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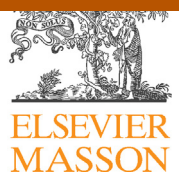

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CLINICAL RESEARCH

Ischaemic postconditioning reduces infarct size: Systematic review and meta-analysis of randomized controlled trials

Réduction de la taille d'infarctus du myocarde par le postconditionnement ischémique : revue systématique et méta-analyse des essais thérapeutiques contrôlés randomisés

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Abbreviations: AUC, area under the curve; CI, confidence interval; CK, creatine kinase; CKMB, creatine kinase myocardial band; CMR, cardiac magnetic resonance; CMR-IS, estimation of IS by CMR; cSTR, complete ST-segment resolution; IPost, ischaemic postconditioning; IS, infarct size; ITT, intention-to-treat; LVEF, left ventricular ejection fraction; PPCI, primary percutaneous coronary intervention; RR, relative risk; SMD, standard mean difference; SPECT, single-photon emission computed tomography; SPECT-IS, direct measurement of IS by SPECT; STEMI, ST-segment elevation myocardial infarction; Tropo, troponin T or I.

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KEYWORDS
Ischaemic postconditioning;
Infarct size reduction;
Meta-analysis;
Randomized controlled trials

Summary
Background. — Infarct size (IS) is a major determinant of patient outcome after acute ST-segment elevation myocardial infarction (STEMI). Interventions aimed at reducing reperfusion injury, such as cardiac ischaemic postconditioning (IPost), may reduce IS and improve clinical outcomes. IPost has been shown to be feasible in patients with STEMI treated by primary percutaneous coronary intervention (PPCI).
Aims. — To provide an updated summary of the efficacy of IPost, assessed by analysing accurate surrogate markers of IS.
Methods. — We performed a meta-analysis of randomized controlled trials that evaluated the efficacy of IPost in STEMI patients undergoing PPCI. The main outcome was area under the curve of serum creatine kinase release (CK-AUC). Secondary outcomes were other surrogate biomarkers of IS, complete ST-segment resolution, direct measurement of IS by single-photon emission computed tomography and estimation of IS by cardiac magnetic resonance (CMR-IS).
Results. — Eleven studies were retrieved, including 1313 STEMI patients undergoing PPCI with or without IPost. Compared with controls, we observed a significant reduction in CK-AUC (standard mean difference [SMD] −2.84 IU/L, 95% CI −5.43 to −0.25 IU/L; $P = 0.03$). Other surrogate markers, such as CMR-IS (SMD −0.36, 95% CI −0.88 to 0.15; $P = 0.16$), showed a non-significant IS reduction in the IPost group.
Conclusions. — This meta-analysis, dealing with accurate surrogate markers of IS, suggests that IPost reduces IS. However, results should be interpreted cautiously because of limited sample sizes and significant heterogeneity. Whether this translates into improvements in cardiac function and patient prognosis still needs to be demonstrated in larger prospective randomized controlled studies that are powered sufficiently.

MOTS CLÉS
Postconditionnement ischémique ;
Réduction de taille d'infarctus ;
Méta-analyse ;
Essai thérapeutique contrôlé randomisé

Résumé
Objectifs. — Synthétiser les données actuelles de la science concernant l'efficacité du postconditionnement ischémique sur la réduction de taille d'infarctus du myocarde (IDM).
Pré-requis. — La taille d'IDM est un déterminant majeur du pronostic des patients au décours d'un STEMI. Les interventions visant à protéger des lésions de reperfusion comme le postconditionnement ischémique pourraient réduire la taille d'IDM et améliorer le pronostic. Des essais cliniques ont montré que le postconditionnement ischémique était réalisable chez les patients revascularisés par angioplastie primaire à la phase aiguë d'un STEMI.
Méthodes. — Nous avons réalisé une méta-analyse des essais thérapeutiques randomisés et contrôlés évaluant l'efficacité du postconditionnement ischémique à la phase aiguë d'un STEMI revascularisé par angioplastie primaire. Le critère majeur était l'aire sous la courbe (AUC) des CPK. Les critères secondaires étaient d'autres biomarqueurs de taille d'IDM, la résolution du segment ST, et la taille d'IDM estimée par scintigraphie ou IRM myocardique.
Résultats. — Onze études incluant 1313 patients ont été retenues. Notre analyse objective une réduction significative de l'AUC des CPK (SMD −2,84, 95 % CI −5,43, −0,25 IU/L, $p = 0,03$) dans le groupe actif. Elle montre une tendance non significative en faveur de cette même réduction dans le groupe actif sur les autres marqueurs de substitution comme l'IRM (SMD −0,36, 95 % CI −0,88, 0,15, $p = 0,16$).
Conclusions. — Nos résultats suggèrent que le postconditionnement ischémique réalisé lors de la revascularisation d'un STEMI par angioplastie primaire permet d'obtenir une réduction de taille d'IDM. Ces résultats sont à interpréter avec prudence en raison de la petite taille des effectifs et d'une hétérogénéité significative. Des essais thérapeutiques contrôlés sur de larges effectifs sont nécessaires pour démontrer l'efficacité de cette réduction sur des critères cliniques et sur le pronostic des patients.

Background

Despite current optimal treatment, coronary heart disease morbidity and mortality remain significant, paving the way for the development of new cardioprotective therapies [1].

Timely reperfusion is the most effective treatment to reduce the size of an infarct resulting from myocardial ischaemia. However, reperfusion has the potential to induce additional lethal injury, identified as reperfusion injury, which can be responsible for up to 40% of the final infarct size (IS).

