EuroIntervention 2014;9:1463-1471

Cardiac remote ischaemic preconditioning reduces periprocedural myocardial infarction for patients undergoing percutaneous coronary interventions: a meta-analysis of randomised clinical trials

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KEYWORDS

- percutaneous coronary intervention
- periprocedural myocardial infarction
- randomised controlled trials
- remote ischaemic preconditioning

Abstract

Aims: To establish the cardioprotective effect of remote ischaemic preconditioning (RIPC) in patients undergoing percutaneous coronary intervention (PCI).

Methods and results: Pubmed (MEDLINE), Cochrane and Embase were systematically searched for randomised controlled trials of RIPC in patients undergoing PCI. Periprocedural myocardial infarction (PMI) was the primary endpoint (defined as troponin elevation >3 times upper reference limit) and C-reactive protein (CRP) was a secondary endpoint. Five studies with 731 patients were included. The median age of the patients was 62 (59-68) years old, 25% were female (23-33), 29% (25-33) had diabetes mellitus, and 26.5% (19-31) presented with multivessel disease. RIPC significantly reduced the incidence of PMI (odds ratio: 0.58 [0.36, 0.93]; I^2 43%), with a greater benefit when performed using the lower limb (0.21 [0.07-0.66]) compared to the upper limb (0.67 [0.46-0.99]). This reduction was enhanced for patients with multivessel disease (beta –0.05 [–0.09;–0.01], p=0.01) and with type C lesion (beta –0.014 [–0.04;–0.010], p=0.01) and did not vary according to age, female gender, diabetes mellitus, use of beta-blockers and of angiotensin converting enzyme inhibitors. Absolute risk difference was –0.10 [–0.19, –0.02], with a number needed to treat of 10 [6-50] patients to avoid one event. CRP –0.69 [–1.69, 0.31] was not significantly reduced by RIPC.

Conclusions: RIPC reduced the incidence of PMI following PCI, especially when performed in the lower limb and for patients with multivessel disease and complex lesions.

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DOI: 10.4244/EIJV9I12A244

Introduction

Reperfusion injury occurs at the time of restoration of blood flow following lethal ischaemia and leads to the generation of superoxide radicals. The free radicals promote oxidative stress, endothelial cell dysfunction and release of pro-inflammatory cytokines. Remote ischaemic preconditioning (RIPC) antagonises these deleterious effects through induction of intracellular kinase and subsequent modification of mitochondrial function within the cells, via opening of ATP-sensitive potassium channels and closure of mitochondrial permeability transition pores[1-10]. In animal models, intermittent, brief ischaemia in a remote organ has been shown to reduce myocardial infarct size when applied immediately before or during the onset of coronary ischaemia, as well as during reperfusion[11].

These experimental data have been translated first into clinical practice for patients undergoing cardiac surgery, especially coronary artery revascularisation. Two recent meta-analyses[12,13] have shown that RIPC reduced the release of troponin after coronary artery bypass grafting (CABG). Moreover, a recent randomised clinical trial[14] has demonstrated a reduction in terms of death for patients undergoing CABG.

Potential benefits of RIPC have also been tested in the setting of percutaneous coronary intervention (PCI). RIPC reduced troponin release for patients presenting with ST-segment elevation myocardial infarction[15], while for patients with stable angina contrasting results are reported, from a reduction[16] of periprocedural myocardial infarction (PMI) to a neutral effect[17]. Similarly, these trials also evaluated RIPC to reduce C-reactive protein (CRP)[18,19], which has been shown to be related to the presence and severity of periprocedural myocardial infarctions, without homogenous results. Release of pro-inflammatory cytokines plays a pivotal role in ischaemia-reperfusion injury (IRI) cascade. Parenchymal damage and instability of subcritical plaques other than the target lesion are two potential consequences of the iatrogenic inflammatory stimulus during percutaneous coronary intervention. Large prospective studies have affirmed high-sensitivity CRP as being a relevant risk factor in the development of unstable atherosclerotic plaques. As outlined in recent European guidelines about cardiovascular disease prevention, specific therapeutic strategies targeting circulating CRP are still lacking. We would like to prove RIPC as a ground-breaking treatment to prevent IRI. CRP may thus represent a useful marker of the effectiveness of preconditioning techniques. Moreover, RIPC recently showed an impressive positive result for acute kidney injury[20].

Thus a meta-analysis was performed to pool available evidence about the potential cardioprotective role of RIPC in reducing periprocedural myocardial infarction.

Methods

DATA SEARCH

Pubmed (MEDLINE), Embase and Cochrane databases were searched using terms such as "ischaemic preconditioning or remote ischaemic (or ischaemic) preconditioning", "percutaneous coronary intervention or PCI", according to optimal search strategies[21]. Moreover, abstract sites for the ESC, TCT, AHA, and ACC were also searched for abstracts of unpublished studies.

The references quoted in the articles included were also reviewed, and no language restriction was performed. All corresponding authors of shortlisted studies were directly contacted for additional data and invited to participate in data analysis and interpretation, as well as suggestions for additional studies.

STUDY SELECTION

Randomised controlled trials which evaluated the effect of RIPC against a control population of patients undergoing PCI were selected. Inclusion criteria were: i) patients undergoing PCI, and ii) evaluation of PMI or reactive CRP levels as endpoint. Exclusion criteria were: i) animal studies, ii) non-randomised clinical studies.

Three investigators (GBZ, EC, FDA) independently reviewed titles, abstracts, and the full texts as needed, to determine whether studies met inclusion criteria. Conflicts between reviewers were resolved through re-review and discussion.

VALIDITY ASSESSMENT

The quality of included trials was explored according to Cochrane, PRISMA and QUORUM statements[22,23]. Methods to obtain sample size, selection bias (allocation and random sequence generation), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment) and attrition bias (incomplete outcome data) were assessed and graphically described.

DATA EXTRACTION, STUDY CHARACTERISTICS AND ENDPOINTS

Three authors (GBZ, EC, FDA) independently abstracted data on study design, setting, RIPC protocols, and age, gender, patients with diabetes mellitus and with diagnosis of multivessel disease.

The rate of PMI was the primary endpoint, while absolute values of CRP after PCI and rates of MACE (major adverse cardiac events) at follow-up were the secondary ones.

