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

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4 16 Objective: the aim of this meta-analysis is to evaluate the effects of ischemic
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6 17 postconditioning therapy (IPC) on clinical hard endpoint.

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8 18 Setting: treatment for STEMI
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11 19 Intervention: IPC
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13 20 Eligible studies: we included randomized trials comparing PPCI in combination with
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16 21 IPC with conventional PPCI in patients with STEMI.
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18 22 The primary and secondary endpoint: The primary end point was all-cause mortality,
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20 23 major adverse cardiac events (MACE) including cardiac death, heart failure, nonfatal MI
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22 24 and revascularization. Secondary end point included each individual component of MACE
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24 25 (cardiac death, heart failure, nonfatal MI and revascularization).
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26

27 26 Results: Nine studies enrolling 3088 patients were included. PPCI in combination with
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29 27 IPC failed to reduce all-cause mortality (RR:0.94, 95% CI: 0.69–1.27, P= 0.68), MACE
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31 28 (RR: 1.14, 95%CI: 0.88-1.46, p=0.32), cardiac death (RR: 1.28, 95%CI: 0.85-1.93,
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33 29 p=0.24), MI (RR: 1.08, 95%CI: 0.38-3.21, p=0.88), heart failure (RR: 1.05, 95%CI:
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35 30 0.62-1.75, p=0.87), and revascularization (RR: 1.35, 95%CI:0.81-2.26, p=0.25)..
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40 31 Conclusion: This meta-analysis suggested that the use of IPC in STEMI patients
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42 32 undergoing PPCI did not reduce all-cause mortality, MACE compared with traditional
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44 33 PPCI.
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47 34 Strengths and limitations of this study
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50 35 1. This meta-analysis included the recent relevant studies and provided the latest RCTs
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52 36 about treatment of STEMI.
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55 37 2. In order to give a solid conclusion, trial sequential analysis was performed to evaluate
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38 the sample size.

39 3. We include the recent DANAMI-3-iPOST study, which randomized 1234 patients with
40 STEMI to conventional PPCI or PPCI with IPC, and may change our opinion on
41 treatment of STEMI.

42 4. A limitation of this meta-analysis is the reduced number of trials included.

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

45
46 Key words: Ischemic postconditioning therapy (IPC); percutaneous coronary
47 intervention (PCI); all-cause mortality; major adverse cardiac events (MACE);
48 meta-analysis

49 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

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51 Background

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

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4 53 with ST-segment elevation myocardial infarction (STEMI) and has become the first-line
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6 54 therapy¹. Although PPCI is effective in restoring blood flow, ischemic reperfusion injury is
7
8 55 not inevitable. Reperfusion injury can also induce deleterious effects with a subsequent
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10 56 increase of infarct size, which accounts for up to 50% of the final size of a myocardial
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12 57 infarct². Furthermore, both animal models of infarction and clinical proof-of-concept
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14 58 studies have shown IPC can effectively protect myocardium from reperfusion injury
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16 59 evaluated by cardiac biomarkers, single-photon emission computed tomography(SPECT),
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18 60 echocardiography, and contrast-enhanced cardiac magnetic resonance(ce-CMR) ³⁻⁷.
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23 61 Related meta-analysis also demonstrated that IPC could rescue cardiomyocytes
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25 62 evaluated by above methods⁸⁻¹⁰. However, whether improvements in these surrogate
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27 63 makers translate into improved clinical outcomes evaluated by hard end points such as
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29 64 all-cause mortality remains controversial. the recent DANAMI-3-iPOST study, which
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31 65 randomized 1234 patients with STEMI to conventional PPCI or PPCI with IPC, did not
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33 66 provide evidences in favor of PPCI with IPC compared with traditional PPCI¹⁰.

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37 67 Given the confusing situations of IPC in PPCI, we performed this meta-analysis. The
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39 68 aim of this meta-analysis was to evaluate whether IPC has a beneficial effect on hard end
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41 69 points such as all-cause mortality and MACE compared with traditional PPCI.
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46 70 **Methods**

47 48 49 50 71 **Search strategy and selection criteria**

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54 72 This meta-analysis is reported in accordance of the Preferred Reporting Items for
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73 System Reviews and Meta-Analyses (PRISMA) Statement and was registered at
74 International Prospective Register of Systematic Reviews (CRD42017063959)¹¹. We
75 systemically searched PubMed, Embase, and Cochrane Library for relevant articles
76 published before April 1, 2017. We used the terms: ischemic postconditioning,
77 postconditioning, percutaneous coronary intervention (PCI), controlled trial, intervention
78 study, and randomized controlled trials (RCTs) to identify randomized controlled trials.
79 MeSH, Emtree, and keyword search terms were used in combination. Results were
80 limited to trials published in English. We manually searched the reference lists of relevant
81 studies and reviews, editorials, and letters to identify further articles.
82 We used Endnote (Thompson ISI ResearchSoft, Philadelphia, USA) to manage relevant
83 articles and remove duplicated articles.

84 **Study criteria, quality assessment, and data extraction**

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

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

94 (cardiac death, heart failure, MI, and revascularization). All clinical endpoints were
95 evaluated according to per protocol definitions, at the longest available follow-up. We
96 judge study quality by evaluating trial procedures for random sequence generation
97 (selection bias), allocation concealment (selection bias), blinding of participants and
98 personnel (performance bias), blinding of outcome assessment (detection bias) and
99 incomplete outcome data (attrition bias). The Cochrane Reviewer's Handbook 4.2 was
100 used to assess risk of bias.

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

107 Data analysis

108 Meta-analysis was performed to calculate the Risk Ratio (RR) and 95% confidence
109 interval (CI) of all-cause mortality , MACE , and each component of MACE. Pooled RRs
110 were computed as the Mantel-Haenszel-weighted average of the RRs for all included
111 studies. Since the true treatment effect of various postconditioning protocols may have
112 varied among the included trials, the random-effects model was used in the analysis.
113 Statistical heterogeneity among the trial-specific RRs was checked and quantified by the
114 I^2 statistic, and a P-value ≤ 0.05 was considered statistical significant. Data analysis will be

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4 115 done on an intention-to-treat basis. All analysis was performed using Review Manger
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6 116 Software (Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen:
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8 117 The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.) and Stata (Stata12.0
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11 118 (StataCorp LP, College Station, Texas).)

119 Outcomes

120 Search results and Bias assessment

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

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

133 **Table 1: detailed characteristics of included studies.**

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

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137 All-cause mortality and MACE

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

142 Based on the pooled results, we did not find that IPC could reduce cardiac death (RR:
143 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
144 (RR: 1.05, 95%CI: 0.62-1.75, $p=0.87$), and revascularization (RR: 1.35, 95%CI:0.81-2.26,
145 $p=0.25$). When all these events (MACE) were considered, the net benefit did not favor IPC
146 during PPCI (RR: 1.14, 95%CI: 0.88-1.46, $p=0.32$, Fig 2).

147 Sensitivity analysis and potential sources of heterogeneity

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

151 There were no heterogeneities between studies with regards the observed effects in
152 all-cause mortality ($I^2=0$, $p=0.63$), cardiac death ($I^2=0$, $p=0.91$), and revascularization ($I^2=0$,
153 $p=0.49$). However, moderate between-study heterogeneity was identified in case of heart
154 failure ($I^2=57\%$, $p=0.02$) and MI ($I^2=53\%$, $p=0.09$). The heterogeneity of heart failure was
155 generated by the Eital 2015 study, excluding these studies from the analysis restored the
156 homogeneity of heart failure dataset($I^2=19\%$, $p=0.28$). The heterogeneity of MI was mainly
157 caused by the Limalanathan 2014 study. When we excluded this study, No heterogeneity

158 was observed ($I^2=0\%$, $p=0.40$). The conclusions were still consistent with previous
 159 analysis. Meta-regression did not find any baseline risk factor, such as age, diabetes,
 160 hypertension et al, was a modifier of the relationship between IPC and all-cause mortality,
 161 MACE. Sensitivity and subgroup analysis did not identify any patient-level or study-level
 162 covariate as a significant source of heterogeneity except for this subgroup analysis (Table
 163 2).

164 **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)
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167 Discussion

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

173 IPC was first introduced by Zhao et al. in 2003¹². Subsequent clinical trials and
 174 meta-analysis found that salutary effect of IPC on infarct size evaluated by CK, CK-MB,
 175 troponin, SPECT, and cardiac function evaluated by left ventricular ejection
 176 fraction(LVEF)^[11-17]. However , opposite results also existed¹³⁻¹⁷. The DANAMI-3-iPOST
 177 trial, which is the largest study to date, did not show that IPC could reduce infarct size,
 178 microvascular obstruction¹³. Furthermore, whether the surrogate end points of infarct size,
 179 myocardial salvage, and resolution of ST-segment elevation can translate into hard
 180 endpoints such as all-cause mortality is really a problem. Unlike these surrogate end
 181 points, all-cause mortality and MACE are, what clinics and patients, really considering.

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

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4 185 play a role in the results of these RCTs. That routine IPC failed in the present study, may
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6 186 on the other hand suggest that some patients may respond to the therapy. A
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8 187 meta-analysis of 19 RCTs concluded that cardioprotection with regard to cardiac enzymes
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10 188 leakage, infarct size and left ventricular function is more prone in patients with LAD artery
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12 189 involvement because of a greater myocardial area being at risk [7]. Zhou et al. performed a
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14 190 meta-analysis consisting of 10 RCTs and found that effects of cardiac protection are more
15
16 191 pronounced among young and male patients, and those in whom direct-stenting
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18 192 techniques were used [8]. IPC protocol is also an important factor in determining the
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20 193 results. IPC may cause myocardial ischemia and expand the infarct area. Many trials
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22 194 chose 4 cycles of 1 minute of reperfusion followed by 1 minute of reocclusion. On the
23
24 195 contrary, other trials chose 4 cycles of 30-second reperfusion followed by 30-second
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26 196 low-pressure balloon occlusion. However, our subgroup analysis did not find the
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28 197 difference. Time of symptoms onset, which is the independent predictor of MACE in
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30 198 patients with STEMI undergoing PPCI, might play a role in the results of these trials.
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32 199 Subgroup analysis did not detect the difference as well.

40 200 Neutral subgroup analysis can result from many reasons. The key reason is that IPC
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42 201 might have no effect on cardioprotection. As a result, our subgroup analysis was neutral.
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44 202 The other reason could not be neglected as well. the sample size of the studies may have
45
46 203 been small to detect minor beneficial effects. Many confounding factors such as patient's
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48 204 baseline characteristics, coexisting diseases, medications, IPC strategies used may partly
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50 205 affect the cardioprotective benefits of IPC. With the use of new antiplatelet and
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52 206 lipid-lowering agents and timely PPCI, the outcome of STEMI improves greatly. The
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207 declining rate of death makes it harder to demonstrate a minor benefit of additional
208 therapy with regard to overall mortality.

209 Limitations

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

220 Conclusions

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

224 Additional Information

225 The authors declare that they have no conflict of interest.

226
227 Contributors ship statement: Xinqun Hu and Zhenhua Xing designed the study and
228 provided methodological expertise in systematic reviews and searching strategies. Jiabing
229 Huang and Xiaofan Peng searched the databases and performed tables. Zhenhua Xing
230 drafted the manuscript. All authors read, provided critical feedback and approved the final
231 manuscript.

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233 Competing interests: none

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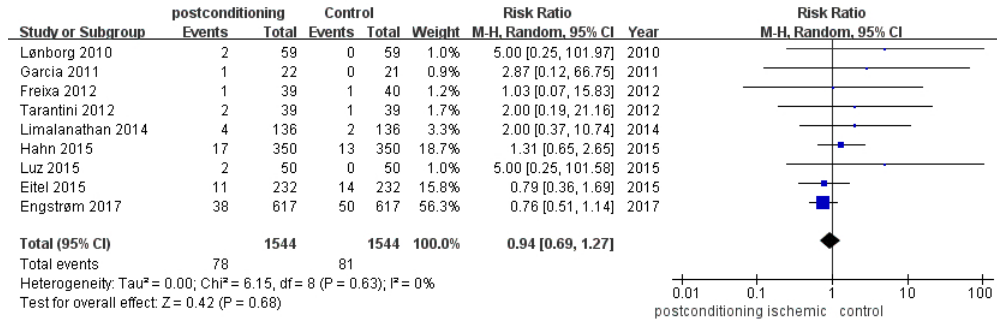
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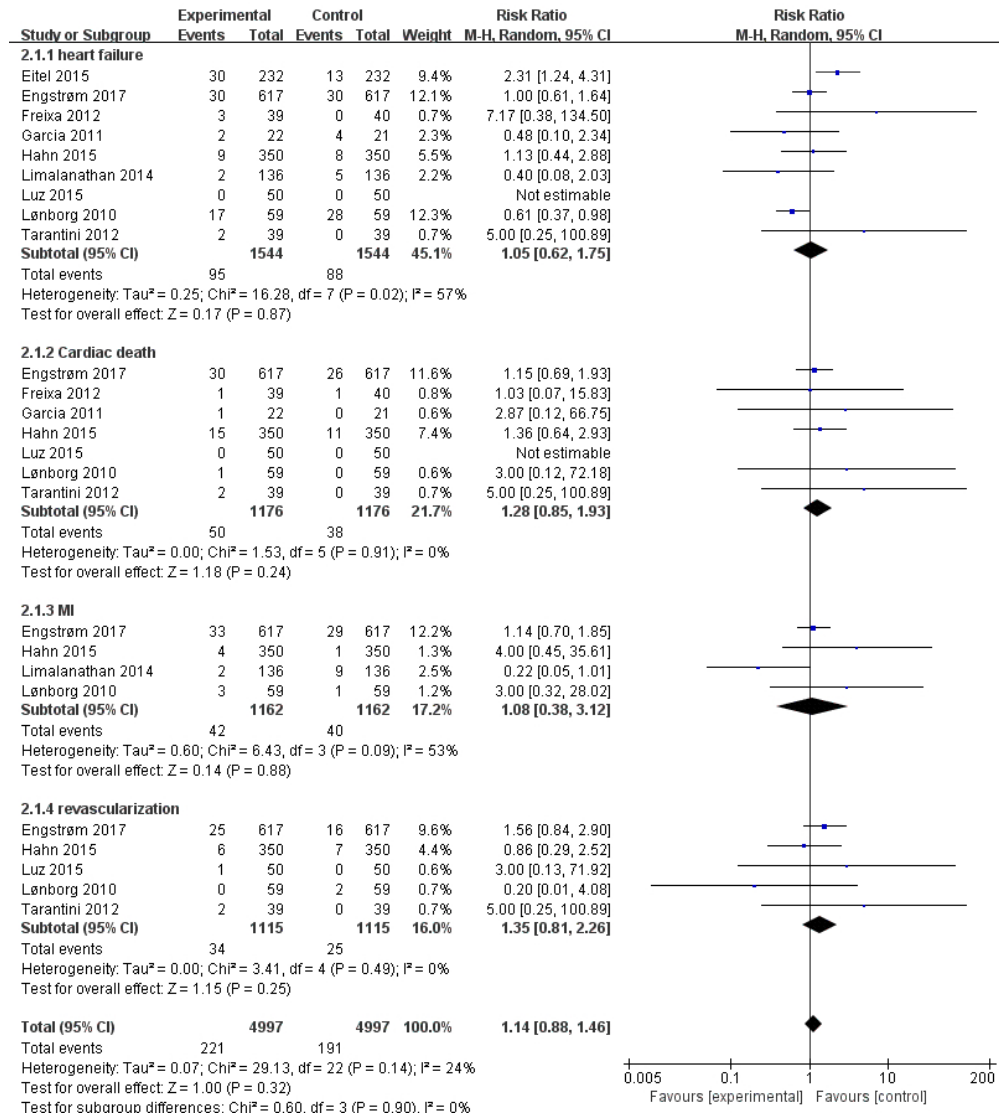
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20 287 **Fig 1: ischemic postconditioning versus traditional PPCI on all-cause mortality in**
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22 288 **patients with STEMI.**

