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Remote Ischemic Perconditioning to Reduce Reperfusion Injury During Acute ST-Segment–Elevation Myocardial Infarction: A Systematic Review and Meta-Analysis

Shelley L. McLeod, PhD(c), MSc; Alla Iansavichene, BS, MLIS; Sheldon Cheskes, MD, CCFP(EM), FCFP

***Background*—**Remote ischemic conditioning (RIC) is a noninvasive therapeutic strategy that uses brief cycles of blood pressure cuff inflation and deflation to protect the myocardium against ischemia–reperfusion injury. The objective of this systematic review was to determine the impact of RIC on myocardial salvage index, infarct size, and major adverse cardiovascular events when initiated before catheterization.

***Methods and Results*—**Electronic searches of Medline, Embase, and Cochrane Central Register of Controlled Trials were conducted and reference lists were hand searched. Randomized controlled trials comparing percutaneous coronary intervention (PCI) with and without RIC for patients with ST-segment–elevation myocardial infarction were included. Two reviewers independently screened abstracts, assessed quality of the studies, and extracted data. Data were pooled using random-effects models and reported as mean differences and relative risk with 95% confidence intervals. Eleven articles (9 randomized controlled trials) were included with a total of 1220 patients (RIC+PCI=643, PCI=577). Studies with no events were excluded from meta-analysis. The myocardial salvage index was higher in the RIC+PCI group compared with the PCI group (mean difference: 0.08; 95% confidence interval, 0.02–0.14). Infarct size was reduced in the RIC+PCI group compared with the PCI group (mean difference: −2.46; 95% confidence interval, −4.66 to −0.26). Major adverse cardiovascular events were lower in the RIC+PCI group (9.5%) compared with the PCI group (17.0%; relative risk: 0.57; 95% confidence interval, 0.40–0.82).

***Conclusions*—**RIC appears to be a promising adjunctive treatment to PCI for the prevention of reperfusion injury in patients with ST-segment–elevation myocardial infarction; however, additional high-quality research is required before a change in practice can be considered. **(*J Am Heart Assoc*. 2017;6:e005522. DOI: 10.1161/JAHA.117.005522.)**

Key Words: ischemia reperfusion injury • meta-analysis • percutaneous coronary intervention • remote ischemic conditioning • ST-segment elevation myocardial infarction

More than 1.4 million patients worldwide are hospitalized each year with an acute coronary syndrome; one third of these patients will have an ST-segment–elevation myocardial infarction (STEMI).[1,2] Prompt restoration of blood flow is crucial to salvage ischemic myocardium.[3–5] Reperfusion strategies such as primary percutaneous coronary intervention (PCI) and thrombolysis have been shown to reduce mortality and infarct size and to improve left ventricular function; however, reperfusion itself may result in adverse events.[6–11] Abrupt reperfusion therapy can lead to reversible impaired myocardial contractility (myocardial stunning), ventricular arrhythmias, and microvascular dysfunction. The pattern of injury that is inflicted on the myocardium has been termed *reperfusion injury*,[12] and the accumulating deleterious effects result in myocyte necrosis and impaired infarct healing and contribute to postinfarction heart failure and other poor outcomes.[13–16] Consequently, the prevention of reperfusion injury and minimization of postinfarction heart

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An accompanying Data S1 is available at http://jaha.ahajournals.org/content/6/5/e005522/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- In this systematic review and meta-analysis of the impact of remote ischemic conditioning on patients undergoing primary percutaneous coronary intervention for acute ST-segment–elevation myocardial infarction, we found a significant improvement in the primary outcome of myocardial salvage index as well as a significant reduction in myocardial infarct size and major adverse cardiovascular events.

What Are the Clinical Implications?

- Remote ischemic conditioning appears to be a promising adjunctive treatment to percutaneous coronary intervention for the prevention of reperfusion injury in patients with ST-segment–elevation myocardial infarction.
- Additional high-quality research focusing on patient-important, clinical outcomes is required before a change in practice can be considered.

failure are considered pivotal goals for improving outcomes in STEMI patients.

Remote ischemic conditioning (RIC) is a noninvasive therapeutic strategy that uses brief cycles of blood pressure cuff inflation and deflation to protect the myocardium against ischemia–reperfusion injury.[17,18] Previous proof-of-concept clinical studies using RIC before (preconditioning) or during (perconditioning) a major ischemic event have demonstrated improvements in surrogate markers of ischemia (eg, increased myocardial salvage and reduced infarct size) in a variety of clinical scenarios including acute STEMI, elective PCI, and coronary artery bypass grafting (CABG) surgery.[19–26] In addition, in patients with STEMI, RIC before PCI has been shown to reduce the incidence of contrast-induced acute kidney injury and has prevented acute kidney injury in patients undergoing cardiopulmonary bypass–assisted cardiac surgery.[27,28]

A systematic review and meta-analysis by Brevoord et al included 23 clinical studies reporting the use of RIC for patients undergoing cardiac surgery, vascular surgery, or elective or acute PCI. Despite reporting significant clinical heterogeneity (eg, clinical scenarios, patient population, RIC protocol), data were pooled for meta-analysis. The authors concluded that no evidence showed that RIC reduced major adverse cardiovascular events (MACE) or mortality associated with ischemic events. RIC, however, did reduce the incidence of periprocedural myocardial infarctions and the release of troponin.[29] More recently, Le Page et al conducted a systematic review and meta-analysis of 53 articles (44 studies) and concluded that RIC was associated with a significant reduction in cardiac biomarkers and long-term morbidity and mortality in situations presenting a risk of myocardial ischemia–reperfusion injury. The authors were unable to extend their conclusions to STEMI patients because too few studies were available at the time of publication.[30] To date, despite multiple systematic reviews, no meta-analysis has explored the effect of RIC exclusively in STEMI patients undergoing emergent PCI, and new randomized trials specifically investigating RIC in STEMI patients have been published.[6,31,32] The primary objective of this systematic review and meta-analysis was to determine the impact of RIC on myocardial salvage index when initiated before catheterization. Secondary outcomes included the impact of RIC on infarct size and MACE including mortality, reinfarction, stroke, and congestive heart failure.

