Reviewer's report

Title: 'Remote ischemic preconditioning to reduce contrast-induced nephropathy'

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Trial registration: ISRCTN76496973

Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

• Introduction section – first paragraph – it would be of relevant if the authors were able to provide some discussion on the biologic rationale and mechanisms by which RIPC may mediated AKI in general and after ischemia/contrast exposure.

• Introduction section – first paragraph – the authors should provide more specific rational and justification for essentially replicating the pilot Renal Protection Trial by Er et al published in Circulation. What are the key elements on the Renal Protection Trial that predispose it to bias and justify this study? How will this proposed smaller trial better clarify the question of whether RIPC is efficacious for prevention CIN?

• Methods section – third paragraph - the authors propose to also include patients receiving both intravenous and intra-arterial contrast. Are the differences in the risk of CIN associated with these routes of delivery of contrast that will a priori be evaluated?

• Methods section – while the author intent to enroll high risk patients – perhaps the integration of a clinical risk score (Mehran risk score) similar to the Renal Protection Trial (Er F et al Circulation 2012) would help benchmark the risk between studies and enable better comparison?

• Methods section – Primary Endpoint - time frame for ascertainment of changes in SCr – I would suggest the authors have a concrete definition for their protocol (i.e., 72 hours) and not a range of 2-3 days (i.e., 48-72 hours) – as there is inherent risk patients may develop the outcome of interest on day three yet be missed. The trial registration website only states 48 hours – not 72 hours.

• Methods section – Adverse events – the authors should specifically list and
define the most commonly anticipated AE expected from the trial.

• Methods section – Power calculation – can the authors justify why they expect RIPC to reduce serum creatinine further below baseline by 14 mcmol/L? Is this expected to be a clinically meaningful change in SCr that correlated with patient-centred events – in particular when a key trial outcome (though secondary) is categorical (CIN - yes/no)?

• Methods section – Statistical analysis – this section would benefit from expansion to clarify the primary and secondary analyses proposed.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

• Study title – this should include “Study Protocol for a Randomized Control Trial” as per journal standards.

• Introduction section – first paragraph – it is uncertain what the authors are referring to when they described “mortality ratio” – is this simply the observed crude mortality? This should be clarified – and perhaps a relative risk of death instead compared with those not developing CIN would also be of benefit to cite.

• Methods section – the trial registration website states biomarkers will be captured from blood/urine at 24 hours after contrast exposure. In addition – the secondary outcome of CIN on the trial registration website is stated as a 25% increase in SCr only – and not a 25% or 0.5 mg/dL change. In addition – the trial registration website states the trial is COMPLETED. These are not discussed in the protocol and inconsistent with the registration website.

Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)?

• Introduction section – first paragraph – “ischaemia”, “pathophysiology” and “the” are spelled incorrectly.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

None to declare.