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Improved long-term clinical outcomes in patients with ST-elevation myocardial infarction undergoing remote ischaemic conditioning as an adjunct to primary percutaneous coronary intervention

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Aims Remote ischaemic conditioning as an adjunct to primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction increases myocardial salvage. We investigated the effect of remote ischaemic conditioning on long-term clinical outcome.

Methods and results From February 2007 to November 2008, 333 patients with a suspected first acute ST-elevation myocardial infarction were randomized to receive primary percutaneous coronary intervention with ($n = 166$) or without ($n = 167$) remote ischaemic conditioning (intermittent arm ischaemia through four cycles of 5-min inflation followed by 5-min deflation of a blood-pressure cuff). Patient follow-up extended from the randomization date until an outcome, emigration or January 2012 (median follow-up = 3.8 years). The primary endpoint was major adverse cardiac and cerebrovascular events (MACCE)—a composite of all-cause mortality, myocardial infarction, readmission for heart failure, and ischaemic stroke/transient ischaemic attack. The individual components of the primary endpoint comprised the secondary endpoints. Outcomes were obtained from Danish nationwide medical registries and validated by medical record review and contact to patients' general practitioner. In the per-protocol analysis of 251 patient fulfilling trial criteria, MACCE occurred for 17 (13.5%) patients in the intervention group compared with 32 (25.6%) patients in the control group, yielding a hazard ratio (HR) of 0.49 (95% confidence interval: 0.27–0.89, $P = 0.018$). The HR for all-cause mortality was 0.32 (95% confidence interval: 0.12–0.88, $P = 0.027$). Although lower precision, the HRs were also directionally lower for all other secondary endpoints.

Conclusion Remote ischaemic conditioning before primary percutaneous coronary intervention seemed to improve long-term clinical outcomes in patients with ST-elevation myocardial infarction.

Keywords Myocardial infarction • Cardioprotection • Ischaemic conditioning • Clinical outcome

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Introduction

Acute myocardial infarction remains a major cause of morbidity and mortality.[1] While advances in reperfusion strategies have improved clinical outcomes,[2–4] evidence is growing that reperfusion injury occurs after revascularization.[5,6] Limiting reperfusion injury has therefore become a treatment target. Remote ischaemic conditioning is a new approach, in which brief episodes of ischaemia distant from the heart are used to protect against myocardial reperfusion injury.[7–9] The stimulus can be applied in a simple, low cost manner using cycles of inflation/deflation of a blood-pressure cuff placed around the upper arm.[10–13]

We have shown that remote ischaemic conditioning initiated in the ambulance during hospital transport for primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction improves myocardial salvage evaluated by single photon emission computed tomography (SPECT).[14] In an echocardiographic subtrial, we have furthermore demonstrated a modest increase in short-term left ventricular function in patients with a large myocardial area at risk and in patients with left anterior descending artery (LAD) infarcts.[15] However, no trial data exist on long-term clinical outcome associated with remote ischaemic conditioning in patients with acute myocardial infarction.

We therefore examined whether the short-term benefits of remote ischaemic conditioning as an adjunct to primary percutaneous coronary intervention translated into improved long-term clinical outcomes in patients with ST-elevation myocardial infarction.

Methods

Design, trial setting, and participants

The parent trial was a randomized, controlled trial performed in the Department of Cardiology, Aarhus University Hospital, Denmark. Patient inclusion and randomization have been described in detail elsewhere.[14] The present trial included all randomized patients from the parent trial. In brief, patients were enrolled in the parent trial from February 2007 to November 2008. Criteria for inclusion were as follows: (i) age $\geq$18 years, (ii) symptom duration of $\leq$12 h prior to admission, and (iii) ST-segment elevation $\geq$0.1 mV in two or more contiguous electrocardiogram leads. Patients were excluded from the analysis based on the following criteria: (i) diagnosis not confirmed upon hospital arrival, (ii) history of previous myocardial infarction, (iii) previous coronary

