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Remote preconditioning and all-cause mortality

During the past three decades, experimental cardiology studies have shown that ischaemic conditioning interventions can lessen the risk of fatal reperfusion injury and reduce infarct size. Murry and colleagues[1] noted that repeated brief episodes of myocardial ischaemia induced before a sustained ischaemic insult preconditioned the heart. Zhao and colleagues[2] reported that a similar intervention applied immediately after (but not before) sustained ischaemic insult could postcondition the heart. Przyklenk and colleagues[3] found that the application of short cycles of non-fatal ischaemia at a remote site (eg, the arm) before, during, or immediately after sustained occlusion of a coronary artery improved resistance to reperfusion injury to the heart compared with unconditioned hearts.

Initially, despite substantial progress in reperfusion therapy, no approaches were proposed to lower the risk of fatal reperfusion injury, be it after focal or global ischaemia reperfusion. The discovery and development of conditioning interventions presented an opportunity to protect various organs affected by ischaemia (eg, the heart, brain, and kidneys) during emergencies (eg, acute myocardial infarction, stroke, cardiac arrest) and scheduled therapeutic interventions (eg, cardiac surgery).[4]

Staat and colleagues[5] showed in a proof-of concept study in patients with ST-segment-elevation myocardial infarction that four cycles of 1 min inflation and 1 min deflation of the angioplasty balloon immediately after reperfusion postconditioned the heart and significantly lessened infarct size, by nearly 40%. Hausenloy and co-workers[6] reported remote conditioning by three cycles of 5 min inflation and 5 min deflation of a blood-pressure cuff on the upper arm, which significantly reduced release of troponin T in patients undergoing elective coronary artery bypass graft (CABG) surgery. Although it could be argued that protective therapies are not needed in low-risk patients undergoing CABG, among whom mortality is already low, more than 40% release cardiac enzymes after surgery that are known to be associated with worsening of short-term and long-term outcomes.[7]

In *The Lancet*, Matthias Thielmann and colleagues[8] report a prospective, randomised, controlled trial into which they enrolled 329 consecutive adults with multivessel coronary artery disease. Patients underwent remote ischaemic preconditioning with a blood-pressure cuff around the upper arm (three cycles of inflation for 5 min and reperfusion for 5 min) or no ischaemic preconditioning before elective isolated first-time CABG. In the remote ischaemic conditioning group the area under the curve for release of cardiac troponin I in the first 72 h after revascularisation was significantly lower than that in the control group (266 ng/mL, 95% CI 237–298 *vs* 321 ng/mL, 287–360; difference 17%, 3–30%). The most important finding of this work, however, is the significant improvement in clinical outcomes induced by remote ischaemic conditioning. In this low-risk population, remote ischaemic preconditioning was associated with reduced incidence of all-cause death (hazard ratio 0·27, 95%CI 0·08–0·98) and myocardial infarction (0·35, 0·15–0·78) at 1 year. We congratulate the researchers on providing the evidence that a conditioning intervention can improve clinical outcomes after CABG, although a limited number of serious adverse events were noted in the study population.

Apart from myocardial protective effects, Thielmann and colleagues noted that reduced release of cardiac

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troponin I was associated with improvements in mortality at 1 year, but not at 30 days. Additionally, the incidence of non-heart-related events, such as sepsis or stroke, was lower in the remote ischaemic preconditioning group than in the control group, albeit of few events overall. These findings suggest that the effect on the heart might be only one aspect of a much wider effect, and that remote conditioning, unlike local conditioning, might lead to persistent protection. This theory is supported by the flexible, transorgan effects on the heart seen after brief remote conditioning in the kidney, liver, and mesentery and skeletal muscles.[9,10] A trial of potent nephron protection induced by ischaemic preconditioning, the RenPro Trial,[11] suggested broad benefits induced by remote ischaemic conditioning. Thus, a simple and cheap method of inducing natural protection in various pathological settings might prove to have substantial clinical effects, possibly closer to those achieved pharmacologically than by focal ischaemic conditioning.[12] If such effects are genuine, whether additive benefit might be expected from the combination of different types of conditioning interventions in various clinical settings could be interesting to investigate.

The exciting findings of Thielmann and colleagues need to be supported by strong experimental evidence and elucidation of the mechanisms underlying the effects of remote conditioning. The results also need to be tested in large phase 3 studies, such as the ERICCA trial[13] or the RIPHeart-Study.[14]

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We declare that we have no conflicts of interest.

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TRILOGY ACS: prasugrel of benefit only after angiography?

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Guidelines[1] recommend that patients with non-ST-segment elevation acute coronary syndrome with moderate-to-high risk features have diagnostic coronary angiography with intent to perform re-vascularisation with percutaneous coronary intervention or coronary artery bypass. However, many patients with unstable angina or non-ST-segment elevation myocardial infarction are treated medically, irrespective of whether coronary angiography or revascularisation is done. Dual antiplatelet treatment with aspirin and clopidogrel is important in these patients.[2,3] New $P2Y_{12}$ inhibitors—eg, prasugrel and ticagrelor—have overcome the limitations of clopidogrel: namely, delayed onset of action, modest effects on platelet inhibition, and wide variation in platelet responsiveness between patients.[4] Prasugrel,

Cardioprotective and prognostic effects of remote ischaemic preconditioning in patients undergoing coronary artery bypass surgery: a single-centre randomised, double-blind, controlled trial

Matthias Thielmann, Eva Kottenberg, Petra Kleinbongard, Daniel Wendt, Nilgün Gedik, Susanne Pasa, Vivien Price, Konstantinos Tsagakis, Markus Neuhäuser, Jürgen Peters, Heinz Jakob, Gerd Heusch

Summary

Background Remote ischaemic preconditioning has been associated with reduced risk of myocardial injury after coronary artery bypass graft (CABG) surgery. We investigated the safety and efficacy of this procedure.