Methods

Literature Search Strategy

The systematic literature searches were conducted in Medline (1946 to October 2016), using both Ovid and PubMed search interfaces; Embase (1947 to October 2016); the Cochrane Central Register of Controlled Trials (October 2016); and electronic bibliographic databases by a research librarian with formal training in electronic literature searching, in consultation with the review authors. A sensitive search strategy (Data S1) included a combination of subject headings and free-text terms using various spelling and endings, such as, but not limited to, the following terms: *ischemic postconditioning, ischemic preconditioning, remote, RIPC* (remote ischemic preconditioning), *myocardial infarction, heart infarction, ST-segment–elevation myocardial infarction, STEMI, myocardial reperfusion injury, thrombolytic therapy, fibrinolytic therapy, percutaneous coronary intervention, angioplasty, ischemic preconditioning,* and *myocardium.*

Study Setting and Population

Randomized controlled trials (RCTs) involving STEMI patients undergoing urgent PCI with RIC initiated before catheterization (eg, in the prehospital setting or on hospital arrival) compared with PCI alone were eligible for inclusion. Studies investigating the use of local ischemic postconditioning (inflation and deflation of the angioplasty balloon) were included only if they also used RIC before reperfusion (perconditioning). Studies comparing the use of local ischemic postconditioning versus PCI alone were excluded from the review because they did not investigate RIC. There was no age restriction. Studies that compared RIC for other ischemic conditions in isolation (eg, elective PCI, CABG, stroke, renal failure) were excluded from this review.

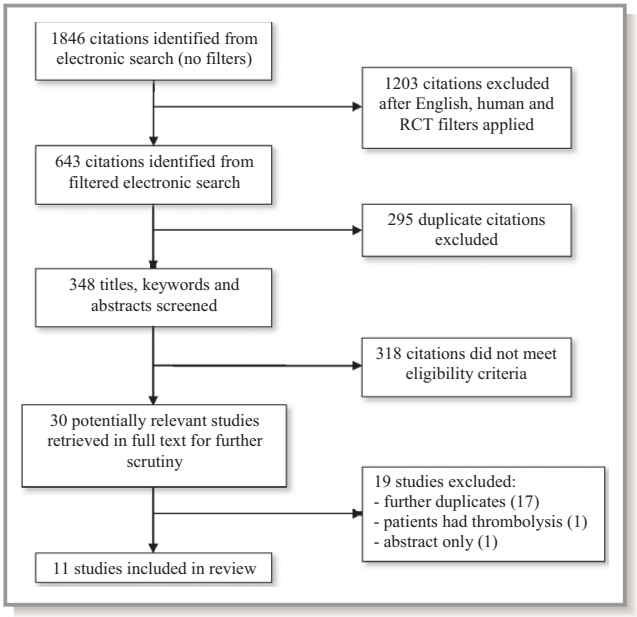

Figure 1. Flow diagram of included studies. RCT indicates randomized controlled trial.

The searches were restricted to studies published in the English language only. An optimized hedges filter and text words were used to refine search results to RCTs and systematic reviews published on the topic. The search strategies were modified for each particular database to include specific terms, search filters, and fields. Reference lists of relevant retrieved articles and reviews were also hand searched for other relevant citations, and the regulatory website ClinicalTrials.gov was searched to identify any unpublished trials. The authors independently screened the search output to identify potentially eligible trials, the full texts of which were retrieved and assessed for inclusion (Figure 1). The extent of agreement between reviewers during final study selection was estimated using Cohen's κ statistic and percentage agreement.

Outcome Measures

The primary outcome was the impact of RIC on myocardial salvage index, defined as the proportion of area at risk of the left ventricle salvaged by treatment following emergent PCI for STEMI. Secondary outcomes included infarct size and MACE including mortality, reinfarction, stroke, and congestive heart failure. Studies that did not report any of these outcomes were excluded from the pooled analyses.

Data Analysis and Risk of Bias Assessment

Using a standardized data collection form, 2 reviewers independently extracted data on patient demographics, sample size, RIC protocol used, and all outcomes data. Risk of bias for the individual trials was independently assessed using the Cochrane Collaboration's tool, and discrepancies in quality assessment scores were resolved by discussion.[33] The following domains were assessed as having a low, unclear (uncertain), or high risk of bias: random sequence generation; allocation concealment; blinding of participants/personnel; blinding of outcome assessment; incomplete outcome data (attrition); and selective outcome reporting.

Direct comparisons were performed using DerSimonian-Laird random-effects models to account for both within- and between-study heterogeneity and reported as relative risks (RRs) with 95% confidence intervals (CIs) using Review Manager 5.3.4 (RevMan; Nordic Cochrane Centre).[34] Secondary outcomes of mortality, reinfarction, stroke, and congestive heart failure were reported as RRs with 95% CIs. In studies with no events in the RIC+PCI or PCI-alone groups, 0.5 was added to each cell of the contingency table (continuity correction) to allow calculation of RR. Studies with no events in both groups were excluded from the meta-analysis. RRs were computed such that a value <1 indicated that RIC+PCI was better than PCI alone for STEMI patients. Statistical significance was defined as $P<0.05$ or 95% CI of the RR that excluded unity.

Statistical heterogeneity was assessed using the I^2 statistic. I^2 describes the percentage of variability in the effect estimates that is due to underlying differences between the studies rather than occurring by chance. I^2 values ≥75% indicated substantial heterogeneity. To explain possible heterogeneity, a priori subgroup analyses were planned to investigate the RIC protocol used by each study as well as the duration of outcome follow-up.

The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) criteria were used to evaluate the quality of evidence by each outcome and were presented using the GRADEpro Guideline Development Tool.[35–37]

Results

The search strategy yielded 1846 potentially relevant citations. After eliminating duplicate citations and studies that did not meet eligibility criteria, 30 full-text articles were retrieved for complete review (Figure 1). Nineteen studies were subsequently excluded, leaving 11 articles (9 RCTs) included in the review with a combined total of 1220 individual patients, 643 in the RIC+PCI group and 577 in the PCI group.[20,21,27,38–45] Percentage agreement for final selection of included trials was 29 of 30 (96.7%) with very good interrater agreement, κ=0.93 (95% CI, 0.81–1.0).