Because IS is known to be a major determinant of patient prognosis, any intervention that reduces its extent may result in a clinical benefit [2].

Ischaemic preconditioning and postconditioning are interventions with multiple and interacting components marshalled against myocardial reperfusion injury by endogenous cardioprotective mechanisms [3]. Cardiac ischaemic postconditioning (IPost) is defined as rapid intermittent interruptions of blood flow in the early phase of myocardial reperfusion, feasible in patients with ST-segment elevation myocardial infarction (STEMI) revascularized by primary percutaneous coronary intervention (PPCI) [3].

Most clinical trials evaluating the benefit of IPost were small single-centre studies that reported conflicting results regarding IS reduction [4,5]. Three meta-analyses investigating the effect of IPost have already been published [6—8]. These meta-analyses either used suboptimal surrogate markers of myocardial IS, such as peak necrosis marker levels, or combined different markers in the same analysis. More evidence is needed before recommending IPost in routine clinical practice.

The aim of this systematic review and meta-analysis was to provide an updated summary of published randomized trials investigating the efficacy of IPost using reliable surrogate markers of IS reduction.

Methods

This review was conducted and reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) criteria [9].

Information sources and search strategy

We searched electronic databases (PubMed, Cochrane) for studies published before December 2013. In order to have comparable information from eligible studies, we collected additional data by communicating directly with the authors.

The following keywords were used: ''ischaemic postconditioning''; ''myocardial infarction''; and ''acute coronary syndrome''. Our search was restricted to human and randomized controlled studies, without any language restriction. We also reviewed the reference lists of published meta-analyses and selected studies.

Eligibility criteria and study selection

The selection of eligible studies was done by two authors (C.T., D.A.), with disagreements resolved by consensus between these two authors.

Inclusion criteria were randomized controlled trials enrolling STEMI patients admitted during the acute phase for PPCI, comparing IPost (active group) with a routine intervention (control group), and evaluating one or more surrogate markers of IS. We decided a priori to exclude studies that systematically used intracoronary adenosine injection at the time of reperfusion, because adenosine is a known activator of cardioprotective signalling pathways, inducing potential pharmacological conditioning, which may dilute the effect of IPost on IS reduction [3].

The following surrogate markers of IS were considered: area under the curve (AUC) of serum creatine kinase (CK) release (CK-AUC); AUC of CK myocardial band release (CKMB-AUC); AUC of troponin (T or I isoforms) release (Tropo-AUC); complete ST-segment resolution (cSTR), defined as STR > 70% after reperfusion; direct measurement of IS by single-photon emission computed tomography (SPECT); or estimation of IS as a percentage of the area at risk by cardiac magnetic resonance (CMR).

Risk of bias in individual studies

One author (C.T.) assessed the methodological quality of the selected trials according to the Cochrane risk of bias criteria. We considered the following domains: random sequence generation and allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); and completeness of the follow-up, intention-to-treat (ITT) analysis and dropouts (attrition bias).

Based on the above criteria, studies were divided into three categories: low (all criteria were at low risk of bias); high (at least one criterion was at high risk of bias); or unclear if otherwise.

Outcomes and comparisons

Our main outcome was the effect of IPost on CK-AUC. Secondary outcomes were: other biological surrogate markers (CKMB-AUC, Tropo-AUC); cSTR as a clinical surrogate marker of ischaemia resolution; and imaging surrogate markers of IS, measured by SPECT (SPECT-IS) or estimated by CMR (CMR-IS).

Data extraction process

Data from eligible trials were extracted by one author (C.T.). We contacted authors by e-mail whenever additional data were needed.

Statistical analysis

We extracted aggregate data from published reports. Summary measures are reported as standard mean difference (SMD) ± standard deviation for continuous variables (CK-AUC, CKMB-AUC, Tropo-AUC, SPECT-IS and CMR-IS) as studies assessed the same outcome but measured it in a variety of ways. Summary risk ratios (RRs) are reported for binary variables (cSTR) with 95% confidence intervals (CIs). We used a fixed-effects model, and if significant heterogeneity was observed, a random-effects model was performed. If heterogeneity persisted after using a random-effects model, we then performed a sensitivity analysis, by excluding one trial at a time. We tried to explore heterogeneity further by considering characteristics at both trial and patient levels. An inverse-variance model was used to pool the data. Statistical heterogeneity across trials was assessed with Chi^2, I^2 and Tau^2 statistics. Heterogeneity was considered significant if the P value was < 0.1 and heterogeneity was considered high if I^2 was > 50%. Risk of bias assessment by visual inspection of funnel plot was not relevant due to the small number