Methods Eligible patients were those scheduled to undergo elective isolated first-time CABG surgery under cold crystalloid cardioplegia and cardiopulmonary bypass at the West-German Heart Centre, Essen, Germany, between April, 2008, and October, 2012. Patients were prospectively randomised to receive remote ischaemic preconditioning (three cycles of 5 min ischaemia and 5 min reperfusion in the left upper arm after induction of anaesthesia) or no ischaemic preconditioning (control). The primary endpoint was myocardial injury, as reflected by the geometric mean area under the curve (AUC) for perioperative concentrations of cardiac troponin I (cTnI) in serum in the first 72 h after CABG. Mortality was the main safety endpoint. Analysis was done in intention-to-treat and per-protocol populations. This trial is registered with ClinicalTrials.gov, number NCT01406678.

Findings 329 patients were enrolled. Baseline characteristics and perioperative data did not differ between groups. cTnI AUC was 266 ng/mL over 72 h (95% CI 237–298) in the remote ischaemic preconditioning group and 321 ng/mL (287–360) in the control group. In the intention-to-treat population, the ratio of remote ischaemic preconditioning to control for cTnI AUC was 0·83 (95% CI 0·70–0·97, p=0·022). cTnI release remained lower in the per-protocol analysis (0·79, 0·66–0·94, p=0·001). All-cause mortality was assessed over 1·54 (SD 1·22) years and was lower with remote ischaemic preconditioning than without (ratio 0·27, 95% CI 0·08–0·98, p=0·046).

Interpretation Remote ischaemic preconditioning provided perioperative myocardial protection and improved the prognosis of patients undergoing elective CABG surgery.

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Introduction

Remote ischaemic preconditioning by brief episodes of ischaemia and reperfusion in a remote organ or vascular territory provides protection from injury by myocardial ischaemia and reperfusion.[1–3] In cardiac and coronary artery bypass graft (CABG) surgery in particular, adverse outcomes relate mainly to peri-procedural myocardial injury.[4] In the translation of remote ischaemic preconditioning from bench to bedside, first proof-of-principle and small randomised, controlled trials have shown decreased release of myocardial biomarkers after aortic,[5] congenital cardiac,[6,7] adult valve,[8–10] and CABG surgery.[11–15] Whether or not such reduction in cardiac biomarkers translates into better clinical outcomes is unclear.

We did a randomised, controlled clinical trial to assess whether remote ischaemic preconditioning reduced concentrations of cardiac troponin I (cTnI) in serum and to analyse the safety and clinical outcomes of remote ischaemic preconditioning after elective, isolated, primary, on-pump CABG surgery.

Methods

Study design and participants

This was a prospective, single-centre, double-blind, randomised, controlled trial. Eligible patients were adults with triple-vessel coronary artery disease, who were scheduled to undergo primary, isolated, elective CABG surgery under cardiopulmonary bypass at the West-German Heart Centre, Essen, Germany, between April, 2008, and October, 2012. Patients were recruited consecutively during preadmission consultations. Exclusion criteria were preoperative renal insufficiency (serum creatinine higher than 200 µmol/L), peripheral vascular disease affecting the upper limbs, acute coronary syndrome within the previous 4 weeks, inotropic or mechanical circulatory support before induction of anaesthesia, any disorder that could potentially increase preoperative cTnI concentrations (eg, percutaneous coronary intervention within the previous 6 weeks), coronary surgery without cardiopulmonary bypass, and emergency, repeat, or concomitant surgery.

Ethics approval was obtained from the institutional review board. Patients gave written informed consent, and the study conforms to the principles of the Declaration of Helsinki.

Randomisation and masking

Patients were randomised on a 1:1 basis. No stratification factors were used and no block randomisation was applied. Codes were computer generated and kept in sealed envelopes at a central location. For each patient randomised the next available code was used. On the day of surgery, patients were assigned to undergo either remote ischaemic preconditioning or no ischaemic preconditioning (control). A junior staff anaesthetist not involved in the study or analysis opened the envelope in the preparation room where anaesthesia was induced. Patients, cardiac surgeons, and intensive-care physicians were unaware of treatment assignment.

Procedures

Anaesthesia was induced with intravenous sufentanil (1 μg/kg), etomidate (0·2 mg/kg), and rocuronium (0·6 mg/kg) and maintained with end-tidal isoflurane (0·6–1·0%) or propofol 0·07–0·15 mg kg^{-1} min^{-1}. After use in some patients, however, we became aware of apparent interference of propofol with remote ischaemic preconditioning and discontinued its use for the remainder of the study.[14,16]