A summary of the characteristics of the included trials can be viewed in Table 1. All 9 RCTs included in this review were conducted outside of North America; 7 (77.8%) were

Table 1. Characteristics of Included Trials

Trial	Inclusion Criteria	RIC Protocol	Main Findings
Bøtker[20] (2010), Denmark	STEMI, symptom onset <12 h, ≥18 y	4×5-min cycles of RIC (200 mm Hg) in ambulance	Mean (SD) myocardial salvage index at 30 d RIC+PCI (n=73): 0.69 (0.27) PCI (n=69): 0.57 (0.26) Mean (SD) infarct size at 30 d RIC+PCI (n=109): 8 (10) PCI (n=110): 12 (13)
Eitel[38] (2015), Germany	STEMI, symptom onset <12 h	3×5-min cycles of RIC (200 mm Hg) on arrival (RIC) followed by 4×30-s cycles after stent deployment (post-IC)	Mean (SD) myocardial salvage index at 3 d RIC+PCI+post-IC (n=158): 0.51 (0.28) PCI (n=160): 0.43 (0.29) Mean (SD) infarct size at 3 d RIC+PCI+post-IC (n=166): 18 (12) PCI (n=168): 20 (14)
Liu[39] (2016), Mongolia	STEMI, symptom onset <12 h, ≥18 y	4×5-min cycles of RIC (200 mm Hg) in ambulance	Mean (SD) infarct size at 3 d RIC+PCI (n=59): 14.2 (6.1) PCI (n=60): 16.6 (6.7) Mean (SD) LVEF at 5 d RIC+PCI (n=59): 0.48 (0.07) PCI (n=60): 0.45 (0.07) MACCE at 1 y RIC+PCI (n=59): 3 (5.1%) PCI (n=60): 8 (13.3%)
Manchurov[40] (2014), Russia	Acute myocardial infarction (45 STEMI, 3 NSTEMI)	4×5-min cycles of RIC (200 mm Hg) before PCI	Brachial artery flow-mediated dilation at 7 d RIC+PCI (n=23): 12.3% PCI (n=25): 7.4%
Munk[41] (2010), Denmark	STEMI, symptom onset <12 h, ≥18 y	4×5-min cycles of RIC (200 mm Hg) in ambulance	Mean (SD) LVEF at 30 d RIC+PCI (n=103): 0.54 (0.08) PCI (n=103): 0.53 (0.10)
Prunier[42] (2014), France	STEMI, symptom onset <6 h, ≥18 y	3×5-min cycles of RIC (200 mm Hg) on arrival to hospital	Mean (SD) CK-MB at 72 h RIC+PCI (n=18): 5038 (3187) RIC+PCI+post-IC (n=20): 5156 (2799) PCI (n=17): 7222 (3021)
Rentoukas[43] (2010), Greece	STEMI, symptom onset <6 h, 35–75 y	3×4-min cycles of RIC (20 mm Hg above systolic arterial pressure) on arrival to hospital	ST-segment resolution ≥80% at 30 min RIC+PCI (n=33): 73% PCI (n=30): 53% Mean (SD) reduction of ST-segment deviation score RIC+PCI (n=33): 69.9% (29.1) PCI (n=30): 53.2% (35.2) Mean (SD) peak troponin I levels (ng/mL) RIC+PCI (n=33): 166.0 (160.8) PCI (n=30): 255.5 (194.5)
Sloth[44] (2014), Denmark	STEMI, symptom onset <12 h, ≥18 y	4×5-min cycles of RIC (200 mm Hg) in ambulance	Composite end point MACCE at 3.8 y RIC+PCI (n=126): 19 (15.1%) PCI (n=125): 37 (29.6%) All-cause mortality at 3.8 y RIC+PCI (n=126): 5 (4.0%) PCI (n=125): 15 (12.0%)
Verouhis[45] (2016), Sweden	STEMI, symptom onset <6 h, ≥18 y	≥1×5-min cycles of RIC (200 mm Hg) on arrival followed by 4×5 min cycles of RIC (200 mm Hg) after reperfusion	Mean (SD) myocardial salvage index at d 4–7 RIC+PCI+post-IC (n=47): 0.49 (0.22) PCI (n=46): 0.49 (0.12) Mean (SD) infarct size at d 4–7 RIC+PCI+post-IC (n=47): 20.6 (13.0) PCI (n=46): 17.9 (8.6)

Continued

Table 1. Continued

Trial	Inclusion Criteria	RIC Protocol	Main Findings
White[21] (2015), UK	STEMI, symptom onset <12 h, 18–80 y	4×5-min cycles of RIC (200 mm Hg) on arrival to hospital	Mean (SD) myocardial salvage index at d 3–6 RIC+PCI (n=43): 0.42 (0.29) PCI (n=40): 0.28 (0.29) Mean (SD) infarct size at d 3–6 RIC+PCI (n=43): 18.0 (10) PCI (n=40): 24.5 (12.0)
Yamanaka[27] (2015), Japan	STEMI, symptom onset <24 h, ≥20 y	3×5-min cycles of RIC (200 mm Hg) on arrival to hospital	CI-AKI at 48–72 h RIC+PCI (n=47): 5 (10.6%) PCI (n=47): 17 (36.2%) Mean (SD) serum creatinine levels at 48–72 h RIC+PCI (n=47): 0.81 (0.21) PCI (n=47): 1.03 (0.61) VF/VT within 24 h RIC+PCI (n=47): 1 (2%) PCI (n=47): 7 (14%)

CI-AKI indicates contrast-induced acute kidney injury; CK-MB, creatine kinase–MB isoenzyme release; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiac and cerebrovascular events; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; post-IC, local ischemic postconditioning; RIC, remote ischemic conditioning; STEMI, ST-segment–elevation myocardial infarction; VT/VT, ventricular fibrillation/ventricular tachycardia.

conducted in Europe,[20,21,38,40,42,43,45] 1 trial was performed in Mongolia,[39] and 1 trial was performed in Japan.[27] The primary outcomes varied among the studies and included surrogate biomarkers of myocardial reperfusion injury, microvascular reperfusion, left ventricular function, and acute kidney injury in STEMI patients. Seven trials (77.8%) used a standard manual, upper arm, blood pressure cuff and a stopwatch for the delivery of RIC before PCI.[20,21,38–40,42,43] The trial by Verouhis et al used a blood pressure cuff around the left thigh connected to an automated device (PeriVasc Cuff Unit; EBIDA) programmed to inflate to 200 mm Hg (or 20 mm Hg above systolic blood pressure if systolic blood pressure was >180 mm Hg) for 5 minutes followed by deflation for 5 minutes in repeated cycles.[45] Yamanaka et al also used an automated continuous blood pressure device (FB-270; Fakuda Denshi) connected to the upper arm that was modified to perform 3 cycles of inflation and deflation automatically.[27] RIC was started by ambulance personnel in 2 (22.2%) of the included studies[20,39] and initiated on arrival at the hospital (before PCI) for the remaining included trials.