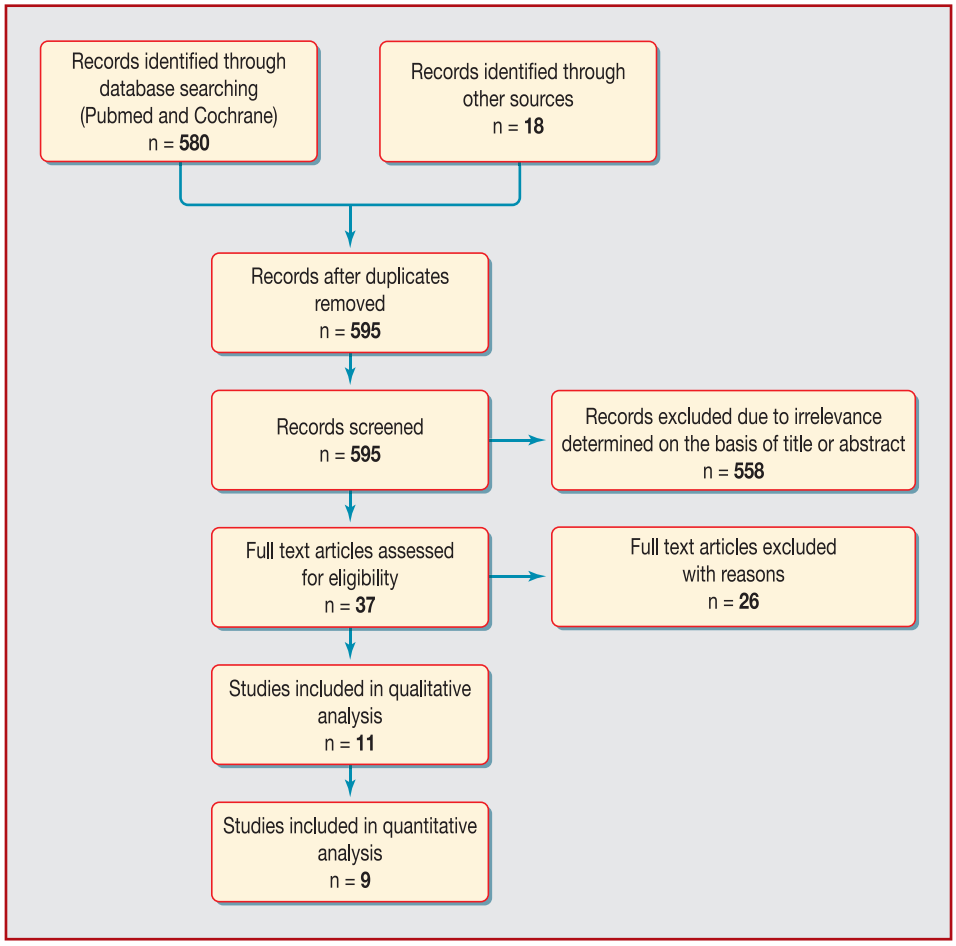

Figure 1. Flow diagram of study selection.

of included studies. Statistical analyses were performed using RevMan software (version 5.1).

Results

Included studies

The numbers of studies identified at each stage of the systemic review are shown in Fig. 1. After removing duplicate references, the searches identified 595 records. Based on title and/or abstract, 37 relevant articles were retrieved for full-text reading. We excluded 22 articles for the following reasons: 16 were not randomized controlled trials; three were meta-analyses; one did not report any surrogate marker of IS; and two dealt with the same database as eligible studies. We excluded a further two trials that systematically used intracoronary adenosine injection at the time of reperfusion and two trials published in Chinese [10,11], as we did not succeed in obtaining data from the authors. Eleven studies [4,5,12–22] were finally included in this review, corresponding to 1313 patients (646 randomized to the IPost group and 667 to the control group) (Table 1). Additional data were obtained by contacting the authors of three studies [4,17,18]. The studies by Lonborg et al. [14,15] and Thuny et al./Mewton et al. [17,20] were reported in two publications each, so we included the data as one study only for each group.

Patients had a mean age of 60.4 years and were predominantly men (Table 1). Patient exclusion criteria in the included studies were homogenous: cardiac arrest; cardiogenic shock; left main coronary artery occlusion or severe stenosis; blood flow in the infarct-related artery > thrombolysis in myocardial infarction (TIMI) grade 1 at the time of the diagnosis coronary angiography; obvious coronary collaterals to the risk region; previous myocardial infarction or preinfarction angina within 48 hours; prior coronary bypass surgery or PCI; and left bundle branch block. IPost protocols were different in the various studies but were all performed within 1 minute of reflow with balloon reinflation at 4 to 6 atm (Fig. 2). Three studies [5,17,19,20] came from the same research group and used the same IPost protocol, with four cycles of 1 minute of balloon reinflation above the index lesion followed by 1 minute of reperfusion immediately after direct stenting. IPost protocols were similar in three other studies [4,13,18], but balloon reinflation was performed at the same location as the PPCI inside the implanted stent. In the five other studies, the IPost protocol was performed before stent implantation, just after balloon angioplasty: four cycles of 1 minute of inflation and 1 minute of deflation [21] or four cycles of 30 seconds of inflation and 30 seconds of deflation [14,15] with stent implantation left

Table 1 Main study characteristics.

Studies	Number of patients		Mean age (years)	Men/women (*n*/*n*)	Ischaemia duration (hours)		IPost protocol	Culprit artery[a]	Summary risk of bias	Outcomes reported
	IPost	Control			IPost	Control				
Yang et al., 2007 [22]	23	18	61	31/10	5.2	4.4	30 s × 3	LAD > RCA > LCX	U	CK-AUC; cSTR; SPECT-IS
Ma et al., 2006 [16]	47	47	64	64/30	6.6	7.1	30 s × 3	LAD > RCA > LCX	H	
Staat et al., 2005 [5]	16	14	57	25/5	5.3	5.5	60 s × 4	RCA > LAD	U	CK-AUC
Thibault et al., 2008 [19]	17	21	56	25/13	4.7	4.9	60 s × 4	LAD > RAD	L	CK-AUC; Tropo-AUC; SPECT-IS
Lonborg et al., 2010 [14,15]	59[b]	59[b]	62	92/26	4.0	4.3	30 s × 4	RCA > LAD > LCX	U	cSTR; CMR-IS
Sorensson et al., 2010 [18]	45[b]	45[b]	63	65/25	2.8	3.1	60 s × 4	RCA > LAD > LCX	U	CKMB-AUC; Tropo-AUC; CMR-IS
Freixa et al., 2012 [4]	39[b]	40[b]	60	62/17	5.4	5.0	60 s × 4	LAD > RCA	L	cSTR[c]; CMR-IS
Fan et al., 2011 [12]	22	28	66	31/19	MD	MD	30 s × 3	MD	U	
Thuny et al., 2012 [17,20]	25	25	57	37/13	4.8	3.6	60 s × 4	LAD > RCA > LCX	U	CMR-IS
Xue et al., 2010 [21]	23	20	58	41/2	4.1	5.4	60 s × 4	LAD > RCA	U	CKMB-AUC; cSTR; SPECT-IS[d]
Hahn et al., 2013 [13]	350	350	60	537/163	3.3	3.2	60 s × 4	LAD > RCA > LCX	L	cSTR
Total	646	667	60.4							

