30″/30″ × 4	44/39	-	3
Garcia 12010	22/21	USA	61/55	86/76	≤12	30″/30″ × 4	36/24	-	41
Freixa 2012	39/40	Spain	59/60	84/72	≤12	60″/60″ × 4	51/39	-	6
Tarantin	39/39	Italy	60/60	85/85	≤6	60″/60″ × 4	41/44	0/2.6	1

i 2012									
Dong 2013	32/30	China	70/68	63/73	≤12	30″/30″ × 3	57/43	-	1
Limalanathan 2014	136/136	Norway	61/60	84/80	≤6	60″/60″ × 4	46/51	29/29	4
Hahn 2015	350/350	South Korea	60/60	79/75	≤12	60″/60″ × 4	47/45	86/86	12
Eitel 2015	232/232	Germany	62/65	76/71	≤12	30″/30″ × 4	42/51	-	6
Luz 2015	43/44	Portugal	57/58	88/82	≤12	60″/60″ × 4	47/43	65/71	14
Engstrøm 2017	617/617	Denmark	63/62	80/79	≤12	30″/30″ × 4	43/40	93/93	38

147 IPC: Ischemic postconditioning group; C; control group (PPCI only); LAD: left descending
148 anterior branch; DES: drug-eluted stent

149 Primary endpoint: heart failure

150 When the data was pooled, the RR for heart failure was 0.88 (95% CI: 0.61,1.26, P=
151 0.47) in the random-effects model (Fig 1). No evident statistical heterogeneity among
152 studies was observed (I^2 = 0, P = 0.51). IPC during PPCI did not reduce heart failure
153 compared to traditional PPCI.

Secondary endpoints: all-cause mortality and MACE

The pooled data showed that IPC did not reduce all-cause mortality compared to traditional PPCI (RR: 0.94, 95% CI: 0.69,1.27, P = 0.68, Fig 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: 0.85,1.93, P = 0.24), MI (RR: 1.08, 95% CI: 0.38,3.12, P = 0.88) and heart failure (RR: 0.85, 95% CI: 0.59,1.23, P = 0.40). When all events (MACE) were considered, IPC during PPCI provided no net benefit of IPC during PPCI (RR: 1.05, 95% CI: 0.83,1.32, P = 0.69, Fig 3).

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 (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).

Table 2: Subgroup analysis.

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

MI: myocardial infarction

Discussion

The current meta-analysis of 10 RCTs, including 3,137 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 (LVEF)[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 ischemia 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 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 to traditional PPCI.

Additional Information

The authors have no conflicts of interest to declare.

Patients consent: No patients, patient advises, and/or the public were involved in this study.

Author contribution statement: Xinqun Hu and Zhenhua Xing designed the study and provided methodological expertise in systematic reviews and searching strategies. Jiabing Huang and Xiaofan Peng searched the databases and constructed the tables. Zhenhua Xing and Liang Tang drafted the manuscript. All authors have read, provided critical feedback, and approved the final manuscript.

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Competing interests: None

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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Figure legends

Fig 1: Effect of PPCI with IPC versus PPCI only on heart failure in STEMI patients undergoing PPCI

PPCI:primary percutaneous coronary intervention, IPC: Ischemic postconditioning group.

Fig 2: Effect of PPCI with IPC versus PPCI only on all-cause mortality in STEMI patients undergoing PPCI.

PPCI:primary percutaneous coronary intervention, IPC: Ischemic postconditioning group.

Fig 3: Effect of PPCI with IPC versus PPCI only on MACE in STEMI patients undergoing PPCI.

PPCI:primary percutaneous coronary intervention, IPC: Ischemic postconditioning group.

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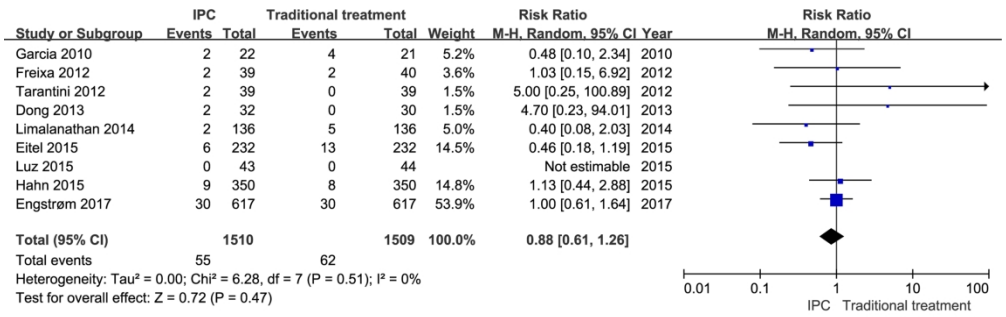

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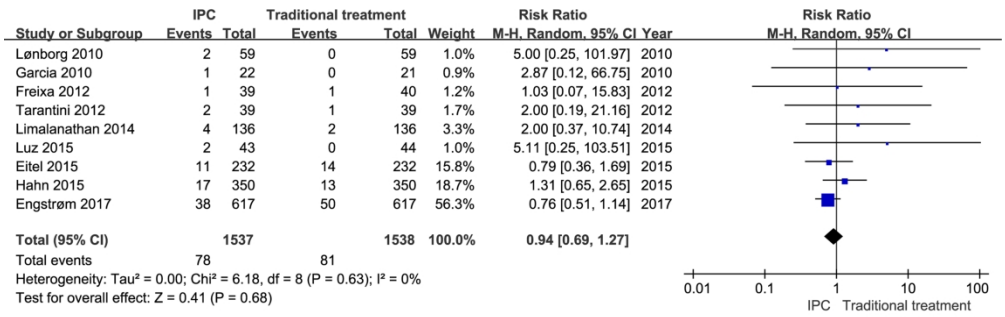