Risk of Bias

Risk of bias was assessed for all 11 articles.[20,21,27,38–45] With respect to random sequence generation, 8 studies (72.7%) were judged to have low risk of bias, and risk was unclear in 3 studies (27.3%; Table 2). Allocation was adequately concealed in 9 (81.2%) and unclear in 2 (18.2%) of the included studies. Because of the application of the blood pressure cuff, blinding of patients and personnel had high risk of bias in all but 1 study. In the trial by Rentoukas et al, it was unclear if patients in the PCI group were blinded to their treatment because they had a manometer cuff placed on their upper arm that was inflated to 20 mm Hg below their diastolic pressure to mimic RIC. Blinding of outcome assessment was judged to be low risk in 9 (81.2%) and unclear in 2 (18.2%) of the included studies. Attrition bias was judged to be high in 8 (72.3%) of the included studies, as many of the enrolled randomized patients did not complete follow-up imaging investigations required to assess the primary outcome or were subsequently excluded from the final analysis, which may have introduced selection bias. Selective reporting of outcomes was judged to have low risk of bias in all included trials.

Data Synthesis

Four of the included trials reported myocardial salvage index with a total of 636 patients (RIC+PCI, n=321; PCI, n=315).[20,21,38,45] The myocardial salvage index was higher in the RIC+PCI group compared with the PCI-alone group (mean difference [MD]: 0.08; 95% CI, 0.02–0.14; Figure 2). Five of the included studies reported infarct size with a total of 848 patients (RIC+PCI, n=424; PCI, n=424).[20,21,38,39,45] Infarct size was reduced in the RIC+PCI group compared with the PCI-alone group (MD: −2.46; 95% CI, −4.66 to −0.26), with moderate statistical heterogeneity among the studies (Figure 3). Four of the included studies reported MACE (Figure 4) with a total of 928 patients (RIC+PCI, n=464; PCI, n=464).[27,38,39,44] MACE was lower in the RIC+PCI group (9.5%) compared with the PCI-alone group (17.0%; RR: 0.57; 95% CI, 0.40–0.82). When the individual components of MACE were considered, there was no statistical difference with respect to mortality, reinfarction, or stroke (Figure 5); however, there was a statistically significant reduction in heart

Table 2. Risk of Bias Summary for Included Trials

Trial	Random Sequence Generation	Allocation Concealment	Blinding of Patients/ Personnel	Blinding of Outcome Assessment	Attrition (%)	Selective Outcome Reporting	Other Bias
Bøtker[20] (2010), Denmark	Low	Low	High*	Low	333 Randomized, 219 included (34.2% attrition)	Low	Low
Eitel[38] (2015), Germany	Low	Low	High*	Low	464 Randomized, 318 included (31.5% attrition)	Low	Low
Liu[39] (2016), Mongolia	Low	Low	High*	Low	141 Randomized, 119 included (15.6% attrition)	Low	Low
Manchurov[40] (2014), Russia	Unclear	Unclear	High*	Unclear	48 Randomized, 48 included (0% attrition)	Low	Low
Munk[41] (2010), Denmark	Low	Low	High*	Low	333 Randomized, 206 included (38.1% attrition)	Low	Low
Prunier[42] (2014), France	Unclear	Low	High*	Low	151 Randomized, 55 included (63.5% attrition)	Low	High†
Rentoukas[43] (2010), Greece	Unclear	Unclear	Unclear	Unclear	63 Randomized, 63 included (0% attrition)	Low	Low
Sloth[44] (2014), Denmark	Low	Low	High*	Low	333 Randomized, 251 included (24.6% attrition)	Low	Low
Verouhis[45] (2016), Sweden	Low	Low	High*	Low	150 Randomized, 93 included (38.0% attrition)	Low	Low
White[21] (2015), UK	Low	Low	High*	Low	323 Randomized, 83 included (74.3% attrition)	Low	High‡
Yamanaka[27] (2015), Japan	Low	Low	High*	Low	125 Randomized, 94 included (24.8% attrition)	Low	Low
Summary score	Low risk of bias	Low risk of bias	High risk of bias	Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias

*Personnel performing remote conditioning and percutaneous coronary intervention were not masked to treatment assignment.
†The extensive exclusion criteria may have introduced selection bias.
‡The authors selected only patients with ST-segment–elevation myocardial infarction and complete occlusion in the infarct-related artery (pre–percutaneous coronary intervention TIMI [Thrombolysis in Myocardial Infarction] flow grade 0), as these patients were less likely to have spontaneously reperfused and therefore most likely to benefit from remote ischemic conditioning.

failure with RIC+PCI (RR: 0.41; 95% CI, 0.20–0.84). All outcomes were judged to be of moderate quality of evidence using GRADE criteria, downgraded for imprecision due to small number of events (Table 3).

Discussion

In this systematic review and meta-analysis of the impact of RIC on patients undergoing primary PCI for acute STEMI, we found a significant improvement in the primary outcome of myocardial salvage index as well as a significant reduction in myocardial infarct size and MACE. Previous systematic reviews have reported the use of RIC for patients undergoing a variety of clinical scenarios including cardiac surgery, vascular surgery, and elective and acute PCI.[6,21,29–32,46,47] In the review by Yetgin et al, 1448 patients with coronary heart disease undergoing elective PCI, emergent PCI, or CABG were randomized to RIC or control. RIC induced by transient limb ischemia was associated with a significant decrease in myocardial injury biomarkers (creatine kinase–myocardial band and troponin) for patients undergoing CABG (standardized MD: −0.34; 95% CI, −0.59 to −0.08) and a nonsignificant reduction for patients undergoing both emergent and elective PCI (standardized MD: −0.21; 95% CI, −0.66 to 0.24). However, when the authors restricted their analysis to the 2 primary PCI studies, they reported a significant positive effect of RIC on myocardial injury (standardized MD: −0.55; 95% CI, −0.77 to −0.32). No data related to myocardial infarct size or clinical outcomes were presented.[47]