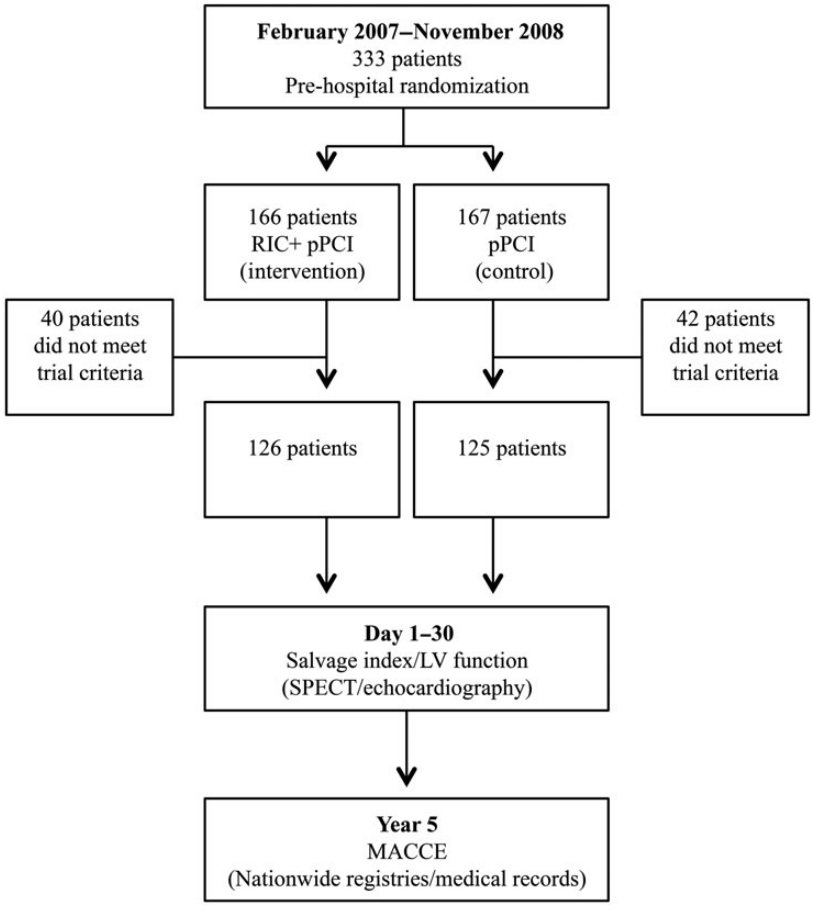

Figure 1 Trial flowchart. RIC, remote ischaemic conditioning; pPCI, primary percutaneous coronary intervention; LV, left ventricular; SPECT, single photon emission computed tomography; MACCE, major adverse cardiac and cerebrovascular events.

Table 1 Number of patients (%) and hazard ratios (95% CI) for the primary composite endpoint of any major adverse cardiac and cerebrovascular events (MACCE) and for the secondary endpoints (all-cause mortality, myocardial infarction, readmission for heart failure, and ischaemic stroke/transient ischaemic attack) in the follow-up period