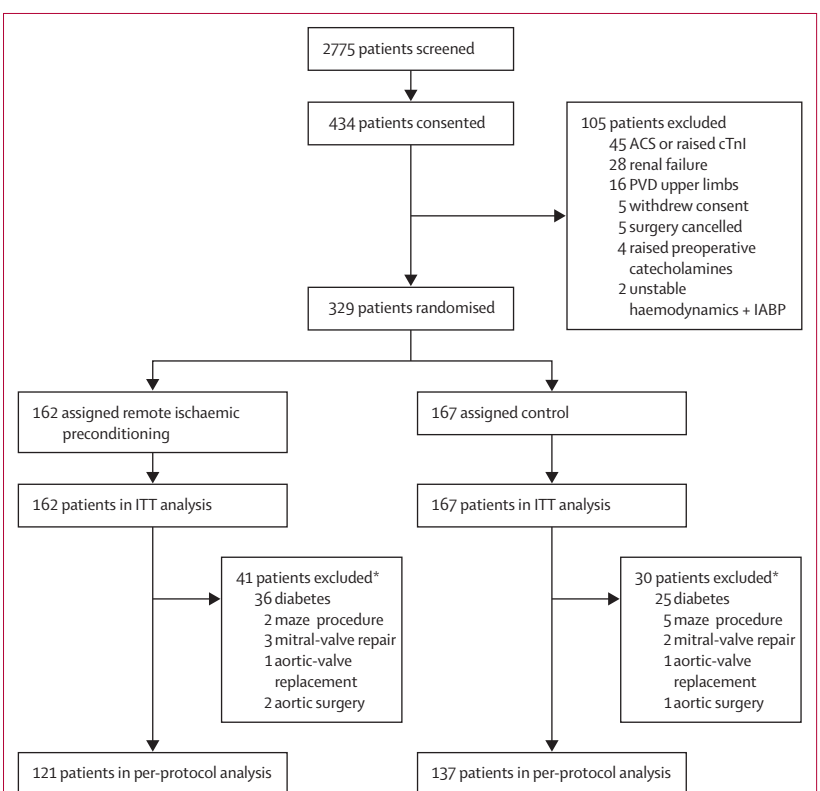

Figure 1: **Trial profile**
ACS=acute coronary syndrome. cTnI=cardiac troponin I. PVD=peripheral-vessel disease. IABP=intra-aortic balloon pump. ITT=intention to treat. *Numbers of excluded patients add up to more than the total because several patients were excluded for more than one reason.

Remote ischaemic preconditioning took place after induction of anaesthesia and before skin incision. Three cycles of 5 min ischaemia, achieved by inflation of a blood-pressure cuff to 200 mm Hg, followed by 5 min reperfusion while the cuff was deflated were applied to the upper left arm. In controls, the cuff was placed around the arm but not inflated.

Surgical revascularisation was achieved through median sternotomy. Internal thoracic arteries and saphenous veins were used as grafts. Heparin was administered to achieve an activated clotting time longer than 400 s. Standard non-pulsatile cardiopulmonary bypass with a membrane oxygenator was used with ascending-aorta and two-stage venous cannulation. During cardiopulmonary bypass, moderate haemodilution with a haematocrit of around 25% and mild systemic hypothermia (32°C) were maintained. A commercially available solution (Dr F Köhler Chemie, Bensheim, Germany) was used to achieve antegrade cold cardioplegia with additional topical cooling and single aortic cross clamping for all distal anastomoses. Proximal anastomoses were constructed with partial side clamping of the ascending aorta. Bypass graft flow was assessed with an ultrasonic transit-time-flow measurement probe (Medistim, Oslo, Norway). After reperfusion and weaning from cardiopulmonary bypass, protamine was administered for heparin reversal. For inotropic support, intravenous epinephrine, norepinephrine, or both, were infused as required. All patients received 500 mg aspirin within 6 h of surgery, followed by 100 mg daily.

Blood sampling and analysis

Venous blood samples were drawn before surgery and at 1, 6, 12, 24, 48, and 72 h after surgery for measurement of cTnI concentrations in serum. We used a specific two-side immunoassay (Dimension Flex, Dade Behring, Marburg, Germany) with a detection range of 0·04–40·00 ng/mL. The reference range was 0–0·05 ng/mL. A cTnI concentration higher than 0·1 ng/mL was deemed abnormal. Creatinine concentrations in serum were measured with a photometrically analysed creatinase assay (Siemens, Erlangen, Germany). We estimated glomerular filtration rate with the modification of diet in renal disease formula. Creatinine and glomerular filtration rate were determined frequently within the first 3 days of surgery, as per normal hospital procedure, and baseline, maximum (for creatinine), minimum (for glomerular filtration rate), and 72 h values were analysed.

Statistical analysis

The primary endpoint was perioperative myocardial injury, as reflected by the geometric mean (95% CI) of the area under the curve (AUC) for cTnI concentration in serum, calculated according to the trapezoidal rule. Missing values were replaced by linear interpolation and

extrapolation. The following secondary endpoints were assessed at 30 days, 1 year, and at completion of follow-up, separately and cumulatively: death from any cause, major adverse cardiac and cerebrovascular events (including postoperative myocardial infarction and cerebrovascular accident or stroke), and the need for repeat revascularisation. Data were obtained from medical records and reviewed by two consultant cardiologists who did not participate in the study. Cardiac and non-cardiac causes of death were assigned by the reviewing cardiologists. Perioperative myocardial infarction (type 5) was defined as cTnI concentration in serum more than five times the 99th percentile of the reference range when associated with new pathological Q-waves, left-bundle-branch block, or angiographically confirmed new or native coronary occlusion. Postoperative myocardial infarction was defined as an increase in cTnI concentration from baseline to at least twice the upper limit of normal, together with evidence of myocardial ischaemia, such as angina symptoms or electrocardiographic changes, including persistent ST-segment or T-wave changes or new Q waves. Cerebrovascular accidents or stroke during or after the index hospital admission were assessed if at least one of the following criteria was fulfilled: any embolic event after the immediate perioperative period (when anaesthesia-induced unconsciousness was completely reversed), a neurological event resulting in new, temporary, or permanent focal or global neurological deficit, or a stroke or permanent neurological event lasting longer than 24 h, or less than 24 h if a cerebral lesion was seen on imaging. Repeat revascularisation was defined as any percutaneous coronary intervention or repeat CABG surgery after the primary CABG surgery.