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24 289 **Fig 2: ischemic postconditioning versus traditional PPCI on MACE in patients with**
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26 290 **STEMI.**

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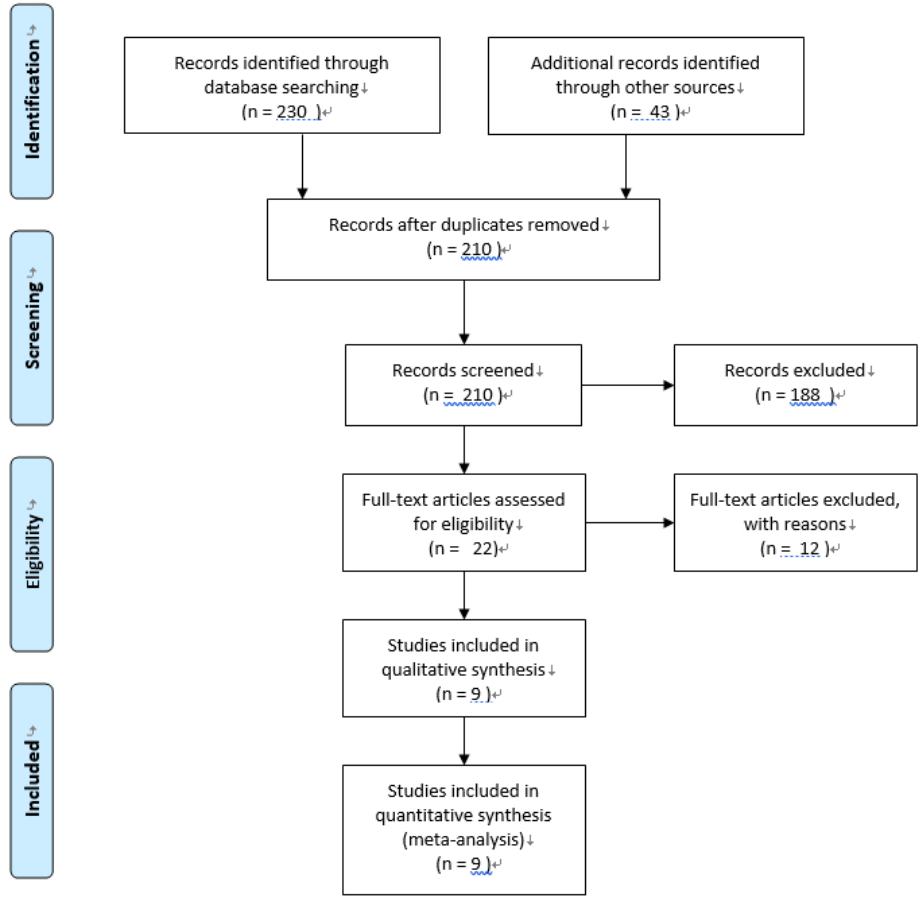


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PRISMA 2009 Flow Diagram



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	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Carcia 2011	?	?	?	?	+	+	+
Eitel 2015	+	+	+	+	+	+	+
Engstrøm 2017	+	+	+	+	+	+	+
Freixa 2012	+	+	+	+	+	+	+
Hahn 2015	+	+	+	+	+	+	+
Limalanathan 2014	+	+	?	?	+	+	+
Luz 2015	+	+	?	?	+	+	+
Lønborg 2010	+	+	+	+	+	+	+
Tarantini 2012	+	+	+	+	+	+	+

209x279mm (200 x 200 DPI)

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

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 undergoing primary percutaneous coronary intervention: a meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-022509.R1
Article Type:	Research
Date Submitted by the Author:	13-Jun-2018
Complete List of Authors:	Xing, Zhenhua; 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

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Manuscripts

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

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

27 Results: Ten studies enrolling 3,137 patients were included. PPCI in combination with
28 IPC failed to reduce heart failure (RR: 0.88, 95% CI: 0.61,1.26, P = 0.47),all-cause
29 mortality (RR: 0.94, 95% CI: 0.69,1.27, P = 0.68),MACE (RR: 1.05, 95% CI: 0.83,1.32, P =
30 0.69), cardiac death (RR: 1.28, 95% CI: 0.85,1.93, P = 0.24), and MI (RR: 1.08, 95% CI:
31 0.38,3.21, P = 0.88).

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

34 Strengths and limitations of this study

35 1. This meta-analysis included recent relevant studies and provided the latest RCTs on
36 STEMI.

37 2. To generate a solid conclusion, sensitivity analysis and subgroup analyses were

38 performed to evaluate the sample size.

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

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

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

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

48 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

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50 Background

51 Primary percutaneous coronary intervention (PPCI) has been proven to be effective

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4 52 in patients with ST-segment elevation myocardial infarction (STEMI) and has become a
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6 53 first-line therapy^[1]. Although PPCI is effective in restoring blood flow, ischemic reperfusion
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8 54 injury is not inevitable. Reperfusion injury can also induce deleterious effects with a
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11 55 subsequent increase in infarct size, which accounts for up to 50% of the final size of a
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13 56 myocardial infarct^[2]. Both animal models of infarction and clinical proof-of-concept studies
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16 57 have shown that reopening of the infarct-related artery (IRA) followed by repetitive brief
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18 58 interruptions of blood flow before sustained reperfusion may protect the myocardium
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21 59 against reperfusion injury, which is evaluated using cardiac biomarkers, single-photon
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23 60 emission computed tomography (SPECT), echocardiography, and contrast-enhanced
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26 61 cardiac magnetic resonance (ce-CMR)^[3-7]. This strategy, known as ischemic
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28 62 postconditioning (IPC), is safe and easy to perform without additional cost^[8]. Related
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31 63 meta-analyses also demonstrated that IPC could rescue cardiomyocytes evaluated by the
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33 64 above methods^[9-11]. However, whether improvements in these surrogate markers can
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36 65 translate into improved clinical outcomes evaluated by hard endpoints, such as heart
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38 66 failure, or all-cause mortality remains controversial. The recent DANAMI-3-iPOST study,
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41 67 which randomized 1,234 patients with STEMI to conventional PPCI or PPCI with IPC did
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43 68 not provide evidence in favor of PPCI with IPC compared to traditional PPCI^[11].

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45 69 Given the confusing situations of IPC during PPCI, we performed this meta-analysis
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48 70 to evaluate whether IPC has a beneficial effect on hard endpoints, such as heart failure,
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51 71 all-cause mortality, and MACE, compared to traditional PPCI.

72 **Methods**

73 **Patients and public involvement**

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

75 **Search strategy and selection criteria**

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

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

89 **Study criteria, quality assessment, and data extraction**

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

91 the study design was a prospective randomized controlled clinical trial (RCT); (2) all
92 patients with STEMI underwent PPCI treatment; (3) patients were randomly assigned to
93 the PPCI in combination with the IPC group or the conventional PPCI group; (4) follow-up
94 time was not less than one month; and (5) relevant data should be retrievable. When
95 relevant data were missing, authors were contacted by e-mail, before excluding the
96 references for inaccessibility of data.

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

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

111 Data analysis

112 Meta-analysis was performed to calculate the risk ratio (RR) and 95% confidence
113 interval (CI). Pooled RRs were computed as the Mantel-Haenszel-weighted average of
114 the RRs for all included studies. Because the true treatment effect of various
115 postconditioning protocols may have varied among the included trials, the random-effects
116 model was used in the analysis. Statistical heterogeneity among the trial-specific RRs was
117 checked and quantified by the I^2 statistic, and a P-value ≤ 0.05 was considered statistically
118 significant. If one study have no events, we did not include this study in the calculation of
119 RR. We performed sensitivity analysis to assess the contribution of each study to the
120 pooled estimation by excluding one trial at a time and recalculating the pooled RR
121 estimation for the remaining studies. To determine the impact of baseline characteristics
122 (symptom onset, different IPC protocol, duration of follow-up et. al.) on the observed
123 clinical benefit, subgroup analyses were performed. All analysis was performed using
124 Review Manager Software (Review Manager (RevMan) [Computer program]. Version 5.3.
125 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.).

126 Outcomes

127 Search results and bias assessment

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

131 3,137 patients^[7, 8, 13-20]. We used the Cochrane Reviewer's Handbook 4.2 to assess risk of
 132 bias (Supplementary Fig 2). No high-risk studies existed. Six of them had a low risk of
 133 bias.

134 The main features of the 10 included RCTs and baseline clinical characteristics of the
 135 patients are presented in Table 1. In the 10 trials, 1,569 patients (50%) were randomly
 136 assigned to postconditioning therapy. The mean age of the trial patients was 61 years,
 137 and 78% of these patients were male. The IPC protocol (ischemia/reperfusion×cycles in
 138 seconds) varied between studies, being 30"/30" × 4 in four studies, 60"/60" × 4 in five
 139 studies, and 30"/30" × 3 in one study. The follow-up in the trials varied from 1 month to 41
 140 months. The time of symptoms onset varied between studies, being 6 hours in 2 studies,
 141 12 hours in 8 studies.

143 **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 (month s)
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	39/39	Italy	60/60	85/85	≤6 h	60"/60" × 4	41/44	0/2.6	1
2012									
Dong	32/30	China	70/68	63/73	≤12 h	30"/30" × 3	57/43	-	1
2013									
Limalanatan	136/136	Norway	61/60	84/80	≤6 h	60"/60" × 4	46/51	29/29	4
han 2014									
Hahn	350/350	South Korea	60/60	79/75	≤12 h	60"/60" × 4	47/45	86/86	12
2015									
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	617/617	Denmark	63/62	80/79	≤12 h	30"/30" × 4	43/40	93/93	38
2017									

144 IPC: Ischemic postconditioning group; C; control group; LAD: left descending anterior

145 branch; DES: drug-eluted stent;

146 **Primary endpoint: heart failure**

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

148 0.47) in the random-effects model (Fig 1). No evident statistical heterogeneity among

149 studies was observed ($I^2 = 0$, $P = 0.51$). IPC during PPCI did not reduce heart failure

150 compared to traditional PPCI.

151 **Second endpoints: all-cause mortality and MACE**

152 Our pooled data showed that IPC does not reduce all-cause mortality compared to
153 traditional PPCI (RR: 0.94, 95%CI: 0.69,1.27, P=0.68, Fig 2). No evident statistical
154 heterogeneity among studies was observed ($I^2=0$, P =0.63). Furthermore, IPC does not
155 reduce cardiac death (RR: 1.28, 95% CI: 0.85,1.93, P = 0.24), MI (RR: 1.08, 95% CI:
156 0.38,3.21, P = 0.88) and heart failure (RR: 0.85, 95% CI: 0.59,1.23, P = 0.40). When all
157 these events (MACE) were considered, the net benefit did not favor IPC during PPCI (RR:
158 1.05, 95% CI: 0.83,1.32, P = 0.69, Fig 3).

159 **Sensitivity analysis and potential sources of heterogeneity**

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

164 There were no heterogeneities with regards to the observed effects on all-cause
165 mortality ($I^2=0$, $p=0.63$) and cardiac death ($I^2=0$, $p=0.91$) between studies. However,
166 moderate between-study heterogeneity was identified in the case of MI ($I^2 = 53%$, P =
167 0.09). MI heterogeneity was mainly caused by the Limalanathan 2014 study. When we
168 excluded this study, no obvious heterogeneity was observed ($I^2 = 0%$, P = 0.40). The
169 conclusions were still consistent with previous analysis. Subgroup analysis did not find
170 any baseline risk factor, such as symptom onset, duration of follow-up, and antiplatelet
171 therapies as a modifier of the relationship between IPC and clinical endpoints (Table 2).

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

174 **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)

175 MI: myocardial infarction; IPC: Ischemic postconditioning group

176 Discussion

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

181 IPC was first introduced by Zhao et al. in 2003^[21]. Subsequent clinical trials and
182 meta-analyses found the salutary effect of IPC on infarct size as evaluated by CK, CK-MB,
183 troponin, SPECT, and cardiac function based on the left ventricular ejection fraction
184 (LVEF)^[3-5]. However, the opposite results have also been reported^[8, 16-19]. The
185 DANAMI-3-iPOST trial, which is the largest study to date, did not show that IPC could
186 reduce infarct size^[8]. Furthermore, whether the surrogate endpoints, such as infarct size,
187 myocardial salvage, and resolution of ST-segment elevation, can translate into hard
188 endpoints, such as heart failure, all-cause mortality, or MACE, remains a point of debate.
189 Unlike these surrogate endpoints, heart failure, all-cause mortality, and MACE are what
190 clinics and patients really consider.

