# Effects of ischaemic conditioning on major clinical outcomes in people undergoing invasive procedures: A systematic review and meta-analysis

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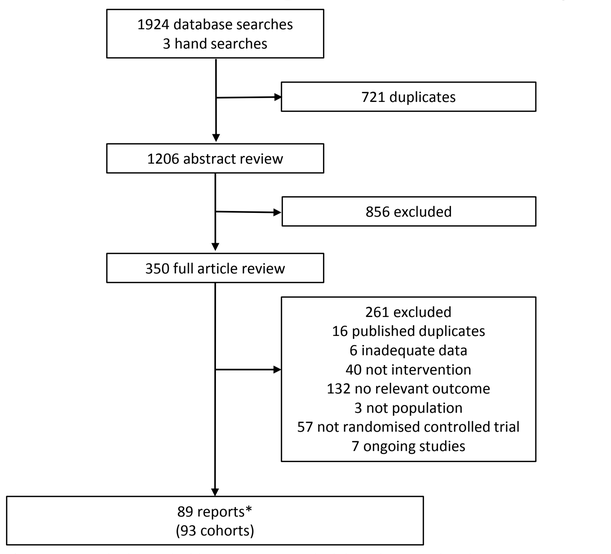
## *Objective:*

To summarise the benefits and harms of ischaemic conditioning on major clinical outcomes.

## *Design:*

Systematic review and meta-analysis. Two authors independently extracted data from individual studies. Random effects models were used to calculate summary estimates for all-cause mortality and other pre-specified clinical outcomes. All-cause mortality and secondary outcomes with a p-value<0.1 were examined for study quality using the GRADE assessment tool, the impact of pre-specified characteristics using meta-regression and Cochran C test, and trial sequential analysis using the Copenhagen Trial Unit Method.

**Figure 1:** PRISMA flow diagram of identification process for eligible studies




*4 reports studied two eligible interventions which have been analysed as separate reports.

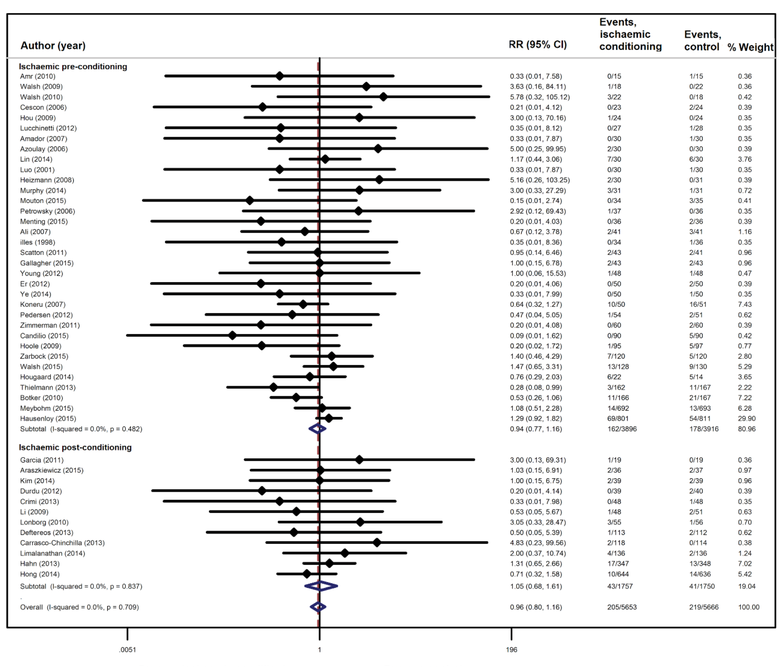
## *Data Sources*

MEDLINE, EMBASE, the Cochrane Databases and the International Clinical Trials Registry platform (ICTRP) from inception through October 2015.

## *Eligibility criteria for selecting studies*

All randomised controlled trials assessing the effects of ischaemic conditioning compared with control on clinical outcomes.

