Why did remote ischaemic conditioning not improve clinical outcomes in acute myocardial infarction in the CONDI-2/ERIC-PPCI trial?

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New treatments are needed to reduce myocardial infarct (MI) size and preserve left ventricular (LV) function, in order to improve clinical outcomes in patients presenting with acute ST-segment elevation myocardial infarction (STEMI) treated by primary percutaneous coronary intervention (PPCI).[1] Remote ischaemic conditioning (RIC), in which brief cycles of ischaemia and reperfusion are applied to an organ or tissue (including a limb) away from the heart, has been shown to reduce MI size in animal models of acute myocardial ischaemia/reperfusion injury (IRI).[2] The ability to deliver the cardioprotective RIC stimulus by simply inflating and deflating a pneumatic cuff placed on the upper arm or thigh, to induce brief cycles of ischaemia and reperfusion[3] has facilitated the translation of RIC into the clinical setting.

The majority of clinical studies have demonstrated improved myocardial salvage (assessed by myocardial nuclear and cardiovascular magnetic resonance imaging)[4-7] and/or 20-30% reductions in MI size (quantified by cardiac biomarkers and cardiac MRI)[8-10] with RIC administered as an adjunct to PPCI in STEMI. Furthermore, two follow-up studies,[11,12] and a single prospective study[13] have suggested that RIC may improve clinical outcomes in STEMI. However, a large, sufficiently powered, prospectively-designed multicentre clinical outcome study has been lacking.

Therefore, we conducted the CONDI-2/ERIC-PPCI trial. The study was an international, multicentre, single-blinded, randomised controlled trial comprising 5401 STEMI patients recruited through 36 centres in the United Kingdom, Denmark, Spain, and Serbia. Patients were randomly assigned to receive either standard (control) treatment or RIC, initiated prior to PPCI. RIC was administered using an automated AutoRIC™ cuff device (CellAegis Devices Inc., Toronto, Canada) placed on the upper arm to deliver 4 alternating cycles of inflation for 5 minutes to 200 mmHg and deflation for 5 minutes. The primary combined end point was cardiac death or hospitalisation for heart failure (HHF) at 12 months post-randomisation. Secondary end points included major cardiovascular and cerebral adverse

events (MACCE, comprising all-cause death, re-infarction, repeat coronary revascularisation, and stroke) at 30 days and 12 months, and MI size in a subset of 2662 patients (quantified as area-under-the-curve [AUC] high-sensitivity troponin T measured 0-48 hours after PPCI). A limited number of pre-specified subgroup analyses (age, diabetic status, left anterior descending [LAD] vs. non-LAD STEMI, pre-angioplasty TIMI flow [0-1 and 2-3], and time elapsed between first medical contact and PPCI) were performed on the primary outcome.

The results of the CONDI-2/ERIC-PPCI trial were presented in a Hot Line Session at the European Society of Cardiology Congress in Paris 2019, and simultaneously published in the Lancet.[14] Unfortunately, there was no difference between the control group (8.6% [n=220]) and the RIC group (9.4% [n=239]) with respect to the combined primary end-point of cardiac death or HHF at 12 months (hazard ratio, 1.10; 95% CI, 0.91 to 1.32; p=0.32), demonstrating that RIC, applied as an adjunct to PPCI, did not improve clinical outcomes in STEMI patients. Similarly, there was no difference between the control group (7.8% [n=197]) and the RIC group (8.4% [n=212]) with respect to MACCE within 12 months of follow-up (hazard ratio, 1.09; 95% CI, 0.90 to 1.32; p=0.38]. These findings are in direct conflict with the CONDI-1 and LIPSIA CONDITIONING follow-up studies. CONDI-1 reported less MACCE (all-cause mortality, myocardial infarction, readmission for heart failure, and ischaemic stroke/transient ischaemic attack) with RIC vs control at a median follow-up of 3.8 years (13.5% vs 25.6%).[11] LIPSIA CONDITIONING reported MACE (cardiac death, reinfarction, and new congestive heart failure) with a combination of RIC and postconditioning vs control at a median follow-up of 3.6 years (10.2% vs 16.9%).[12] Similarly, the single-centre prospective RIC-STEMI trial reported less cardiac death or HHF at a median follow-up of 2.1 years with RIC vs control (hazard ratio, 0.35; 95% CI, 0.15 to 0.78).[13] All three studies had extended follow-up, whereas the CONDI-2/ERIC-PPCI trial had a relatively short-term follow-up period of 12 months, which may not have been long enough to observe any effect of RIC on clinical outcomes.