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

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4 197 myocardial area being at risk.^[9] Zhou et al. performed a meta-analysis of 10 RCTs and
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6 198 found that the effects of cardiac protection are more pronounced among young and male
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8 199 patients and those who received direct-stenting^[10]. The IPC protocol is also an important
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11 200 factor in determining the effectiveness of IPC. IPC may cause myocardial ischemia and
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13 201 expand the infarct area. Several trials chose four cycles of 1 min of reperfusion followed
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15 202 by 1 min of reocclusion. However, other trials selected four cycles of 30-s reperfusion
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18 203 followed by 30-s low-pressure balloon occlusion. However, our subgroup analyses did not
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21 204 find the effectiveness of IPC.any differences.

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23 205 Time of symptoms onset, which is an independent predictor of MACE in patients with
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25 206 STEMI undergoing PPCI, may have influenced the results of these trials. Subgroup
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28 207 analysis did not detect the effectiveness of IPC either.

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30 208 The result of subgroup analyses did not support IPC. The key reason is that IPC
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33 209 might have no effect on cardioprotection. Furthermore, the sample size of the studies may
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35 210 have been too small to detect minor beneficial effects. Several confounding factors, such
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38 211 as patient's baseline characteristics, coexisting diseases, medications, and IPC strategies
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40 212 used, may influence the cardioprotective benefits of IPC. With the use of novel antiplatelet
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43 213 and lipid-lowering agents and timely PPCI, the outcome of STEMI has significantly
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45 214 improved. The decreasing mortality rate also makes it harder to demonstrate the minor
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48 215 benefits of using additional therapy.

51 216 Limitations

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55 217 This study has a number of limitations. First, although no apparent heterogeneity in
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4 218 statistical analysis was observed, variations in the methodology among studies, such as
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6 219 different risk profiles of the included patients, IPC strategies, and follow-up time, were
7
8 220 inevitable. However, we performed subgroup analysis and did not find that these
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10 221 heterogeneities affected our conclusion. In addition, we based our conclusion on the
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12 222 random effects model, which can account for a certain degree of heterogeneity. Second,
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14 223 although we performed an extensive search strategy, some studies might not be included
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16 224 in this meta-analysis. However, this meta-analysis is the largest population-based
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18 225 analysis of IPC. Third, additional RCTs are necessary to evaluate long-term clinical
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23 226 outcomes.

227 **Conclusions**

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

231 **Additional Information**

232 The authors have no conflicts of interest to declare.

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

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

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

237 Huang and Xiaofan Peng searched the databases and constructed the tables. Zhenhua

238 Xing drafted the manuscript. All authors have read, provided critical feedback, and

239 approved the final manuscript.

240 Funding: None

241 Competing interests: None

242 Data sharing statement: No additional data available.

243

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- 244
- 245
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8 305 Figure legends

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11 306 **Fig 1: Ischemic postconditioning versus traditional PPCI on heart failure in STEMI**

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13 307 **patients undergoing PPCI**

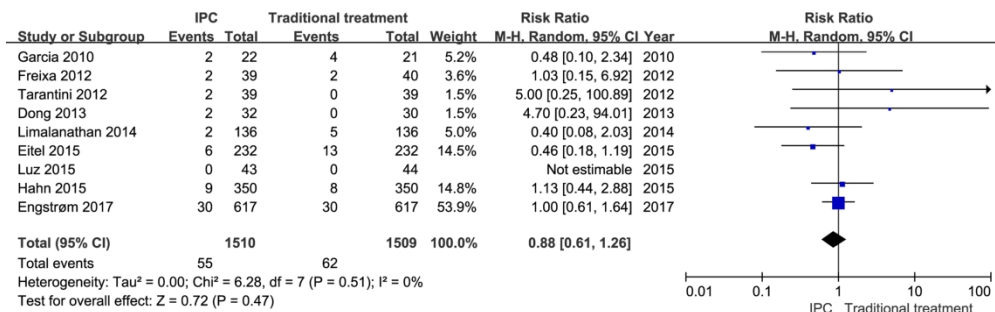
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15 308 **Fig 2: Ischemic postconditioning versus traditional PPCI on all-cause mortality in**

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17 309 **STEMI patients undergoing PPCI.**

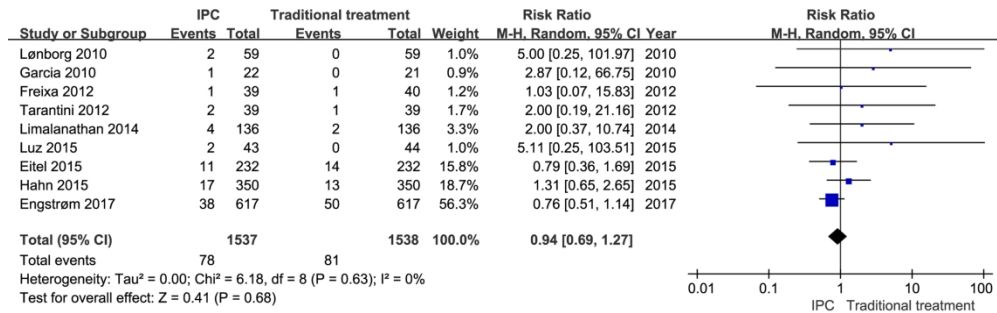
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19 310 **Fig 3: Ischemic postconditioning versus traditional PPCI on MACE in STEMI patients**

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21 311 **undergoing PPCI.**

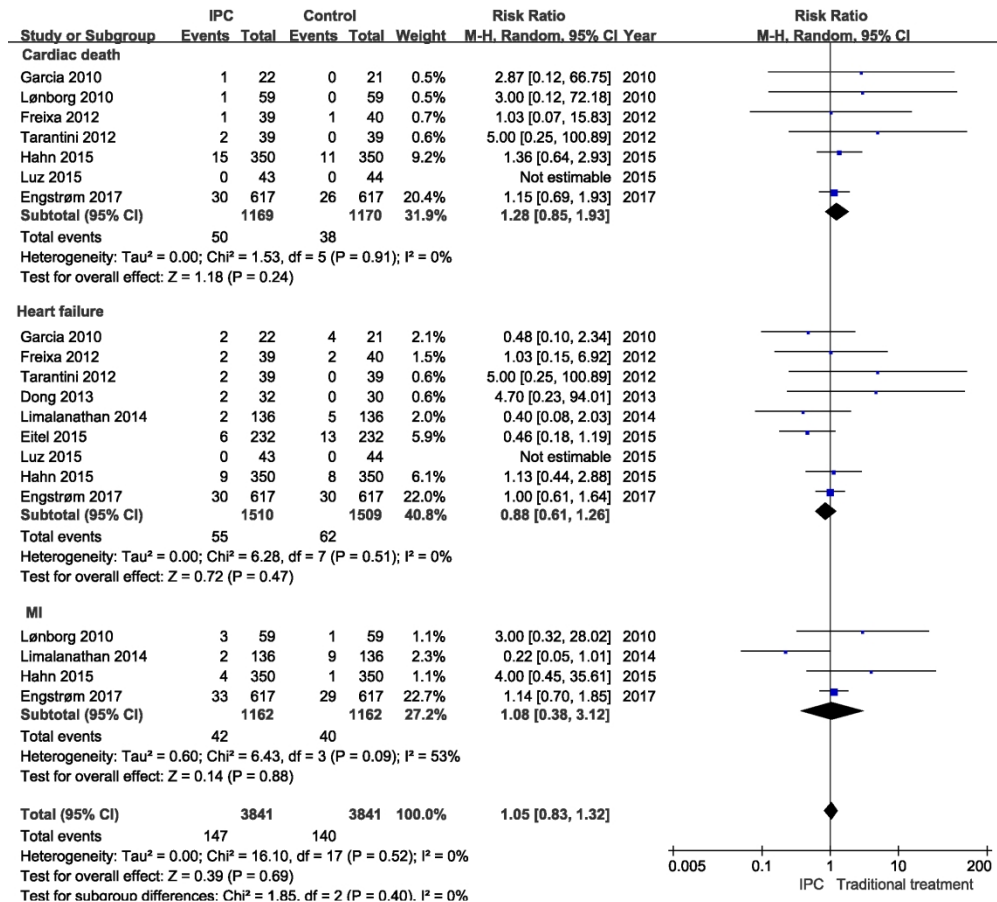
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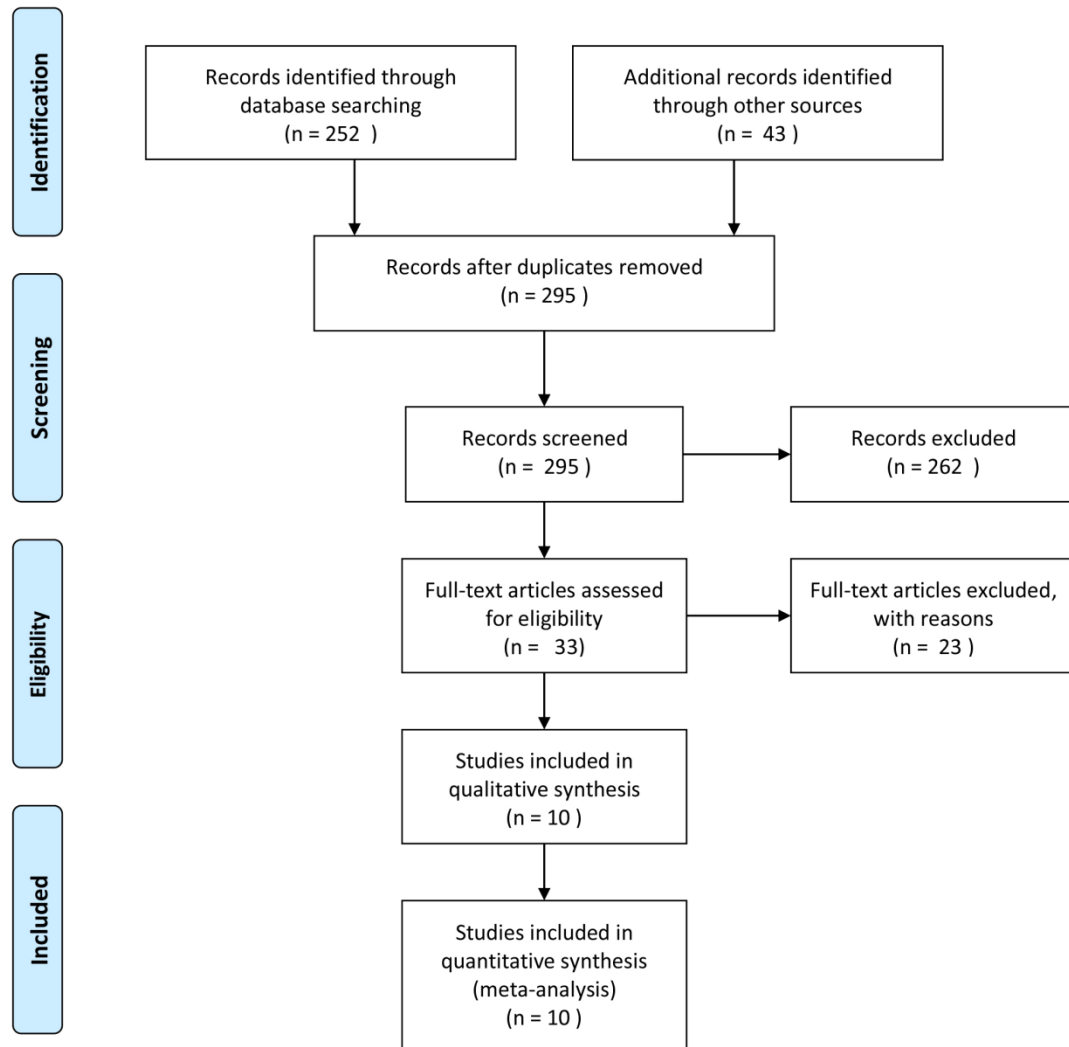
PubMed

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)	-	-	-

**PRISMA 2009 Flow Diagram**

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Dong 2013	?	?	?	?	+	+	+
Eitel 2015	+	+	+	+	+	+	+
Engstrøm 2017	+	+	+	+	+	+	+
Freixa 2012	+	+	+	+	+	+	+
Garcia 2010	?	?	?	?	+	+	+
Hahn 2015	+	+	+	+	+	+	+
Limalanathan 2014	+	+	?	?	+	+	+
Luz 2015	+	+	?	?	+	+	+
Lønborg 2010	+	+	+	+	+	+	+
Tarantini 2012	+	+	+	+	+	+	+

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

For more information, visit: www.prisma-statement.org.

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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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

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Manuscripts

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

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

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

27 Results: Ten studies that had enrolled 3,137 patients were included. PPCI combined
28 with IPC failed to reduce heart failure (RR: 0.88, 95% CI: 0.61,1.26, P = 0.47), all-cause
29 mortality (RR: 0.94, 95% CI: 0.69,1.27, P = 0.68), MACE (RR: 1.05, 95% CI: 0.83,1.32, P
30 = 0.69), cardiac death (RR: 1.28, 95% CI: 0.85,1.93, P = 0.24), and MI (RR: 1.08, 95% CI:
31 0.38,3.12, P = 0.88).