QUANTITATIVE DATA SYNTHESIS

Random effects models were exploited to compute the odds ratio and risk difference for periprocedural myocardial infarction. The number needed to treat was reported as 1/absolute risk difference. Fixed effects models were also tested, and their results reported only if different from random effect.

Using event rates as a dependent variable, a meta-regression was performed to test whether there was an interaction between baseline clinical features (age, female gender, diabetes mellitus and multivessel disease) and rates of periprocedural myocardial infarction.

Hypothesis testing for statistical homogeneity was set at the two-tailed 0.10 level and based on Cochran's Q test, with I^2 values of 25%, 50%, and 75% representing, respectively, mild, moderate, and extensive statistical heterogeneity. Funnel plots were explored to identify small study biases by the Duval and Tweedie trim and fill method. Statistical analyses were performed with Review Manager 4.2.4 (Windows; Microsoft, Redmond, WA, USA), and Comprehensive Meta-Analysis (CMA; Biostat, Inc., Englewood, NJ, USA).

Results

A total of 294 citations were initially screened, and appraised using the abstracts; nine articles were selected, among which four were excluded, because of not evaluating clinical endpoints[15,20,24,25] **(Figure 1)**. Finally, five studies were included in our analysis[16,17,26-28].

Seven hundred and thirty-one patients were randomised to remote ischaemic preconditioning or control. Their median age was 62 (59-68) years old, 25% were female (23-33), 29% (25-33) reported a diagnosis of diabetes mellitus, 81% (78-82) were treated with beta-blockers and 56% (51-62) with angiotensin converting enzyme inhibitors; 26.5% (19-31) of patients presented with multivessel disease and 39.5% (31-52) with a type C lesion **(Table 1)**.

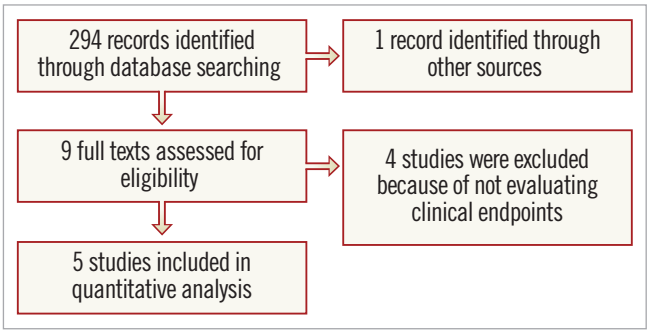


Figure 1. *Profile of the review.*

The protocol of RIPC was similar, with only one study using the lower limb[24], and the definition of periprocedural myocardial infarction was consistent among studies, i.e., an increase of troponin greater than three times the 99th percentile URL **(Table 2)**.

RIPC significantly reduced the incidence of PMI (0.58 [0.36, 0.93]; I^2 43%, **Figure 2**), with an increased benefit when performed at the lower limb (0.21 [0.07-0.66]) compared to the upper limb (0.67 [0.46-0.99]) **(Figure 3)**. This reduction was enhanced for patients with multivessel disease (beta –0.05 [–0.09;–0.01], p=0.01) and with type C lesion (beta –0.014 [–0.04;–0.010], p=0.01) and did not vary according to age (beta 0.06 [–0.03;0.17], p=0.19), female gender (beta –0.03 [–0.06;0.009], p=0.14), diabetes mellitus (beta –0.03 [–0.07;0.005], p=0.09), use of beta-blockers (beta –0.05 [–0.15;0.05], p=0.35) and use of angiotensin converting enzyme inhibitors (beta 0.01 [–0.02;0.04], p=0.47, **Figure 4**, **Figure 5**). Absolute risk difference was –0.10 [–0.19, –0.02], with a number needed to treat of 10 [6-50] patients to avoid one event.

RIPC did not significantly reduce global release of CRP (OR –0.69 [–1.69, 0.31]) **(Figure 6)** or MACE after a follow-up of 12 (1-42) months **(Figure 6)**, although a significant difference was noted in the study with the longest follow-up.

Table 1. Main features of patients of included studies.

	Number of patients (active:control)	Age	Female gender n (%)	Diabetes mellitus n (%)	Clinical indications for PCI	Beta-blockers n (%)	Angiotensin converting enzyme inhibitors n (%)	Multivessel disease n (%)	Type C lesion n (%)
Ahmed, 13	77:72	54±7	20 (13)	77 (52)	Elective PCI	65 (81)	44 (55)	34 (25)	22 (15)
Ghaemian, 13	40:40	61±8	42 (51)	29 (36)	Elective PCI			36 (45)	62 (77)
Hoole, 09	104:98	62±9	44 (25)	44 (22)	Elective PCI	160 (80)	149 (74)	34 (17)	70 (36)
Luo, 13	101:104	60±8	49 (25)	57 (27)	Elective PCI	169 (83)	139 (57)	57 (28)	–
Prasad, 12	47:48	66±11	16 (17)	26 (27)	Elective PCI 65%, unstable angina 35%	70 (73)	38 (38)	18 (17)	42 (43)

Table 2. Procedural features of included studies.

	Protocol of preconditioning	Time between RIPC and PCI	Definition of periprocedural myocardial infarction	Region of recruitment	Period of recruitment
Ahmed, 13	Three cycles of alternating 5 min inflation and 5 min deflation of a standard upper-arm blood-pressure cuff to 200 mmHg	Immediately before PCI	An increase of cTnT greater than 3 times the 99th percentile URL	Asia	March-November 2012
Ghaemian, 13	2 cycles of lower-limb ischaemia and reperfusion, using a 15 cm-wide lower-limb tourniquet placed over the patient's upper thigh contralateral to the femoral puncture site	45 minutes after end of RIPC protocol	An increase of cTnT greater than 3 times the 99th percentile URL	Asia	2009-2009
Hoole, 09	Three cycles of alternating 5 min inflation and 5 min deflation of a standard upper-arm blood-pressure cuff to 200 mmHg	60 minutes after start of RIPC protocol	An increase of cTnT greater than 3 times the 99th percentile URL	Europe	July 2006 - November 2007
Luo, 13	Three cycles of alternating 5 min inflation and 5 min deflation of a standard upper-arm blood-pressure cuff to 200 mmHg	Less than 120 minutes after start of RIPC protocol	An increase of cTnT greater than 3 times the 99th percentile URL	Asia	March 2012 - August 2012
Prasad, 12	Three cycles of alternating 3 min inflation and 3 min deflation of a standard upper-arm blood-pressure cuff to 200 mmHg		An increase of cTnT greater than 3 times the 99th percentile URL	North America	November 2006 - November 2008