In the CONDI-2/ERIC-PPCI trial there was also no effect of RIC on MI size when compared to control (evaluated by high-sensitivity troponin T - ratio of means, 1.05; 95% CI, 0.92 to 1.18; p=0.48). This finding confirms that RIC appeared to have no biological effect - a finding, which is consistent with the observed lack of effect of clinical outcomes at 12 months. Several other studies have failed to demonstrate a beneficial effect of RIC on MI size when quantified by cardiac biomarkers despite salutatory effects on myocardial salvage and clinical outcomes,[4,5,11-13] questioning the reliability of using MI size quantified by cardiac biomarkers to assess cardioprotective efficacy. Because CMR is a more sensitive technique for assessing cardioprotective efficacy, the results of the CMR study from the CONDI-2/ERIC-PPCI trial, which will report the effect of RIC on MI size and myocardial salvage, are eagerly awaited.

Even though MI size is known to be a critical determinant of clinical outcomes post-PPCI in STEMI, it has not been conclusively shown that a reduction in MI size by a cardioprotective intervention applied as an adjunct to PPCI, can be translated into improved clinical outcomes within the range of infarct sizes achieved with contemporary reperfusion therapy. Interestingly, the RIC-STEMI trial failed to demonstrate a reduction in MI size (using 48 hr AUC Troponin I), but still found improved clinical outcomes after 2 years' follow-up.[13] The unexpected and discordant effects of RIC on MI size and clinical outcomes in the RIC-STEMI trial may have been due to a type 1 error, as only 516 STEMI patients were randomised, and the number of events were relatively small (3 RIC vs 11 control for cardiac mortality and 8 RIC vs 17 control for HHF). An alternative explanation may be that the primary effect of RIC was on post-STEMI left ventricular (LV) remodelling rather than acute MI size – but this is not supported by experimental animal studies, which have shown RIC reducing acute MI size.[2]

Other reasons why RIC may have failed to reduce MI size and improve clinical outcomes in

the CONDI-2/ERIC-PPCI trial include:

1. **The RIC protocol itself:** In the CONDI-2/ERIC-PPCI trial, four 5-min cycles of upper arm cuff inflations/deflations were used, a RIC protocol which has been shown in prior studies to increase myocardial salvage index[4] and reduce MI size[6]. However, the optimal RIC protocol in terms of arm vs leg, number of cycles, duration of ischaemia/reperfusion cycles and unilateral vs bilateral limbs, has not been established in humans. Interestingly, the RIC-STEMI study, which showed improved clinical outcomes with RIC, used 3 cycles of inflation/deflation of a pneumatic cuff placed on the thigh.[13]
2. **Timing of the RIC protocol:** Clinical studies have reported efficacy with RIC administered in the ambulance or on arrival at the hospital (prior to PPCI), during PPCI, and even at the onset of reperfusion after PPCI. In the CONDI-2/ERIC-PPCI trial, there were no differences in clinical outcomes whether the RIC protocol was performed in the ambulance or at the hospital. Furthermore, there was no difference in clinical outcomes whether the full 4 cycles of the RIC protocol were completed prior to onset of PPCI or not.
3. **Comedications and comorbidities:** Experimental studies have shown that certain co-morbidities (such as age and diabetes) and co-medications (such as platelet $P2Y_{12}$ inhibitors), can attenuate the cardioprotective efficacy of ischemic conditioning strategies, although specific evidence for RIC is limited.[15] However, in the CONDI-2/ERIC-PPCI trial, age, the presence of diabetes, or the administration of the $P2Y_{12}$ receptor antagonist, ticagrelor, did not interfere with clinical outcomes between the control and the RIC groups.
4. **Pre-PPCI TIMI flow and coronary artery territory:** The efficacy of cardioprotective interventions applied at reperfusion in STEMI patients are closely related to MI size and pre-PPCI TIMI flow, with most benefit reported for patients with anterior infarcts and an occluded artery on presentation (pre-PPCI TIMI flow ≤1).[4] However, pre-specified subgroup analyses in the CONDI-2/ERIC-PPCI revealed no differences in clinical outcomes with RIC vs control when considered according to MI location and pre-PPCI TIMI flow.

In summary, the findings from the CONDI-2/ERIC-PPCI trial provide definitive and conclusive

evidence that RIC offers no benefits on either MI size or clinical outcomes in STEMI patients treated by PPCI. This is unfortunate as RIC had been the most promising cardioprotective strategy for improving clinical outcomes following STEMI, and few other therapeutic options exist. Further studies are needed to identify novel cardioprotective targets and innovative approaches to cardioprotection such as combination multi-target therapy. RIC may still have benefit in other condition such as renal transplantation, stroke and elective PCI.

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Declaration of interests

HEB is a shareholder in CellAegis Inc. DJH has no conflicts of interest.

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