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

35 Strengths and limitations of this study

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4 36 1. Unlike previous studies, we focused on clinical outcomes such as heart failure, or
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6 37 all-cause mortality.
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10 38 2. The recent DANAMI-3-iPOST study, which randomized 1,234 patients with STEMI to
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12 39 conventional PPCI or PPCI with IPC, was included, which may alter the conclusion
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14 40 regarding STEMI treatment.
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18 41 3. In order to give a solid conclusion, sensitivity and subgroup analyses were performed.
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21 42 4. A limitation of this meta-analysis is the inclusion of a relatively low number of
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23 43 patients.
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30 45 Key words: Ischemic postconditioning therapy (IPC); percutaneous coronary
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32 46 intervention (PCI); all-cause mortality; major adverse cardiac events (MACE);
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35 47 meta-analysis
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38 48 **Background**

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43 49 Primary percutaneous coronary intervention (PPCI) has been proven to be effective
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45 50 in patients with ST-segment elevation myocardial infarction (STEMI) and has become a
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47 51 first-line therapy^[1]. Although PPCI is effective in restoring blood flow, ischemic reperfusion
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49 52 injury is not inevitable. Reperfusion injury can also induce deleterious effects with a
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51 53 subsequent increase in infarct size, which accounts for up to 50% of the final size of a
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53 54 myocardial infarct^[2]. Both animal models of infarction and clinical proof-of-concept studies
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4 55 have shown that reopening of the infarct-related artery (IRA), followed by repetitive brief
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6 56 interruptions of blood flow before sustained reperfusion, may protect the myocardium
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9 57 against reperfusion injury, which is evaluated using cardiac biomarkers, single-photon
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11 58 emission computed tomography (SPECT), echocardiography, and contrast-enhanced
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13 59 cardiac magnetic resonance (ce-CMR)^[3-7]. This strategy, known as ischemic
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15 60 postconditioning (IPC), is safe and easy to perform without additional cost^[8]. Related
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17 61 meta-analyses, using the above methods for evaluation, have also demonstrated that IPC
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19 62 can rescue cardiomyocytes^[9-11]. However, whether improvements in these surrogate
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21 63 markers translate into improved clinical outcomes, such as reduction in heart failure
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23 64 and/or all-cause mortality, remains controversial. The recent DANAMI-3-iPOST study,
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25 65 which randomized 1,234 patients with STEMI to conventional PPCI or PPCI with IPC did
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27 66 not provide evidence indicating that PPCI with IPC leads to better clinical outcomes
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29 67 compared to traditional PPCI^[11].

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36 68 Given the confusion surrounding the different results related to IPC combined with
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38 69 PPCI, a meta-analysis was done to evaluate whether IPC has a beneficial effect on hard
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40 70 endpoints, such as heart failure, all-cause mortality, and MACE, compared to traditional
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42 71 PPCI.

43 44 45 46 47 48 72 **Methods**

49 50 51 52 73 **Patient and Public Involvement**

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55 74 Qualitative patient data were the focus of this synthesis; however, patients and the

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4 75 public were not involved in the design of the study or analysis of the data.
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7 76 **Search strategy and selection criteria**

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11 77 This meta-analysis is reported in accordance to the Preferred Reporting Items for
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13 78 System Reviews and Meta-Analyses (PRISMA) Statement and was registered at
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16 79 International Prospective Register of Systematic Reviews (CRD42017063959)^[12].
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18 80 PubMed, Embase, and Cochrane Library were systematically searched for relevant
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21 81 articles published before May 1, 2018. The terms “ischemic postconditioning”,
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23 82 “postconditioning”, “percutaneous coronary intervention (PCI)”, “controlled trial”,
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26 83 “intervention study”, and “randomized controlled trials (RCTs)” were used to identify
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28 84 randomized controlled trials. MeSH, Emtree, and keyword search terms were used in
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31 85 combination (Supplementary file). The results were limited to trials published in English.
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33 86 The reference lists of relevant studies and reviews, editorials, and letters were manually
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36 87 searched to identify additional articles. Endnote (Thompson ISI ResearchSoft,
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38 88 Philadelphia, PA, USA) was used to manage relevant articles and remove duplicate
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44 90 **Study criteria, quality assessment, and data extraction**

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47 91 Studies were included in the meta-analysis when they met the following criteria: (1)
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50 92 the study design was a prospective randomized controlled clinical trial (RCT); (2) all
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53 93 patients with STEMI underwent PPCI treatment; (3) patients were randomly assigned to
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56 94 the PPCI in combination with the IPC group or the conventional PPCI group; (4) follow-up
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95 time was not less than one month; and (5) relevant data were retrievable. When relevant
96 data were missing, the authors were contacted by e-mail before excluding the references
97 for inaccessibility of data.

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

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

112 Data analysis

113 Meta-analysis was performed to calculate the risk ratio (RR) and 95% confidence
114 interval (CI). Pooled RRs were computed as the Mantel-Haenszel-weighted average of

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4 115 the RRs for all included studies. Because the true treatment effect of various IPC
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6 116 protocols may have varied among the included trials, the random-effects model was used
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9 117 in the analysis. Statistical heterogeneity among the trial-specific RRs was checked and
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11 118 quantified by the I^2 statistic, and a P-value ≤ 0.05 was considered statistically significant.
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14 119 We performed sensitivity analysis to assess the contribution of each study to the pooled
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16 120 estimation by excluding one trial at a time and recalculating the pooled RR estimation for
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18 121 the remaining studies. Subgroup analyses were conducted in terms of time of symptom
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20 122 onset, IPC protocols, antiplatelet therapies. Data analysis was performed on an
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22 123 intention-to-treat basis. All analysis was performed using Review Manager Software
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24 124 (Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic
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26 125 Cochrane Centre, The Cochrane Collaboration, 2014.).
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126 Outcomes

127 Search results and bias assessment

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40 128 Supplementary Figure 1 shows that the combined search strategy identified 273
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42 129 potential relevant manuscripts, from which 33 studies were retrieved for more detailed
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44 130 assessment. A total of 10 RCTs, involving 3137 patients, are included in this
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46 131 meta-analysis^[7, 8, 13-20]. The Cochrane Reviewer's Handbook 4.2 was used to assess risk
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48 132 of bias (Supplementary Fig 2). No high-risk studies were identified and six studies had a
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50 133 low risk of bias.
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55 134 The main features of the 10 included RCTs and the baseline clinical characteristics of
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135 the patients are presented in Table 1. In the 10 trials, 1,569 patients (50%) were randomly
 136 assigned to PPCI with IPC. The mean age of the trial patients was 61 years and 78% of
 137 the patients were male. The IPC protocol (cycles × ischemia/reperfusion in seconds)
 138 varied between studies and were as follows: 30"/30" × 4 in four studies, 60"/60" × 4 in five
 139 studies, and 30"/30" × 3 in one study. Follow-up among trials varied from 1 month to 41
 140 months. The time of symptom onset varied between studies from 6 hours in 2 studies to
 141 12 hours in 8 studies.

142 **Table 1: Detailed characteristics of included studies.**

Study	Patient s (IPC/C)	Countr y	Age (years,IP C/C)	Male (%,IPC/C)	Symptom onset (hours)	Protocol (duration×cycl es)	LAD (%,IP C/C)	DES (%,IPC/ C)	Follow-up (months)
Lønborg 2010	59/59	Denma rk	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
Limalan athan 2014	136/13 6	Norway	61/60	84/80	≤6	60"/60" × 4	46/51	29/29	4
Hahn 2015	350/35 0	South Korea	60/60	79/75	≤12	60"/60" × 4	47/45	86/86	12
Eitel 2015	232/23 2	Germa ny	62/65	76/71	≤12	30"/30" × 4	42/51	-	6
Luz 2015	43/44	Portug al	57/58	88/82	≤12	60"/60" × 4	47/43	65/71	14
Engstrø m 2017	617/61 7	Denma rk	63/62	80/79	≤12	30"/30" × 4	43/40	93/93	38

143 IPC: Ischemic postconditioning group; C; control group(PPCI only); LAD: left descending

144 anterior branch; DES: drug-eluted stent

145 **Primary endpoint: heart failure**

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

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4 147 0.47) in the random-effects model (Fig 1). No evident statistical heterogeneity among
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6 148 studies was observed ($I^2 = 0$, $P = 0.51$). IPC during PPCI did not reduce heart failure
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9 149 compared to traditional PPCI.

150 **Secondary endpoints: all-cause mortality and MACE**

151 The pooled data showed that IPC did not reduce all-cause mortality compared to
152 traditional PPCI (RR: 0.94, 95% CI: 0.69,1.27, $P = 0.68$, Fig 2). No evident statistical
153 heterogeneity among studies was observed ($I^2=0$, $P = 0.63$). Furthermore, IPC did not
154 reduce cardiac death (RR: 1.28, 95% CI: 0.85,1.93, $P = 0.24$), MI (RR: 1.08, 95% CI:
155 0.38,3.12, $P = 0.88$) and heart failure (RR: 0.85, 95% CI: 0.59,1.23, $P = 0.40$). When all
156 events (MACE) were considered, IPC during PPCI provided no net benefit of IPC during
157 PPCI (RR: 1.05, 95% CI: 0.83,1.32, $P = 0.69$, Fig 3).

158 **Sensitivity analysis and potential sources of heterogeneity**

159 Sensitivity analysis was performed by excluding each included study, one at a time,
160 and recalculating the overall effects. The direction of the overall effects, in terms of heart
161 failure, MI, cardiac death, and all-cause mortality, were not influenced no matter which
162 study was excluded (Supplementary Table 1).

163 There were very little heterogeneities between studies with regard to the observed
164 effects on all-cause mortality ($I^2=0$, $p=0.63$) and cardiac death ($I^2=0$, $p=0.91$). However,
165 moderate between-study heterogeneity was identified in the case of MI ($I^2 = 53\%$, $P =$
166 0.09). MI heterogeneity was mainly caused by the Limalanathan 2014 study. When this

167 study was excluded, no heterogeneity was observed ($I^2 = 0\%$, $P = 0.40$) and the
 168 conclusions were still consistent with the previous analysis. Subgroup analysis did not
 169 identify any baseline risk factor, such as symptom onset, duration of follow-up, or
 170 antiplatelet therapies as a modifier of the relationship between IPC and clinical endpoints
 171 (Table 2). Sensitivity and subgroup analysis did not identify any patient- or study-level
 172 covariate as a significant source of heterogeneity, except for this subgroup analysis.

173 **Table 2: Subgroup analysis.**

	Cardiac death	Heart failure	MI	AI-cause mortality
Symptom onset				
≤6 hours	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)

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

175 Discussion

176 The current meta-analysis of 10 RCTs, including 3,137 patients with STEMI
 177 undergoing PPCI, showed that no reduction in heart failure, all-cause mortality, or MACE
 178 when comparing PPCI in combination with IPC to traditional PPCI over a mean follow-up
 179 of 20 months. Similarly, no improvement in clinical outcomes was shown in the subgroup
 180 analysis.

181 IPC was first introduced by Zhao et al. in 2003^[21]. Subsequent clinical trials and
 182 meta-analyses found a salutary effect of IPC on infarct size as evaluated by CK, CK-MB,
 183 troponin, SPECT, and cardiac function based on the left ventricular ejection fraction

184 (LVEF)^[3-5]. However, opposite results have also been reported^[8, 16-19]. The
185 DANAMI-3-iPOST trial, which is the largest study to date, showed that IPC did not reduce
186 infarct size^[8]. Furthermore, whether surrogate endpoints, such as infarct size, myocardial
187 salvage, and resolution of ST-segment elevation, translate into hard endpoints, such as
188 heart failure, all-cause mortality, or MACE, remains a point of debate. Unlike the above
189 surrogate endpoints, heart failure, all-cause mortality, and MACE are what are generally
190 considered to be most important by both clinicians and patients.

191 Previous meta-analyses mainly focused on cardiac biomarkers, cardiac imaging, and
192 cardiac function; however clinical outcomes are also very consequential. In the current
193 meta-analysis IPC was not shown to improve clinical outcomes, though several factors
194 may influence its effectiveness. A meta-analysis of 19 RCTs concluded that
195 cardioprotection as evaluated by cardiac enzyme leakage, infarct size, and left ventricular
196 function is more likely in patients with LAD artery involvement because of a greater
197 myocardial area is at risk.^[9] Zhou et al. performed a meta-analysis of 10 RCTs and found
198 that the effects of cardiac protection were more pronounced among young and male
199 patients and those who received direct-stenting^[10]. The IPC protocol is also an important
200 factor in determining the IPC efficacy. IPC may cause myocardial ischemia and expand
201 the infarct area. Several trials chose four cycles of 1 min of reperfusion followed by 1 min
202 of reocclusion. However, other trials selected four cycles of 30-s reperfusion followed by
203 30-s low-pressure balloon occlusion. However, the subgroup analyses in the current study
204 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 events, such as heart failure, the sample size is relatively small. Nonetheless, this meta-analysis is

225 the largest population-based analysis of IPC. Additional RCTs are necessary to evaluate
226 long-term clinical outcomes.

227 **Conclusions**

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

231 **Additional Information**

232 The authors have no conflicts of interest to declare.

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

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

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241 Competing interests: None

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4 242 Data sharing statement: All data generated and research materials used during this
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6 243 systematic review and meta-analysis are available from the corresponding author on
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9 244 reasonable request.
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For peer review only

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10 307 Figure legends

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13 308 **Fig 1: Effect of PPCI with IPC versus PPCI only on heart failure in STEMI patients**

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16 309 **undergoing PPCI**

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19 310 PPCI:primary percutaneous coronary intervention;IPC: Ischemic postconditioning

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22 311 group;STEMI:ST-segment elevation myocardial infarction

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25 312 **Fig 2: Effect of PPCI with IPC versus PPCI only on all-cause mortality in STEMI**

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28 313 **patients undergoing PPCI.**

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31 314 PPCI:primary percutaneous coronary intervention;IPC: Ischemic postconditioning

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34 315 group;STEMI:ST-segment elevation myocardial infarction

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37 316 **Fig 3: Effect of PPCI with IPC versus PPCI only on MACE in STEMI patients**

