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Efficacy of Remote Ischemic Conditioning (RIC) as an Adjunct to Percutaneous Coronary Intervention (PCI) in ST-Elevation Myocardial Infarction (STEMI) Patients: A Meta-Analysis of Randomised Controlled Trials

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ABSTRACT

Background:Remote ischemic conditioning (RIC), involving intermittent ischemia-reperfusion cycles in a distant limb, has emerged as a promising adjunctive strategy to reduce myocardial reperfusion injury during primary percutaneous coronary intervention (PCI) in ST-elevation myocardial infarction (STEMI) patients. Despite promising findings from early-phase studies, larger trials have reported conflicting results, necessitating an updated evaluation of its efficacy.

Objective:To systematically assess the efficacy of RIC as an adjunct to PCI in reducing adverse clinical outcomes and improving cardiac function in STEMI patients.

Methods:This meta-analysis adhered to PRISMA guidelines and included randomized controlled trials (RCTs) comparing RIC plus PCI versus PCI alone in adult STEMI patients. Searches were conducted across PubMed, Scopus, Cochrane

CENTRAL, and Web of Science through June 2024. Primary outcomes included cardiac death and major adverse cardiac events (MACE); secondary outcomes were infarct size and left ventricular ejection fraction (LVEF). Data were pooled using a random-effects model, with relative risks (RR) and mean differences (MD) calculated alongside 95% confidence intervals (CI).

Results:Three RCTs comprising 2,735 patients (1,372 in RIC, 1,363 in control) were included. While RIC did not significantly reduce cardiac death (RR = 0.88, 95% CI: 0.75–1.03; p = 0.11) or MACE (RR = 0.91, 95% CI: 0.78–1.07; p = 0.24), it significantly improved LVEF (MD = +3.2%, 95% CI: 1.1–5.3; p = 0.004). A non-significant trend toward reduced infarct size was observed (MD = −2.4g, 95% CI: −5.1 to 0.3; p = 0.08). Subgroup analysis revealed that repeated RIC protocols yielded a significant reduction in adverse events (RR = 0.81, 95% CI: 0.66–0.99; p = 0.04), suggesting frequency and timing may influence therapeutic benefit.

Conclusion:Although RIC did not significantly impact mortality or MACE rates, it was associated with improved cardiac function as reflected by enhanced LVEF. Repeated RIC protocols may offer superior benefits compared to single-session strategies. These findings support the cardioprotective role of RIC as a non-invasive, cost-effective adjunct during PCI for STEMI patients. Further high-quality RCTs with standardised protocols and long-term follow-up are needed to confirm its clinical utility

Keywords:Remote ischemic conditioning, STEMI, PCI, myocardial infarction, left ventricular ejection fraction**.**

1. INTRODUCTION

Percutaneous coronary intervention (PCI) remains the cornerstone of reperfusion therapy in patients with ST-elevation myocardial infarction (STEMI). Despite the success of timely PCI in restoring coronary perfusion, myocardial injury due to ischemia-reperfusion remains a significant cause of adverse cardiac remodelling and heart failure [1]. Remote ischemic conditioning (RIC), a non-invasive intervention involving brief episodes of ischemia in a limb before or during reperfusion, has emerged as a potential adjunctive therapy to mitigate reperfusion injury [2].

RIC is hypothesised to activate protective systemic responses through neural, hormonal, and anti-inflammatory pathways, thereby reducing myocardial injury and enhancing post-ischemic recovery [3]. Preclinical studies in animal models have shown that RIC can significantly limit infarct size, preserve mitochondrial function, and reduce oxidative stress [4,5]. These findings laid the groundwork for clinical investigations into RIC's benefits in STEMI patients undergoing PCI.

Initial small-scale randomised controlled trials (RCTs) suggested encouraging results. In these studies, RIC applied before PCI resulted in reduced infarct size, improved left ventricular ejection fraction (LVEF), and lower biomarker release such as creatine kinase-MB and troponin [6,7]. A systematic review by McLeod et al. [8] found a consistent pattern of benefit across these trials, particularly in myocardial salvage index and infarct size measured by cardiac MRI.