	Per-protocol analysis				Intention-to-treat analysis			
	RIC + pPCI (*n* = 126)	pPCI (*n* = 125)	HR (95% CI)	*P*-value	RIC + pPCI (*n* = 166)	pPCI (*n* = 167)	HR (95% CI)	*P*-value
Primary composite endpoint								
MACCE	17 (13.5%)	32 (25.6%)	0.49 (0.27–0.89)	0.018	30 (18.1%)	46 (27.5%)	0.62 (0.39–0.99)	0.045
Vessel patency on admission[a]								
Occluded vessel on admission (TIMI 0–1)	10 (7.9%)	23 (18.4%)	0.44 (0.21–0.93)	0.031	16 (9.7%)	27 (16.1%)	0.55 (0.30–1.03)	0.061
Non-occluded vessel on admission (TIMI 2–3)	7 (5.6%)	9 (7.2%)	0.64 (0.24–1.73)	0.380	14 (8.4%)	19 (11.4%)	0.74 (0.37–1.47)	0.383
Infarct location[a]								
LAD infarct	12 (9.5%)	19 (15.2%)	0.63 (0.30–1.29)	0.206	18 (10.9%)	24 (14.4%)	0.73 (0.40–1.35)	0.321
Non-LAD infarct	5 (4.0%)	13 (10.4%)	0.26 (0.05–1.23)	0.089	12 (7.2%)	22 (13.1%)	0.59 (0.21–1.62)	0.302
Secondary endpoints								
All-cause mortality	5 (4.0%)	15 (12.0%)	0.32 (0.12–0.88)	0.027	11 (6.6%)	21 (12.6%)	0.51 (0.25–1.07)	0.074
Cardiac mortality	2 (1.6%)	5 (4.0%)	0.39 (0.08–2.00)	0.258	4 (2.4%)	9 (5.4%)	0.44 (0.13–1.41)	0.167
Non-cardiac mortality	3 (2.4%)	10 (8.0%)	0.28 (0.08–1.03)	0.056	7 (4.2%)	12 (7.2%)	0.57 (0.23–1.45)	0.241
Myocardial infarction	8 (6.4%)	11 (8.8%)	0.69 (0.28–1.71)	0.423	9 (5.4%)	17 (10.2%)	0.51 (0.23–1.15)	0.105
STEMI	2 (1.6%)	4 (3.2%)	0.47 (0.09–2.58)	0.386	3 (1.8%)	7 (4.2%)	0.42 (0.11–1.61)	0.205
N-STEMI	6 (4.8%)	7 (5.6%)	0.81 (0.27–2.42)	0.711	6 (3.6%)	10 (6.0%)	0.58 (0.21–1.60)	0.291
Readmission for heart failure	4 (3.2%)	7 (5.6%)	0.54 (0.16–1.85)	0.327	9 (5.4%)	11 (6.6%)	0.81 (0.34–1.95)	0.636
Decompensated chronic/acute heart failure	3 (2.4%)	3 (2.4%)	0.94 (0.19–4.67)	0.941	6 (3.6%)	6 (3.6%)	0.98 (0.32–3.03)	0.968
Device implantation (ICD/BIV-pacemaker)	1 (0.8%)	4 (3.2%)	0.24 (0.03–2.14)	0.200	3 (1.8%)	5 (3.0%)	0.60 (0.14–2.52)	0.488
Ischaemic stroke/transient ischaemic attack	3 (2.4%)	4 (3.2%)	0.72 (0.16–3.23)	0.670	5 (3.0%)	7 (4.2%)	0.71 (0.23–2.25)	0.562
Ischaemic stroke	2 (1.6%)	4 (3.2%)	0.49 (0.09–2.65)	0.403	4 (2.4%)	6 (3.6%)	0.67 (0.19–2.38)	0.537
Transient ischaemic attack	1 (0.8%)	0 (0.0%)	-	-	1 (0.8%)	1 (0.6%)	-	-

[a]Subgroup analysis. RIC, remote ischaemic conditioning; pPCI, primary percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.
LAD, left anterior descending; STEMI, ST-elevation myocardial infarction; N-STEMI, non-ST-elevation myocardial infarction; ICD, implantable cardioverter defibrillator; BIV,biventricular.

artery bypass grafting (CABG), and (iv) chest pain >12 h prior to admission.

In total, 333 patients with a tentative diagnosis of ST-elevation myocardial infarction were enrolled during ambulance transfer and randomized to receive remote ischaemic conditioning as an adjunct to primary percutaneous coronary intervention ($n = 166$) or to receive standard treatment with primary percutaneous coronary intervention alone ($n = 167$). The remote ischaemic conditioning intervention was initiated in the ambulance during transport to the interventional centre using intermittent arm ischaemia. Arm ischaemia was achieved by means of four cycles of alternating 5-min inflation (200 mmHg) followed by 5-min deflation of a blood pressure cuff placed on the upper arm. Of the 333 patients initially enrolled in the pre-hospital setting, 82 patients were excluded on hospital arrival because they did not meet the trial criteria, as described above (*Figure 1*).