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40 317 **undergoing PPCI.**

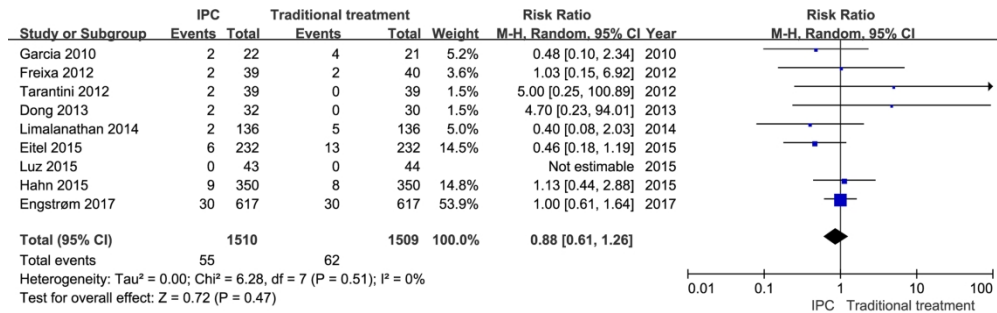
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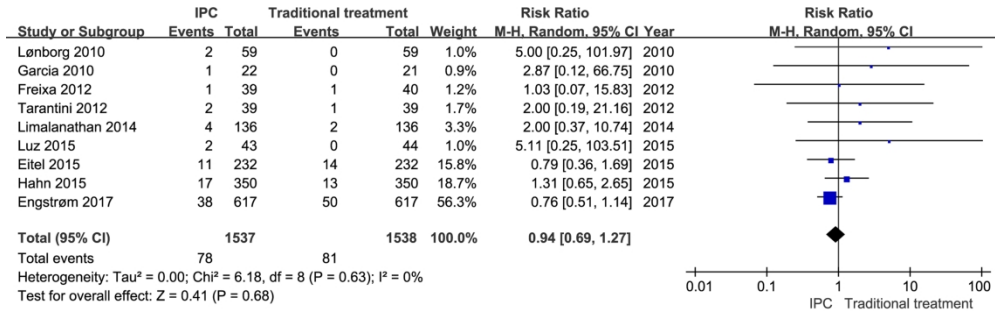
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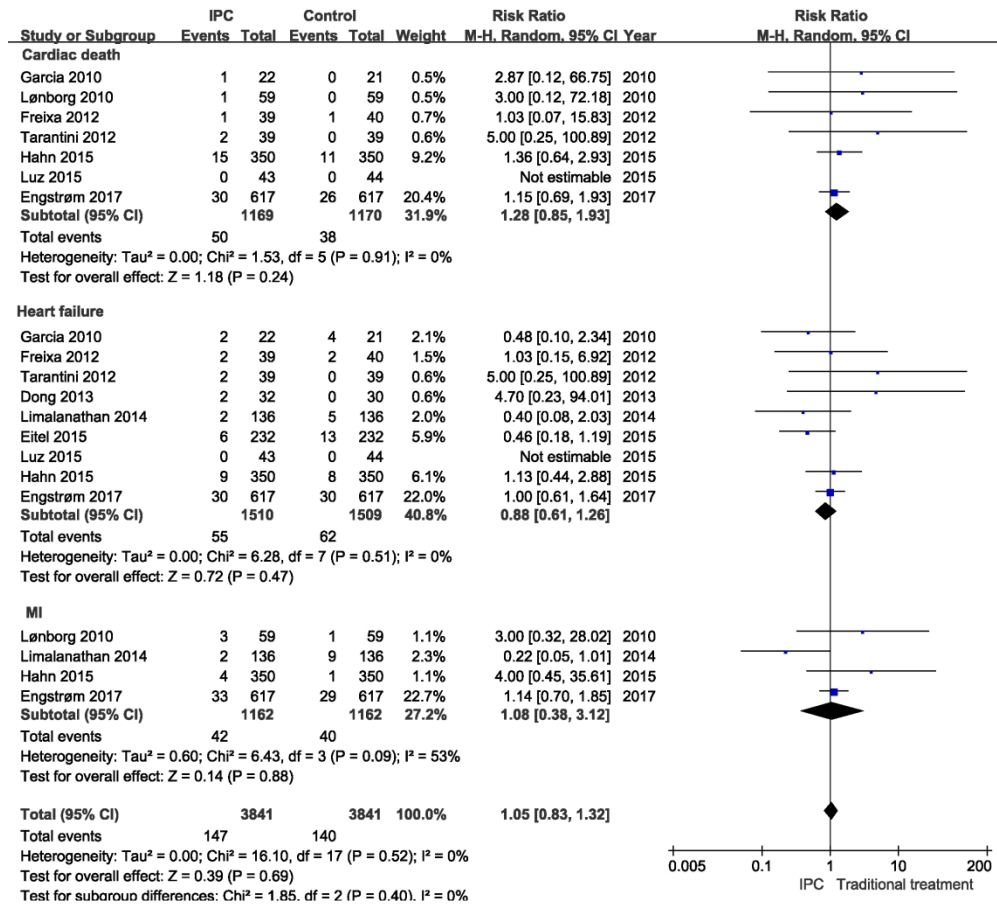
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5 Effects of ischemic postconditioning on outcomes of
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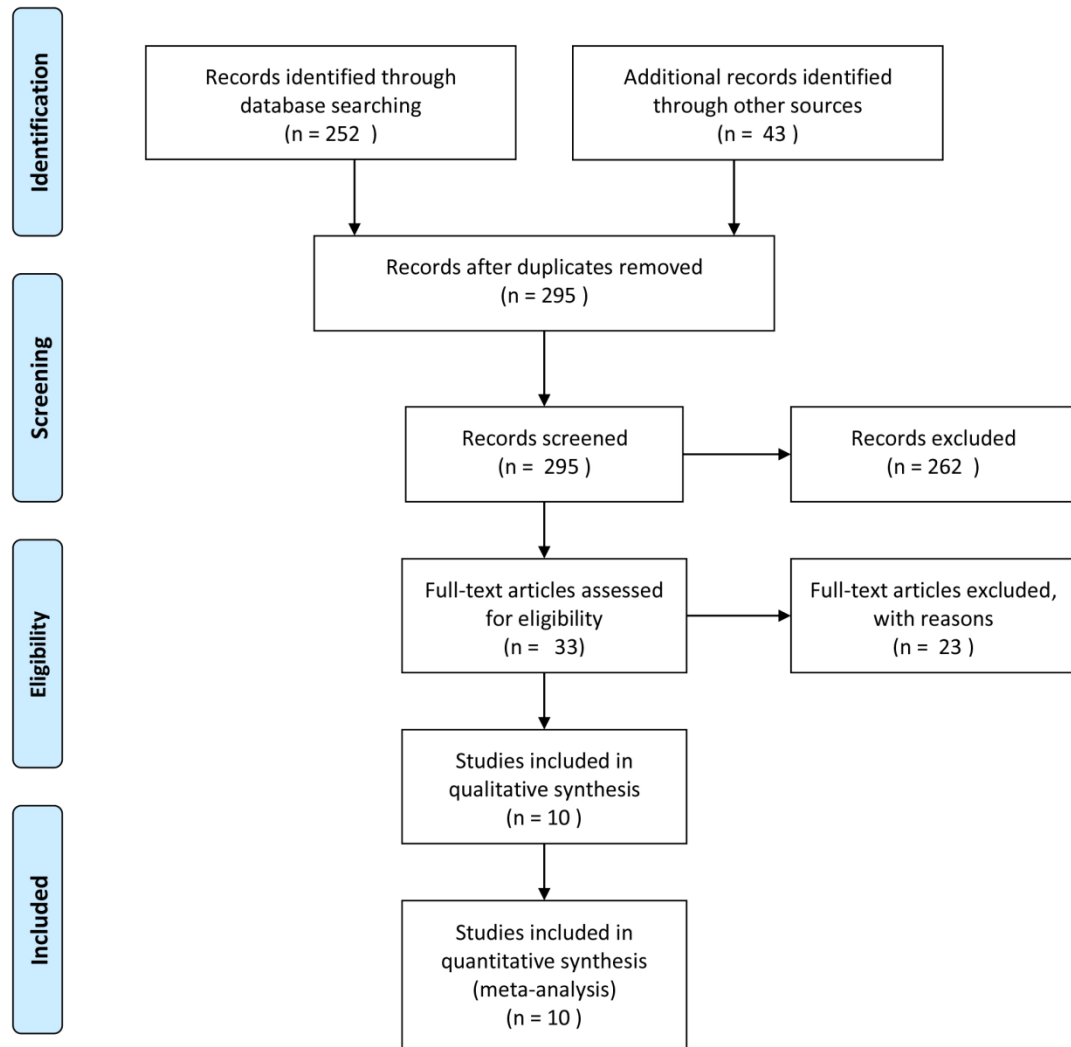
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- #2 Search conditioning[Title/Abstract] 55132
- #3 Search percutaneous coronary intervention[MeSH Terms] 46594
- #4 Search PCI[Title/Abstract] 21330
- #5 Search (PCI[Title/Abstract]) OR percutaneous coronary intervention[MeSH Terms] 55884
- #6 Search (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)	-	-	-



PRISMA 2009 Flow Diagram



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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Dong 2013	?	?	?	?	+	+	+
Eitel 2015	+	+	+	+	+	+	+
Engstrøm 2017	+	+	+	+	+	+	+
Freixa 2012	+	+	+	+	+	+	+
Garcia 2010	?	?	?	?	+	+	+
Hahn 2015	+	+	+	+	+	+	+
Limalanathan 2014	+	+	?	?	+	+	+
Luz 2015	+	+	?	?	+	+	+
Lønborg 2010	+	+	+	+	+	+	+
Tarantini 2012	+	+	+	+	+	+	+

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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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
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Manuscripts

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

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4 16 Objective: The aim of this meta-analysis was to evaluate the effects of ischemic
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6 17 postconditioning therapy (IPC) on hard clinical endpoints in ST-segment elevation
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9 18 myocardial infarction (STEMI) patients who underwent primary percutaneous coronary
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12 19 intervention (PPCI).

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14 20 Design: Systematic review and meta-analysis to evaluate the effects of IPC on the
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17 21 outcomes of patients with STEMI.

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19 22 Data sources: PubMed, Embase, and the Cochrane Library were systematically
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22 23 searched for relevant articles published prior to May 1, 2018.

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24 24 Eligibility criteria for selecting studies: Randomized trials comparing conventional
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27 25 PPCI to PPCI combined with IPC in STEMI patients were included. The primary endpoint
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30 26 was heart failure. Secondary endpoints were all-cause mortality and major adverse cardiac
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33 27 events (MACE), including cardiac death, heart failure, and myocardial infarction (MI). The
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36 28 Cochrane Reviewer's Handbook 4.2 was used to assess the risk of bias.

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38 29 Data extraction and synthesis: Relevant data were extracted by two independent
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41 30 investigators. We derived pooled risk ratios (RRs) with random effects models. Sensitivity
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44 31 and subgroup analyses were performed.

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46 32 Results: Ten studies that had enrolled 3,137 patients were included. PPCI combined
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49 33 with IPC failed to reduce heart failure (RR: 0.88, 95% CI: 0.61, 1.26, P = 0.47), all-cause
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52 34 mortality (RR: 0.94, 95% CI: 0.69, 1.27, P = 0.68), MACE (RR: 1.05, 95% CI: 0.83, 1.32, P
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55 35 = 0.69), cardiac death (RR: 1.28, 95% CI: 0.85, 1.93, P = 0.24), and MI (RR: 1.08, 95% CI:
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58 36 0.38, 3.12, P = 0.88).

59 37 Conclusions: IPC combined with PPCI does not reduce heart failure, MACE, and all-
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4 38 cause mortality compared to traditional PPCI in patients with STEMI. (CRD42017063959)

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9 40 Key words: Ischemic postconditioning therapy (IPC); percutaneous coronary
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11 41 intervention (PCI); all-cause mortality; major adverse cardiac events (MACE); meta-
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14 42 analysis

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19 44 Strengths and limitations of this study

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22 45 1. Unlike previous studies, we focused on clinical outcomes such as heart failure, or all-
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24 46 cause mortality.

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27 47 2. The recent DANAMI-3-iPOST study, which randomized 1,234 patients with STEMI to
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29 48 conventional PPCI or PPCI with IPC, was included, which may alter the conclusion
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31 49 regarding STEMI treatment.

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34 50 3. In order to give a solid conclusion, sensitivity and subgroup analyses were performed.

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37 51 4. A limitation of this meta-analysis is the inclusion of a relatively low number of patients.

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41 42 43 44 53 **Background**

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47 54 Primary percutaneous coronary intervention (PPCI) has been proven to be effective
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49 55 in patients with ST-segment elevation myocardial infarction (STEMI) and has become a
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51 56 first-line therapy^[1]. Although PPCI is effective in restoring blood flow, ischemic reperfusion
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53 57 injury is not inevitable. Reperfusion injury can also induce deleterious effects with a
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55 58 subsequent increase in infarct size, which accounts for up to 50% of the final size of a
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4 59 myocardial infarct^[2]. Both animal models of infarction and clinical proof-of-concept studies
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6 60 have shown that reopening of the infarct-related artery (IRA), followed by repetitive brief
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9 61 interruptions of blood flow before sustained reperfusion, may protect the myocardium
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12 62 against reperfusion injury, which is evaluated using cardiac biomarkers, single-photon
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15 63 emission computed tomography (SPECT), echocardiography, and contrast-enhanced
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17 64 cardiac magnetic resonance (ce-CMR)^[3-7]. This strategy, known as ischemic
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20 65 postconditioning (IPC), is safe and easy to perform without additional cost^[8]. Related meta-
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23 66 analyses, using the above methods for evaluation, have also demonstrated that IPC can
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26 67 rescue cardiomyocytes^[9-11]. However, whether improvements in these surrogate markers
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29 68 translate into improved clinical outcomes, such as reduction in heart failure and/or all-
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32 69 cause mortality, remains controversial. The recent DANAMI-3-iPOST study, which
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35 70 randomized 1,234 patients with STEMI to conventional PPCI or PPCI with IPC did not
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38 71 provide evidence indicating that PPCI with IPC leads to better clinical outcomes compared
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41 72 to traditional PPCI^[11].

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43 73 Given the confusion surrounding the different results related to IPC combined with
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46 74 PPCI, a meta-analysis was done to evaluate whether IPC has a beneficial effect on hard
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49 75 endpoints, such as heart failure, all-cause mortality, and MACE, compared to traditional
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52 76 PPCI.
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77 **Methods**

78 **Patient and Public Involvement**

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

81 **Search strategy and selection criteria**

82 This meta-analysis is reported in accordance to the Preferred Reporting Items for
83 System Reviews and Meta-Analyses (PRISMA) Statement and was registered at
84 International Prospective Register of Systematic Reviews (CRD42017063959)^[12]. PubMed,
85 Embase, and Cochrane Library were systematically searched for relevant articles
86 published before May 1, 2018. The terms “ischemic postconditioning”, “postconditioning”,
87 “percutaneous coronary intervention (PCI)”, “controlled trial”, “intervention study”, and
88 “randomized controlled trials (RCTs)” were used to identify randomized controlled trials.
89 MeSH, Emtree, and keyword search terms were used in combination (Supplementary file).
90 The results were limited to trials published in English. The reference lists of relevant studies
91 and reviews, editorials, and letters were manually searched to identify additional articles.
92 Endnote (Thompson ISI ResearchSoft, Philadelphia, PA, USA) was used to manage
93 relevant articles and remove duplicate articles.