RIC before cardiac surgery has been shown to improve biomarkers of ischemic and reperfusion injury in patients undergoing cardiac surgery, but uncertainty about clinical outcomes remains.[24,25,28,48,49] Meybohm et al conducted a prospective, blinded, multicenter RCT involving adults who were scheduled for elective cardiac surgery requiring cardiopulmonary bypass under anesthesia with intravenous

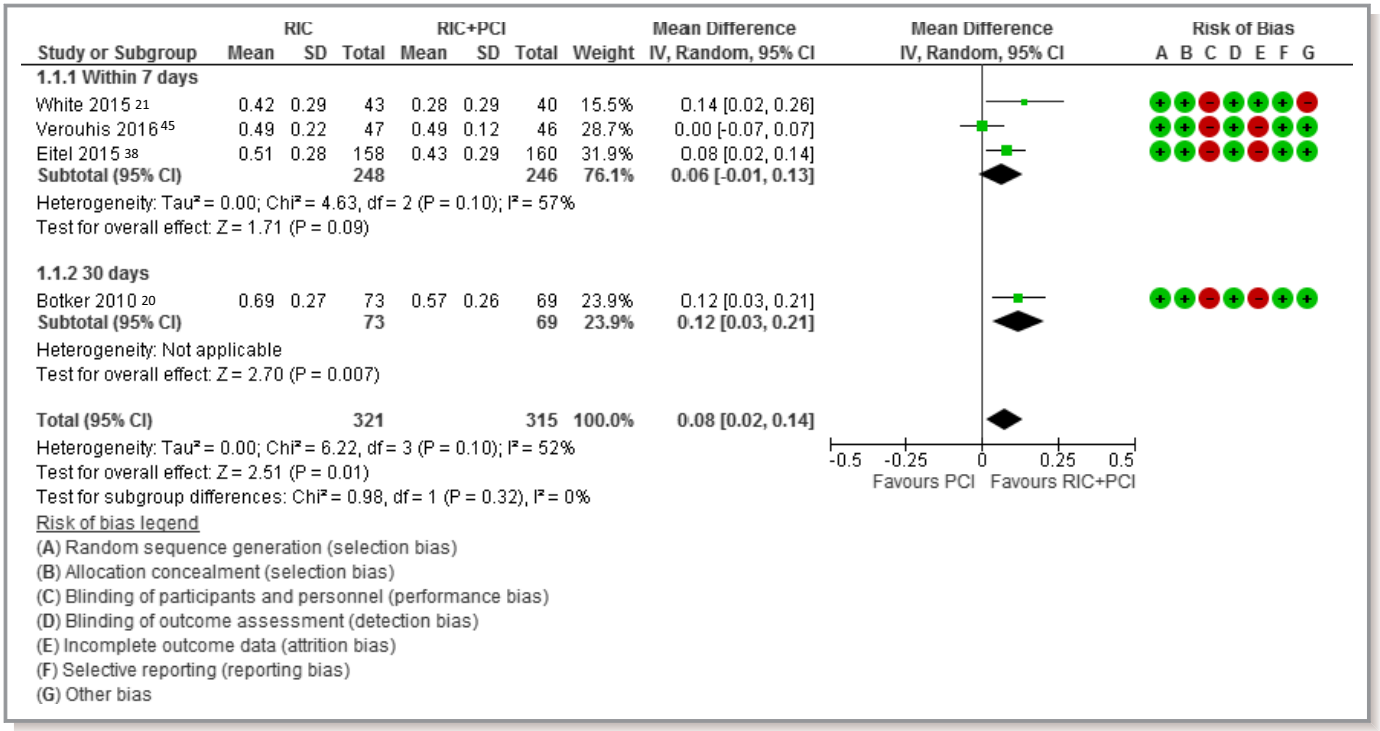

Figure 2. Myocardial salvage index, defined as the proportion of area at risk of the left ventricle salvaged by treatment following emergent percutaneous coronary intervention for ST-segment–elevation myocardial infarction. CI indicates confidence interval; IV, inverse variance method; PCI, percutaneous coronary intervention; random, random-effects model; RIC, remote ischemic perconditioning.

propofol. The primary end point was a composite measure of death, myocardial infarction, stroke, or acute renal failure up to the time of hospital discharge. There was no difference in the composite primary end point in the RIC group (14.3%) compared with the sham-RIC group (14.6%) and no difference reported for any of the individual component outcomes.[48] Similarly, Walsh et al performed an RCT to evaluate the effect of RIC on markers of heart and kidney injury after cardiac surgery. RIC did not reduce myocardial injury (absolute MD in creatine kinase–myocardial band: 0.15; 95% CI, −0.07 to 0.36) or kidney injury (absolute MD in creatinine: 0.06; 95% CI, −0.10 to 0.23) during cardiac surgery. When 6-month clinical outcomes were assessed, there was no difference between the RIC and sham groups for myocardial infarction (RR: 1.35; 95% CI, 0.85–2.17), acute kidney injury (RR: 1.10; 95% CI, 0.68–1.78), stroke (RR: 1.02; 95% CI, 0.34–3.07), or mortality (RR: 1.47; 95% CI, 0.65–3.31), although the number of events was noted to be small. The authors concluded RIC is unlikely to substantially improve patient-important outcomes in cardiac surgery.[49] Both studies are consistent with the most recent meta-analysis by the Remote Preconditioning Trialists' Group, which included 23 trials of RIC involving a total of 2200 patients undergoing cardiovascular surgery. In that meta-analysis, RIC did not have a significant effect on clinical end points, including death, myocardial infarction, acute renal failure, stroke, or mesenteric ischemia.[50]