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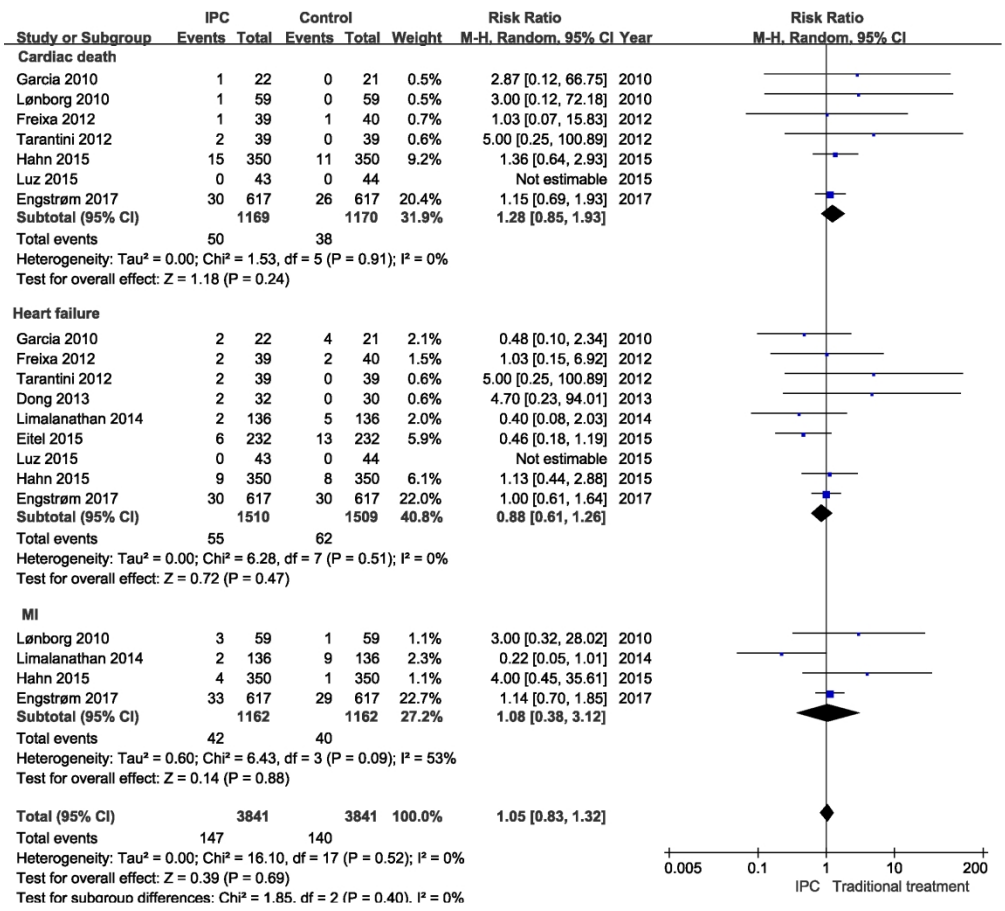

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Effects of ischemic postconditioning on outcomes of patients with ST-segment elevation myocardial infarction who underwent primary percutaneous coronary intervention: a meta-analysis

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Search Query Items found

#1 Search ischemic postconditioning[MeSH Terms] 849

#2 Search conditioning[Title/Abstract] 55132

#3 Search percutaneous coronary intervention[MeSH Terms] 46594

#4 Search PCI[Title/Abstract] 21330

#5 Search (PCI[Title/Abstract]) OR percutaneous coronary intervention[MeSH Terms] 55884

