**Methods for Systematic Review and Meta-analysis of Remote Ischemic Conditioning in Patients with ST Elevation Myocardial Infarction**

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**Methods**

The methods of this review will be registered prospectively.(www.github.com/grahamnichol) A Boolean search strategy will be applied to the Pubmed database (See Appendix 1). This will include application of the Cochrane sensitivity- and precision-maximizing search strategy for randomized controlled trials, and will be restricted to clinical studies that are reported in the English language:1

Included will be studies that described use of remote ischemic conditioning (RIC) in adults aged 18 years or older with acute ST-elevation myocardial infarction, and that reported survival and/or major adverse cardiac events (MACE) or biochemical injury, other measure of infarct size, or ejection fraction. Studies that described only RIC without a comparison group will not be included. If a study describes use of multiple (RIC or non-RIC) methods, these data will be aggregated prior to inclusion in the systematic review.

Unique citations will be reviewed to confirm eligibility by two individuals (LG, DM), and relevant data extracted (LG, DM). The primary author of each included study will be asked to confirm that the data have been extracted correctly. If the primary author for a study is unable or unwilling to do so,2 the data extracted for that study will be confirmed by a second member of the review team (GN). Differences in either study eligibility or data abstraction will be resolved by consensus. The methodological quality of included randomized studies will be assessed independently by two individuals (LG, DM) with differences resolved by consensus including a third member of the review team (GN) using the Cochrane Collaboration’s risk of bias tool.(https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials) This includes seven domains of potential bias and is scored as low, high or uncertain risk of bias.

The primary outcome to be evaluated by this review is survival to hospital discharge. If vital status at discharge is not available, we will substitute survival to 28 or 30 days. Secondary outcomes will include: major adverse cardiac events (MACE) which includes death, reinfarction, target vessel revascularization, cardiogenic shock or hospitalization for heart failure. We will also evaluate survival and MACE to the end of study follow-up. Myocardial injury will be assessed as peak troponin or peak creatinine kinase. Cardiac function will be assessed as any report of ejection fraction, regardless of the method of ascertainment.

If relevant data are not included in the primary publication, we will contact the primary author to request that they provide the missing information if it is available.

Results will be summarized qualitatively and quantitatively using standard meta-analytic techniques.3 Analyses will be performed for the overall results, as well as grouped by study origin (United States [US] vs. outside the US); location of RIC (upper extremity vs. lower extremity), location of infarct (anterior vs. non-anterior), method of revascularization (primary PCI vs. fibrinolytics vs. neither), timing of RIC (before initiation of revascularization vs. after vs. unknown.) Statistical heterogeneity will be assessed using tau2, inconsistency index I2 and a test of heterogeneity with the related p value. A p-value of 0.05 will be considered significant. Publication bias will be assessed using a regression test for funnel plot asymmetry. A random effects model (i.e., DerSimonian-Laird) will be used to calculate risk differences for each outcome. Funnel plots will be used to visually check for possible selection or publication bias in combination with a test for funnel plot asymmetry based on a linear weighted regression. Secondary analysis will use a fixed effects model (Mantel-Haenszel) to calculate risk differences for survival and other clinical outcomes. Pooled measures of myocardial injury (i.e., peak troponin, peak CK) will be calculated as standardized mean differences. Pooled measures of heart function (i.e., ejection fraction) will be calculated as weighted mean differences. The level of statistical significance will be set *a priori* at alpha = 0.05. Meta-analysis will be performed using jamovi (Version 0.9, retrieved from https://www.jamovi.org) with its ‘major’ package. This will be supplemented by using R (Version 3.5.0, retrieved from https://www.r-project.org/) with its ‘meta’ package.

**References**

1. Zhang L, Ajiferuke I, Sampson M. Optimizing search strategies to identify randomized controlled trials in MEDLINE. *BMC Med Res Methodol*. May 9 2006;6:23. doi:10.1186/1471-2288-6-23

2. Forkmann M, Kolschmann S, Holzhauser L, et al. Target temperature management of 33 degrees C exerts beneficial haemodynamic effects after out-of-hospital cardiac arrest. *Acta Cardiol*. Aug 2015;70(4):451-9.

3. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. Jul 21 2009;339:b2700. doi:10.1136/bmj.b2700