These findings are difficult to extrapolate to and compare with acute STEMI, which represents an entirely different clinical condition. Propofol, a sedative-hypnotic agent that binds neurotransmitter γ-aminobutyric acid receptors, has been shown to attenuate the efficacy of RIC by affecting mitochondrial permeability and adenosine triphosphate synthesis.[51] Consequently, propofol should be used cautiously, if at all, in any conditions associated with reperfusion injury. Many of the RIC trials in CABG used propofol anesthesia, potentially mitigating the impact of RIC. In addition, the degree of myocardial ischemia during elective cardiac surgery while the heart is under cardioplegia cannot be assumed to be similar to that occurring during STEMI. It is clear from RCTs involving STEMI that the maximal benefit from RIC appears to occur in patients with the greatest degree of cardiac ischemia (eg, TIMI [Thrombolysis in Myocardial Infarction] 0–1 flow), which is not comparable to the flow state to the myocardium during elective cardiac surgery.[20,38] Although underpowered, Sloth et al were able to demonstrate significant improvements in STEMI patients treated with RIC for rates of MACE (hazard ratio: 0.49; 95% CI, 0.27–0.89) and all-cause mortality (hazard ratio: 0.32; 95% CI, 0.12–0.88).[44] The majority of benefits from RIC on clinical outcomes such as MACE and all-cause mortality appear to occur after 1 year of follow-up, suggesting that, at least in STEMI, the assessment of the benefit of RIC pertaining to clinical outcomes may require a

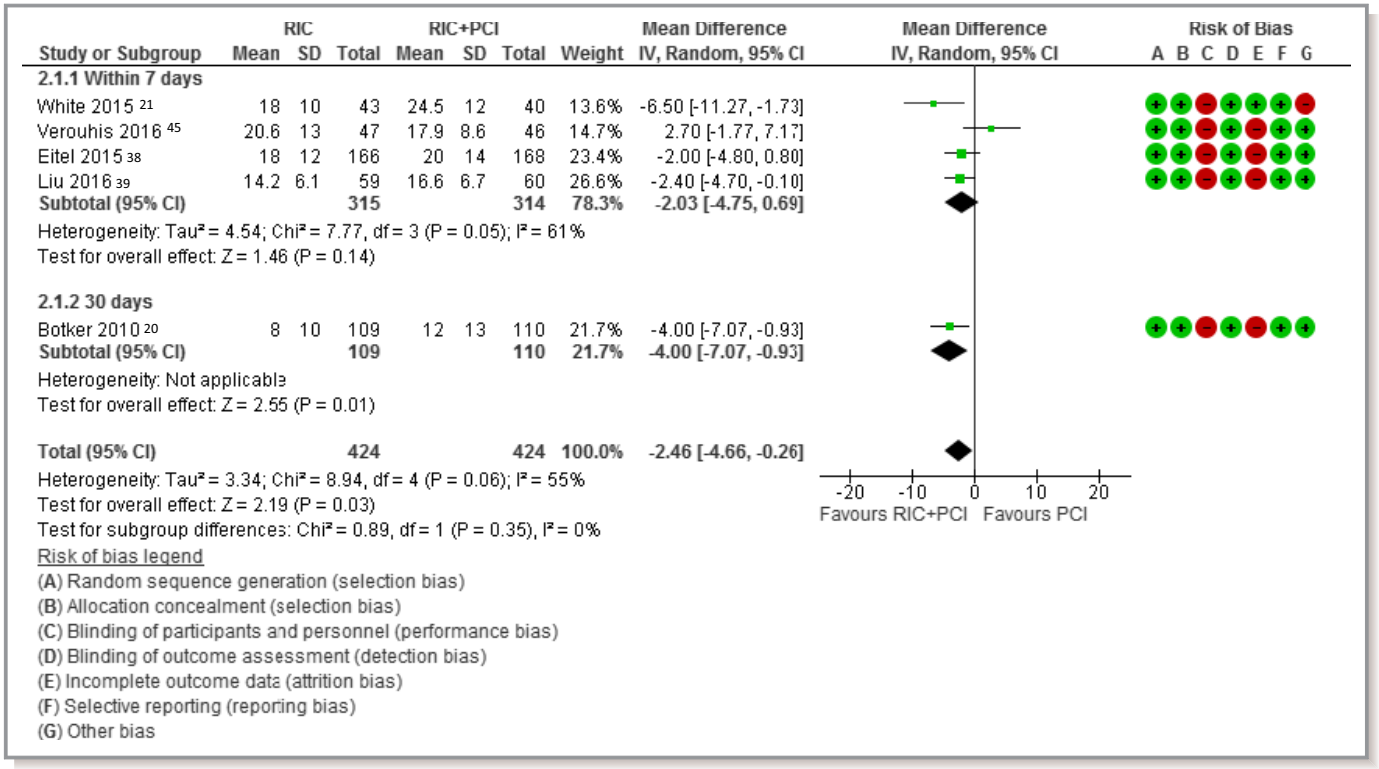

Figure 3. Infarct size as a percentage of left ventricle with and without RIC before primary PCI for patients with ST-segment–elevation myocardial infarction. CI indicates confidence interval; IV, inverse variance method; PCI, percutaneous coronary intervention; random, random-effects model; RIC, remote ischemic conditioning.

longer period of follow-up than noted in the aforementioned cardiac surgery RCTs.

As noted in the perspective by Rosello and Yellon, many cardioprotective therapies aimed at reducing myocardial reperfusion injury that have been successfully examined in the preclinical setting have not demonstrated a reduction in infarct size at the bedside or demonstrated clinical benefits.[52] The authors suggest that the failure to translate cardioprotective therapies into the clinical setting may be attributed to many factors, such as patient comorbidities (eg, diabetes