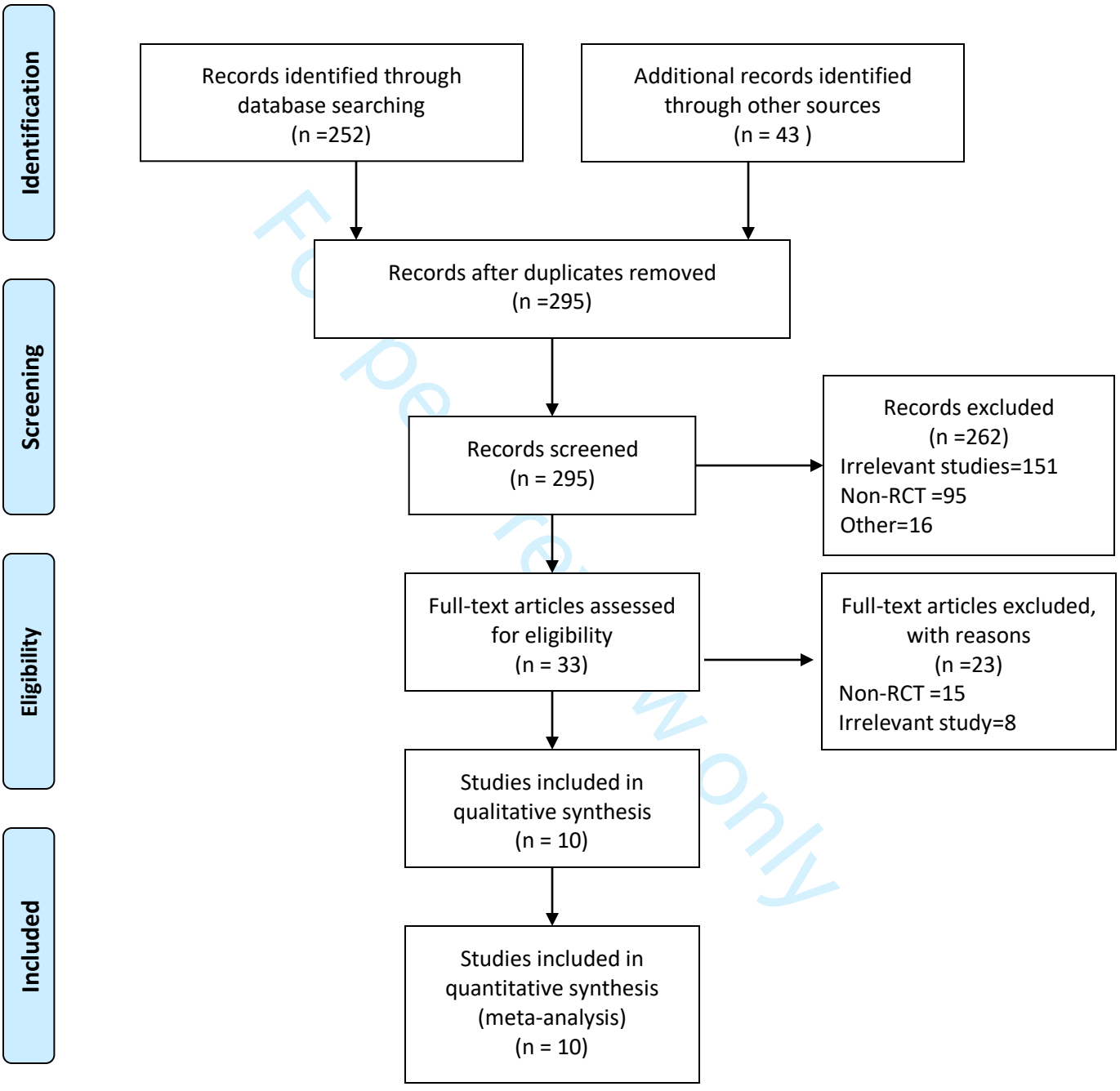
#6 Search (conditioning[Title/Abstract]) OR ischemic postconditioning[MeSH Terms] 55763

#7 Search (((conditioning[Title/Abstract]) OR ischemic postconditioning[MeSH Terms])) AND ((PCI[Title/Abstract]) OR percutaneous coronary intervention[MeSH Terms]) 153

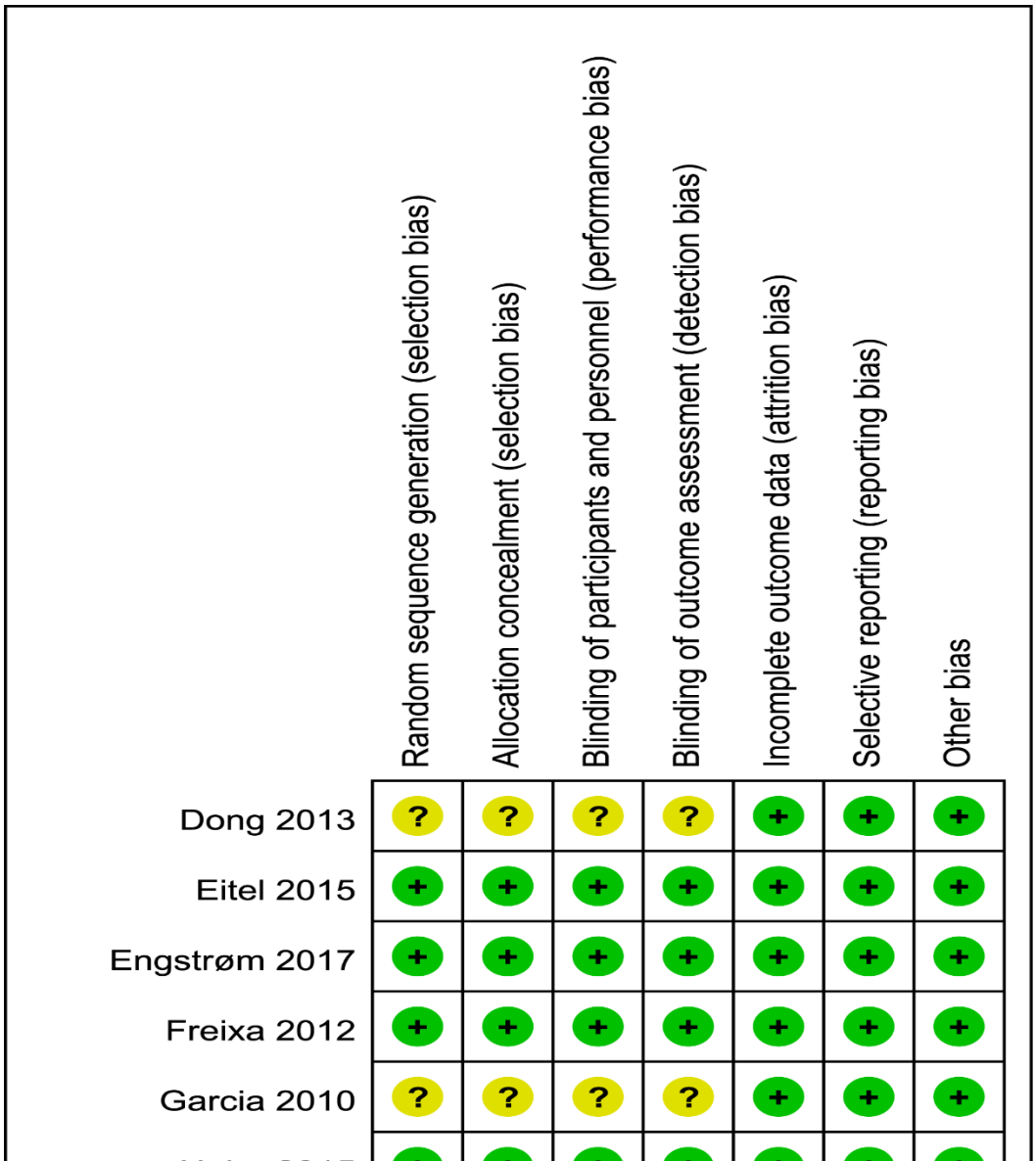
Supplementary table 1: Sensitivity analysis