For the primary endpoint we hypothesised a reduction by 40% of its SD (standardised difference 0·4) with remote ischaemic preconditioning. To achieve 95% power and a two-sided α of 5%, we calculated that 164 patients would be required per treatment group. Data of all randomised patients were included in the efficacy analyses, according to the intention-to-treat principle. Although the original study protocol excluded patients with diabetes and those undergoing combined surgical procedures, we extended the study programme in 2012, with the approval of the institutional review board, to include such patients to see whether they might also benefit from remote ischaemic preconditioning. We did a separate per-protocol analysis that excluded these patients and others with protocol violations.

Descriptive statistics are summarised for categorical variables as frequency (%) and were compared between groups with Fisher's exact test. Continuous variables, expressed as mean (SD), were compared between groups with the unpaired Student's *t* test. The cTnI AUC, creatinine, and glomerular-filtration-rate data were log-transformed and analysed with one-way ANOVA. The ratios (95% CI) of ischaemic preconditioning to control were obtained by back-transformation of the ANOVA results. For time-to-event variables the survival functions were estimated with the Kaplan-Meier method and compared by Cox's proportional hazard regression, which was also used to obtain hazard ratios (HRs); the proportional hazards assumption was verified with log-log survival plots. Additionally, Kaplan-Meier survival functions were compared with log-rank tests. A subgroup analysis was done for patients who received propofol anaesthesia. All statistical analyses were done with SAS (version 9.2). The trial is registered at ClinicalTrials.gov, number NCT01406678.

	RIPC (n=162)	Control (n=167)
Demographics		
Age (years)	68·2 (10·3)	69·1 (9·2)
Sex (male/female)	134 (83%)/28 (17%)	135 (80%)/32 (20%)
Bodyweight (kg)	85·3 (15·8)	83·4 (16·5)
Risk factors and comorbidities		
Diabetes mellitus	36 (22%)	25 (15%)
Hypertension	114 (70%)	130 (78%)
Hyperlipidaemia	62 (38%)	79 (47%)
Peripheral vessel disease	19 (12%)	21 (13%)
COPD	14 (9%)	25 (15%)
Renal disease (creatinine >200 μmol/L)	22 (14%)	16 (10%)
Cardiac status		
Angina CCS III–IV	34 (21%)	46 (28%)
Previous myocardial infarction	24 (15%)	24 (14%)
Left-ventricular ejection fraction (%)	51·4 (10·1)	51·1 (9·8)
Medication		
Aspirin	139 (86%)	144 (86%)
Clopidogrel	52 (32%)	47 (28%)
β blockers	107 (66%)	120 (72%)
Statins	121 (75%)	136 (81%)
ACE inhibitors or ARBs	77 (48%)	75 (45%)
Risk scores		
Additive EuroSCORE	4·7 (1·9)	4·9 (2·0)
Logistic EuroSCORE (%)	4·1 (2·8)	4·6 (4·0)
EuroSCORE II (%)	1·2 (0·5)	1·2 (0·5)

Data are mean (SD) or number (%). RIPC=remote ischaemic preconditioning. COPD=chronic obstructive pulmonary disease. CCS=Canadian Cardiovascular Society score. ACE=angiotensin-converting enzyme. ARBs=angiotensin-II-receptor blockers. EuroSCORE=European system for cardiac operative risk evaluation.

***Table 1*: Baseline characteristics**

Role of funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 2775 patients screened for the trial, 329 patients were randomised to remote ischaemic preconditioning (n=162) or to the control group (n=167) and included in

the intention-to-treat analysis (figure 1). The baseline and intraoperative characteristics did not differ between groups (tables 1 and 2). 258 patients were included in the per-protocol analysis (figure 1).