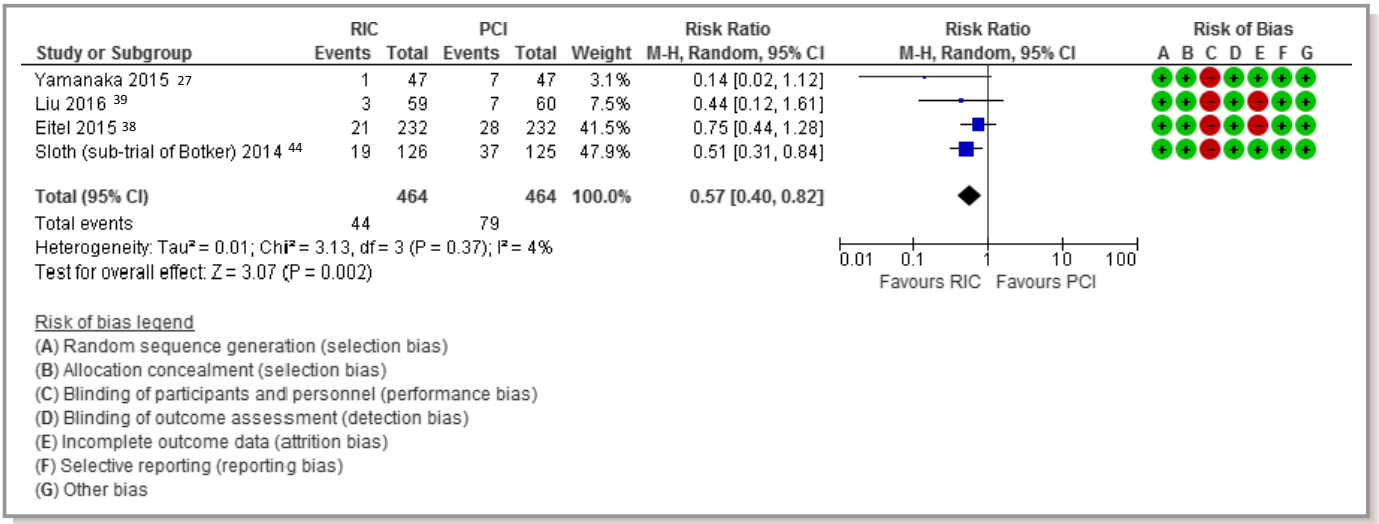

Figure 4. Major adverse cardiac events with and without RIC before primary PCI for patients with ST-segment–elevation myocardial infarction. CI indicates confidence interval; M-H, Mantel–Haenszel method; PCI, percutaneous coronary intervention; random, random-effects model; RIC, remote ischemic conditioning.

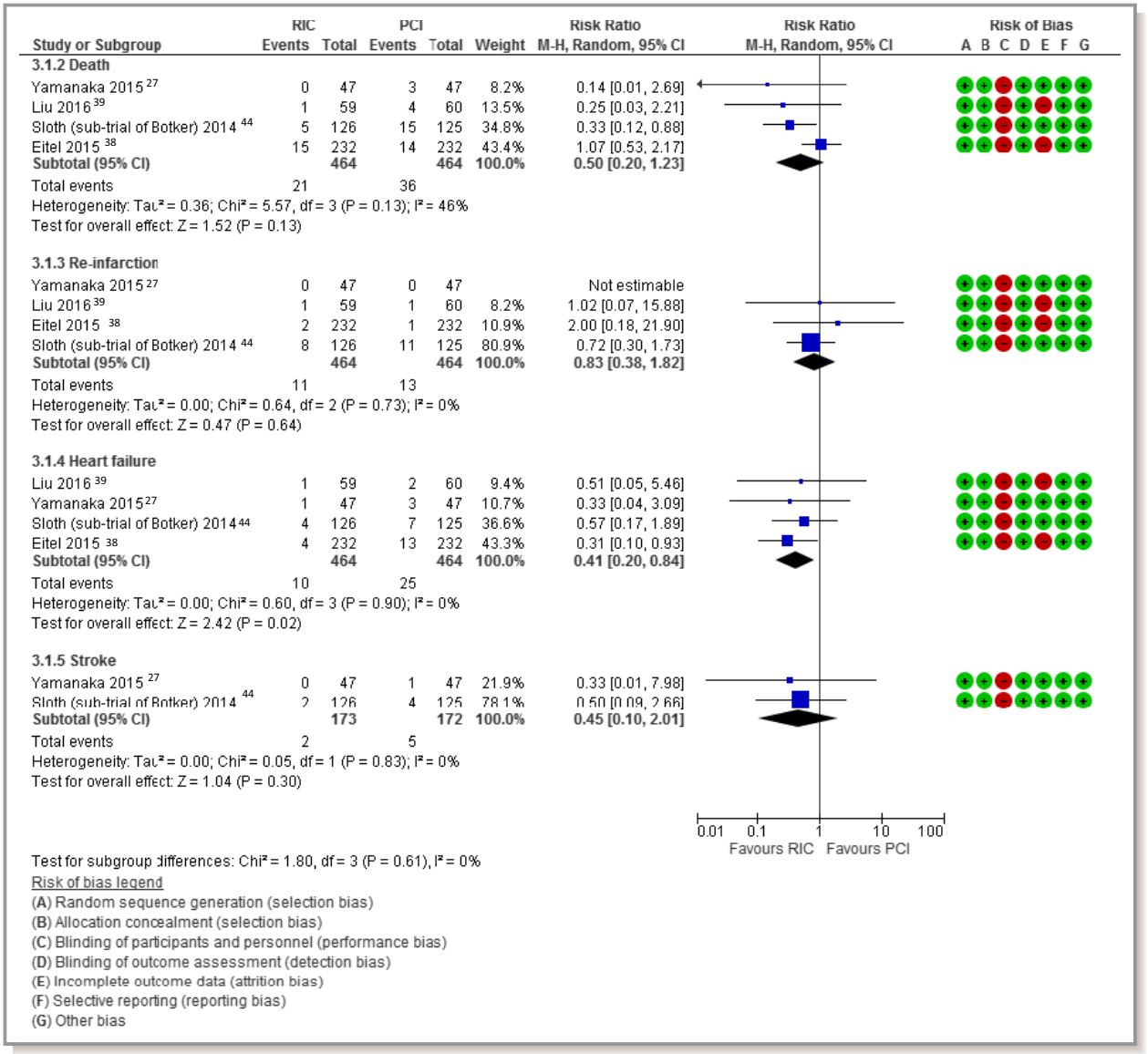

Figure 5. Breakdown of major adverse cardiac events with and without RIC before primary PCI for patients with ST-segment–elevation myocardial infarction. *0.5 added to each cell of 2×2 contingency table because no events were found in one of comparison groups. CI indicates confidence interval; M-H, Mantel–Haenszel method; PCI, percutaneous coronary intervention; random, random-effects model; RIC, remote ischemic conditioning.

mellitus, advanced age) and medications (eg, β-blockers, anticoagulants) that may limit the proposed benefit of RIC. These factors have not been addressed or adequately controlled for in any of the RCTs to date. Future studies should attempt to address these issues in the study design.

Limitations

Our systematic review and meta-analysis has several limitations. Only RCTs in English were evaluated for inclusion. The majority of the included studies were small and focused on the effect of RIC on biomarker release and other surrogate indicators of organ injury as opposed to clinical outcomes. For the included trials that did report clinical outcomes, only 2 studies extended the assessment beyond 6 months, and the number of reported events was small.[39,44] Patient follow-up of <1 year may be too short to detect long-term benefit for patients undergoing RIC as an adjunct to primary PCI.