AUC: area under the curve; CK: creatine kinase; CKMB: creatine kinase myocardial band; CMR: cardiac magnetic resonance; cSTR: complete ST-segment resolution; H: high risk of bias; IPost: ischaemic postconditioning; IS: infarct size; L: low risk of bias; LAD: left anterior descending artery; LCX: left circumflex artery; MD: missing data; RCA: right coronary artery; SPECT: single-photon emission computed tomography; U: unclear risk of bias.

[a] Culprit artery: refers to the most frequent location (in percentages) of the artery responsible for ST-segment elevation myocardial infarction in each article.

[b] Not intention-to-treat.

[c] Results were reported as average STR in each group (instead of cSTR defined by STR > 70%) and hence could not be used for the quantitative meta-analysis.

[d] Results were reported in the form of a score (semi-quantitative method) and hence could not be used for the quantitative meta-analysis.

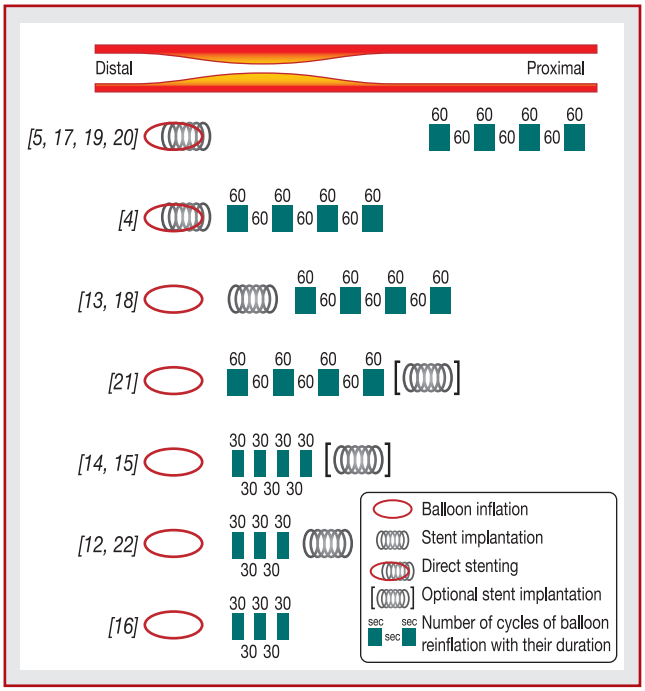

Figure 2. Different ischaemic postconditioning (IPost) protocols performed in studies included in the qualitative analysis. Stent implantation was performed using direct stenting or after first balloon inflation or after IPost sequences. Brackets indicate that stent implantation was not part of the protocol and was therefore left to the operator's preference. Black squares represent intracoronary balloon reinflation (at 4 to 6 atm) after revascularization and localization inside the infarct-related artery.

to the discretion of the operator; three cycles of 30 seconds of inflation and 30 seconds of deflation followed by stenting [12,22] or without stenting [16].

Only three studies [4,13,19] were at low risk of bias for all considered criteria, and one [16] was considered at high risk of bias because of a randomization method based on the date of admission. The other seven studies were considered as having an unclear risk of bias (Table 1).

Eight studies provided at least partial data on IS surrogates (Table 1) and could be included in the quantitative analysis. Three studies provided data on CK-AUC, two on CKMB-AUC, two on Tropo-AUC, four on cSTR, three on SPECT-IS (although one [21] presented results in a way that prevented comparison with the results from the two other studies) and four on CMR-IS.

Surrogates biomarkers of infarct size: CK-AUC, CKMB-AUC and Tropo-AUC

IPost was associated with a significant reduction in CK-AUC (SMD −2.84 IU/L, 95% CI −5.43 to −0.25 IU/L; $P = 0.03$) in three studies [5,19,22] (Fig. 3), but with significant heterogeneity ($Chi^2 = 47.1$, $P < 0.001$; $I^2 = 96\%$; $Tau^2 = 4.88$). In the sensitivity analysis, heterogeneity disappeared with the exclusion of the study by Yang et al. [22]; this study was different from the two other studies [5,19] regarding patient profiles (more hypertension and diabetes) and patient selection (no age limitation, no specification for the time from chest pain onset to PPCI). Of note, the two other studies were performed by the same research group. CK dosage methods were different in the study by Yang et al. (automated analyser Synchron LX20; Beckman Coulter, Brea, CA, USA) compared with the other two studies (CK Kit; Beckman Coulter). In addition, the IPost protocol was different in the study by Yang et al. compared with the other two studies (Fig. 2).

IPost was not associated with a significant reduction in CKMB-AUC (SMD −0.35 IU/L, 95% CI −0.96 to 0.26 IU/L; $P = 0.27$) in two studies [18,21] (Fig. 3), with moderate heterogeneity ($Chi^2 = 2.58$; $P = 0.11$; $I^2 = 61\%$; $Tau^2 = 0.12$). Heterogeneity between the two studies could be explained by the use of different dosage methods for blood analysis and by fewer blood samplings in the study by Xue et al. [21].