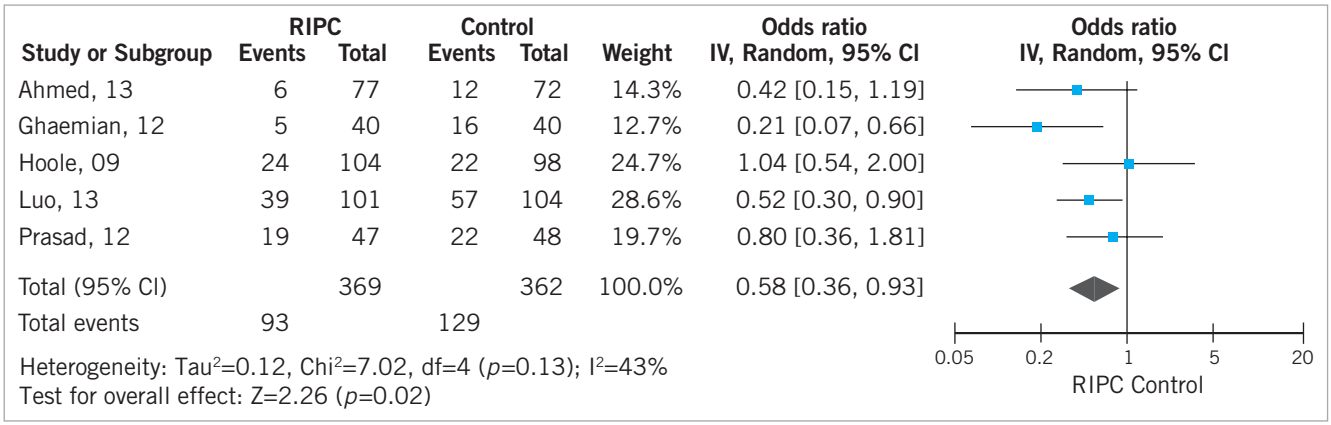


Figure 2. *Pooled analysis of periprocedural myocardial infarction according to randomisation group.*

As shown in panel A of **Figure 7**, publication bias towards positive studies may be present, but Duval and Tweedie's trim and fill showed significant reduction both for observed and adjusted methods. Moreover, risk of bias was small (**Figure 7**, panel B).

Discussion

To the best of our knowledge this is the largest meta-analysis demonstrating, for the first time, a cardioprotective effect of RIPC during non-emergent PCI.

RIPC significantly reduced PMI with an estimated 10 patients needed to be treated to avoid one adverse event. Reduction of periprocedural myocardial infarction was increased for patients with multivessel disease. These observations are consistent with the benefit of RIPC we have recently reported in a meta-analysis of studies among patients with diffuse coronary disease undergoing surgical revascularisation[12], highlighting the concept that positive effects of preconditioning may be more relevant and easier to detect in patients with a larger amount of cardiac damage. This may account for the fact that some investigations with a small sample size and in relatively low-risk patients[16,17] (i.e., low frequency of diabetics and multivessel disease) did not demonstrate a benefit of RIPC on PMI. An interesting and hypothesis-generating

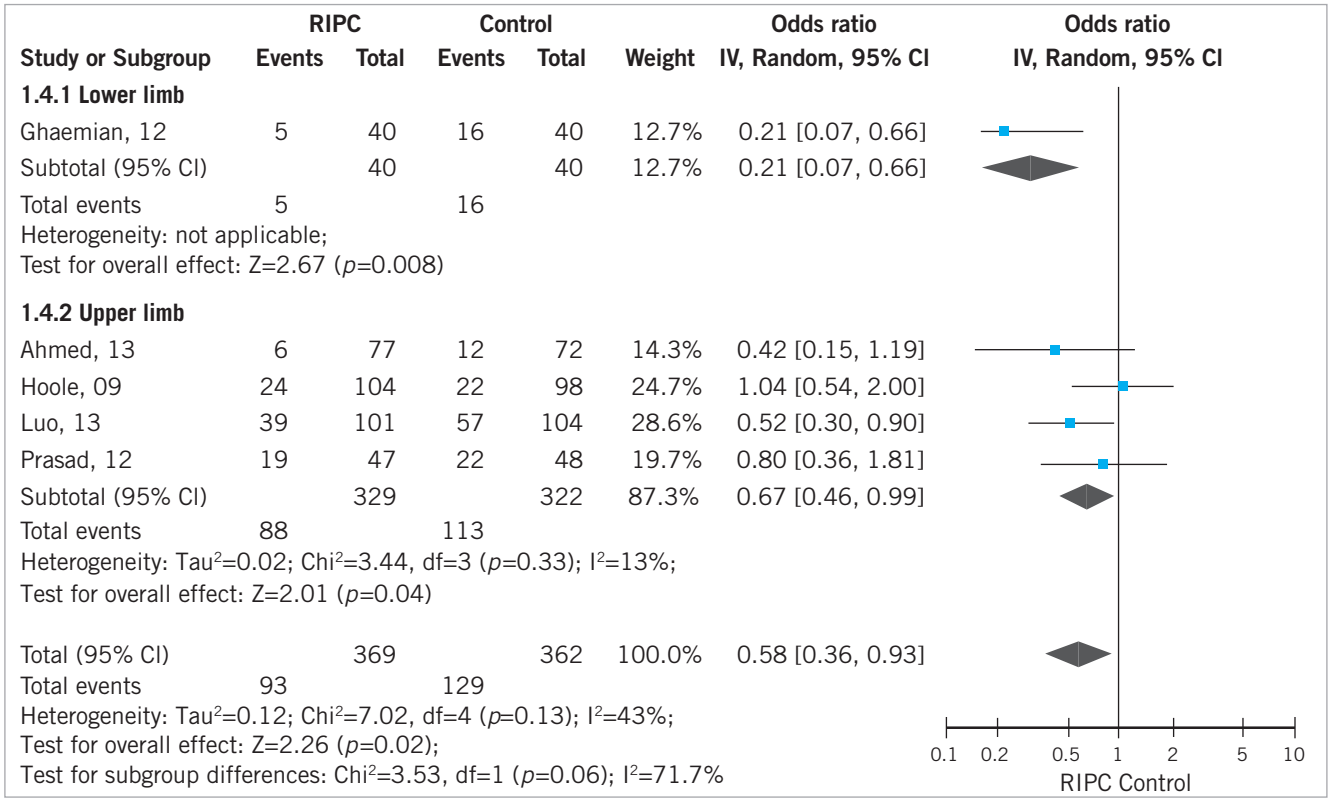


Figure 3. *Pooled analysis of periprocedural myocardial infarction according to site or RIPC.*

