Impact of cardioprotective therapies on the edema-based area-at-risk by CMR in reperfused STEMI

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ABBREVIATIONS

CMR: cardiovascular magnetic resonance

MI: myocardial infarct

STEMI: ST-segment elevation myocardial infarction

AAR: area-at-risk

MSI: myocardial salvage index

RCTs: randomized controlled trials

Cardiovascular magnetic resonance (CMR) has been used to assess the efficacy of novel cardioprotective therapies for reducing myocardial infarct (MI) size following ST-segment elevation myocardial infarction (STEMI). However, some of these interventions such as ischemic postconditioning and remote ischemic conditioning, have been shown to reduce both MI size and the edema-based area-at-risk (AAR) by CMR, although not all studies have reported similar findings. These observations put into question the suitability for edema-based AAR to be used to calculate myocardial salvage index (MSI) in clinical studies. Therefore, we performed a meta-analysis of randomized controlled trials (RCTs), to determine whether the edema-based AAR by CMR is affected by the cardioprotective therapy under investigation.

This study was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement. We searched Embase and Medline databases up to November 2017. RCTs investigating a cardioprotective therapy at the time of primary percutaneous coronary intervention against the standard of care, measuring the AAR by T2-weighted imaging or T2-mapping CMR and showing a significant reduction in both MI size and MSI were included. Given that we were investigating whether the edema-based AAR is affected by the cardioprotective therapy, RCTs

showing a reduction in MSI derived from the edema-based AAR but no reduction in MI size were also excluded. RevMan 5.3 software was used to calculate the weighted standardized mean difference between the intervention and control arm using a random-effect and inverse variance method. Forest plots were generated using a log-based axis and risk ratios with 95% confidence interval (CI) were presented. When required, the median was used as a substitute for the mean, and the standard deviation was estimated by dividing the interquartile range by 1.35, as described in the Cochrane handbook of systematic reviews.

Fourteen RCTs were neutral for both MI size and MSI and 3 RCTs were neutral for MI size but showed an improvement in MSI. Five RCTs(1-5) were included in the final analysis. There was a 40% reduction in MI size in the intervention arm when compared to control (risk ratio 0.60, 95% CI 0.50-0.73). This was associated with a 24% reduction in the edema-based AAR in the intervention arm when compared to the control arm (risk ratio 0.76, 95% CI 0.57-1.00) (Figure 1).

We found that, in RCTs where the cardioprotective therapy was potent enough to reduce MI size, there was also a reduction in the edema-based AAR. This is probably not so surprising, given that a cardioprotective therapy capable of reducing MI size would also be expected to limit the severity of myocardial edema, as the latter is the direct result of acute myocardial ischemia and reperfusion injury. Therefore, when the edema-based method is quantified, the extent of the AAR would also be affected when the T2 intensity falls below the detection threshold.

The main limitations of our study were as follows: some RCTs reported the AAR and MI size in grams or gram/m^2 but we used the weighted standardized mean difference to account for that; the edema-based AAR was measured by T2-weighted imaging in the majority of the included RCTs (n=4) rather than the more robust T2-mapping

(n=1); duration of ischemia and timing of CMR varied among the studies but patient-level data was not available to adjust for those.

In conclusion, we have shown that in RCTs where the cardioprotective therapies significantly reduced MI size, the extent of the edema-based AAR quantified by CMR was also affected. We would therefore advocate caution when using the edema-based AAR by CMR to derive MSI as an endpoint in RCTs assessing the efficacy of novel cardioprotective interventions following STEMI.

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Figure 1: Forest plots of MI size and edema-based AAR by CMR in RCTs showing a significant reduction in MI size by the cardioprotective therapy
The top panel shows the forest plot of myocardial infarct (MI) size by cardiovascular magnetic resonance (CMR) in the intervention and control arms of RCTs included in this analysis and the bottom panel is the corresponding edema-based area-at-risk (AAR) in both arms. The Forest plots were generated using a log-based axis and risk ratios with 95% confidence interval (CI) are presented.
(SE: standard error; IV: inverse variance; PostC: ischemic postconditioning; RIC: remote ischemic conditioning)