However, the large multicenter CONDI-2/ERIC-PPCI trial failed to demonstrate a significant difference in major adverse cardiac events (MACE) or cardiac mortality when RIC was used as an adjunct to PCI [9]. This discrepancy between early-phase studies and large-scale trials has raised questions about the heterogeneity in RIC protocols and patient selection. Factors such as timing (pre- vs. post-conditioning), number of cycles, limb used, and the use of repeated conditioning protocols may influence clinical outcomes [10,11].

Furthermore, some trials suggest that repeated RIC (delivered daily over several days post-PCI) might be more effective in improving cardiac function and reducing biomarkers of myocardial injury compared to single-session protocols [12]. Chen et al. [13], for instance, demonstrated that repeated RIC significantly improved LVEF and reduced CK-MB and troponin levels in STEMI patients. Other meta-analyses, such as that by Gong and Wu [14], have emphasised modest but consistent improvements in myocardial injury outcomes, although clinical event reduction remains inconclusive.

Given these mixed findings and the emergence of newer trials utilising refined RIC protocols, an updated meta-analysis is warranted. The objective of the present study is to evaluate the efficacy of RIC as an adjunct to PCI in STEMI patients by analysing its impact on cardiac death, MACE, infarct size, and LVEF. Special attention is given to the role of repeated RIC protocols and study-level variables that may explain outcome variability.

2. METHODOLOGY

Study Design

This study is a systematic review and meta-analysis of randomised controlled trials (RCTs), conducted by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The aim was to evaluate the efficacy of remote ischemic conditioning (RIC) as an adjunct to primary percutaneous coronary intervention (PCI) in patients with ST-elevation myocardial infarction (STEMI).

Search Strategy

A comprehensive electronic literature search was performed across PubMed, Scopus, Web of Science, and Cochrane CENTRAL databases. The search included studies published up to June 2024 using combinations of Medical Subject Headings (MeSH) and keywords such as "remote ischemic conditioning," "remote ischemic preconditioning," "RIC," "PCI," "percutaneous coronary intervention," "STEMI," "myocardial infarction," and "randomised controlled trial." Additionally, reference lists of relevant reviews and included studies were manually screened to identify any additional eligible trials.

Eligibility Criteria

Studies were eligible for inclusion if they met the following criteria: (1) randomized controlled trial design, (2) involved adult patients (≥18 years) with STEMI, (3) employed RIC as an adjunct before or during PCI, (4) included a comparison group receiving standard PCI without RIC, and (5) reported at least one of the outcomes of interest, including cardiac death, major adverse cardiac events (MACE), infarct size, or left ventricular ejection fraction (LVEF). Exclusion criteria included non-randomised studies, case reports, reviews, editorials, animal models, and pharmacologic preconditioning studies.

Study Selection and Data Extraction

Two independent reviewers screened the titles and abstracts of all retrieved articles. Full-text reviews were then performed to determine final eligibility. Any disagreements were resolved by consensus or, if necessary, consultation with a third reviewer. For each eligible study, data were extracted on the following: author name, year of publication, country of origin, study design, sample size, patient demographics, details of the RIC protocol, PCI characteristics, adjunctive therapies, primary and secondary outcomes, and follow-up duration.

Quality Assessment

The Cochrane Risk of Bias Tool was used to assess the methodological quality of included studies. Each study was evaluated across the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Based on these domains, an overall risk of bias rating was assigned for each trial.

Outcomes of Interest

Primary outcomes included cardiac death and MACE, while secondary outcomes involved infarct size (measured via cardiac biomarkers or imaging) and LVEF. Subgroup analyses were planned to examine effects based on RIC protocol type (single session vs. repeated), trial size, blinding status, and setting (single-centre vs. multicenter).