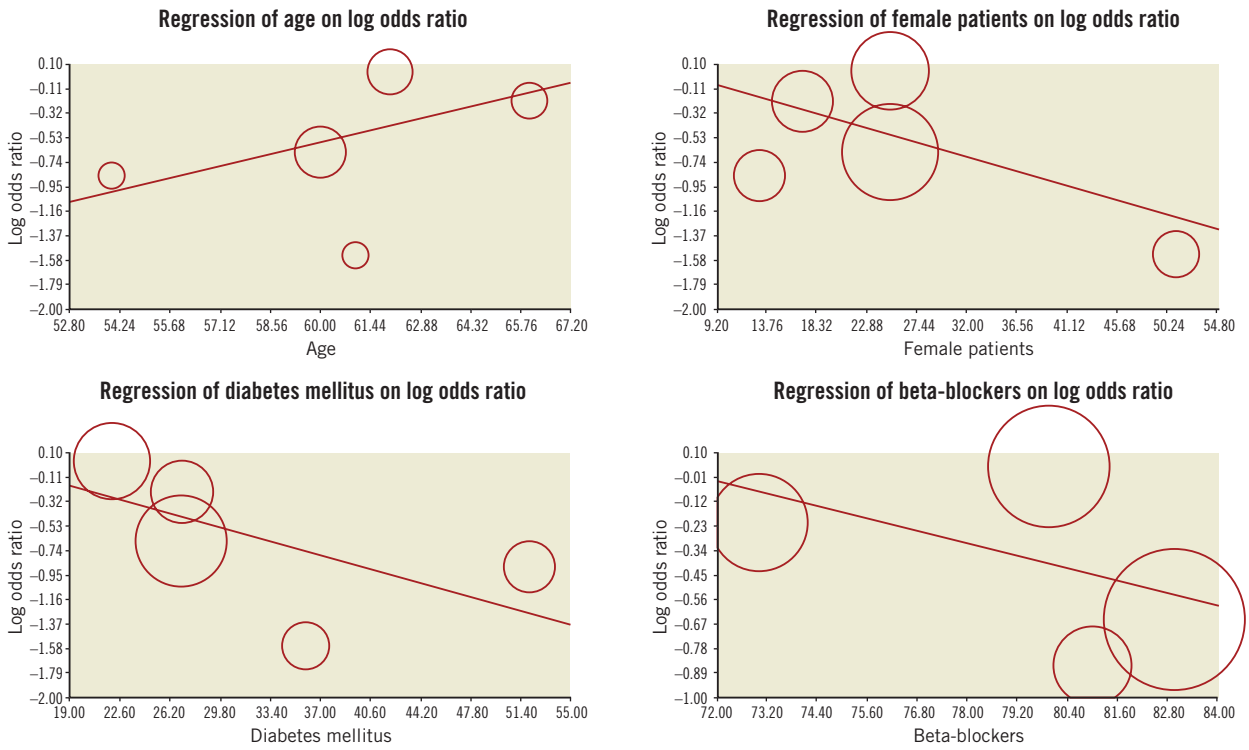


Figure 4. *Meta-regression of clinical variables on reduction of periprocedural myocardial infarction (no significant interaction was noted).*

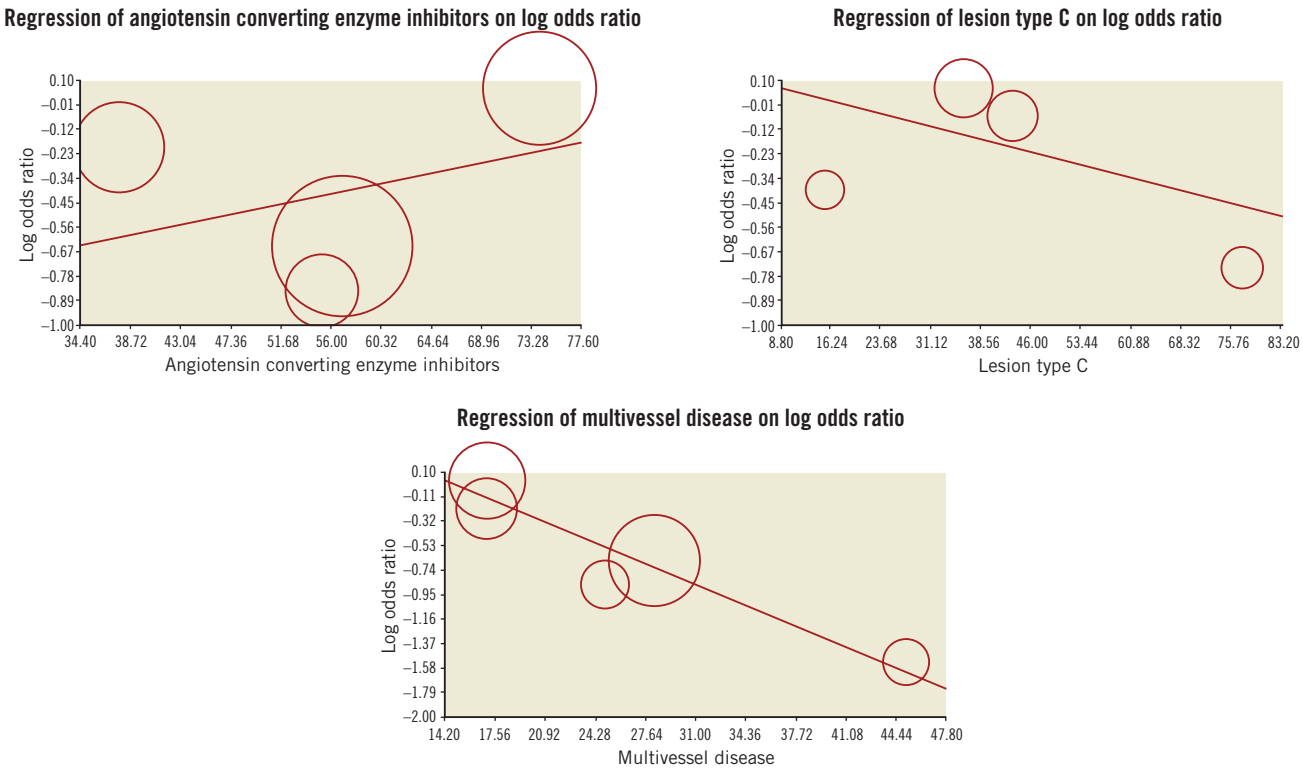
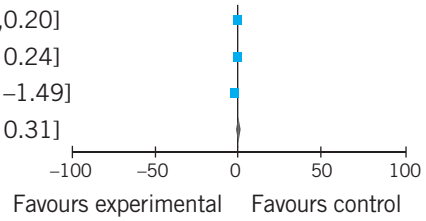