Excluded study	Heart failure	MI	Cardiac death	All-cause mortality
Lønborg 2010	-	0.90(0.25,3.24)	1.49(0.74,2.99)	0.90(0.69,1.27)
Garcia 2010	0.91(0.62,1.31)	-	1.26(0.84,1.91)	0.95(0.70,1.29)
Freixa 2012	0.86(0.58,1.28)	-	1.29(0.85,1.95)	0.96(0.70,1.30)
Tarantini 2012	0.85(0.59,1.22)	-	1.25(0.83,1.89)	0.95(0.70,1.29)
Limalanathan 2014	0.91(0.63,1.32)	1.26(0.79,2.00)	-	0.94(0.69,1.27)
Hahn 2015	-	0.84(0.25,2.84)	1.23(0.77,2.03)	0.90(0.65,1.25)
Eitel 2015	0.98(0.66,1.45)	-	-	1.00(0.72,1.38)
Luz 2015	0.88(0.61,1.26)	-	1.28(0.85,1.93)	0.94(0.69,1.27)
Engstrøm 2017	0.75(0.44,1.28)	1.20(0.78,1.32)	1.54(0.78,3.04)	1.28(0.81,2.00)
Dong 2013	0.85(0.59,1.23)	-	-	-

PRISMA 2009 Flow Diagram



Supplementary Figure 1: Flow diagram of literature searched for meta-analysis.



Supplementary Fig2. Bias assessment using Cochrane Reviewer's Handbook 4.2

PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5
Synthesis of results	21	Present the main results of the review. If meta-analyses done, include for each, confidence intervals and measures of consistency.	5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	5
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	6
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	9

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

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

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Complete List of Authors:	Xing, Zhenhua; Second Xiangya Hospital Tang, Liang; Second Xiangya Hospital Huang, Jiabing; Second Xiangya Hospital Peng, Xiaofan; Second Xiangya Hospital Hu, Xinqun; Second Xiangya Hospital
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Ischemic postconditioning therapy, percutaneous coronary intervention, all-cause mortality, major adverse cardiac events, meta-analysis

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

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Objective: The aim of this meta-analysis was to evaluate the effects of ischemic postconditioning therapy (IPC) 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: Randomized 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 myocardial infarction (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 3,137patients were included. PPCI combined with IPC failed to reduce heart failure (RR: 0.88, 95% CI: 0.61,1.26, 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: 0.69,1.27, P = 0.68; absolute risk: 5.07% in the IPC group and 5.27% in the PPCI only), MACE (RR: 1.05, 95% CI: 0.83,1.32, P = 0.69; absolute risk: 9.37% in the IPC group and 8.93% in the PPCI only), cardiac death (RR: 1.28, 95% CI: 0.85,1.93, 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: 0.38,3.12, 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 to traditional PPCI in patients with STEMI. (CRD42017063959)

Key words: Ischemic postconditioning therapy (IPC); percutaneous coronary intervention (PCI); all-cause mortality; major adverse cardiac events (MACE); meta-analysis

Strengths and limitations of this study

1. Unlike previous studies, we focused on clinical outcomes such as heart failure, or all-cause mortality.
2. The recent DANAMI-3–iPOST study, which randomized 1,234 patients with STEMI to conventional PPCI or PPCI with IPC, was included, which may alter the conclusion regarding STEMI treatment.
3. In order to give a solid conclusion, sensitivity and subgroup analyses were performed.
4. 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, ischemic 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 (IRA), 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 computed tomography (SPECT), echocardiography, and contrast-enhanced cardiac magnetic resonance (ce-CMR)[3-7]. This strategy, known as ischemic 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 randomized 1,234 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 to 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 to 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 System Reviews and Meta-Analyses (PRISMA) Statement and was registered at International Prospective Register of Systematic Reviews (CRD42017063959)[12]. PubMed, Embase, and Cochrane Library were systematically searched for relevant articles published before May 1, 2018. The terms “ischemic postconditioning”, “postconditioning”, “percutaneous coronary intervention (PCI)”, “controlled trial”, “intervention study”, and “randomized controlled trials (RCTs)” were used to identify randomized controlled trials. MeSH, Emtree, and keyword search terms were used in combination (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 (Thompson 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 randomized controlled clinical trial (RCT); (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 one 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 myocardial infarction (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 risk of bias.