	RIPC (n=162)	Control (n=167)	HR (95% CI)	p value
Intraoperative characteristics				
Time from end of RIPC or sham to skin incision (min)	7 (6)	8 (6)	..	0·631
Time from end of RIPC or sham to reperfusion (min)	128 (30)	124 (23)	..	0·754
Aortic cross-clamp duration (min)	67 (19)	67 (19)	..	0·876
Cardioplegia (mL)	1585 (263)	1545 (279)	..	0·227
Reperfusion time (min)	33 (15)	34 (17)	..	0·863
Number of bypass grafts	2·7 (1·0)	2·6 (1·3)	..	0·172
Number of distal anastomoses	3·2 (1·0)	3·3 (1·0)	..	0·250
Transit time graft flow (mL/min)	69 (34)	74 (35)	..	0·766
Postoperative characteristics				
Time on mechanical ventilation (h)	7 (15)	9 (17)	..	0·582
ICU/IMC stay (days)	3·5 (2·7)	3·9 (3·9)	..	0·446
Hospital stay (days)	10·7 (2·6)	10·3 (2·4)	..	0·577
cTnI concentration				
>15 ng/mL	32 (20%)	40 (24%)	..	0·424
>20 ng/mL	21 (13%)	35 (21%)	..	0·057
>30 ng/mL	6 (4%)	32 (19%)	..	<0·0001
Perioperative myocardial infarction (type 5)	2 (1%)	11 (7%)	..	0·020
Clinical outcomes				
All-cause mortality				
30 days	3 (1·9%)	6 (3·6%)	0·51 (0·13–2·02)	0·335
1 year	3 (1·9%)	11 (6·9%)	0·27 (0·08–0·98)	0·046
End of follow-up	3 (1·9%)	11 (6·9%)	0·27 (0·08–0·98)	0·046
Cardiac death				
30 days	1 (0·6%)	5 (3·0%)	0·20 (0·02–1·73)	0·145
1 year	1 (0·6%)	7 (4·5%)	0·14 (0·02–1·16)	0·069
End of follow-up	1 (0·6%)	7 (4·5%)	0·14 (0·02–1·16)	0·069
MACCE				
30 days	3 (1·9%)	14 (8·4%)	0·21 (0·06–0·75)	0·016
1 year	4 (2·6%)	19 (12·0%)	0·21 (0·07–0·61)	0·040
End of follow-up	8 (13·9%)	23 (18·9%)	0·32 (0·14–0·71)	0·005
Stroke	0	2 (1·2%)	NA	0·995
Myocardial infarction	8 (13·9%)	21 (17·8%)	0·35 (0·15–0·78)	0·011
Repeat revascularisation				
30 days	3 (1·9%)	5 (3·0%)	0·61 (0·15–2·55)	0·496
1 year	3 (1·9%)	7 (4·4%)	0·43 (0·11–1·66)	0·220
End of follow-up	7 (4·3%)	9 (17·1%)	0·70 (0·26–1·88)	0·477
PCI	6 (8·3%)	9 (17·1%)	0·59 (0·21–1·68)	0·325
CABG	1 (0·6%)	0	NA	0·998
Combined secondary outcomes at end of follow-up*	15 (22·1%)	35 (34·4%)	0·38 (0·21–0·70)	0·002

Data are mean (SD) or number (%) unless stated otherwise. RIPC=remote ischaemic preconditioning. HR=hazard ratio. ICU=intensive-care unit. IMC=intermediate-care unit. cTnI=cardiac troponin I. MACCE=major adverse cardiac and cerebrovascular event. NA=not analysed. PCI=percutaneous coronary intervention. CABG=coronary artery bypass graft surgery. *All-cause mortality, MACCE, and repeat revascularisation.

***Table 2*: Characteristics and outcomes during and after surgery**

All baseline cTnI concentrations were lower than 0·1 ng/mL and remote ischaemic preconditioning was associated with reduced cTnI concentrations in serum in the first 72 h after CABG (figure 2). The geometric mean cTnI AUC was significantly less for the remote ischaemic preconditioning group than for the control group (266 ng/mL, 95% CI 237–298 *vs* 321 ng/mL, 287–360). The estimated ratio for remote ischaemic preconditioning to control for cTnI AUC was 0·83 (95% CI 0·70–0·97; p=0·022). In the per-protocol analysis, the ratio was 0·79 (0·66–0·94; p=0·001). A subgroup analysis for the patients who received propofol anaesthesia revealed a cTnI AUC ratio of 0·95 (95% CI 0·69–1·31; p=0·753).

Preoperative creatinine concentrations in serum and glomerular filtration rates were similar in the remote ischaemic preconditioning and control groups. The ratio for creatinine was 0·95 (95% CI 0·90–1·01; p=0·094) at its maximum and 0·91 (0·85–0·97; p=0·004) at 72 h. The ratio for glomerular filtration rate was 1·06 (0·99–1·13; p=0·086) at its minimum and 1·12 (1·04–1·20; p=0·003) at 72 h.

No safety concerns were related to remote ischaemic preconditioning. Individual causes of death are shown

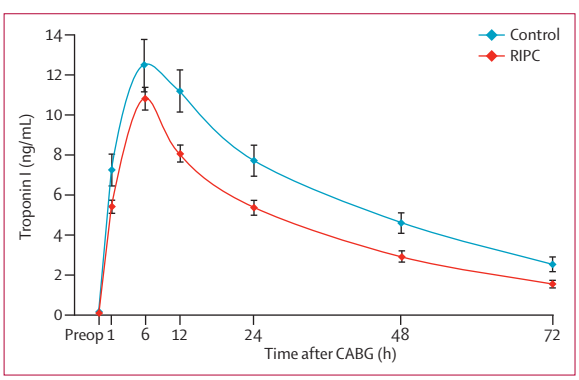

***Figure 2*: Mean (SEM) perioperative concentrations of cardiac troponin I in serum**
RIPC=remote ischaemic preconditioning. Preop=before surgery. CABG=coronary artery bypass graft surgery.

	RIPC (time after surgery)	Control (time after surgery)
Ischaemic colitis with perforation	1 (day 5)	0
PMI associated with acute graft failure	1 (day 15)	0
Sepsis	1 (day 20)	2 (days 20 and 274)
PMI associated with LCOS	0	3 (days 0, 2, and 9)
Sudden cardiac death	0	2 (days 7 and 9)
Aortic free-wall rupture	0	1 (day 7)
Stroke	0	1 (day 32)
Unknown	0	2 (days 33 and 36)

RIPC=remote ischaemic preconditioning. PMI=perioperative myocardial infarction. LCOS=low-cardiac-output syndrome.