IPost was not associated with a significant reduction in Tropo-AUC (SMD −0.28 IU/L, 95% CI −1.04 to 0.48 IU/L; $P = 0.48$) in two studies [18,19] (Fig. 3), with significant heterogeneity between studies ($Chi^2 = 3.67$; $P = 0.06$; $I^2 = 73\%$; $Tau^2 = 0.22$). Heterogeneity between the two studies could be explained by the use of different troponin isoforms (isoform I in the study by Thibault et al. [19] versus isoform T in the study by Sorensson et al. [18]) and different dosage methods.

Clinical surrogate of ischaemia resolution: cSTR

IPost was not associated with a significantly improved cSTR, with only 10% patients experiencing STR > 70% after IPost in four studies [13–15,21,22] (RR 1.10, 95% CI 0.95 to 1.27; $P = 0.20$), with significant heterogeneity between studies ($Chi^2 = 6.56$; $P = 0.09$; $I^2 = 54\%$) (Fig. 4).

In addition to the different IPost protocols across studies (Table 1 and Fig. 2), heterogeneity may also be explained by the different timings for ST-segment resolution evaluation: 120 minutes for Xue et al. and Yang et al. [21,22], 90 minutes for Lonborg et al. [14,15] and 30 minutes for Hahn et al. [13]. Of note, different methods were used for electrocardiogram analysis: a trained technician for Xue et al. [21], dedicated software (LIFENET) for Lonborg et al. [14,15], a cardiologist for Yang et al. [22] and an independent laboratory for Hahn et al. [13].

Imaging surrogates of infarct size: SPECT-IS (% of the LV) and CMR-IS (% of the LV)

IPost was not associated with a significant reduction in SPECT-IS (SMD −0.42, 95% CI −0.88 to 0.03; $P = 0.06$) in two studies [19,22] (Fig. 5), without significant heterogeneity between studies ($Chi^2 = 0.68$; $P = 0.41$; $I^2 = 0\%$).

IPost was not associated with significant reduction in CMR-IS (SMD −0.36, 95% CI −0.88 to 0.15; $P = 0.16$) in four studies [4,14,15,17,18,20] (Fig. 5), with significant heterogeneity between studies ($Chi^2 = 13.6$; $P = 0.004$; $I^2 = 78\%$; $Tau^2 = 0.21$). Sensitivity analyses did not identify one specific study responsible for heterogeneity. Forest plot visual inspection indicates that two studies (Lonborg et al. and Thuny et al./Mewton et al. [14,15,17,20]) showed significant reductions in CMR-IS, while the two others (Freixa et al. and Sorensson et al. [4,18]) showed no reduction. This finding could be partially explained by differences in timing of CMR