Relevant data were extracted by two independent investigators (XF Peng and JB Huang). Disagreements were resolved by consensus or a third investigator (XQ Hu). 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% confidence interval (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, antiplatelet therapies. Data analysis was performed on an intention-to-treat basis. All analysis was performed using Review Manager Software (Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.).

Outcomes

Search results and bias assessment

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 showed in 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 risk of bias (Supplementary Fig 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, 1,569 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 protocol (cycles*ischemia/reperfusion in seconds) varied between studies and were as follows: 30″/30″ × 4 in four studies, 60″/60″ × 4 in five studies, and 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 2 studies to 12 hours in 8 studies.

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 2010	59/59	Denmark	61/62	69/74	≤12	30″/30″ × 4	44/39	-	3
Garcia 12010	22/21	USA	61/55	86/76	≤12	30″/30″ × 4	36/24	-	41
Freixa 2012	39/40	Spain	59/60	84/72	≤12	60″/60″ × 4	51/39	-	6
Tarantin	39/39	Italy	60/60	85/85	≤6	60″/60″ × 4	41/44	0/2.6	1

i 2012									
Dong 2013	32/30	China	70/68	63/73	≤12	30″/30″ × 3	57/43	-	1
Limalanathan 2014	136/136	Norway	61/60	84/80	≤6	60″/60″ × 4	46/51	29/29	4
Hahn 2015	350/350	South Korea	60/60	79/75	≤12	60″/60″ × 4	47/45	86/86	12
Eitel 2015	232/232	Germany	62/65	76/71	≤12	30″/30″ × 4	42/51	-	6
Luz 2015	43/44	Portugal	57/58	88/82	≤12	60″/60″ × 4	47/43	65/71	14
Engstrøm 2017	617/617	Denmark	63/62	80/79	≤12	30″/30″ × 4	43/40	93/93	38

151 IPC: Ischemic postconditioning group; C; control group (PPCI only); LAD: left descending
152 anterior branch; DES: drug-eluted stent

153 ## Primary endpoint: heart failure

154 When the data was pooled, the RR for heart failure was 0.88 (95% CI: 0.61,1.26, P=
155 0.47; absolute risk: 3.64% in the IPC group and 4.11% in the PPCI only group) in the
156 random-effects model (Fig 1). No evident statistical heterogeneity among studies was
157 observed (I^2 = 0, P = 0.51). IPC during PPCI did not reduce heart failure compared to

traditional PPCI.

Secondary endpoints: all-cause mortality and MACE

The pooled data showed that IPC did not reduce all-cause mortality compared to traditional PPCI (RR: 0.94, 95% CI: 0.69,1.27, P = 0.68; absolute risk: 5.07% in the IPC group and 5.27% in the PPCI only group, Fig 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: 0.85,1.93, 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: 0.38,3.12, 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: 0.59,1.23, 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: 0.83,1.32, P = 0.69; absolute risk: 9.37% in the IPC group and 8.93% in the PPCI only group, Fig 3).

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 (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).

Table 2: Subgroup analysis.

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

Clopidogrel	1.28 (0.85,1.93)	0.98 (0.66,1.45)	1.08 (0.38,3.12)	0.97 (0.69,1.35)
GPIIb/IIIa inhibitors	1.23 (0.81,1.88)	0.84 (0.56,1.27)	1.08 (0.38,3.12)	0.93 (0.67,1.30)
Bivalirudin	1.44 (0.70,2.94)	0.98 (0.47,2.03)	0.84 (0.77,14.24)	1.48 (0.81,2.69)

MI: myocardial infarction

Discussion

The current meta-analysis of 10 RCTs, including 3,137 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 (LVEF)[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 ischemia 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 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 to traditional PPCI.

Additional Information

The authors have no conflicts of interest to declare.

Patients consent: No patients, patient advises, and/or the public were involved in this study.

Author contribution statement: Xinqun Hu and Zhenhua Xing designed the study and provided methodological expertise in systematic reviews and searching strategies. Zhenhua Xing and Liang Tang drafted the manuscript. Jiabing Huang and Xiaofan Peng searched the databases and constructed the tables. All authors have read, provided critical feedback, and approved the final manuscript.

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Competing interests: None

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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Figure legends

Fig 1: Effect of PPCI with IPC versus PPCI only on heart failure in STEMI patients undergoing PPCI

PPCI:primary percutaneous coronary intervention, IPC: Ischemic postconditioning group.

Fig 2: Effect of PPCI with IPC versus PPCI only on all-cause mortality in STEMI patients undergoing PPCI.

PPCI:primary percutaneous coronary intervention, IPC: Ischemic postconditioning group.

Fig 3: Effect of PPCI with IPC versus PPCI only on MACE in STEMI patients undergoing PPCI.

PPCI:primary percutaneous coronary intervention, IPC: Ischemic postconditioning group.