***Table 3*: Causes of death**

in table 3. All-cause mortality in the intention-to-treat population was lower in the remote ischaemic conditioning group than in the control group at all time-points, as was cardiac mortality (table 2). At completion of follow-up, data for 507 patient-years had been recorded with 100% completeness. When deaths from sepsis were excluded, all-cause mortality remained lower at 1 year and at completion of follow-up, but not significantly so (two [1·2%] *vs* nine [5·5%], p=0·056). Similar patterns were seen in the per-protocol analysis (figure 3, appendix p 1). During surgery, 47 patients in the ischaemic preconditioning group and 32 controls received propofol, but the remainder received isoflurane. Among patients who received propofol to maintain anaesthesia, two deaths occurred, both in the control group.

The rates of recorded major adverse cardiac and cerebrovascular events in the intention-to-treat population were lower in the remote ischaemic preconditioning group than in the control group (table 2, figure 4). At completion of follow-up, data for 489 patient-years had been recorded. Results remained similar in the per-protocol analysis (figure 4, appendix p 1). The rate of repeat revascularisation did not differ between the remote ischaemic preconditioning and control groups in the intention-to-treat (table 2) and the per-protocol populations (figure 5, appendix p 1). At the completion of follow-up, data for 492 patient-years had been recorded. The combined endpoint of all-cause mortality, major adverse cardiac and cerebrovascular events, and repeat revascularisation was lower in the remote ischaemic preconditioning group

See Online for appendix

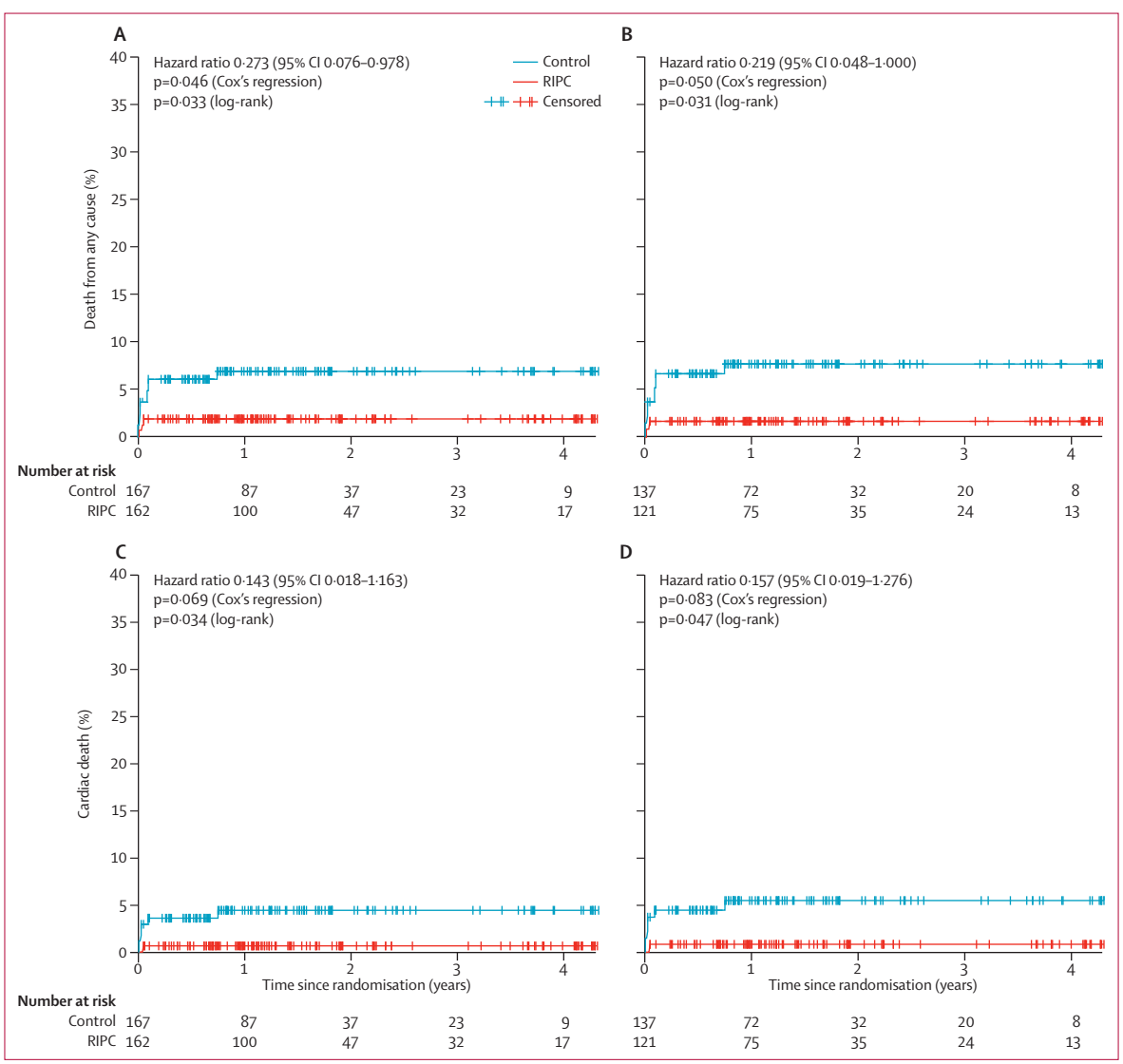

***Figure 3*: Kaplan-Meier time-to-event curves for all-cause mortality and cardiac mortality for the complete follow-up period**
(A) All-cause mortality in the intention-to-treat population. (B) All-cause mortality in the per-protocol population. (C) Cardiac mortality in the intention-to-treat population. (D) Cardiac mortality in the per-protocol population. RIPC=remote ischaemic preconditioning.