94 **Study criteria, quality assessment, and data extraction**

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

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4 96 the study design was a prospective randomized controlled clinical trial (RCT); (2) all
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6 97 patients with STEMI underwent PPCI treatment; (3) patients were randomly assigned to
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9 98 the PPCI in combination with the IPC group or the conventional PPCI group; (4) follow-up
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12 99 time was not less than one month; and (5) relevant data were retrievable. When relevant
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14 100 data were missing, the authors were contacted by e-mail before excluding the references
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17 101 for inaccessibility of data.

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19 102 The primary endpoint was heart failure. Secondary endpoints were all-cause mortality
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22 103 and major adverse cardiac events (MACE), including cardiac death, heart failure, and
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24 104 myocardial infarction (MI). All clinical endpoints were evaluated according to per protocol
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27 105 definitions, at the longest available follow-up. Study quality was judged by evaluating trial
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30 106 procedures for random sequence generation (selection bias), allocation concealment
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33 107 (selection bias), blinding of participants and personnel (performance bias), blinding of
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35 108 outcome assessment (detection bias), and incomplete outcome data (attrition bias). The
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38 109 Cochrane Reviewer's Handbook 4.2 was used to assess risk of bias.

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40 110 Relevant data were extracted by two independent investigators (XF Peng and JB
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43 111 Huang). Disagreements were resolved by consensus or a third investigator (XQ Hu). The
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46 112 following data were abstracted from the selected articles: first author, publication date,
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49 113 study design, onset of symptoms, characteristics of included participants, total number of
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52 114 IPC and conventional groups, events of the IPC and conventional groups, stent type, and
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54 115 follow-up time.
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116 Data analysis

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

130 Outcomes

131 Search results and bias assessment

132 Supplementary Figure 1 shows that the combined search strategy identified 273
133 potential relevant manuscripts, from which 33 studies were retrieved for more detailed
134 assessment. A total of 10 RCTs, involving 3137 patients, are included in this meta-
135 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

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Li i 2012									
Dong	32/30	China	70/68	63/73	≤12	30"/30" × 3	57/43	-	1
2013									
Limalan	136/13	Norway	61/60	84/80	≤6	60"/60" × 4	46/51	29/29	4
athan	6								
2014									
Hahn	350/35	South	60/60	79/75	≤12	60"/60" × 4	47/45	86/86	12
2015	0	Korea							
Eitel	232/23	Germa	62/65	76/71	≤12	30"/30" × 4	42/51	-	6
2015	2	ny							
Luz	43/44	Portug	57/58	88/82	≤12	60"/60" × 4	47/43	65/71	14
2015		al							
Engstrø	617/61	Denma	63/62	80/79	≤12	30"/30" × 4	43/40	93/93	38
m 2017	7	rk							

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.

154 **Secondary endpoints: all-cause mortality and MACE**

155 The pooled data showed that IPC did not reduce all-cause mortality compared to
156 traditional PPCI (RR: 0.94, 95% CI: 0.69,1.27, P = 0.68, Fig 2). No evident statistical
157 heterogeneity among studies was observed ($I^2=0$, P = 0.63). Furthermore, IPC did not
158 reduce cardiac death (RR: 1.28, 95% CI: 0.85,1.93, P = 0.24), MI (RR: 1.08, 95% CI:
159 0.38,3.12, P = 0.88) and heart failure (RR: 0.85, 95% CI: 0.59,1.23, P = 0.40). When all
160 events (MACE) were considered, IPC during PPCI provided no net benefit of IPC during
161 PPCI (RR: 1.05, 95% CI: 0.83,1.32, P = 0.69, Fig 3).

162 **Sensitivity analysis and potential sources of heterogeneity**

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

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

175 **Table 2: Subgroup analysis.**

	Cardiac death	Heart failure	MI	AI-cause mortality
Symptom onset				
≤6 hours	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)

176 **MI: myocardial infarction**

177 Discussion

178 The current meta-analysis of 10 RCTs, including 3,137 patients with STEMI
179 undergoing PPCI, showed that no reduction in heart failure, all-cause mortality, or MACE
180 when comparing PPCI in combination with IPC to traditional PPCI over a mean follow-up
181 of 20 months. Similarly, no improvement in clinical outcomes was shown in the subgroup
182 analysis.

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

193 Previous meta-analyses mainly focused on cardiac biomarkers, cardiac imaging, and
194 cardiac function; however clinical outcomes are also very consequential. In the current
195 meta-analysis IPC was not shown to improve clinical outcomes, though several factors
196 may influence its effectiveness. A meta-analysis of 19 RCTs concluded that
197 cardioprotection as evaluated by cardiac enzyme leakage, infarct size, and left ventricular

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4 198 function is more likely in patients with LAD artery involvement because of a greater
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6 199 myocardial area is at risk.^[9] Zhou et al. performed a meta-analysis of 10 RCTs and found
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9 200 that the effects of cardiac protection were more pronounced among young and male
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11 201 patients and those who received direct-stenting^[10]. The IPC protocol is also an important
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14 202 factor in determining the IPC efficacy. IPC may cause myocardial ischemia and expand
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17 203 the infarct area. Several trials chose four cycles of 1 min of reperfusion followed by 1 min
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19 204 of reocclusion. However, other trials selected four cycles of 30-s reperfusion followed by
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22 205 30-s low-pressure balloon occlusion. However, the subgroup analyses in the current study
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25 206 found no differences in the effectiveness of IPC when comparing different protocols.

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27 207 Time of symptom onset, which is an independent predictor of MACE in patients with
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30 208 STEMI undergoing PPCI, may have influenced the results of these trials. However,
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33 209 subgroup analysis in this study did not detect differences between trials related to time of
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36 210 symptom onset. The key reason is that IPC might have no effect on cardioprotection, thus
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39 211 the results of the subgroup analysis in this study were neutral. Furthermore, the sample
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42 212 size of the studies may have been too small to detect minor beneficial effects. Several
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45 213 confounding factors, such as baseline characteristics of patients, coexisting diseases,
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48 214 medications, and IPC strategies used, may have influenced the cardioprotective benefits
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51 215 of IPC. With the use of novel antiplatelet and lipid-lowering agents and timely PPCI, the
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54 216 outcome of STEMI has significantly improved. The decreasing mortality rate also makes it
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57 217 harder to demonstrate minor benefits of using additional therapy.

218 **Limitations**

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

229 **Conclusions**

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

233 **Additional Information**

234 The authors have no conflicts of interest to declare.

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

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

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244 Competing interests: None

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

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9 309 Figure legends

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11 310 **Fig 1: Effect of PPCI with IPC versus PPCI only on heart failure in STEMI patients**

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14 311 **undergoing PPCI**

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17 312 PPCI:primary percutaneous coronary intervention, IPC: Ischemic postconditioning
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19 313 group.

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22 314 **Fig 2: Effect of PPCI with IPC versus PPCI only on all-cause mortality in STEMI**

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24 315 **patients undergoing PPCI.**

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27 316 PPCI:primary percutaneous coronary intervention, IPC: Ischemic postconditioning
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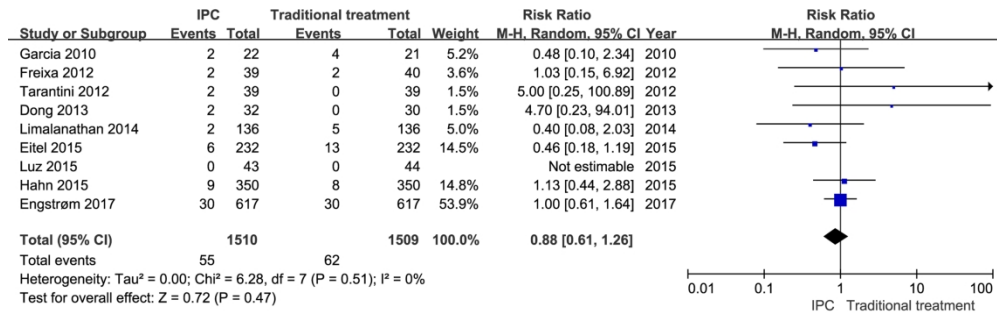
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32 318 **Fig 3: Effect of PPCI with IPC versus PPCI only on MACE in STEMI patients**

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34 319 **undergoing PPCI.**

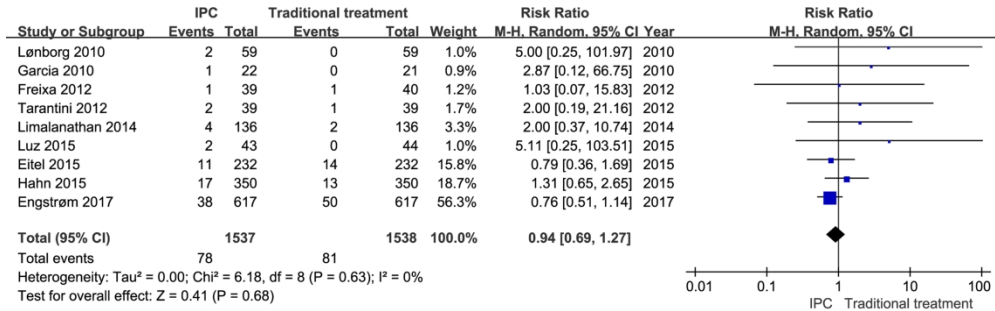
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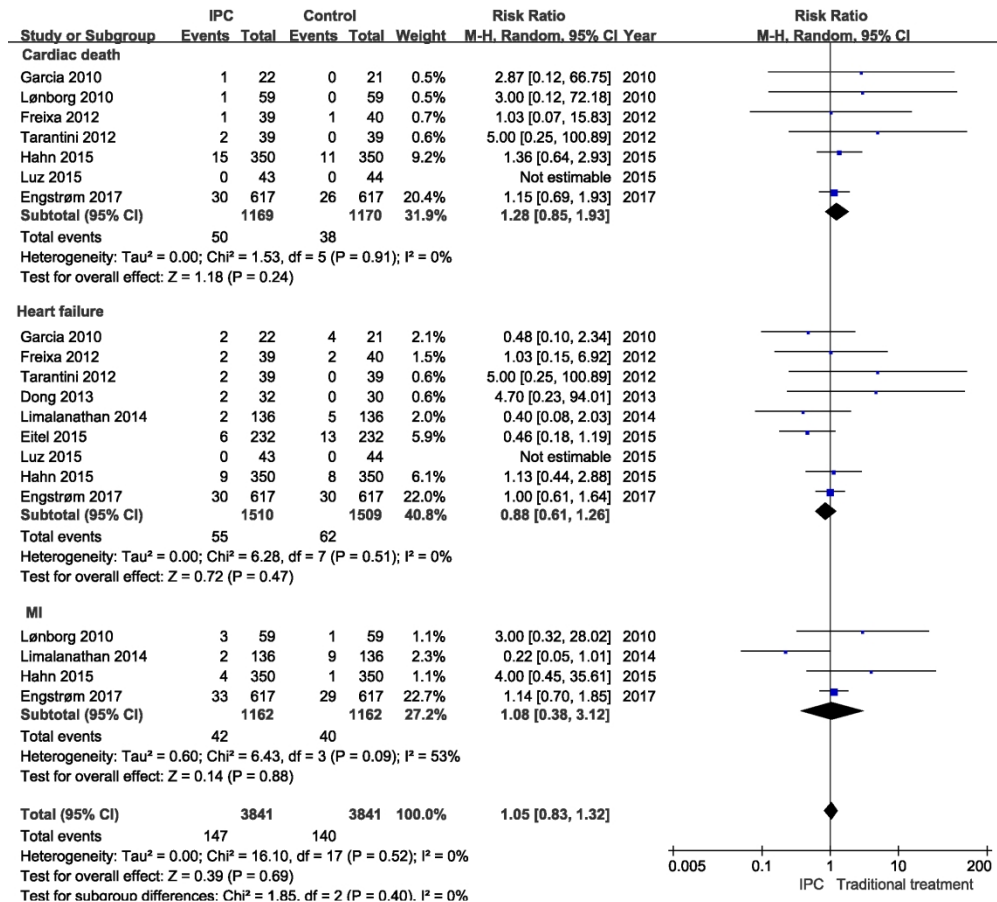
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5 1 Effects of ischemic postconditioning on outcomes of
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10 3 underwent primary percutaneous coronary intervention: a
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12 4 meta-analysis
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PubMed