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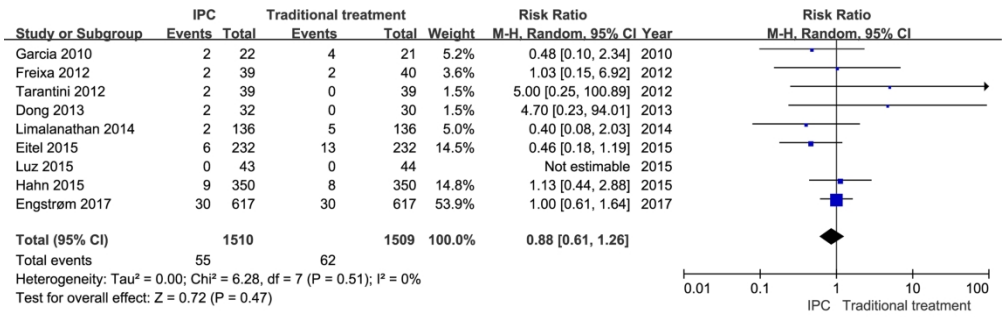

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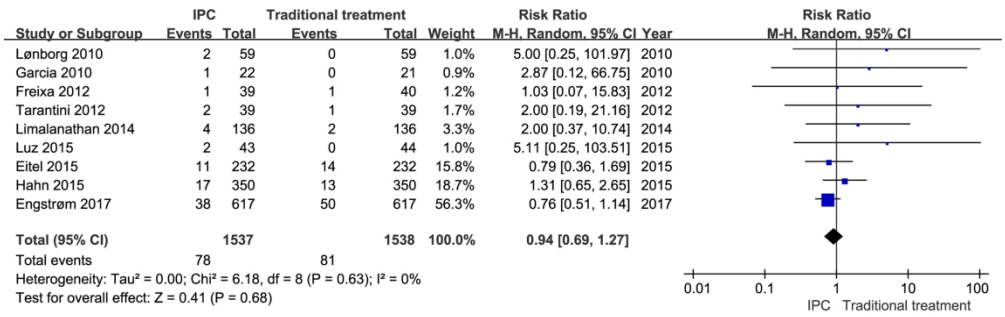

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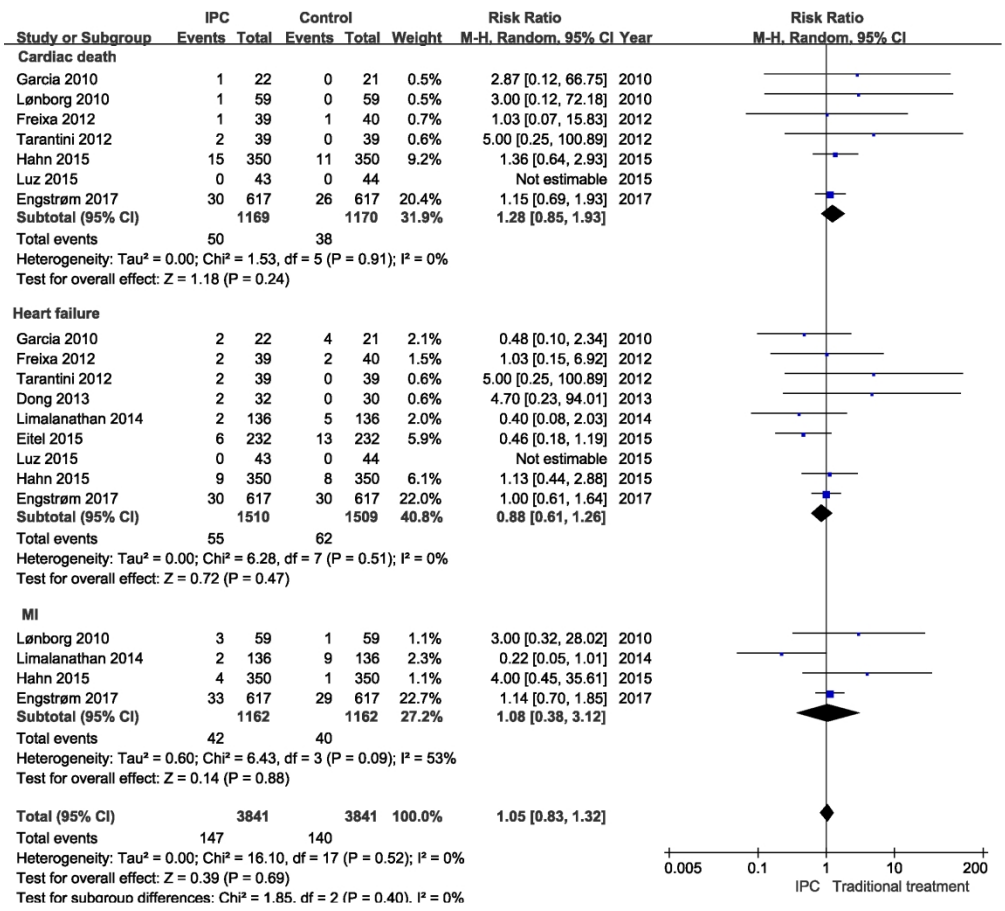

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Effects of ischemic postconditioning on outcomes of patients with ST-segment elevation myocardial infarction who underwent primary percutaneous coronary intervention: a meta-analysis