Endpoints

The primary endpoint was major adverse cardiac and cerebrovascular events (MACCE), defined as a composite of all-cause mortality, myocardial infarction, readmission for heart failure, and ischaemic stroke/transient ischaemic attack. The individual components of the primary endpoint comprised the secondary endpoints.

All-cause mortality was defined as death from any cause in the follow-up period. Death causes were divided into cardiac and non-cardiac death causes. Cardiac death causes were defined as death from an evident cardiac cause or death from unknown cause.

Myocardial infarction was defined as a myocardial reinfarction (within 28 days of index admission) or a recurrent myocardial infarction occurring >28 days after index admission. The diagnoses of myocardial infarction were made according to existing guidelines,[16] and furthermore divided into ST-elevation myocardial infarction and non-ST-elevation myocardial infarction.

Readmission for heart failure was defined as readmission for decompensated chronic heart failure, acute heart failure (lung oedema or cardiogenic shock), or device implantation due to chronic heart failure [biventricular pacemaker and/or prophylactic implantable cardioverter defibrillator (ICD)] in the follow-up period.

Ischaemic stroke was defined as new neurological deficit persisting for >24 h and a computed tomography (CT) or magnetic resonance imaging (MRI) verifying acute brain infarction and transient ischaemic attack as new neurological deficit resolving within 24 h and a CT scan or MRI without acute brain infarction in the follow-up period.

Data collection

We followed all trial patients from the date of randomization until an outcome, emigration, or January 2012, whichever occurred first. Outcome data were collected from Danish nationwide medical registries. Each Danish citizen is given a unique 10-digit personal identification number at birth or upon immigration, which can be used to link data among administrative and medical registries.[17]

We identified all-cause mortality from the Danish Civil Registration System.[17] This registry has collected information on the vital status of all Danish citizens, including date of death, since 1968. All death certificates contain the underlying and contributing causes of death and are submitted to the Danish Registry of Causes of Death by the physician who verified the death. We used the Danish Registry of Causes of Death to identify cardiac and non-cardiac deaths.[18]

We identified all non-fatal outcomes from the Danish National Registry of Patients.[19] This registry has collected data on all hospital admissions since 1977. At discharge, each hospitalization is coded by the treating physician with one primary diagnosis, and, when appropriate, one or more secondary diagnoses, according to the *International Classification of Diseases* (ICD) system, 10th revision (from 1994 onwards).

To ensure high-quality data, we validated all cardiovascular readmissions and causes of death using medical records or by contacting the patient's general practitioner. Events occurring during the patients' index admission were also obtained from medical records. Trial staff members responsible for collection and analyses of follow-up data were blinded to treatment assignment.

The trial protocol was approved by the Regional Ethics Committee and the Danish Data Protection Agency. The trial was registered with ClinicalTrials.gov, number NCT01665365.

Statistical analyses

Two types of analyses were performed: (i) a per-protocol analysis of patients fulfilling trial criteria ($n = 251$) and (ii) an intention-to-treat analysis of all randomized patients ($n = 333$). We used Cox proportional hazards regression to calculate hazard ratios (HRs) with 95% confidence intervals (CIs), with and without adjustment for differences in baseline characteristics (age, sex, and hypertension). Using the Kaplan–Meier estimator, we illustrated graphically the cumulative incidence function of MACCE, all-cause mortality, cardiac mortality, and non-cardiac mortality.

A two-tailed P-value <0.05 was considered statistically significant. Statistical analyses were conducted using the SAS software (version 9.2).