**Figure 2:** Effect of ischaemic conditioning on all-cause mortality*

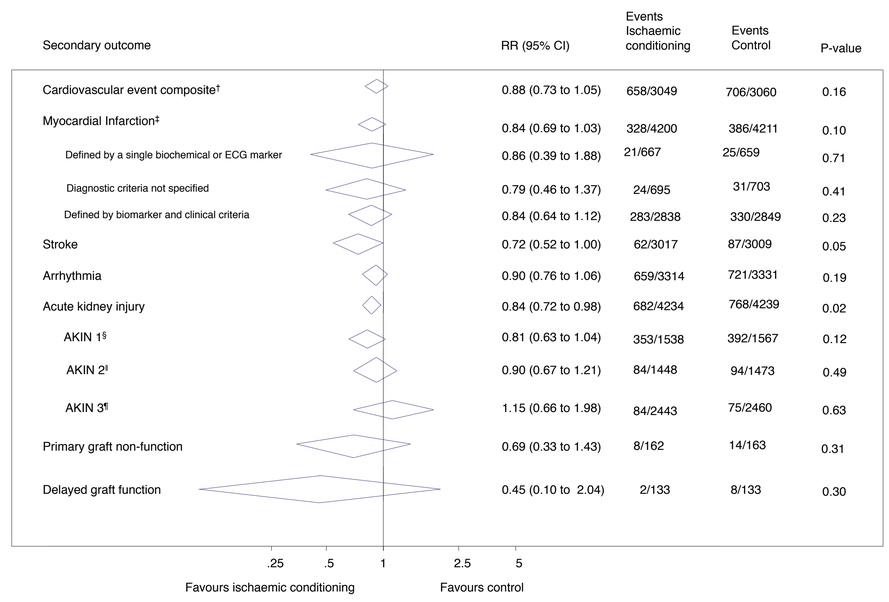



* Does not include trials with 0 events in both arms

## *Results*

Eighty-nine trials were identified with a median 79 participants (interquartile range (IQR) 55, 123) and median 1 month (IQR 0.5, 10) intended duration. Ischaemic conditioning had no impact on all-cause mortality (67 trials, 424 events, 11,614 participants, RR 0.96, 95% confidence interval 0.80 to 1.16, p=0.68, GRADE: moderate quality evidence) regardless of the clinical setting in which it was used or the particular intervention-related characteristics. Ischaemic conditioning may reduce the rates of some secondary outcomes including stroke (18 trials, 5,995 participants, 149 events, RR 0.72, 95%CI 0.52 to 0.997, p=0.048, GRADE: very low quality evidence) and acute kidney injury (36 trials, 8,613 participants, 1,450 events, RR 0.84, 95%CI 0.72 to 0.98, p=0.02, GRADE: low quality evidence) although the benefits appear to be confined to non-surgical settings and to mild episodes of acute kidney injury only. To confirm the observed effect size reflects true benefit would require future trials to increase the number of studied participants by 4420% for mortality, 520% for stroke and 170% for acute kidney injury.

**Figure 3:** Effect of ischaemic conditioning on secondary outcomes *

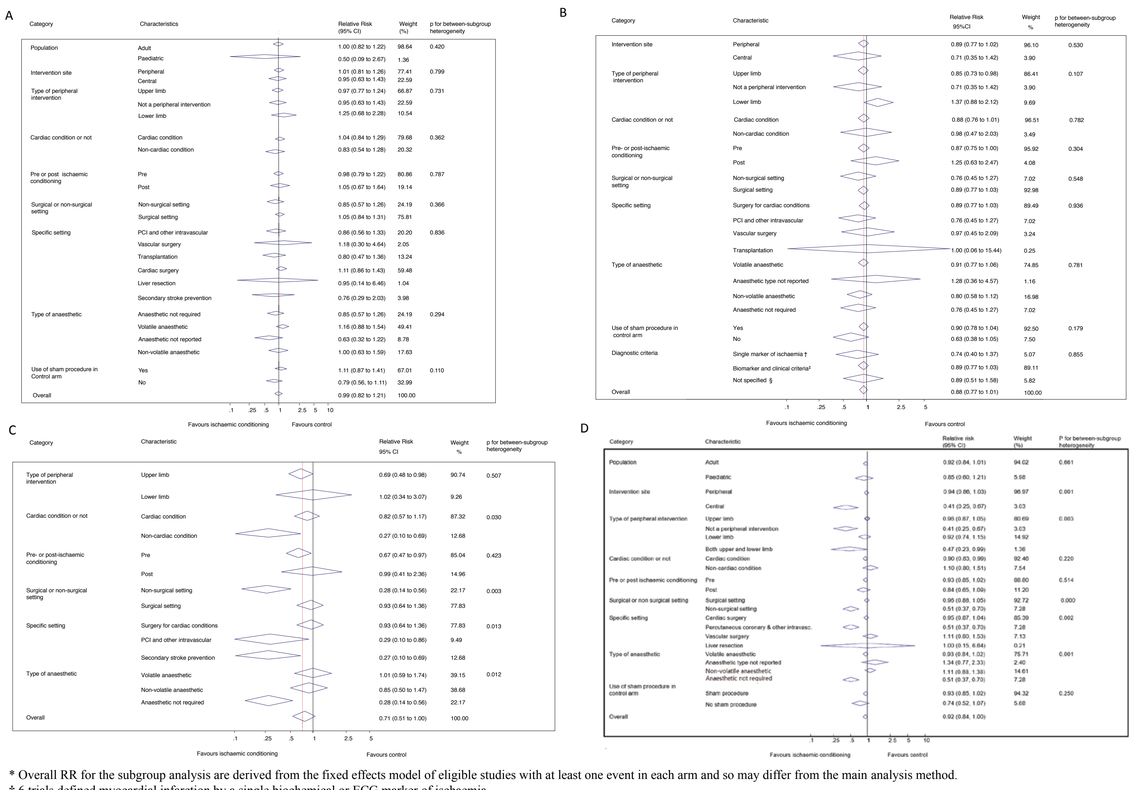



* Does not include studies with 0 events in both arms
† Composite of major adverse cardiovascular events as defined by study authors
‡ As defined by study authors
§ Acute kidney injury network criterion 1 derived where available from study author definition as per Appendix table 2
‖ Acute kidney injury network criterion 2 derived where available from study author definition as per Appendix table 2
¶ Acute kidney injury network criterion 3 derived where available from study author definition as per Appendix table 2

## *Conclusions*

Ischaemic conditioning has no overall effect on the risk of death. Possible effects on stroke and AKI are uncertain given methodological concerns and low event rates. Adoption of ischaemic conditioning cannot be recommended for routine use unless further, sufficient high quality evidence demonstrates benefit.

**Figure 4:** Subgroup analyses of the effect of ischaemic conditioning on all-cause mortality (A), myocardial infarction (B), stroke (C) and acute kidney injury (D)*




* Overall RR for the subgroup analysis are derived from the fixed effects model of eligible studies with at least one event in each arm and so may differ from the main analysis method.
† 6 trials defined myocardial infarction by a single biochemical or ECG marker of ischaemia
‡ 16 trials defined myocardial infarction by a biomarker and clinical criteria
§ 14 trials did not describe their diagnostic criteria

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DOI: 10.3252/pso.eu.53era.2016
ePosters supported by F. Hoffmann- La Roche Ltd.
53rd CONGRESS ERA-EDTA VIENNA AUSTRIA MAY 21st-24th, 2016
Held jointly with Österreichische Gesellschaft für Nephrologie
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