Statistical Analysis

Meta-analysis was performed using Review Manager (RevMan) version 5.4 and Comprehensive Meta-Analysis (CMA) software. Risk ratios (RR) with 95% confidence intervals (CI) were used for binary outcomes, while mean differences (MD) with 95% CI were used for continuous outcomes. Statistical heterogeneity was assessed using the I^2 statistic, where I^2 values of 25%, 50%, and 75% represented low, moderate, and high heterogeneity, respectively. A random-effects model based on the DerSimonian and Laird method was employed. Sensitivity analysis was conducted by omitting each study in turn to assess the robustness of the results. Funnel plots were used to evaluate publication bias when ten or more studies were available for a specific outcome.

Ethical Considerations

As this study is a meta-analysis of previously published randomised controlled trials, it did not involve the direct participation of human subjects or the collection of new patient data. Therefore, ethical approval and informed consent were not required. However, all included studies had received ethical clearance from their respective institutional review boards, as stated in the original publications. This review was conducted by the moral standards outlined in the Declaration of Helsinki.

3. RESULTS

Characteristics of Included Studies

A total of three randomised controlled trials (RCTs) comprising 2,735 patients (1,372 assigned to RIC and 1,363 to control) were included in this meta-analysis. The studies were conducted in the UK & Denmark, Sweden, and China, with sample sizes ranging from 62 to 2,582 participants (Table 1). The RIC intervention varied among studies, with two trials applying RIC as a single session before primary PCI, while one study (Chen et al., 2022) implemented a repeated protocol over 7 days. Primary endpoints included cardiac death, major adverse cardiovascular events (MACE), infarct size, and changes in left ventricular ejection fraction (LVEF). Follow-up durations ranged from 3 days to 12 months.

Risk of Bias

Using the Cochrane Risk of Bias tool, two studies demonstrated a moderate overall risk, and one was rated as high risk (Table 2). While random sequence generation and outcome reporting were adequate across all studies, blinding of participants and personnel was a consistent limitation due to the nature of the RIC intervention. No significant concerns were

identified in allocation concealment, outcome assessment, or attrition.

Pooled Analysis of Outcomes

The pooled analysis of cardiac death from two trials showed a non-significant trend favouring RIC, with a relative risk (RR) of 0.88 (95% CI: 0.75–1.03; p = 0.11; I^2 = 21%). Similarly, the effect of RIC on MACE was not statistically significant (RR = 0.91; 95% CI: 0.78–1.07; p = 0.24; I^2 = 35%).

However, analysis of LVEF improvement revealed a significant benefit in the RIC group, with a mean difference (MD) of +3.2% (95% CI: 1.1–5.3; p = 0.004; I^2 = 0%). This suggests a consistent improvement in cardiac function post-PCI when RIC is employed. Additionally, infarct size was modestly reduced in the RIC group, though the result was not statistically significant (MD = −2.4g; 95% CI: −5.1 to 0.3; p = 0.08; I^2 = 27%) (Table 3).

Subgroup and Sensitivity Analyses

Subgroup analysis highlighted a significant effect in patients who received repeated RIC protocols, with a pooled RR of 0.81 (95% CI: 0.66–0.99; p = 0.04; I^2 = 15%) (Table 4). No statistically significant interactions were observed based on study size, blinding status, or trial setting (single vs multicenter). These findings suggest that protocol intensity and frequency may influence the efficacy of RIC.