Results

Follow-up data were available for all 333 randomized patients, with no patients lost to follow-up. There was no difference in follow-up time between the intervention and control groups [median follow-up time = 3.8 years (95% CI: 3.3 years to 4.2 years) and maximum follow-up time = 4.9 years]. Baseline characteristics and medical procedure data have previously been published in detail and did not differ in the two groups except for hypertension, which was more common in the intervention group.[14] Adjustments for the differences in baseline characteristics did not change the results substantially, and we therefore only report the crude HRs.

In the per-protocol analysis ($n = 251$), the primary composite endpoint (MACCE) occurred in 17 (13.5%) patients in the intervention group and in 32 (25.6%) patients in the control group (*Table 1*). The HR for MACCE was 0.49 (95% CI: 0.27–0.89, $P = 0.018$) in favour of the intervention (*Figure 2*). When the MACCE definition included only cardiac mortality, rather than all-cause mortality, the composite endpoint was experienced in 15 (11.9%) patients in the intervention group and in 25 (20.0%) patients in the control group, yielding an HR of 0.56 (95% CI: 0.30–1.06, $P = 0.075$).

Among the secondary endpoints, all-cause mortality was reduced in the intervention group compared with the control group [5 deaths (4.0%) vs. 15 deaths (12.0%), HR = 0.32 (95% CI: 0.12–0.88, $P = 0.027$)]. Causes of death are listed in *Table 2*, where cancer was the most common non-cardiac death cause. The HRs for MACCE were reduced independently of vessel patency before procedure and infarct location (*Table 1*). Although lower precision, the HRs were also directionally lower for all other secondary endpoints (myocardial infarction, readmission for

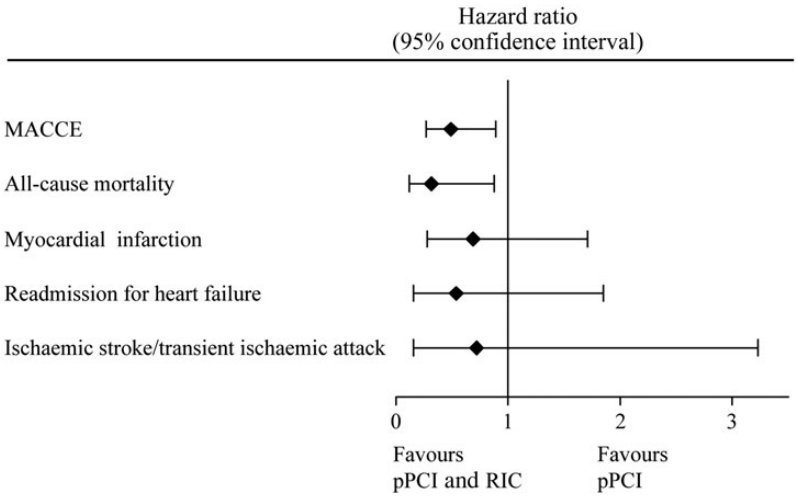

Figure 2 Hazard ratio for the primary composite endpoint (major adverse cardiac and cerebrovascular events) and for the secondary endpoints (all-cause mortality, myocardial infarction, readmission for heart failure, and ischaemic stroke/transient ischaemic attack) in the follow-up period (per-protocol analysis).

Table 2 Death causes (per-protocol and intention-to-treat analysis)