Figure 5. *Meta-regression of clinical variables on reduction of periprocedural myocardial infarction (significant interaction with multivessel disease and lesion type C).*

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std mean difference IV, random, 95% CI
Ahmed, 13	5.6	7.2	77	6.64	10.35	72	33.7%	–0.12 [–0.44 ,0.20]
Hoole, 09	1.9	5.3	104	2.1	6.8	98	34.1%	–0.03 [–0.31, 0.24]
Prasad, 12	5	1	47	7	1	48	32.2%	–1.98 [–2.48, –1.49]
Total (95% CI)			228			218	100.0%	–0.69 [–1.69, 0.31]

Heterogeneity: Tau²=0.75; Chi²=48.98, df=2 (p<0.00001); I²=96%;
Test for overall effect: Z=1.35 (p=0.18)



Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds ratio IV, random, 95% CI
Ghaemian, 12	4	40	2	40	24.5%	2.11 [0.36, 12.24]
Hoole, 09	4	95	13	97	37.4%	0.28 [0.09, 0.91]
Prasad, 12	7	47	7	48	38.1%	1.02 [0.33, 3.19]
Total (95% CI)		182		185	100.0%	0.76 [0.25, 2.30]
Total events	15		22			

Heterogeneity: Tau²=0.51; Chi²=4.27, df=2 (p=0.12); I²=53%;
Test for overall effect: Z=0.49 (p=0.62)

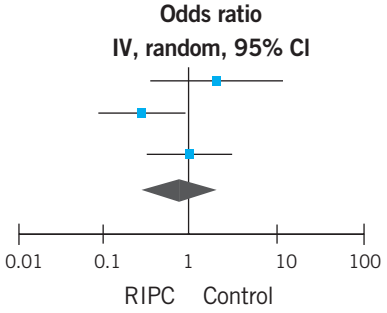


Figure 6. *Pooled analysis of CRP according to randomisation group (above). Pooled analysis of MACE according to randomisation group (below).*

observation from our analysis is that the benefits of RIPC may be enhanced when ischaemia and reperfusion therapy is performed in the lower limbs. This raises the question as to whether RIPC is an "all-or-nothing" or a dose-dependent phenomenon[29]. If the latter theory is true, the lower limb, with its significantly larger bulk of skeletal muscle, may confer maximal cardiac protection.

An alternative to RIPC is direct cardiac preconditioning. Laskey[29] demonstrated that direct ischaemic preconditioning performed in

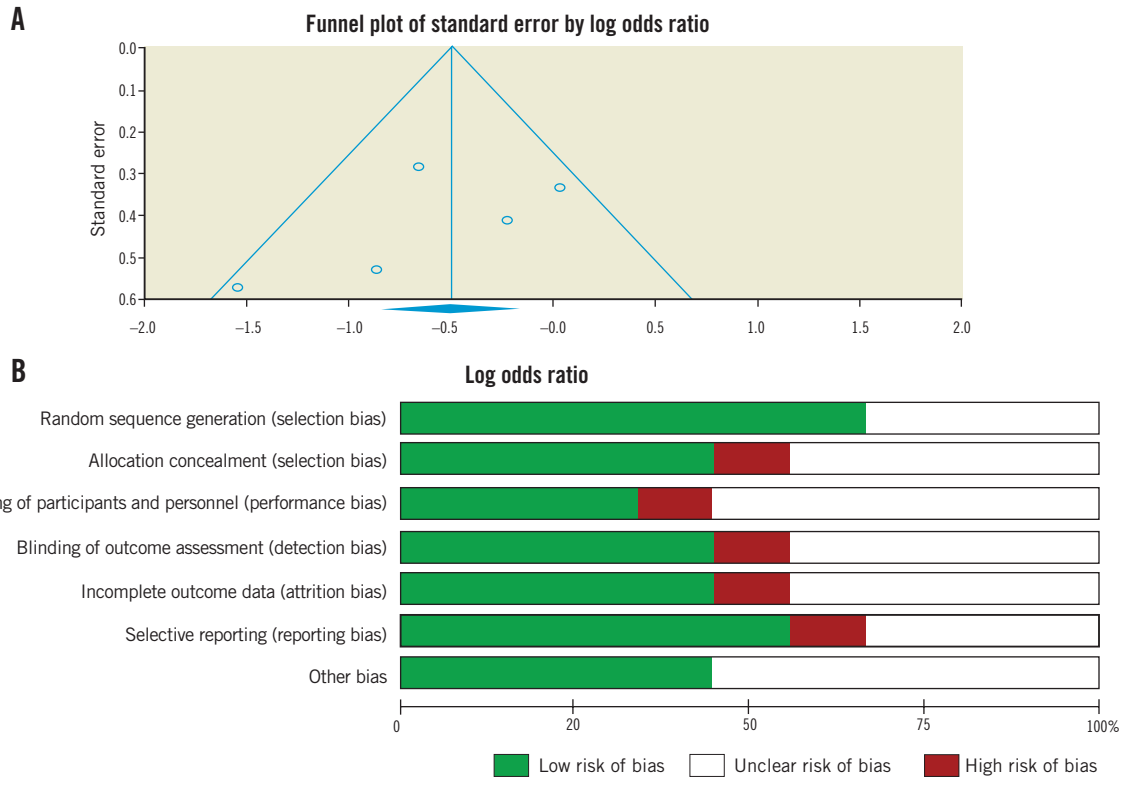


Figure 7. *A) Funnel plot describing risk of publication bias. B) Risk of bias percentages of studies with low, unclear or high risk of selection, attrition, reporting and blinding bias are reported.*