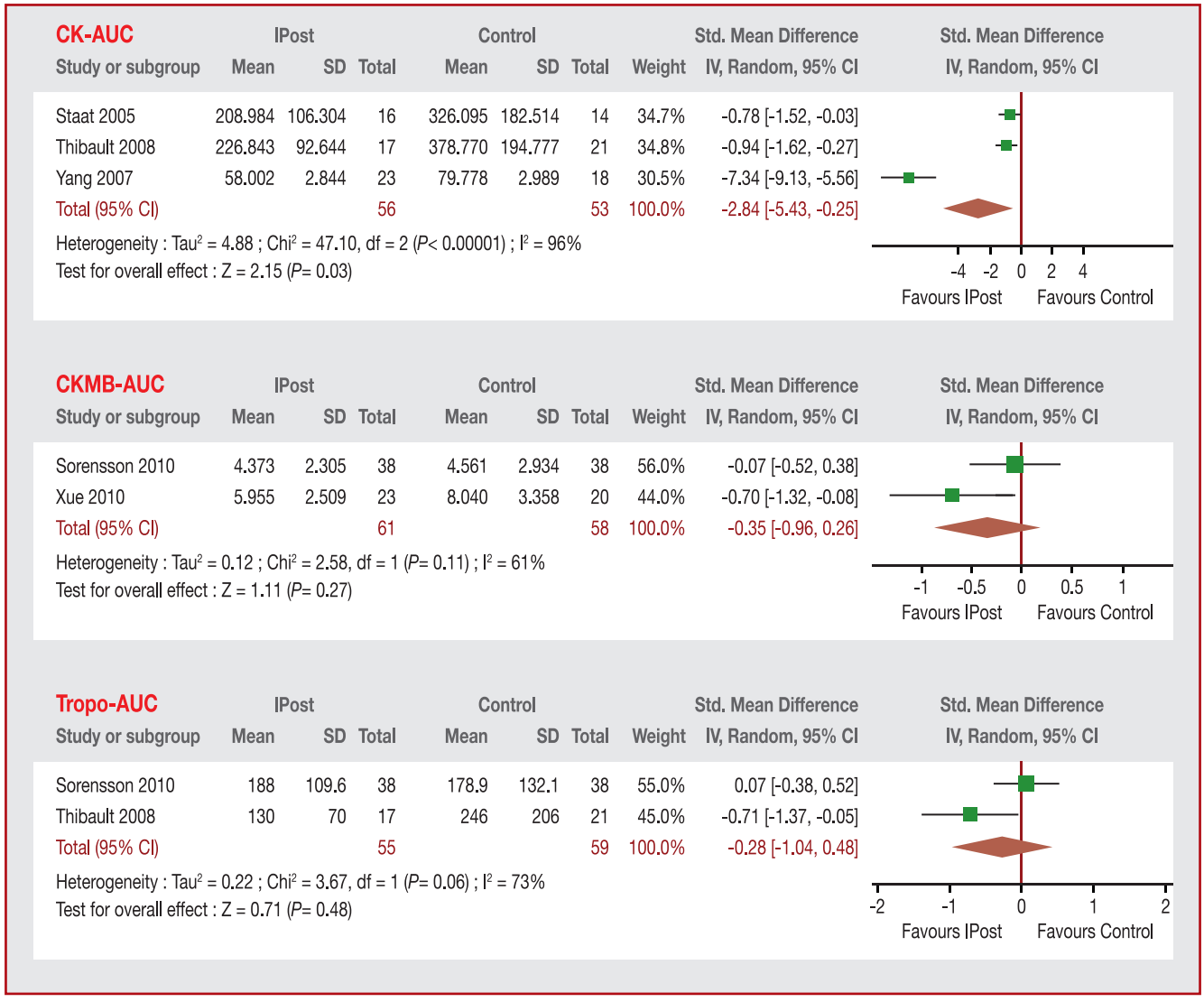

Figure 3. Forest plots of biological surrogate markers of infarct size. Results are presented as the standard (Std.) mean difference. A random-effects model was performed. AUC: area under the curve; CI: confidence interval; CK: creatine kinase; CKMB: creatine kinase myocardial band; IPost: ischaemic postconditioning; IV: inverse-variance; SD: standard deviation; Tropo: troponin T or I.

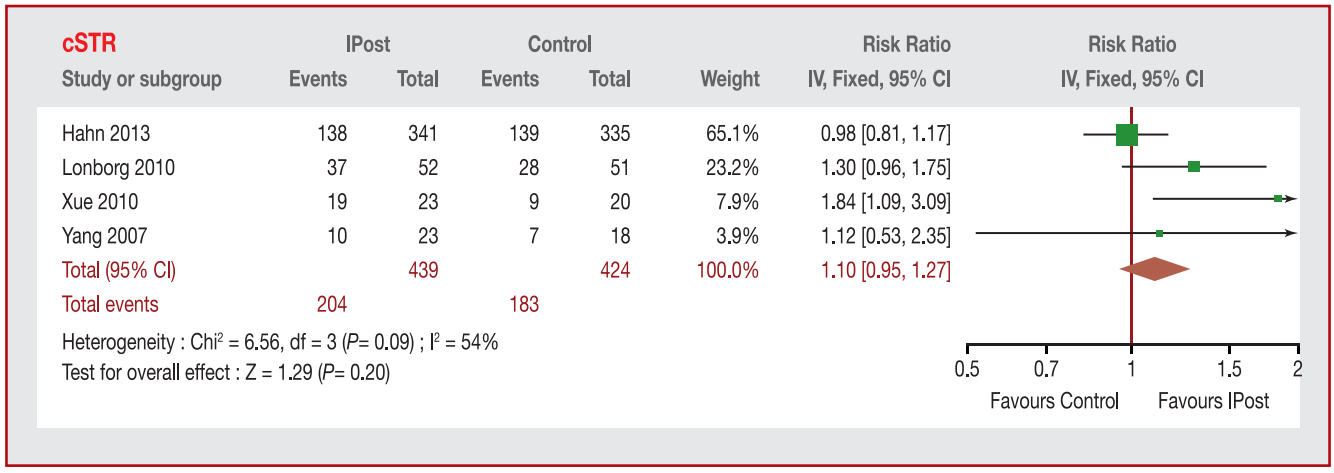

Figure 4. Forest plot of complete ST-segment resolution (cSTR). cSTR was defined as the difference in ST-segment elevation between the baseline electrocardiogram (ECG) and the ECG recorded after reperfusion, divided by the ST-segment elevation in baseline ECG > 70%. Results are presented as the risk ratio. A fixed-effects model was performed. CI: confidence interval; IPost: ischaemic postconditioning; IV: inverse-variance.