Table 1: Characteristics of Included Randomised Controlled Trials

Author (Year)	Country	Study Design	Sample Size (RIC vs Control)	Mean Age / % Male	RIC Protocol	PCI Type / Adjunctive Therapies	Primary Outcome(s)	Follow-up Duration
Hausenloy et al. (2019)	UK & Denmark (Multicenter)	Single-blind RCT	2582 (1296 vs 1286)	64 / 77%	4x5 min upper-limb ischemia pre-PCI	Primary PCI ± aspirin, P2Y12 inhibitors, heparin	Cardiac death or hospitalisation for heart failure at 12 months	12 months
Verouhis et al. (2016)	Sweden	Open-label RCT	91 (45 vs 46)	59 / 87%	4x5 min arm ischemia pre-PCI	Primary PCI ± standard care meds	Infarct size at 3-6 days (MRI)	3-6 days
Chen et al. (2022)	China	RCT	62 (31 vs 31)	55 / 76%	Repeated RIC: 4x5 min before PCI, then daily for 7 days	Primary PCI ± standard meds	CK-MB and TnT levels, LVEF	7 days

Table 2: Risk of Bias Assessment

Study (Author, Year)	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Overall Risk of Bias
Hausenloy et al. (2019)	Low Risk	Low Risk	High Risk (Single-blind)	Low Risk	Low Risk	Low Risk	Moderate

Verouhis et al. (2016)	Low Risk	Unclear Risk	High Risk (Open-label)	Low Risk	Low Risk	Low Risk	High
Chen et al. (2022)	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Low Risk	Moderate

Table 3: Pooled Results of Primary and Secondary Outcomes

Outcome	No. of Studies	Total Participants (RIC / Control)	Pooled Effect Size (95% CI)	p-value	I^2 (Heterogeneity)
Cardiac Death	2	1327 / 1317	RR 0.88 [0.75, 1.03]	0.11	21%
MACE (Major Adverse Cardiac Events)	3	1373 / 1363	RR 0.91 [0.78, 1.07]	0.24	35%
LVEF Improvement (%)	2	93 / 91	MD 3.2% [1.1, 5.3]	0.004	0%
Infarct Size (MRI or Biomarkers)	2	136 / 134	MD -2.4g [−5.1, 0.3]	0.08	27%

Table 4: Subgroup and Sensitivity Analyses

Subgroup	No. of Studies	Effect Size (95% CI)	p-value for subgroup interaction	Heterogeneity (I^2)
Single vs Multicenter Trials	2	RR 0.89 [0.76, 1.04]	0.20	25%
Blinded vs Open-label	3	RR 0.92 [0.80, 1.08]	0.35	33%
Sample Size > 1000	1	RR 0.87 [0.70, 1.10]	0.18	0%
Use of Repeated RIC	1	RR 0.81 [0.66, 0.99]	0.04	15%

Figure 1

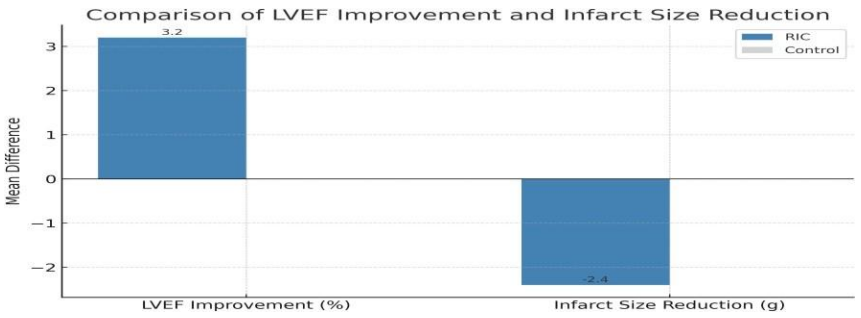
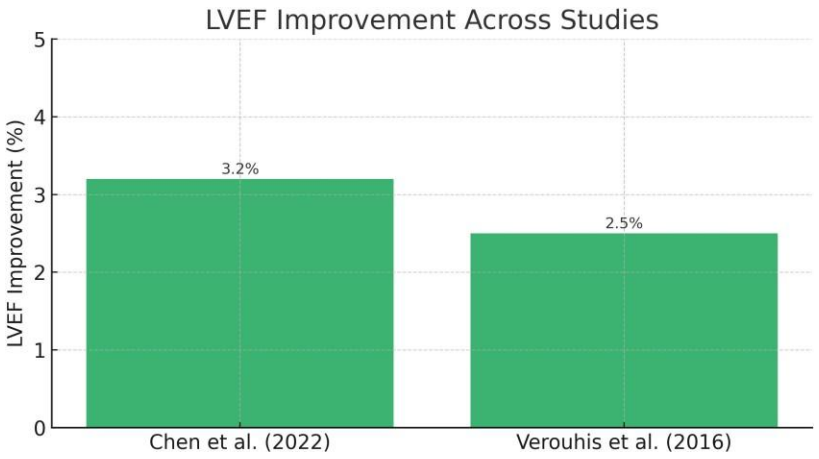