the coronary vascular bed prior to PTCA by two 90-second cycles of ischaemia induced by balloon inflations, separated by five minutes of reperfusion, significantly reduced post-procedural creatine kinase elevation. However, direct preconditioning has the potential disadvantage of inducing complications such as macro- or microembolisation, ventricular arrhythmia or mechanical trauma to the vessel. In contrast, RIPC represents a safe, quick and cost-effective way to reduce PMIs, with a low number of patients needed to be treated to avoid one event[30]. This is comparable to a recent trial of statin use before PCI[31], showing that 10 patients given atorvastatin were needed to reduce one event.

Although the cardioprotective mechanism of RIPC remains incompletely understood, preconditioning has been postulated to stabilise vulnerable plaques through platelet inhibition and antithrombotic effects[32]. Preclinical studies have shown that humoral mediators such as adenosine and bradykinin or neurogenic pathways probably play a crucial role in RIPC[33]. Also, endogenous myocardial mediators such as erythropoietin, nitric oxide, delta 1-opioid, and free radicals are involved[9,34,35].

PMI can occur through a variety of mechanisms. A recent study using magnetic resonance imaging for delayed enhancement with gadolinium has shown that both impairment of flow in coronary side branches and distal embolisation of atheromatous material contribute to myocardial necrosis during PCI[36,37]. When substantial elevations of CK-MB of troponin are recorded, side branch occlusion though plaque shift is the most probable mechanism. On the contrary, smaller increases in cardiac enzymes are more likely due to microembolisation of thrombotic or atherosclerotic material. Moreover, some studies advocate that the presence of an enhanced inflammatory state could predispose patients to thrombosis as well as vasospasm, playing a role in the microembolism mechanism[38,39]. The lack of effect of RIPC on the CRP levels in our analysis suggests that modulation of inflammation may not be the predominant mechanism of action of preconditioning.

The majority of PMI, especially when measured with a sensitive biomarker such as troponin, probably represent a marker of atherosclerotic burden and procedural complexity. Nevertheless, large PMI are likely to affect prognosis, and strategies to limit them are worth pursuing[38]. The Joint ESC/ACCF/AHA/WHF Task Force Universal definition of Myocardial Infarction 2007[40] defined PMI (type 4a) during PCI as an elevation of serum biomarkers (preferably cardiac troponins) above three times the 99th percentile upper reference limit (URL) after PCI, in patients with a normal baseline troponin value. Testa et al[41] in a recent meta-analysis of 15 studies incorporating 7,578 patients demonstrated that these patients were at high risk of further adverse events both during the hospital stay and at 18 months. However, the accuracy of these results was limited by the use in the included studies of troponin cut-off values higher than the currently recommended 99th percentile. The incidence of PMI in selected studies of our review was about 15-20%, being higher in those studies with relevant rates of multivessel disease[26,27], i.e., with larger atherosclerotic disease and more complex interventions. Recently, a revised universal definition of PMI has been proposed[42], although the selected threshold of >5×99th percentile is, as acknowledged by the authors, arbitrary and without demonstrated correlation with prognosis[43]. The studies included in our study predated this definition and hence did not use it. Moreover, in our pooled analysis, RIPC did not influence prognosis. This finding should be confirmed in larger studies. Actually, the lower rates of adverse events after a PCI for stable angina require a larger sample size to drive a significant reduction; interestingly, the only positive trial was the one with the longest follow-up.

Limitations

Our work has several limitations. First, a small number of studies were included which enrolled a small sample size due to the relatively recent interest in the clinical application of RIPC, which represented a limitation both for main analysis, and for meta-regression. Moreover, there is a lack of economic interest in this procedure. A second publication bias was noted towards positive effects, even if Duval and Tweedie's trim and fill produced a negative result. In the included trials, overall quality was good, with a low risk of blinding and of selection bias.

Conclusion

The preliminary data for RIPC are very encouraging. However, confirmation in larger randomised multicentre studies that are adequately powered to assess major clinical endpoints is required. Unfortunately, the size of trials required to demonstrate benefits in hard clinical endpoints makes mortality trials unlikely, necessitating reliance on composite measures together with softer endpoints.

Impact on daily practice

The potential applications of remote preconditioning span a wide range of clinical situations targeting the heart, brain, kidney, and liver. Owing to its easy delivery, its safety and cheapness, the preconditioning treatment looks like an encouraging therapeutic tool for various different clinical scenarios of ischaemia-reperfusion injury syndromes. RIPC antithrombotic effects may be particularly useful in cardiology to reduce periprocedural complications of percutaneous interventions, especially periprocedural myocardial infarction.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Das M, Das DK. Molecular mechanism of preconditioning. *IUBMB Life.* 2008;60:199-203.

2. Halestrap AP, Clarke SJ, Khaliulin I. The role of mitochondria in protection of the heart by preconditioning. *Biochim Biophys Acta.* 2007;1767:1007-31.

3. Wolfrum S, Schneider K, Heidbreder M, Nienstedt J, Dominiak P, Dendorfer A. Remote preconditioning protects the

heart by activating myocardial PKCepsilon-isoform. *Cardiovasc Res.* 2002;55:583-9.

4. Weinbrenner C, Nelles M, Herzog N, Sarvary L, Strasser RH. Remote preconditioning by infrarenal occlusion of the aorta protects the heart from infarction: a newly identified non-neuronal but PKC-dependent pathway. *Cardiovasc Res.* 2002;55:590-601.