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Search Query Items found

#1 Search ischemic postconditioning[MeSH Terms] 849

#2 Search conditioning[Title/Abstract] 55132

#3 Search percutaneous coronary intervention[MeSH Terms] 46594

#4 Search PCI[Title/Abstract] 21330

#5 Search (PCI[Title/Abstract]) OR percutaneous coronary intervention[MeSH Terms] 55884

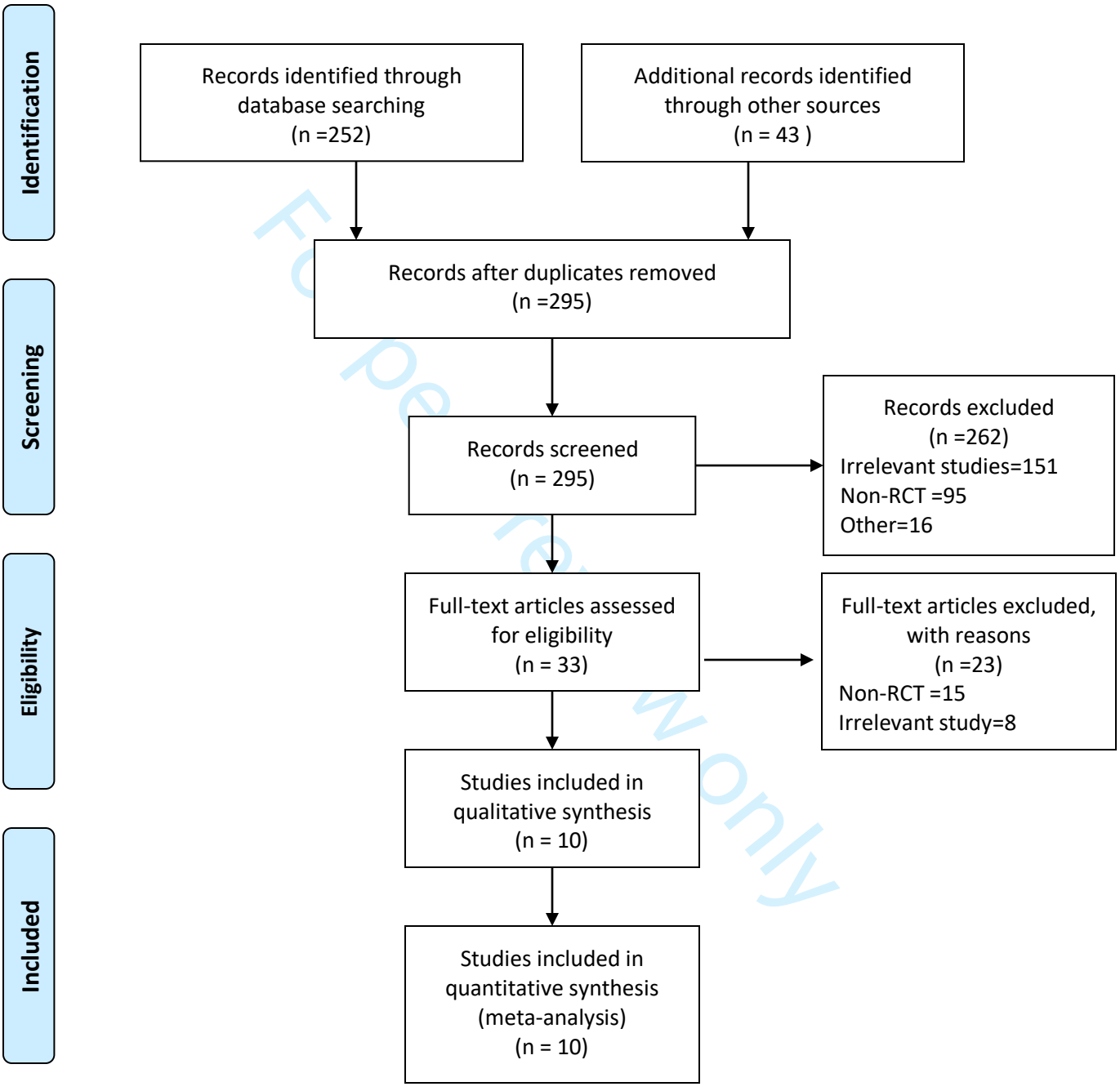
#6 Search (conditioning[Title/Abstract]) OR ischemic postconditioning[MeSH Terms] 55763

#7 Search (((conditioning[Title/Abstract]) OR ischemic postconditioning[MeSH Terms])) AND ((PCI[Title/Abstract]) OR percutaneous coronary intervention[MeSH Terms]) 153