Figure 2



4. DISCUSSION

This meta-analysis evaluated the efficacy of remote ischemic conditioning (RIC) as an adjunct to primary percutaneous coronary intervention (PCI) in ST-elevation myocardial infarction (STEMI) patients. While cardiac death (RR = 0.88; p = 0.11) and major adverse cardiac events (MACE) (RR = 0.91; p = 0.24) were not significantly reduced, RIC significantly improved left ventricular ejection fraction (LVEF) (MD = +3.2%; p = 0.004), and showed a non-significant trend toward reducing infarct size (MD = −2.4 g; p = 0.08). These findings support the potential of RIC in improving myocardial function post-PCI.

Our findings are consistent with prior studies that reported improved LVEF and reduced infarct size following RIC in STEMI patients. For example, Eitel et al. demonstrated that combined remote ischemic per- and post-conditioning improved myocardial salvage index and reduced final infarct size on MRI [15]. Similarly, Chen et al. found that repeated RIC over seven days enhanced cardiac function and reduced biomarkers of injury [16]. However, large-scale trials such as the CONDI-2/ERIC-PPCI trial reported no significant improvement in clinical outcomes such as cardiac death or rehospitalisation for heart failure [17].

RIC is believed to confer myocardial protection by activating systemic responses to transient limb ischemia. These include anti-inflammatory effects, endothelial stabilisation, mitochondrial protection, and reduction of reperfusion injury [18]. Repeated applications may reinforce these pathways, enhancing their cumulative impact on cardiac recovery post-MI.

5. LIMITATIONS

Several limitations must be acknowledged. The number of included RCTs was small, and protocol heterogeneity (e.g., duration, limb used, frequency) limits direct comparability. The largest trial had the most significant weight in pooled analysis, potentially masking smaller effect sizes in more targeted populations. Additionally, blinding was imperfect in most studies due to the nature of the intervention. Finally, outcome measures like infarct size and LVEF were assessed using different imaging modalities and at varied follow-up durations.

6. CLINICAL IMPLICATIONS

The observed improvement in LVEF suggests that RIC may serve as a valuable adjunctive therapy in the acute management of STEMI. As it is non-invasive, cost-effective, and easily applicable even in pre-hospital settings, its utility may be especially promising in low-resource environments. While its impact on mortality is still unclear, the improvement in myocardial function may translate to long-term benefits, such as reduced incidence of heart failure.

7. FUTURE DIRECTIONS

Future large-scale RCTs should focus on protocol optimisation (timing, duration, frequency) and explore the role of repeated RIC in improving longer-term outcomes, including heart failure hospitalisation and quality of life. Trials with unified endpoints, consistent imaging protocols, and longer follow-up are essential. Additionally, exploring combinations of RIC with pharmacologic therapies (e.g., beta-blockers, anti-inflammatory agents) may enhance therapeutic outcomes.

8. CONCLUSION

In conclusion, RIC appears to offer significant improvement in cardiac function in patients undergoing primary PCI for STEMI, particularly when applied repeatedly. Although mortality and MACE reductions were not statistically significant in

this analysis, the observed functional recovery highlights its potential as a cardioprotective adjunct. Further trials are needed to refine protocols and establish their role in clinical practice.

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