5. Kristiansen SB, Henning O, Kharbanda RK, Nielsen-Kudsk JE, Schmidt MR, Redington AN, Nielsen TT, Bøtker HE. Remote preconditioning reduces ischemic injury in the explanted heart by a KATP channel-dependent mechanism. *Am J Physiol Heart Circ Physiol.* 2005;288:H1252-6.

6. Wang L, Oka N, Tropak M, Callahan J, Lee J, Wilson G, Redington A, Caldarone CA. Remote ischemic preconditioning elaborates a transferable blood-borne effector that protects mitochondrial structure and function and preserves myocardial performance after neonatal cardioplegic arrest. *J Thorac Cardiovasc Surg.* 2008;136:335-42.

7. Hausenloy DJ, Yellon DM. Remote ischaemic preconditioning: underlying mechanisms and clinical application. *Cardiovasc Res.* 2008;79:377-86.

8. Konstantinov IE, Arab S, Kharbanda RK, Li J, Cheung MM, Cherepanov V, Downey GP, Liu PP, Cukerman E, Coles JG, Redington AN. The remote ischemic preconditioning stimulus modifies inflammatory gene expression in humans. *Physiol Genomics.* 2004;19:143-50.

9. Loukogeorgakis SP, Williams R, Panagiotidou AT, Kolvekar SK, Donald A, Cole TJ, Yellon DM, Deanfield JE, MacAllister RJ. Transient limb ischemia induces remote preconditioning and remote postconditioning in humans by a K(ATP)-channel dependent mechanism. *Circulation*. 2007;116:1386-95.

10. Prasad A, Stone G, Holmes D, Gersh B. Reperfusion injury, microvascular dysfunction and cardioprotection: the "dark side" of reperfusion. *Circulation*. 2009;120:2105-12.

11. Kerendi F, Kin H, Halkos ME, Jiang R, Zatta AJ, Zhao ZQ, Guyton RA, Vinten-Johansen J. Remote postconditioning. Brief renal ischemia and reperfusion applied before coronary artery reperfusion reduces myocardial infarct size via endogenous activation of adenosine receptors. *Basic Res Cardiol.* 2005;100:404-12.

12. D'Ascenzo F, Cavallero E, Moretti C, Omedè P, Sciuto F, Rahman IA, Bonser RS, Yunseok J, Wagner R, Freiberger T, Kunst G, Marber MS, Thielmann M, Ji B, Amr YM, Modena MG, Zoccai GB, Sheiban I, Gaita F. Remote ischaemic preconditioning in coronary artery bypass surgery: a meta-analysis. *Heart.* 2012;98:1267-71.

13. Brevoord D, Kranke P, Kuijpers M, Weber N, Hollmann M, Preckel B. Remote ischemic conditioning to protect against ischemia-reperfusion injury: a systematic review and meta-analysis. *PLoS One.* 2012;7:e42179.

14. Thielmann M, Kottenberg E, Kleinbongard P, Wendt D, Gedik N, Pasa S, Price V, Tsagakis K, Neuhäuser M, Peters J, Jakob H, Heusch G. Cardioprotective and prognostic effects of remote ischaemic preconditioning in patients undergoing coronary artery bypass surgery: a single-centre randomised, double-blind, controlled trial. *Lancet.* 2013;382:597-604.

15. Bøtker HE, Kharbanda R, Schmidt MR, Bøttcher M, Kaltoft AK, Terkelsen CJ, Munk K, Andersen NH, Hansen TM, Trautner S, Lassen JF, Christiansen EH, Krusell LR, Kristensen SD, Thuesen L, Nielsen SS, Rehling M, Sørensen HT, Redington AN, Nielsen TT. Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial. *Lancet.* 2010;375:727-34.

16. Hoole SP, Heck PM, Sharples L, Khan SN, Duehmke R, Densem CG, Clarke SC, Shapiro LM, Schofield PM, O'Sullivan M, Dutka DP. Cardiac Remote Ischemic Preconditioning in Coronary Stenting (CRISP Stent) Study: a prospective, randomized control trial. *Circulation*. 2009;119:820-7.

17. Prasad A, Gössl M, Hoyt J, Lennon RJ, Polk L, Simari R, Holmes DR Jr, Rihal CS, Lerman A. Remote ischemic preconditioning immediately before percutaneous coronary intervention does not impact myocardial necrosis, inflammatory response, and circulating endothelial progenitor cell counts: a single center randomized sham controlled trial. *Catheter Cardiovasc Interv.* 2013;81:930-6.

18. Veselka J, Hájek P, Malý M, Zemánek D, Adlová R, Tomašov P, Martinkovičová L, Tesař D, Cervinka P. Predictors of coronary intervention-related myocardial infarction in stable angina patients pre-treated with statins. *Arch Med Sci.* 2011;7:67-72.

19. Patti G, Mangiacapra F, Ricottini E, Cannatà A, Cavallari I, Vizzi V, D'Ambrosio A, Dicuonzo G, Di Sciascio G. Correlation of platelet reactivity and C-reactive protein levels to occurrence of peri-procedural myocardial infarction in patients undergoing percutaneous coronary intervention (from the ARMYDA-CRP study). *Am J Cardiol.* 2013;111:1739-44.

20. Er F, Nia AM, Dopp H, Hellmich M, Dahlem KM, Caglayan E, Kubacki T, Benzing T, Erdmann E, Burst V, Gassanov N. Ischemic preconditioning for prevention of contrast medium-induced nephropathy: randomized pilot RenPro Trial (Renal Protection Trial). *Circulation*. 2012;126:296-303.

21. Wilczynski NL, Haynes RB; Hedges Team. Developing optimal search strategies for detecting clinically sound prognostic studies in MEDLINE: an analytic survey. *BMC Med.* 2004;2:23.

22. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ.* 2009;339:b2535.

23. Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, Gøtzsche PC, Lang T, CONSORT GROUP (Consolidated Standards of Reporting Trials). The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med.* 2001;134:663-94.

24. Iliodromitis EK, Kyrzopoulos S, Paraskevaidis IA, Kolocassides KG, Adamopoulos S, Karavolias G, Kremastinos DT. Increased C reactive protein and cardiac enzyme levels after coronary stent implantation. Is there protection by remote ischaemic preconditioning? *Heart.* 2006;92:1821-6.