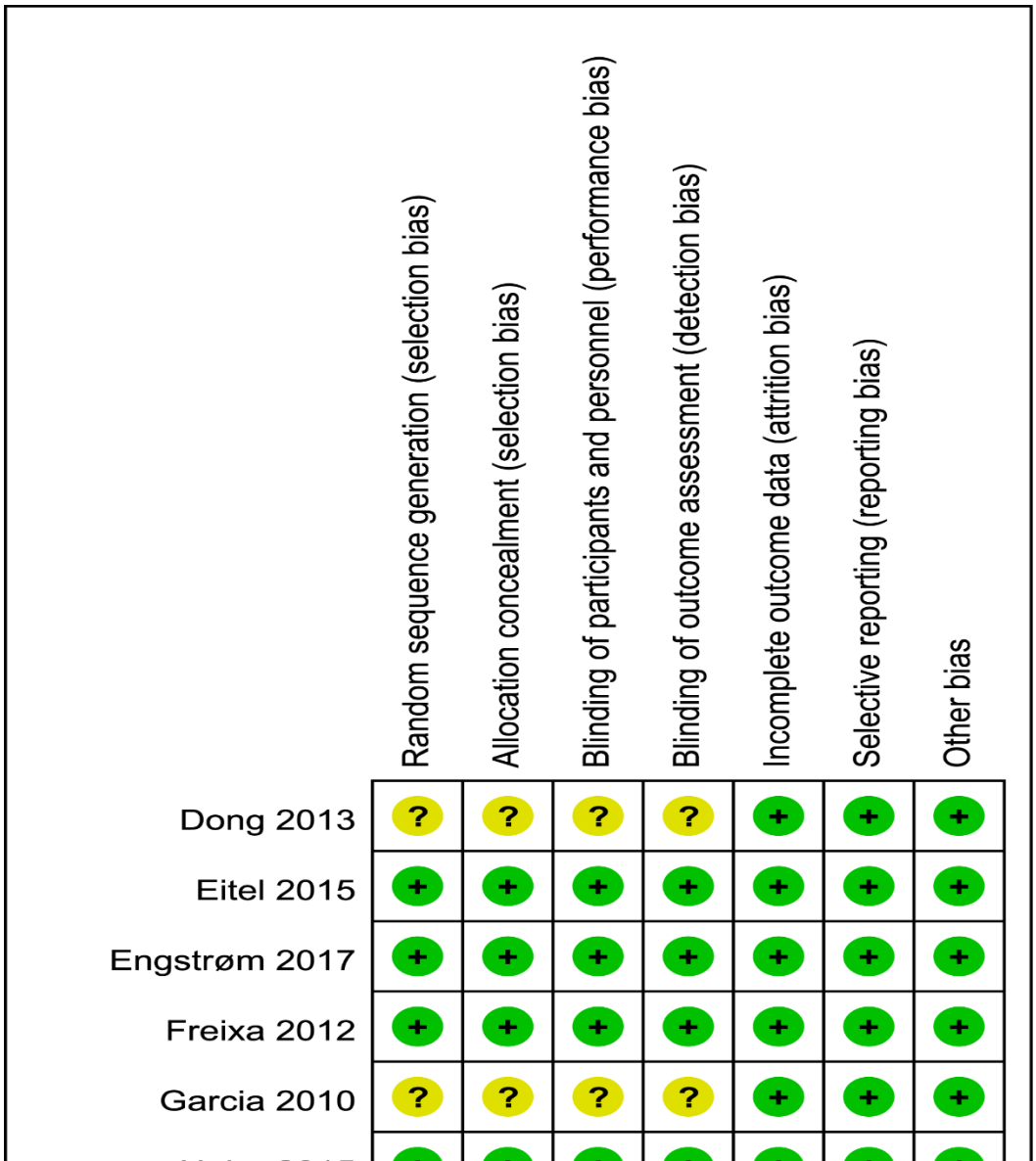
Supplementary table 1: Sensitivity analysis

Excluded study	Heart failure	MI	Cardiac death	All-cause mortality
Lønborg 2010	-	0.90(0.25,3.24)	1.49(0.74,2.99)	0.90(0.69,1.27)
Garcia 2010	0.91(0.62,1.31)	-	1.26(0.84,1.91)	0.95(0.70,1.29)
Freixa 2012	0.86(0.58,1.28)	-	1.29(0.85,1.95)	0.96(0.70,1.30)
Tarantini 2012	0.85(0.59,1.22)	-	1.25(0.83,1.89)	0.95(0.70,1.29)
Limalanathan 2014	0.91(0.63,1.32)	1.26(0.79,2.00)	-	0.94(0.69,1.27)
Hahn 2015	-	0.84(0.25,2.84)	1.23(0.77,2.03)	0.90(0.65,1.25)
Eitel 2015	0.98(0.66,1.45)	-	-	1.00(0.72,1.38)
Luz 2015	0.88(0.61,1.26)	-	1.28(0.85,1.93)	0.94(0.69,1.27)
Engstrøm 2017	0.75(0.44,1.28)	1.20(0.78,1.32)	1.54(0.78,3.04)	1.28(0.81,2.00)
Dong 2013	0.85(0.59,1.23)	-	-	-

PRISMA 2009 Flow Diagram



Supplementary Figure 1: Flow diagram of literature searched for meta-analysis.



Supplementary Fig2. Bias assessment using Cochrane Reviewer's Handbook 4.2

PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5
Synthesis of results	21	Present the main results of the review. If meta-analyses done, include for each, confidence intervals and measures of consistency.	5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	5
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	6
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	9

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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

Xing Z, Tang L, Huang J, *et al*. Effects of ischaemic postconditioning on outcomes of patients with ST-segment elevation myocardial infarction who underwent primary percutaneous coronary intervention: a meta-analysis. *BMJ Open* 2019;9:e022509. doi: 10.1136/bmjopen-2018-022509

This article was previously published with an error.

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BMJ Open 2019;**9**:e022509corr1. doi:10.1136/bmjopen-2018-022509corr1