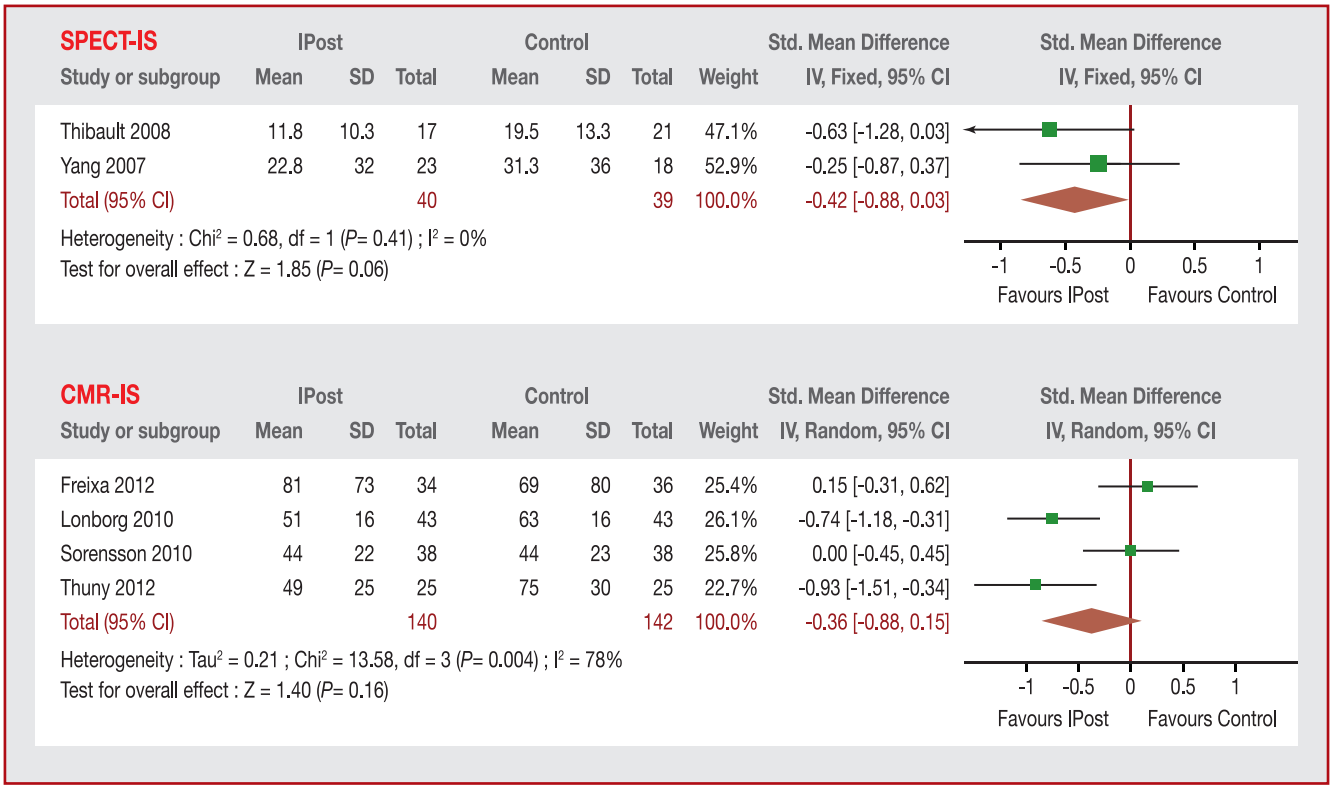

Figure 5. Forest plots of imaging surrogate markers of infarct size (IS). Results are presented as the standard (Std.) mean difference. A fixed-effects model was performed for SPECT-IS and a random-effects model was performed for CMR-IS. CI: confidence interval; CMR: cardiac magnetic resonance; IPost: ischaemic postconditioning; IV: inverse-variance; SD: standard deviation; SPECT: single-photon emission computed tomography.

analysis. CMR was performed 2 days after admission in the study by Thuny et al./Mewton et al. [17,20], 7 days after admission in the studies by Sorensson et al. and Freixa et al. [4,18] and 3 months after admission in the study by Lonborg et al. [14,15].

Left ventricular ejection fraction (LVEF), measured by either transthoracic echocardiography or CMR, showed no significant differences between groups at short (7-day) and long (6-month) follow-up (data not shown).

Discussion

Our study is the first meta-analysis analysing the effects of IPost on the following surrogates of IS: CK-AUC, CKMB-AUC and Tropo-AUC. Our results suggest that IPost significantly decreases CK-AUC. Although not statistically significant, results for CKMB-AUC, Tropo-AUC, cSTR, SPECT-IS and CMR-IS showed a trend towards a beneficial effect of IPost. Regarding CMR analysis, this may be related to significant discrepancy between studies regarding CMR timing after myocardial infarction. In addition, CMR determination of the area at risk has recently been the subject of controversy because of other potential causes of myocardial oedema [23].

Reducing IS through the prevention of reperfusion injuries is a new frontier in myocardial infarction therapy. Apart from IPost, other procedures have produced encouraging results: injection of cardioprotective agents, such as cyclosporine or metoprolol [24,25]; and remote ischaemic conditioning [26,27]. So far, no large prospective randomized clinical trials with hard clinical endpoints evaluating these procedures have been published; they are therefore still in transition from bench to bedside. Performing meta-analyses combining data from small clinical trials may provide interesting insights for both researchers and clinicians regarding the benefit of these procedures.

We can summarize the results of the three meta-analyses already published [6—8] as follows. The meta-analysis by Hansen et al. [6] published in 2010 included six studies (244 patients) and showed a significant decrease in peak CK and an increase in LVEF in IPost patients compared with usual care. Two recent meta-analyses [7,8] published in 2012 had different inclusion/exclusion criteria, leading to differences in included studies and reported outcomes. The meta-analysis by Wei et al. [7] included 13 studies (673 patients) and showed: a significant decrease in peak CK; a significant decrease in peak CKMB; a significant reduction in SPECT-IS; no significant improvement in cSTR; and significant improvement in long-term LVEF. The meta-analysis by Zhou et al. [8] included 10 studies (560 patients) and showed a significant reduction in necrosis biomarkers and significant improvement in LVEF.

The novelty of our meta-analysis comes from the inclusion of the latest and largest published clinical trial by Hahn et al. [13], the analysis of different surrogate markers of IS and the methodology. Compared with the meta-analyses by Hansen et al. and Wei et al. [6,7], we used AUC and not

peak of biomarkers as a surrogate marker for IS. According to Gibbons et al. [28], peak CKMB can be used as a substitute for AUC if a sufficient number of samples are measured to detect true peak values. Turer et al. [29] showed that peak CK, peak CKMB and AUC calculations had significant correlation with functional outcomes (LVEF and SPECT-IS) and death in the setting of STEMI. Lopes et al. [30] showed that the observed CKMB measures (AUC and peak) and measures obtained from sophisticated curve fitting also had significant correlations with clinical endpoints, such as 90-day death and heart failure. However, this may not be true in studies in which CKMB values are measured less frequently. At least, five CKMB measurements are necessary to fit a log-normal model to the CKMB curve. It is still possible to calculate observed CKMB-AUC using fewer than five measurements, but the validity is questionable [30]. In line with the article by Gibbons et al. [28], we favoured AUC rather than peak values. Besides, we analysed IS as a percentage of the area at risk, estimated by CMR (CMR-IS) in four studies, whereas Hansen et al. [6] did not consider CMR-IS and Wei et al. [7] only analysed CMR-IS for two studies.