RIC + pPCI ($n = 166$)	**pPCI** ($n = 167$)
Cardiac death ($n = 4$)	**Cardiac death** ($n = 9$)
(1) Cardiac tamponade (perforated LAD)[a]	(1) Sudden cardiac arrest[a]
(2) Respiratory insufficiency (combination of pulmonary oedema/acute exacerbation in chronic obstructive pulmonary disease)	(2) Cardiogenic shock[a]
(3) Cardiogenic shock[a]	(3) Sudden cardiac arrest[a]
(4) Cardiac arrest (found dead at home − autopsy not performed)	(4) Repeated stent thrombosis
	(5) Sudden cardiac arrest (during readmission for myocardial infarct/heart failure)
	(6) Cardiac arrest (found dead at home—autopsy not performed)
	(7) Chronic heart failure
	(8) Cardiogenic shock[a]
	(9) Pulmonary oedema[a]
Non-cardiac death ($n = 7$)	**Non-cardiac death** ($n = 12$)
(1) Cancer (diffuse large B-cell lymphoma)[a]	(1) Post-operative respiratory insufficiency and bleeding (surgery for rectal cancer)[a]
(2) Post-operative bleeding (surgery for rectal tumour)[a]	(2) Cancer (lung cancer)[a]
(3) Cancer (bladder cancer)	(3) Cancer (colon cancer)[a]
(4) Parkinson's disease	(4) Sepsis (peritonitis)[a]
(5) Cancer (breast cancer)[a]	(5) Cancer (prostate cancer)[a]
(6) Cancer (acute myeloid leukaemia)	(6) Suspected cancer (the patient was not interested in further diagnostic examination)[a]
(7) Diffuse bleeding/thrombocytopenia (aetiology unknown)	(7) Alcohol intoxication
	(8) Cancer (oesophagus cancer)
	(9) Cancer (cerebral cancer)[a]
	(10) Sepsis[a]
	(11) Cancer (rectal cancer)[a]
	(12) Cancer (lung cancer)[a]

[a]Per-protocol analysis. RIC, remote ischaemic conditioning; pPCI, primary percutaneous coronary intervention. LAD, left anterior descending.

heart failure, and ischaemic stroke/transient ischaemic attack). The cumulative incidence curves for MACCE, all-cause mortality, cardiac mortality and non-cardiac mortality are shown in *Figure 3A–D*. The intention-to-treat analysis supported the per-protocol analysis (*Table 1* and Supplementary material online, *Figures S4* and *S5A–D*).