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

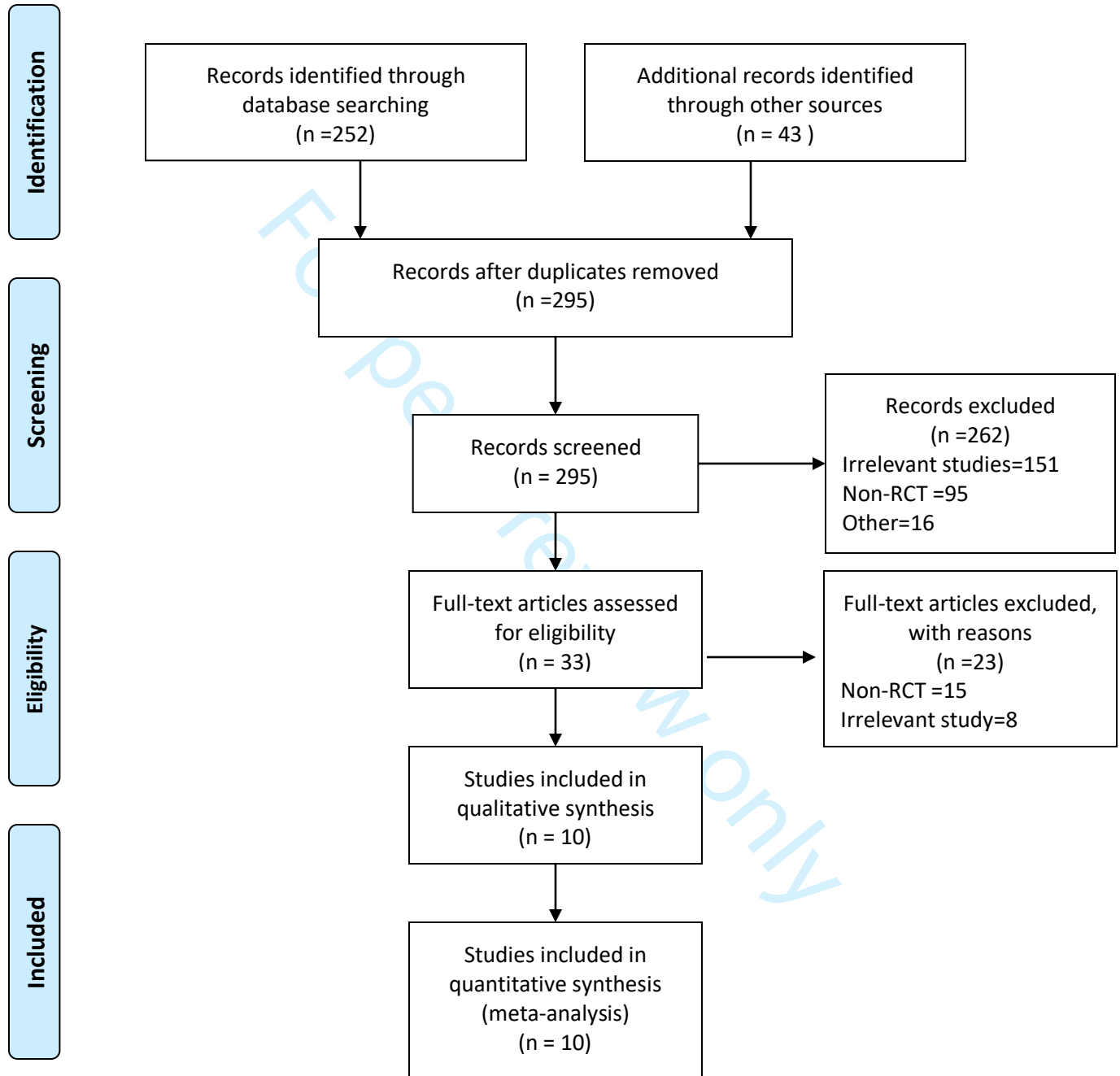
#4 Search PCI[Title/Abstract] 21330

#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.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Dong 2013	?	?	?	?	+	+	+
Eitel 2015	+	+	+	+	+	+	+
Engstrøm 2017	+	+	+	+	+	+	+
Freixa 2012	+	+	+	+	+	+	+
Garcia 2010	?	?	?	?	+	+	+
Hahn 2015	+	+	+	+	+	+	+
Limalanathan 2014	+	+	?	?	+	+	+
Luz 2015	+	+	?	?	+	+	+
Lønborg 2010	+	+	+	+	+	+	+
Tarantini 2012	+	+	+	+	+	+	+

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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Manuscript ID	bmjopen-2018-022509.R4
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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

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Manuscripts

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

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4 16 Objective: The aim of this meta-analysis was to evaluate the effects of ischemic
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6 17 postconditioning therapy (IPC) on hard clinical endpoints in ST-segment elevation
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9 18 myocardial infarction (STEMI) patients who underwent primary percutaneous coronary
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12 19 intervention (PPCI).

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14 20 Design: Systematic review and meta-analysis to evaluate the effects of IPC on the
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17 21 outcomes of patients with STEMI.

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19 22 Data sources: PubMed, Embase, and the Cochrane Library were systematically
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22 23 searched for relevant articles published prior to May 1, 2018.

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24 24 Eligibility criteria for selecting studies: Randomized trials comparing conventional
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27 25 PPCI to PPCI combined with IPC in STEMI patients were included. The primary endpoint
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30 26 was heart failure. Secondary endpoints were all-cause mortality and major adverse cardiac
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33 27 events (MACE), including cardiac death, heart failure, and myocardial infarction (MI). The
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36 28 Cochrane Reviewer's Handbook 4.2 was used to assess the risk of bias.

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38 29 Data extraction and synthesis: Relevant data were extracted by two independent
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41 30 investigators. We derived pooled risk ratios (RRs) with random effects models. Sensitivity
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44 31 and subgroup analyses were performed.

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46 32 Results: Ten studies that had enrolled 3,137 patients were included. PPCI combined
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49 33 with IPC failed to reduce heart failure (RR: 0.88, 95% CI: 0.61, 1.26, $P = 0.47$; absolute risk:
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52 34 3.64% in the IPC group and 4.11% in the PPCI only group), all-cause mortality (RR: 0.94,
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55 35 95% CI: 0.69, 1.27, $P = 0.68$; absolute risk: 5.07% in the IPC group and 5.27% in the PPCI
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58 36 only), MACE (RR: 1.05, 95% CI: 0.83, 1.32, $P = 0.69$; absolute risk: 9.37% in the IPC group
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60 37 and 8.93% in the PPCI only), cardiac death (RR: 1.28, 95% CI: 0.85, 1.93, $P = 0.24$;

38 absolute risk: 4.28% in the IPC group and 3.25% in the PPCI only group), and MI (RR:
39 1.08, 95% CI: 0.38,3.12, P = 0.88; absolute risk: 3.61% in the IPC group and 3.44% in the
40 PPCI only group).

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

43
44 Key words: Ischemic postconditioning therapy (IPC); percutaneous coronary
45 intervention (PCI); all-cause mortality; major adverse cardiac events (MACE); meta-
46 analysis

47 48 Strengths and limitations of this study

- 49 1. Unlike previous studies, we focused on clinical outcomes such as heart failure, or all-
50 cause mortality.
- 51 2. The recent DANAMI-3-iPOST study, which randomized 1,234 patients with STEMI to
52 conventional PPCI or PPCI with IPC, was included, which may alter the conclusion
53 regarding STEMI treatment.
- 54 3. In order to give a solid conclusion, sensitivity and subgroup analyses were performed.
- 55 4. A limitation of this meta-analysis is the inclusion of a relatively low number of patients.

56 57 **Background**

58 Primary percutaneous coronary intervention (PPCI) has been proven to be effective

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4 59 in patients with ST-segment elevation myocardial infarction (STEMI) and has become a
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6 60 first-line therapy^[1]. Although PPCI is effective in restoring blood flow, ischemic reperfusion
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9 61 injury is not inevitable. Reperfusion injury can also induce deleterious effects with a
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12 62 subsequent increase in infarct size, which accounts for up to 50% of the final size of a
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14 63 myocardial infarct^[2]. Both animal models of infarction and clinical proof-of-concept studies
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17 64 have shown that reopening of the infarct-related artery (IRA), followed by repetitive brief
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20 65 interruptions of blood flow before sustained reperfusion, may protect the myocardium
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23 66 against reperfusion injury, which is evaluated using cardiac biomarkers, single-photon
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25 67 emission computed tomography (SPECT), echocardiography, and contrast-enhanced
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28 68 cardiac magnetic resonance (ce-CMR)^[3-7]. This strategy, known as ischemic
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31 69 postconditioning (IPC), is safe and easy to perform without additional cost^[8]. Related meta-
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34 70 analyses, using the above methods for evaluation, have also demonstrated that IPC can
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37 71 rescue cardiomyocytes^[9-11]. However, whether improvements in these surrogate markers
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40 72 translate into improved clinical outcomes, such as reduction in heart failure and/or all-
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43 73 cause mortality, remains controversial. The recent DANAMI-3-iPOST study, which
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46 74 randomized 1,234 patients with STEMI to conventional PPCI or PPCI with IPC did not
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49 75 provide evidence indicating that PPCI with IPC leads to better clinical outcomes compared
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52 76 to traditional PPCI^[11].

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56 77 Given the confusion surrounding the different results related to IPC combined with
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59 78 PPCI, a meta-analysis was done to evaluate whether IPC has a beneficial effect on hard
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79 endpoints, such as heart failure, all-cause mortality, and MACE, compared to traditional
80 PPCI.

81 **Methods**

82 **Patient and Public Involvement**

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

85 **Search strategy and selection criteria**

86 This meta-analysis is reported in accordance to the Preferred Reporting Items for
87 System Reviews and Meta-Analyses (PRISMA) Statement and was registered at
88 International Prospective Register of Systematic Reviews (CRD42017063959)^[12]. PubMed,
89 Embase, and Cochrane Library were systematically searched for relevant articles
90 published before May 1, 2018. The terms “ischemic postconditioning”, “postconditioning”,
91 “percutaneous coronary intervention (PCI)”, “controlled trial”, “intervention study”, and
92 “randomized controlled trials (RCTs)” were used to identify randomized controlled trials.
93 MeSH, Emtree, and keyword search terms were used in combination (Supplementary file).
94 The results were limited to trials published in English. The reference lists of relevant studies
95 and reviews, editorials, and letters were manually searched to identify additional articles.
96 Endnote (Thompson ISI ResearchSoft, Philadelphia, PA, USA) was used to manage
97 relevant articles and remove duplicate articles.

98 **Study criteria, quality assessment, and data extraction**

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

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4 100 the study design was a prospective randomized controlled clinical trial (RCT); (2) all
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6 101 patients with STEMI underwent PPCI treatment; (3) patients were randomly assigned to
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9 102 the PPCI in combination with the IPC group or the conventional PPCI group; (4) follow-up
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11 103 time was not less than one month; and (5) relevant data were retrievable. When relevant
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14 104 data were missing, the authors were contacted by e-mail before excluding the references
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17 105 for inaccessibility of data.

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19 106 The primary endpoint was heart failure. Secondary endpoints were all-cause mortality
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21
22 107 and major adverse cardiac events (MACE), including cardiac death, heart failure, and
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25 108 myocardial infarction (MI). All clinical endpoints were evaluated according to per protocol
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28 109 definitions, at the longest available follow-up. Study quality was judged by evaluating trial
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31 110 procedures for random sequence generation (selection bias), allocation concealment
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34 111 (selection bias), blinding of participants and personnel (performance bias), blinding of
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37 112 outcome assessment (detection bias), and incomplete outcome data (attrition bias). The
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40 113 Cochrane Reviewer's Handbook 4.2 was used to assess risk of bias.

41 114 Relevant data were extracted by two independent investigators (XF Peng and JB
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43 115 Huang). Disagreements were resolved by consensus or a third investigator (XQ Hu). The
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46 116 following data were abstracted from the selected articles: first author, publication date,
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49 117 study design, onset of symptoms, characteristics of included participants, total number of
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52 118 IPC and conventional groups, events of the IPC and conventional groups, stent type, and
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55 119 follow-up time.
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120 Data analysis

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

134 Outcomes

135 Search results and bias assessment

136 Supplementary Figure 1 shows that the combined search strategy identified 273
137 potential relevant manuscripts, from which 33 studies were retrieved for more detailed
138 assessment(detailed search strategies for PubMed is showed in complementary file). A
139 total of 10 RCTs, involving 3137 patients, are included in this meta-analysis^[7, 8, 13-20]. The

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4 140 Cochrane Reviewer's Handbook 4.2 was used to assess risk of bias (Supplementary Fig
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6 141 2). No high-risk studies were identified and six studies had a low risk of bias.
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9 142 The main features of the 10 included RCTs and the baseline clinical characteristics of
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11 143 the patients are presented in Table 1. In the 10 trials, 1,569 patients (50%) were randomly
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13 144 assigned to PPCI with IPC. The mean age of the trial patients was 61 years and 78% of
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15 145 the patients were male. The IPC protocol (cycles*ischemia/reperfusion in seconds) varied
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17 146 between studies and were as follows: 30"/30" × 4 in four studies, 60"/60" × 4 in five studies,
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19 147 and 30"/30" × 3 in one study. Follow-up among trials varied from 1 month to 41 months.
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23 148 The time of symptom onset varied between studies from 6 hours in 2 studies to 12 hours
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25 149 in 8 studies.
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30 150 **Table 1: Detailed characteristics of included studies.**
31

Study	Patient s (IPC/C)	Countr y	Age (years,IP C/C)	Male (%,IPC/C)	Symptom onset (hours)	Protocol (duration×cycl es)	LAD (%,IP C/C)	DES (%,IPC/ C)	Follow-up (months)
Lønborg 2010	59/59	Denma rk	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

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2012									
Dong	32/30	China	70/68	63/73	≤12	30"/30" × 3	57/43	-	1
2013									
Limalan	136/13	Norway	61/60	84/80	≤6	60"/60" × 4	46/51	29/29	4
athan	6								
2014									
Hahn	350/35	South	60/60	79/75	≤12	60"/60" × 4	47/45	86/86	12
2015	0	Korea							
Eitel	232/23	Germa	62/65	76/71	≤12	30"/30" × 4	42/51	-	6
2015	2	ny							
Luz	43/44	Portug	57/58	88/82	≤12	60"/60" × 4	47/43	65/71	14
2015		al							
Engstrø	617/61	Denma	63/62	80/79	≤12	30"/30" × 4	43/40	93/93	38
m 2017	7	rk							

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

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4 158 traditional PPCI.
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8 **159 Secondary endpoints: all-cause mortality and MACE**
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11 160 The pooled data showed that IPC did not reduce all-cause mortality compared to
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13 161 traditional PPCI (RR: 0.94, 95% CI: 0.69,1.27, P = 0.68; absolute risk: 5.07% in the IPC
14
15 162 group and 5.27% in the PPCI only group, Fig 2). No evident statistical heterogeneity among
16
17 163 studies was observed ($I^2=0$, P = 0.63). Furthermore, IPC did not reduce cardiac death (RR:
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19 164 1.28, 95% CI: 0.85,1.93, P = 0.24; absolute risk: 4.28% in the IPC group and 3.25% in the
20
21 165 PPCI only group), MI (RR: 1.08, 95% CI: 0.38,3.12, P = 0.88, absolute risk: 3.61% in the
22
23 166 IPC group and 3.44% in the PPCI only group) and heart failure (RR: 0.85, 95% CI:
24
25 167 0.59,1.23, P = 0.40; absolute risk: 3.64% in the IPC group and 4.11% in the PPCI only
26
27 168 group). When all events (MACE) were considered, IPC during PPCI provided no net benefit
28
29 169 of IPC during PPCI (RR: 1.05, 95% CI: 0.83,1.32, P = 0.69; absolute risk: 9.37% in the IPC
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31 170 group and 8.93% in the PPCI only group, Fig 3).
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41 **171 Sensitivity analysis and potential sources of heterogeneity**
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44 172 Sensitivity testing was performed by excluding each included study, one at a time, and
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46 173 recalculating the overall effects. The direction of the overall effects, in terms of heart failure,
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48 174 MI, cardiac death, and all-cause mortality, were not influenced no matter which study was
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50 175 excluded (Supplementary Table 1).
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52
53 176 There were very little heterogeneities between studies with regard to the observed
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55 177 effects on all-cause mortality ($I^2=0$, $p=0.63$) and cardiac death ($I^2=0$, $p=0.91$). However,
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178 moderate between-study heterogeneity was identified in the case of MI ($I^2 = 53\%$, $P = 0.09$).