Compared with the meta-analysis by Zhou et al. [8], we followed a different methodology: each myocardial necrosis biomarker was analysed separately, while Zhou et al. aggregated all biomarkers (i.e. the more relevant available marker was chosen for each study, resulting in a non-homogeneous comparisons of IS surrogates).

Preclinical studies have suggested that only the first few minutes of myocardial reperfusion following the index ischaemic period offer a window for IPost protection against ischaemia reperfusion injuries. Emerging evidence suggests that several signalling pathways are recruited at the time of myocardial reperfusion, including cell-surface receptors, a diverse array of protein kinase cascades, including the reperfusion injury salvage kinase (RISK) pathway and the survivor activating factor enhancement (SAFE) pathway, redox signalling and the mitochondrial permeability transition pore (mPTP) [3,31]. In addition, significant myocardial ischaemic injury is needed to gain any significant IS reduction from procedures preventing reperfusion injuries. Miura et al. [32] suggested that the intervention would need to be potent enough to limit the fraction of the risk zone infarcting from 75% in the untreated patient to $\leq$ 40% in patients with an area at risk that is > 20% of the left ventricle. Of note, most of the clinical trials included in our meta-analysis did not give any details regarding the area at risk.

As depicted in our work, the IPost protocols differed between studies. This may have induced variability regarding the efficacy of IS reduction. Four studies used direct stenting, four others implanted the stent after the IPost protocol and four studies only allowed the use of thrombus aspiration before stenting [4,13—15,17,20]. This is important, because thrombus aspiration may reduce post PCI distal embolization that may play an important role in the ''no-reflow'' phenomenon. A recent clinical trial showed no clinical benefit of systematic thrombus aspiration in STEMI patients [33]. Some studies did not specifically mention in their protocol that balloon reinflation was performed after retraction above the implanted stent. Balloon reinflation inside the implanted stent may have triggered thrombus fragmentation and distal embolization, leading to microvascular occlusion, jeopardizing myocardial revascularization and potential IPost efficacy [4]. Our data do not allow us to draw any conclusion regarding the best IPost protocol to protect the myocardium against reperfusion injuries at the time of PPCI. Of note, animal models used to establish IPost efficacy and mechanisms could not address this concern either. In animal models, myocardial ischaemia is provoked by experimental non-atherothrombotic coronary occlusion subsequently revascularized without coronary stenting.

As mentioned above, our meta-analysis included the recent publication by Hahn et al. [13] reporting the largest clinical trial comparing IPost with control in 700 patients undergoing PPCI for STEMI. In this study, the primary endpoint (percentage of ST-segment resolution > 70% measured 30 minutes after PPCI) was not different between treated and control groups. The weight of this study was important; its integration in our analysis turned the effect of IPost on cSTR reduction to statistically non-significant. However, some limitations of this study that may have jeopardized the potential beneficial effect of IPost need to be acknowledged: balloon reinflation within the stent at the location of the culprit lesion; and a large number of infarct-related artery predilatations and thrombus aspirations before stenting, which may have delayed the subsequent IPost procedure. These limitations have been discussed extensively in a report by Ovize et al. [34].

Although our meta-analysis produced encouraging results regarding IS reduction, we must acknowledge that IPost may not be easy to translate into clinical practice because of the burden of immediate balloon reinflation after coronary revascularization during PPCI. Of note, preclinical studies have suggested that IPost may not be efficient in patients with metabolic disorders such as hyperlipidaemia and diabetes [35]. Other strategies, such as remote conditioning [27] and/or pharmacological conditioning [25], may be easier to translate into clinical practice.

Study limitations

Our meta-analysis has several limitations, mainly due to the characteristics of the studies. Included studies had small numbers of patients and poorly reported methodological aspects, such as random sequence generation, allocation concealment and performance bias. Of note, three of the included studies did not have an intention-to-treat analysis [4,14,15,18]. Several outcomes (CK-AUC, Tropo-AUC and CMR-IS) were heterogeneously reported. Methods used to measure CK-AUC or cSTR were also heterogeneous. This led us to present several Forest plots with a small number of studies for each endpoint. In addition, high heterogeneity (I^2 > 50%) was observed for almost all analysed outcomes. We discussed several possible causes of heterogeneity, but could not identify a major cause. The relevance of performing a meta-analysis may be questionable in case of persisting heterogeneity, despite the use of a random-effects model or subgroup analysis. On the other hand, performing a meta-analysis allowed us to provide graphical representation of the summary of evidence regarding IPost-related IS reduction; it also provided quantitative estimates of such a reduction on various outcomes, which could be taken into account when designing future clinical trials. Our results suggest a small benefit of IPost on surrogate markers of IS, with no data regarding clinical outcomes. Both IS reduction

and clinical outcomes remain to be investigated in large clinical trials.

Conclusions

Using CK-AUC as a surrogate marker, our results suggest a small benefit of IPost on IS, which is a major determinant of a patient's clinical outcome after acute myocardial infarction; hence, this reduction could significantly improve post myocardial infarction cardiac function and patient prognosis. Published clinical trials evaluating IPost were neither tailored nor conceived to detect clinical benefits on major adverse cardiac events, such as heart failure or mortality. There is a need for large prospective randomized controlled studies with intention-to-treat analysis, using hard clinical endpoints.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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