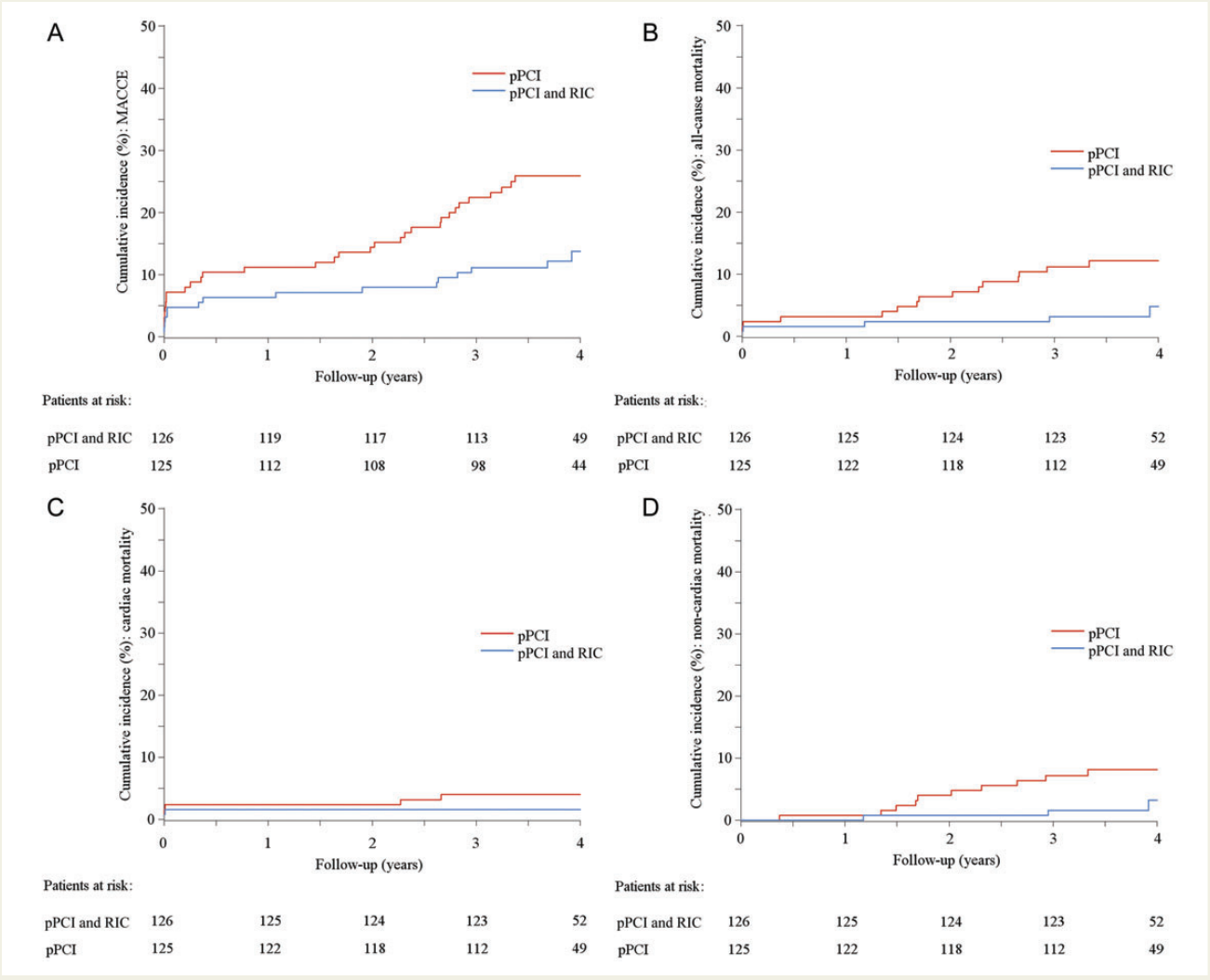

Figure 3 (*A*) Cumulative incidence (%) of major adverse cardiac and cerebrovascular events (MACCE) by year since randomization (per-protocol analysis). $P = 0.010$. (*B*) Cumulative incidence (%) of all-cause mortality by year since randomization (per-protocol analysis). $P = 0.019$. (*C*) Cumulative incidence of cardiac mortality (%) by year since randomization (per-protocol analysis). $P = 0.248$. (*D*) Cumulative incidence of non-cardiac mortality (%) by year since randomization (per-protocol analysis). $P = 0.045$.

Discussion

We found that remote ischaemic conditioning as an adjunct to primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction seemed to improve long-term clinical outcomes.

This is the first trial to evaluate the effect of remote ischaemic conditioning as an adjunct to primary percutaneous coronary intervention on long-term clinical outcomes in patients with myocardial infarction. A recent meta-analysis including 23 randomized trials investigating the effect of remote ischaemic conditioning on clinical outcomes showed a reduction in cardiac biomarker release and peri-procedural myocardial infarction, but did not demonstrate an effect on major adverse cardiovascular events or mortality.[20] However, the meta-analysis was mainly based on trials in low-risk patients undergoing elective cardiac procedures and only investigated short-term clinical outcomes, i.e. up to 6 months after the index event. Only one trial besides our parent trial was conducted in high-risk patients with ST-elevation myocardial infarction and this trial did not evaluate clinical outcomes, but only the effect of remote ischaemic conditioning on the release of biochemical myocardial necrosis markers and ST-segment resolution.[21]

More recently, results from the CRISP stent trial in patients undergoing elective percutaneous coronary intervention have demonstrated a lower MACCE rate in the remote ischaemic preconditioning group compared with the control group after 6 years of follow-up [23 vs. 36, HR = 0.58 (95% CI: 0.35–0.97), $P = 0.039$].[22] Additionally, a trial in patients undergoing elective CABG randomized to remote ischaemic preconditioning or standard therapy has showed a reduction in MACCE [13.9 vs. 18.9%, HR = 0.32 (95% CI: 0.14–0.71), $P = 0.05$] and all-cause mortality [1.9 vs. 6.9%, HR = 0.27 (95% CI: 0.08–0.98), $P = 0.046$] after a mean

follow-up duration of 1.54 years.[23] While these two trials reported an effect of remote ischaemic conditioning on long-term clinical outcomes in *a priori* low-risk patients undergoing elective cardiac procedures, our results demonstrate an effect of remote ischaemic conditioning on long-term clinical outcomes in patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction.