179 MI heterogeneity was mainly caused by the Limalanathan 2014 study. When this study was

180 excluded, no heterogeneity was observed ($I^2 = 0\%$, $P = 0.40$) and the conclusions were still

181 consistent with the previous analysis. Subgroup analysis did not identify any baseline risk

182 factor, such as symptom onset, duration of follow-up, or antiplatelet therapies as a modifier

183 of the relationship between IPC and clinical endpoints (Table 2).

184 **Table 2: Subgroup analysis.**

	Cardiac death	Heart failure	MI	AI-cause mortality
Symptom onset				
≤6 hours	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)

185 **MI: myocardial infarction**

186 Discussion

187 The current meta-analysis of 10 RCTs, including 3,137 patients with STEMI
 188 undergoing PPCI, showed that no reduction in heart failure, all-cause mortality, or MACE
 189 when comparing PPCI in combination with IPC to traditional PPCI over a mean follow-up
 190 of 20 months. Similarly, no improvement in clinical outcomes was shown in the subgroup
 191 analysis.

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

202 Previous meta-analyses mainly focused on cardiac biomarkers, cardiac imaging, and

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4 203 cardiac function; however clinical outcomes are also very consequential. In the current
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6 204 meta-analysis IPC was not shown to improve clinical outcomes, though several factors
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9 205 may influence its effectiveness. A meta-analysis of 19 RCTs concluded that
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11 206 cardioprotection as evaluated by cardiac enzyme leakage, infarct size, and left ventricular
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14 207 function is more likely in patients with LAD artery involvement because of a greater
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17 208 myocardial area is at risk.^[9] Zhou et al. performed a meta-analysis of 10 RCTs and found
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19 209 that the effects of cardiac protection were more pronounced among young and male
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21 210 patients and those who received direct-stenting^[10]. The IPC protocol is also an important
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23 211 factor in determining the IPC efficacy. IPC may cause myocardial ischemia and expand
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26 212 the infarct area. Several trials chose four cycles of 1 min of reperfusion followed by 1 min
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29 213 of reocclusion. However, other trials selected four cycles of 30-s reperfusion followed by
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31 214 30-s low-pressure balloon occlusion. However, the subgroup analyses in the current study
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34 215 found no differences in the effectiveness of IPC when comparing different protocols.

37 216 Time of symptom onset, which is an independent predictor of MACE in patients with
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39 217 STEMI undergoing PPCI, may have influenced the results of these trials. However,
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41 218 subgroup analysis in this study did not detect differences between trials related to time of
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44 219 symptom onset. The key reason is that IPC might have no effect on cardioprotection, thus
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47 220 the results of the subgroup analysis in this study were neutral. Furthermore, the sample
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50 221 size of the studies may have been too small to detect minor beneficial effects. Several
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53 222 confounding factors, such as baseline characteristics of patients, coexisting diseases,
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56 223 medications, and IPC strategies used, may have influenced the cardioprotective benefits
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59 224 of IPC. With the use of novel antiplatelet and lipid-lowering agents and timely PPCI, the
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225 outcome of STEMI has significantly improved. The decreasing mortality rate also makes it
226 harder to demonstrate minor benefits of using additional therapy.

227 **Limitations**

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

238 **Conclusions**

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

242 Additional Information

243 The authors have no conflicts of interest to declare.

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

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

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253 Competing interests: None

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

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9 318 Figure legends

10
11 319 **Fig 1: Effect of PPCI with IPC versus PPCI only on heart failure in STEMI patients**

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14 320 **undergoing PPCI**

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17 321 PPCI:primary percutaneous coronary intervention, IPC: Ischemic postconditioning
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19 322 group.

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22 323 **Fig 2: Effect of PPCI with IPC versus PPCI only on all-cause mortality in STEMI**

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24 324 **patients undergoing PPCI.**

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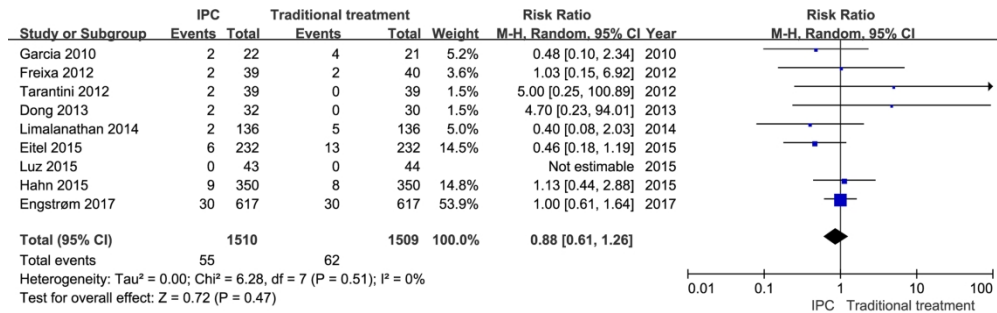
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32 327 **Fig 3: Effect of PPCI with IPC versus PPCI only on MACE in STEMI patients**

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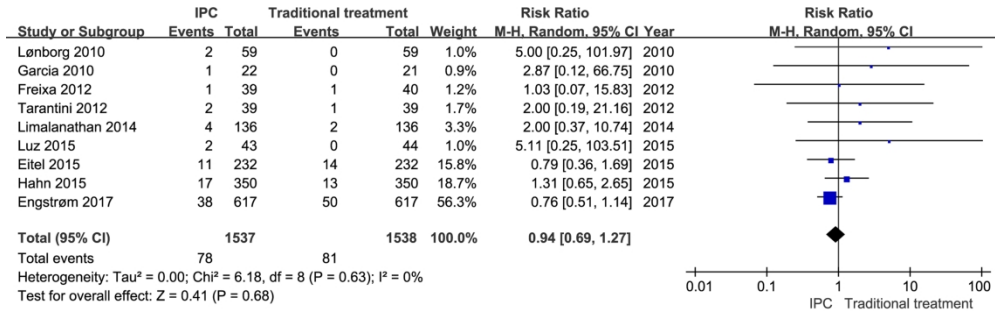
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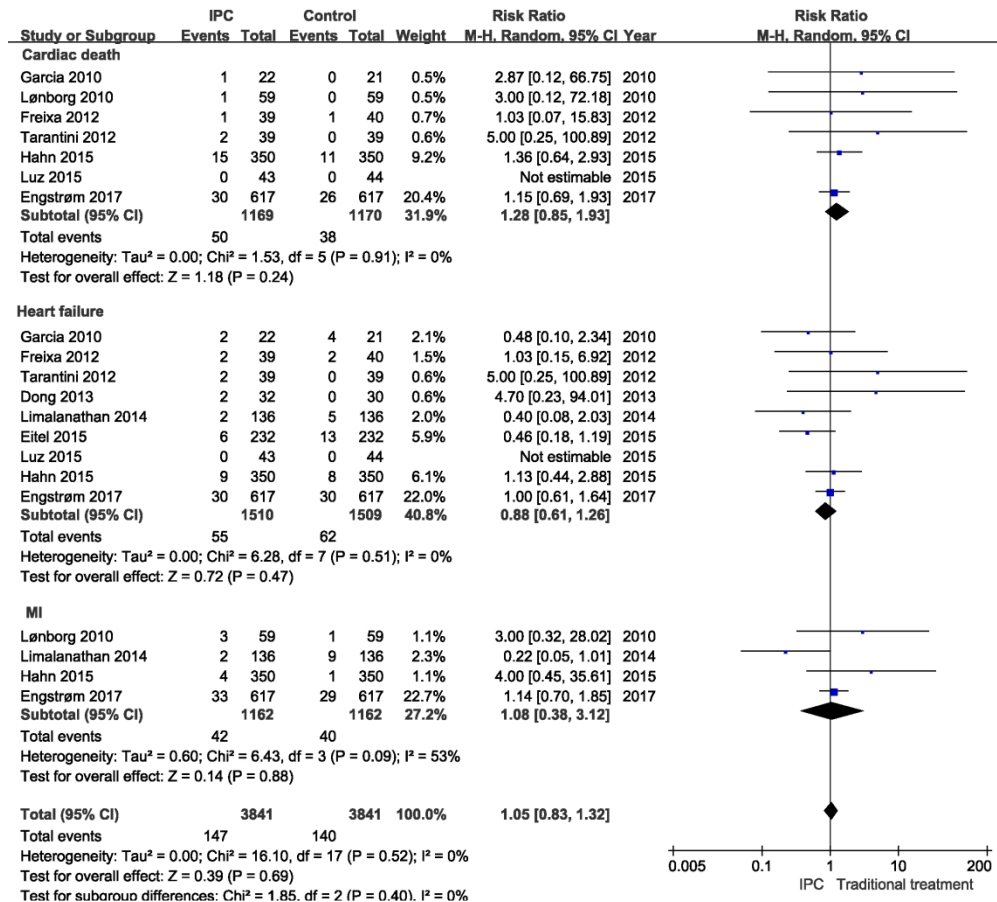
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5 1 Effects of ischemic postconditioning on outcomes of
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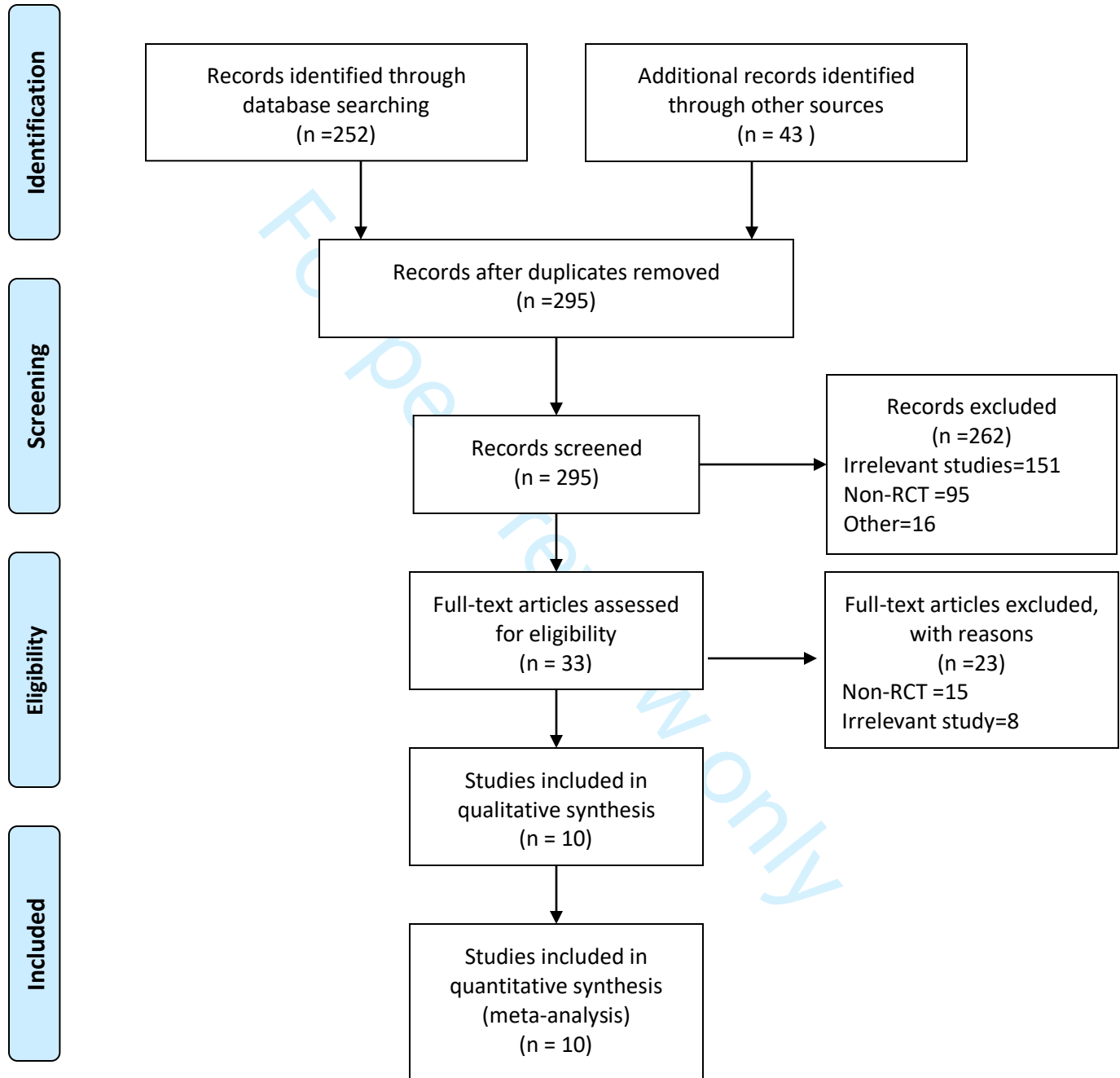
- #1 Search ischemic postconditioning[MeSH Terms] 849
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- #3 Search percutaneous coronary intervention[MeSH Terms] 46594
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- #6 Search (conditioning[Title/Abstract]) OR ischemic postconditioning[MeSH 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.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Dong 2013	?	?	?	?	+	+	+
Eitel 2015	+	+	+	+	+	+	+
Engstrøm 2017	+	+	+	+	+	+	+
Freixa 2012	+	+	+	+	+	+	+
Garcia 2010	?	?	?	?	+	+	+
Hahn 2015	+	+	+	+	+	+	+
Limalanathan 2014	+	+	?	?	+	+	+
Luz 2015	+	+	?	?	+	+	+
Lønborg 2010	+	+	+	+	+	+	+
Tarantini 2012	+	+	+	+	+	+	+

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

For more information, visit: www.prisma-statement.org.

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.

Central South University was omitted in the author affiliations. The correct affiliation of authors is:

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