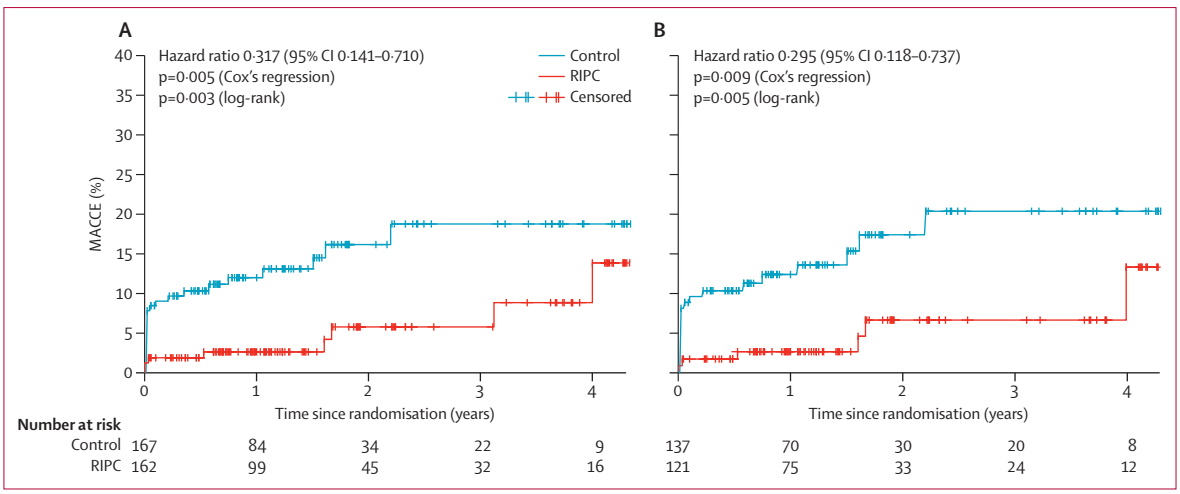

***Figure 4*: Kaplan-Meier time-to-event curves for MACCE for the complete follow-up period**
(A) Intention-to-treat population. (B) Per-protocol population. RIPC=remote ischaemic preconditioning. MACCE=major adverse cardiac and cerebrovascular events.

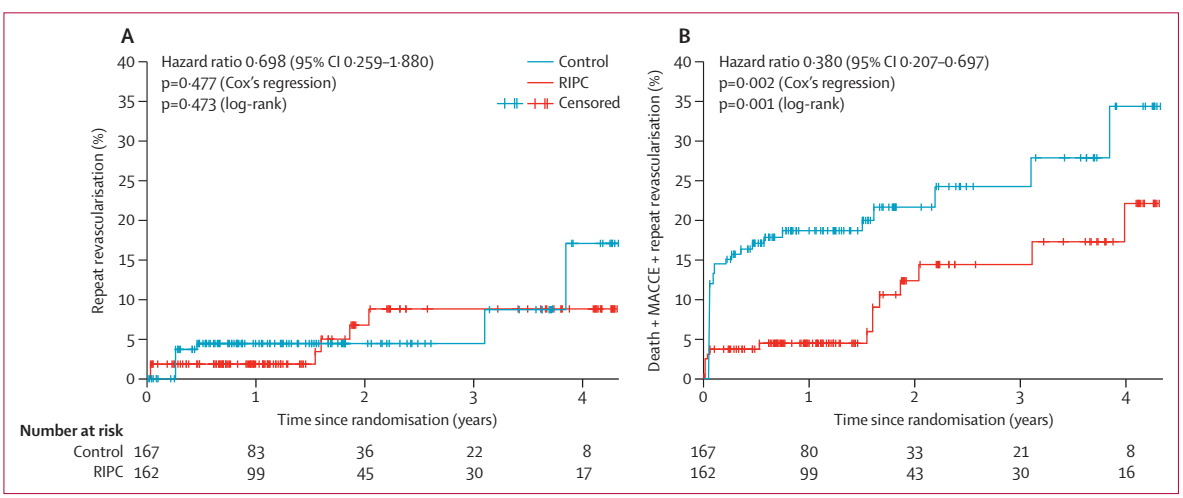

***Figure 5*: Kaplan-Meier time-to-event curves for the rate of revascularisation and the combined secondary endpoints for the complete follow-up period**
(A) Rate of revascularisation in the intention-to-treat population (B) Combined secondary endpoints in the intention-to-treat population. RIPC=remote ischaemic preconditioning. MACCE=major adverse cardiac and cerebrovascular events.

than in the control group in the intention-to-treat and per-protocol populations (table 2, figure 5, appendix p 1).

Discussion

This study confirms in a large cohort the findings of previous reports[11–15] that remote ischaemic preconditioning reduces perioperative myocardial injury during elective CABG surgery (panel, appendix pp 2–7).[3] The cardioprotective effects were measured as a 17·3% reduction in the cTnI AUC by remote ischaemic preconditioning. We further showed a persistent benefit from remote ischaemic preconditioning, with better survival and lower numbers of major adverse cardiac and cerebrovascular events than without ischaemic preconditioning.