We have presented per-protocol as well as intention-to-treat data. Although intention-to-treat data increase sample size and hence statistical power, we focused on the per-protocol analysis in accordance with the conclusion in our parent trial that was based on an improvement in myocardial salvage index per-protocol.[14]

The reduction in our primary endpoint MACCE was mainly driven by a reduction in all-cause mortality. Evaluating specific death causes, the point estimates suggested a reduction in both cardiac and non-cardiac mortality. The reduction in cardiac mortality was expected from the parent trial results. The reduction in non-cardiac mortality was not and most likely arose by chance. Importantly, the results for MACCE when excluding non-cardiac mortality supported our conclusion. We note that the previously demonstrated improvement in myocardial salvage index and left ventricular function may translate into a reduction in the post-infarction heart failure rate driven by fewer device implantations due to chronic heart failure. However, the overall number of post-infarction heart failure diagnoses was too low to draw firm conclusions.

In the parent trial a subgroup analysis of myocardial salvage index stratified by vessel patency and infarct location showed that the effect of remote ischaemic conditioning was most pronounced in patients with an occluded vessel on admission and in patients with LAD infarcts.[14] Although our subgroup analyses did not allow firm conclusions, our results do not reject the assumption that a beneficial effect is predominantly achieved in patients with an occluded vessel on admission consistent with the hypothesis that the effect of remote ischaemic conditioning is mainly associated with an attenuation of reperfusion injury. On the other hand, the clinical effect of remote ischaemic conditioning was independent on infarct location, indicating that all patients with ST-elevation myocardial infarction may benefit from this low-risk treatment.

The present trial has limitations. The power calculation in the parent trial was based on the myocardial salvage index. Here, we report long-term clinical outcomes. Importantly, despite wide CIs due to the sample size, all point estimates supported a beneficial effect. We defined heart failure as readmission for heart failure. We may have underestimated the rate of heart failure, because outpatient diagnoses were not included. However, this potential misclassification would bias the estimates towards null and thus cannot explain the reduced HR for heart failure. Substantial confounding is less likely owing to the randomized design and because the intention-to-treat analysis supported the results from the per-protocol analysis. Also, adjustment for the difference in hypertension frequency among the groups at baseline did not change the results.

The outcome of this first trial to evaluate the effect of remote ischaemic conditioning on long-term clinical outcomes in patients with ST-elevation myocardial infarction is encouraging. A simple, cost-effective intervention, which can easily be applied in the prehospital setting in patients with acute cardiac events, may in fact have the potential to reduce morbidity and mortality. However, our results need to be confirmed in a larger multicentre trial before remote ischaemic conditioning can be implemented in guidelines as an adjunct to primary percutaneous coronary intervention.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contributions

A.D.S. had full access to all data in the trial and takes responsibility for the integrity of the data and accuracy of the data analysis.

Trial concept and design: H.E.B., A.D.S., M.R.S., H.T.S.

Data collection: A.D.S.

Statistical analyses: L.P., A.D.S.

Interpretation of data: A.D.S., M.R.S., K.M., H.E.B., S., M.S., L.P., H.T.S.

Drafting of paper: A.D.S. Critical revision of the paper: M.R.S., K.M., H.E.B., M.S., L.P., H.T.S., R.K.K., A.N.R.

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Conflict of interest: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. M.R.S., R.K.K., A.N.R., and H.E.B. are shareholders in CellAegis. No other disclosures were reported.

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