Attrition bias was judged to be high in 8 (72.7%) of the included studies because many of the randomized patients did not complete imaging investigations required to assess the primary outcome (eg, myocardial infarct size) or were subsequently excluded from the final analysis, which may have introduced selection bias. These missing patient outcome data present a threat to the internal and external validity of the individual trial and our summary findings.

Table 3. The GRADE Criteria Were Used to Evaluate the Certainty of Evidence by Each Outcome

Quality Assessment							No. of Patients		Effect			
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other	RIC+PCI	PCI Alone	Relative (95% CI)	Absolute	Quality	Importance
Myocardial salvage index (better indicated by lower values)												
4	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious*	None	321	315	…	MD 0.08 higher (0.02–0.14 higher)	⊕⊕⊕O Moderate	Critical
Infarct size (better indicated by lower values)												
5	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious*	None	424	424	…	MD 2.46 lower (4.66–0.26 lower)	⊕⊕⊕O Moderate	Critical
Major adverse cardiac events												
4	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious*	None	44/464 (9.5%)	79/464 (17.0%)	RR 0.57 (0.40–0.82)	73 fewer per 1000 (from 31 fewer to 102 fewer)	⊕⊕⊕O Moderate	Critical

CI indicates confidence interval; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; MD, mean difference; PCI, percutaneous coronary intervention; RIC, remote ischemic conditioning.
*Rated down because of the small number of events.

To be included in our systematic review, studies investigating the use of RIC initiated after catheterization were included only if they also used RIC before balloon inflation. This, along with variation in cycles of RIC before PCI, may have introduced an element of heterogeneity into the treatment protocols. Studies comparing the use of local ischemic conditioning after catheterization versus PCI alone were excluded from the review. In addition, for all included studies, the RIC protocol had to be initiated before reperfusion (perconditioning); therefore, randomization occurred before PCI and before a definitive decision could be made as to whether the patient had met specific inclusion criteria. It is unknown how many cycles of RIC were completed before PCI for the included studies and whether that affects the effect of RIC for acute STEMI patients. Finally, all studies included in our review excluded patients who presented with cardiogenic shock or who underwent PCI following STEMI complicated by cardiac arrest, a subgroup of patients who may gain maximal benefit from the RIC technique.

Conclusions

This systematic review and meta-analysis suggests that RIC is emerging as a promising adjunctive treatment to PCI for the prevention of reperfusion injury in STEMI patients; however, additional high-quality research is required before a change in practice can be considered. Ongoing multicenter clinical trials should help elucidate the effect of RIC on clinical outcomes such a hospitalization, heart failure, and mortality.

Disclosures

None.

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SUPPLEMENTAL MATERIAL

Data S1. Search strategy.

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present (October, 2016)

#	*Searches*	*Results*	*Search Type*
1	ischemic postconditioning/ or exp ischemic preconditioning/	7347	Advanced
2	((ischemi$ or ischaemi$) and (conditioning$ or postconditioning$ or preconditioning$ or perconditioning$ or post-conditioning$ or pre-conditioning$ or per-conditioning$)).mp.	11571	Advanced
3	or/1-2	11571	Advanced
4	remote$.mp.	54497	Advanced
5	(RIPC or RPC).tw.	1333	Advanced
6	(3 and 4) or 5	1990	Advanced
7	exp Myocardial Infarction/ or (myocardial$ adj3 infarct$).mp.	212232	Advanced
8	(((myocardial$ or cardiac$ or heart$ or cardial$) adj3 infarct$) or (heart adj3 attack$)).mp.	211201	Advanced
9	(STEMI or (((ST-segment$ or ST segment$) adj4 elevat$) or (ST adj3 elevat$) or (non-ST adj3 elevat$) or (ST-elevation$ or non-ST-elevation$))).tw.	20246	Advanced
10	or/7-9	220643	Advanced
11	6 and 10	271	Advanced
12	Myocardial Reperfusion Injury/	12203	Advanced
13	(myocardi$ adj3 injur$).mp.	20516	Advanced
14	or/12-13	20516	Advanced
15	6 and 14	266	Advanced
16	exp Thrombolytic Therapy/ or exp Fibrinolytic Agents/ or Mechanical Thrombolysis/	162766	Advanced
17	(thrombolys$ or thrombolytic$ or fibrinolytic or fibrolytic$ or alteplase or antifibrinolytic$ or enoxaparin or fibrinogen or fibrinolysis or plasminogen or streptokinase or tenecteplase or		

	urokinase or reteplase or clexane or drotrecogin).tw.		124965	Advanced
18	or/16-17		239943	Advanced
19	6 and 18		27	Advanced
20	exp percutaneous coronary intervention/	39914		Advanced
21	(percutaneous adj3 coronar$ adj3 (angioplast$ or intervention$ or revascularization$)).tw.		28091	Advanced
22	((primary or percutaneous or coronary) and (PCI or PPCI or PTCA)).tw.		18621	Advanced
23	angioplast$.tw.	38275		Advanced
24	or/20-23		73628	Advanced
25	6 and 24		82	Advanced
26	exp Myocardium/ or myocardi$.mp.		498663	Advanced
27	6 and 26		508	Advanced
28	Ischemic Preconditioning, Myocardial/	3570		Advanced
29	28 and (4 or 5)		260	Advanced
30	**11 or 15 or 19 or 25 or 27 or 29**		**530**	**Advanced**
31	random$.tw. or randomized controlled trial/		916900	Advanced
32	30 and 31		195	Advanced
33	limit 30 to "therapy (best balance of sensitivity and specificity)"		162	Advanced
34	32 or 33		198	Advanced
35	systematic review/ or meta analysis.mp,pt. or MEDLINE.tw. or systematic review.tw.		172397	Advanced
36	30 and 35		27	Advanced
37	**34 or 36**		**202**	**Advanced**
38	37 not (exp Animals/ not (Human/ and exp Animals/))	158		Advanced
39	38 not (mice or rat or rats or cat$1 or cattle$1 or dog$1 or goat$1 or horse$1 or rabbit$1 or sheep$1 or swine$1 or pig$1 or canine$1 or feline$1 or porcine$ or calf or murine).ti.		155	Advanced

40	39 not ("20387183" or "22108640" or "25306677" or "25512268" or "26027222").an. [5 non-English citations]	**150**	**Advanced**