Several landmark phase 2 studies and small randomised controlled trials provided compelling proof-of-concept evidence that remote ischaemic preconditioning lessens the risk of myocardial injury in patients with acute ST-segment-elevation myocardial infarction[17,18] and in those undergoing elective percutaneous coronary interventions[19] and various other types of vascular[4] and cardiac surgical procedures.[6–15]

In cardiac surgery, perioperative myocardial injury is closely associated with postoperative morbidity and mortality in the short and long terms.[4] In a previous study in more than 3300 consecutive CABG patients, we identified a cutoff cTnI value of 10·5 ng/mL to distinguish clinically innocent release inherent to the procedure from that indicating perioperative myocardial infarction.[20] This peak value corresponds to a cTnI AUC of about 300 ng/mL over 72 h.[13] Remote ischaemic preconditioning could represent a promising and simple strategy to provide additional protection to the myocardium and improve

postoperative outcomes. Such improvements would be particularly welcome owing to the increasingly challenging risk profiles of patients who are referred for cardiac surgery.

The patients in this trial were at low risk of poor postoperative outcomes. In our original protocol patients with diabetes were excluded because of potential interference with cardioprotective signalling.[21] Patients scheduled to undergo combined surgery were also excluded because ischaemic conditioning strategies are meant to protect the myocardium from ischaemia and reperfusion rather than from surgical trauma. We extended the inclusion criteria, however, because we wanted to see whether remote ischaemic preconditioning also provides benefit to patients at increased risk. Therefore, we included 61 patients with diabetes. Future studies should be done to confirm whether remote ischaemic preconditioning is protective in high-risk populations, although in two consensus conferences, increased protection with conditioning strategies in patients at raised risk was suggested.[22,23]

In some trials remote ischaemic preconditioning has not led to significant differences from controls or shown increased benefits.[24–27] These inconsistent findings are probably related to differences in study protocols, confounding comorbidities, anaesthetic regimens, and in surgical procedures, techniques, and protection regimens. We previously reported a lack of significant protection with remote ischaemic preconditioning in patients receiving propofol during anaesthesia,[14,16] and this finding was supported by this study in a larger cohort of patients.

In this study remote ischaemic preconditioning provided prognostic benefits beyond cardioprotection in patients undergoing elective on-pump CABG surgery. Improvements in all-cause mortality were sustained at completion of follow-up, more than 4 years after surgery. This finding is in accordance with data from preliminary randomised, controlled trials of patients with ST-segment-elevation myocardial infarction or undergoing elective percutaneous coronary interventions.[28,29] When looking at secondary endpoints individually, remote ischaemic preconditioning protected patients from injury to myocardium, brain, kidney, as shown previously,[30] but not from the underlying atherosclerotic process, because the rate of repeat revascularisation was not affected compared with control.

The study had some limitations. Although large, it was a single-centre trial and it was only powered adequately to analyse prospectively one surrogate cardiac biomarker, cTnI. The secondary endpoints, for which the study was not powered but which were legitimate to assess in view of a significant primary endpoint, indicated improved prognosis in patients undergoing remote ischaemic preconditioning. All-cause mortality included death from sepsis, which is not intuitively related to cardioprotection. Remote ischaemic preconditioning elicits a systemic response that differs from a local response to preconditioning or postconditioning of ischaemic or reperfused myocardium and protects other organs from which sepsis could arise.[30] Mortality remained lower in the remote ischaemic preconditioning group than in the control group when deaths from sepsis were excluded, but no longer significantly so. Most deaths occurred early after CABG (within 30 days), but remote ischaemic preconditioning also protected from late stroke (one occurred in the control group and led to death). Speculatively, cardioprotection by remote ischaemic preconditioning might have prevented subsequent atrial fibrillation and hence stroke. Finally, cardiac mortality was lower with remote ischaemic preconditioning than without. Nevertheless, the numbers of outcomes for the secondary endpoints in our study were small and the CIs were wide. Further study with different clinical outcomes as primary endpoints, therefore, is clearly warranted.

The ERICCA trial, a large, prospective, multicentre, randomised trial, is being done to investigate clinical outcome in patients undergoing CABG surgery with or without and remote ischaemic preconditioning (NCT01247545). At this point, causal relations between cardioprotection and improved clinical outcome must remain speculative. Nevertheless, our findings indicate that remote ischaemic preconditioning is a safe perioperative method that provides cardioprotection and improves prognosis in patients undergoing elective CABG surgery.

Panel: Research in context

Systematic review

We searched Current Contents, Medline, and PubMed for original articles published up to April 24, 2013, with the terms "cardioprotection", "human", "infarct size", "patient", "remote preconditioning". We identified 34 studies (appendix pp 2–7). The weighted average reduction in infarct size with remote ischaemic preconditioning was 19%, but no benefits in clinical outcomes have yet been reported.

Interpretation

Remote ischaemic preconditioning was associated with reduced perioperative concentrations of cardiac troponin I in serum in patients undergoing elective coronary artery bypass graft surgery for triple-vessel disease compared those in controls (difference 17·3%). All-cause mortality and major adverse cardiac and cerebrovascular events were also less frequent in the remote ischaemic preconditioning group, although the rate of coronary revascularisation did not differ. The improvements in clinical outcomes must be confirmed in prospective studies.

Contributors

MT and GH were the principal investigators and designed the trial. MT, EK, and PK coordinated the trial. MT, EK, DW, SP, KT, JP, and HJ administered the treatment protocol. MT, EK, PK, NG, and MN, analysed the data and MT, EK, and GH interpreted the data. EK and JP were the senior anaesthetists and MT, DW, SP, KT, and HJ were the study cardiothoracic surgeons. The manuscript was written by MT, MN, and GH. All authors saw and approved the final version of the manuscript.

Conflicts of interest

We declare that we have no conflicts of interest.

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