25. Rentoukas I, Giannopoulos G, Kaoukis A, Kossyvakis C, Raisakis K, Driva M, Panagopoulou V, Tsarouchas K, Vavetsi S, Pyrgakis V, Deftereos S. Cardioprotective role of remote ischemic

periconditioning in primary percutaneous coronary intervention: enhancement by opioid action. *JACC Cardiovasc Interv.* 2010;3:49-55.

26. Ahmed RM, Mohamed EH, Ashraf M, Maithili S, Nabil F, Rami R, Mohamed TI. Effect of remote ischemic preconditioning on serum troponin T level following elective percutaneous coronary intervention. *Catheter Cardiovasc Interv.* 2013;82:E647-53.

27. Ghaemian A, Nouraei SM, Abdollahian F, Naghshvar F, Giussani DA, Nouraei SA. Remote ischemic preconditioning in percutaneous coronary revascularization: a double-blind randomized controlled clinical trial. *Asian Cardiovasc Thorac Ann.* 2012;20:548-54.

28. Luo SJ, Zhou YJ, Shi DM, Ge HL, Wang JL, Liu RF. Remote ischemic preconditioning reduces myocardial injury in patients undergoing coronary stent implantation. *Can J Cardiol.* 2013;29:1084-9.

29. Laskey WK. Beneficial impact of preconditioning during PTCA on creatine kinase release. *Circulation*. 1999;99:2085-9.

30. Gritsopoulos G, Iliodromitis EK, Zoga A, Farmakis D, Demerouti E, Papalois A, Paraskevaidis IA, Kremastinos DT. Remote postconditioning is more potent than classic postconditioning in reducing infarct size in anesthetized rabbits. *Cardiovasc Drug Ther.* 2009;23:193-8.

31. Patti G, Pasceri V, Colonna G, Miglionico M, Fischetti D, Sardella G, Montinaro A, Di Sciascio G. Atorvastatin pretreatment improves outcomes in patients with acute coronary syndromes undergoing early percutaneous coronary intervention: results of the ARMYDA-ACS randomized trial. *J Am Coll Cardiol.* 2007;49:1272-8.

32. Babu GG, Walker JM, Yellon DM, Hausenloy DJ. Peri-procedural myocardial injury during percutaneous coronary intervention: an important target for cardioprotection. *Eur Heart J.* 2011;32:23-31.

33. Veighey K, Macallister RJ. Clinical applications of remote ischemic pre-conditioning. *Cardiol Res Pract.* 2012;2012:620681.

34. Serejo FC, Rodrigues LF Jr, Silva Tavares KC, de Carvalho AC, Nascimento JH. Cardioprotective properties of humoral factors released from rat hearts subject to ischemic preconditioning. *J Cardiovasc Pharmacol.* 2007;49:214-22.

35. Kant R, Diwan V, Jaggi AS, Singh N, Singh D. Remote renal preconditioning-induced cardioprotection: a key role of hypoxia inducible factor-prolyl 4-hydroxylases. *Mol Cell Biochem.* 2008;312:25-31.

36. Porto I, Selvanayagam JB, Van Gaal WJ, Prati F, Cheng A, Channon K, Neubauer S, Banning AP. Plaque volume and occurrence and location of periprocedural myocardial necrosis after percutaneous coronary intervention: insights from delayed-enhancement magnetic resonance imaging, thrombolysis in myocardial infarction myocardial perfusion grade analysis, and intravascular ultrasound. *Circulation*. 2006;114:662-9.

37. Prasad A, Herrmann J. Myocardial infarction due to percutaneous coronary intervention. *N Engl J Med.* 2011;364:453-64.

38. Selvanayagam JB, Porto I, Channon K, Petersen SE, Francis JM, Neubauer S, Banning AP. Troponin elevation after percutaneous coronary intervention directly represents the extent of irreversible myocardial injury: insights from cardiovascular magnetic resonance imaging. *Circulation*. 2005;111:1027-32.

39. D'Ascenzo F, Agostoni P, Abbate A, Castagno D, Lipinski MJ, Vetrovec GW, Frati G, Presutti DG, Quadri G, Moretti C, Gaita F, Zoccai GB. Atherosclerotic coronary plaque regression and the risk of adverse cardiovascular events: a meta-regression of randomized clinical trials. *Atherosclerosis.* 2013;226:178-85.

40. Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *Eur Heart J.* 2007;28:2525-38.

41. Testa L, Van Gaal WJ, Biondi Zoccai GG, Agostoni P, Latini RA, Bedogni F, Porto I, Banning AP. Myocardial infarction after percutaneous coronary intervention: a meta-analysis of troponin elevation applying the new universal definition. *QJM.* 2009;102:369-78.

42. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD; Joint ESC/ACCF/AHA/WHF Task Force for Universal Definition of Myocardial Infarction; Authors/Task Force Members Chairpersons, Thygesen K, Alpert JS, White HD; Biomarker Subcommittee, Jaffe AS, Katus HA, Apple FS, Lindahl B, Morrow DA; ECG Subcommittee, Chaitman BR, Clemmensen PM, Johanson P, Hod H; Imaging Subcommittee, Underwood R, Bax JJ, Bonow JJ, Pinto F, Gibbons RJ; Classification Subcommittee, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW; Intervention Subcommittee, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasche P, Ravkilde J; Trials & Registries Subcommittee, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML; Trials & Registries Subcommittee, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G; Trials & Registries Subcommittee, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D; Trials & Registries Subcommittee, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S; ESC Committee for Practice Guidelines (CPG), Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S; Document Reviewers, Morais J, Aguiar C, Almahmeed W, Arnar DO, Barili F, Bloch KD, Bolger AF, Botker HE, Bozkurt B, Bugiardini R, Cannon C, de Lemos J, Eberli FR, Escobar E, Hlatky M, James S, Kern KB, Moliterno DJ, Mueller C, Neskovic AN, Pieske BM, Schulman SP, Storey RF, Taubert KA, Vranckx P, Wagner DR. Third universal definition of myocardial infarction. *J Am Coll Cardiol.* 2012;60:1581-98.

43. Woudstra P, Grundeken MJ, van de Hoef TP, Wallentin L, Fox KA, de Winter RJ, Damman P. Prognostic relevance of PCI-related myocardial infarction. *Nat Rev Cardiol.* 2013;10:231-6.