Remote Ischemic Preconditioning Improves Outcome at 6 Years After Elective Percutaneous Coronary Intervention  

The CRISP Stent Trial Long-term Follow-up

William R. Davies, PhD, MRCP; Adam J. Brown, MRCP; William Watson, MRCP; Liam M. McCormick, MRCP; Nick E.J. West, MD, FRCP; David P. Dutka, MD, FRCP; Stephen P. Hoole, MA, DM, MRCP

Background—Postprocedural myocardial infarction (type 4a) has been shown to be an adverse prognostic indicator after elective percutaneous coronary intervention (PCI). The Cardiac Remote Ischemic Preconditioning in Coronary Stenting (CRISP Stent) study demonstrated that remote ischemic preconditioning reduced procedural symptoms, ECG ST-segment deviation, and cardiac troponin I release after elective PCI and reduced the major adverse cardiac and cerebral event (MACCE) rate at 6 months. We were interested to confirm if this early benefit in MACCE rate in the remote ischemic preconditioning group was sustained long-term.

Methods and Results—Patients were telephoned by researchers blinded to the randomization details. MACCE, defined as all-cause mortality, nonfatal myocardial infarction, transient ischemic attack or stroke, and heart failure requiring hospital admission, were adjudicated by case note and national database review. One hundred ninety-two (89.3%) of the 225 patients with elective PCI randomized in the original study were available for long-term follow-up (mean time to event or last follow-up: 1579.7±603.6 days). There were a total of 59 (30.7%) MACCEs. Patients with an MACCE had a higher mean cardiac troponin I after PCI (±SD): 2.07±6.99 versus 0.91±2.07 ng/mL (P=0.05). The MACCE rate at 6 years remained lower in the remote ischemic preconditioning group (hazard ratio, 0.58; 95% confidence interval, 0.35–0.97; P=0.039; absolute risk reduction=0.13 and number needed to treat=8 to prevent the MACCE at 6 years).

Conclusions—Remote ischemic preconditioning reduces the incidence of postprocedural cardiac troponin I after elective PCI and confers an MACCE-free survival benefit at both short- and long-term follow-up.


Key Words: cardioprotection ■ ischemia reperfusion injury ■ outcome ■ percutaneous coronary intervention
WHAT IS KNOWN

- Remote ischemic preconditioning (RIPC) has emerged as a therapy to limit ischemia reperfusion injury in other tissues.
- In the Cardiac Remote Ischemic Preconditioning in Coronary Stenting (CRISP Stent) study, we observed that RIPC increased the tolerance of the myocardium to ischemia during elective percutaneous coronary intervention (PCI) and significantly attenuated cardiac troponin release measured 24 hours after stent implantation.
- Whether this early benefit translated into a long-term clinical benefit in patients undergoing PCI was unknown.

WHAT THE STUDY ADDS

- The present study has confirmed that the initial early benefit observed after RIPC translates to a reduction in long-term clinical events in patients undergoing elective PCI.
- Delays between the conditioning stimulus and subsequent PCI should be minimized to maximize the full beneficial effect of RIPC in this clinical setting.
- Patients should be considered for RIPC immediately before elective PCI in an attempt to reduce postprocedural troponin release and to abrogate adverse clinical events.

a signal of reduced major adverse cardiac and cerebral events (MACCEs) in the RIPC group compared with the control group at 6 months. We were interested to assess if the early benefits seen in the RIPC group would be sustained long-term, particularly because procedure-related cTn release has been shown to be detrimental to prognosis, and this was also attenuated by RIPC.

Methods

Full methodological details have previously been published.\textsuperscript{14} In brief, patients undergoing elective PCI between July 2006 and November 2007 at a single specialist cardiothoracic center were identified and invited to participate in the study. There were 7 inclusion/exclusion criteria: (1) age at enrollment could not be <18 years, (2) the patient had to be able to give informed consent, (3) elective PCI was performed, (4) preprocedural cTnI was below the lower limit of the laboratory reference range, (5) women could not be of childbearing age, (6) the subject could not be taking either nicorandil (preconditioning mimetic) or glibenclamide (preconditioning blocking), and (7) the subject had a life expectancy of >6 months, as subjectively assessed by their clinician. Consenting patients were randomized electronically by an independent Research and Development Unit.

Procedural Interventions

All participants were advised to avoid strenuous activity that might provoke their usual angina on the day of elective admission. One hour before the procedure, the patients randomized to RIPC had a blood pressure cuff placed around their nondominant upper arm. This was inflated to 200 mmHg pressure for 5 minutes and released to allow reperfusion for further 5 minutes. A total of 3 cycles was performed. Control patients had a cuff placed around their upper arm in a similar fashion, but the cuff was not inflated.

Patients then underwent elective PCI by an interventional cardiologist blinded to the randomization. Patients received either a drug-eluting stent or a bare metal stent and a dual antiplatelet therapy in accordance with local practice and national recommendations.

Venous blood was drawn 24 hours after the procedure and assayed for cTnI (Bayer ADVIA IMS Troponin I Ultra method; Bayer, Berlin, Germany) and creatinine. The cTnI assay precision and sensitivity complied with European Society of Cardiology and American College of Cardiology recommendations. The 99th percentile of the cTnI level in a reference population (upper reference limit) of healthy volunteers was below the lower limit of detection of 0.04 ng/mL. A cTnI>0.2 ng/mL was therefore considered to fulfill the 2012 definition of MI4a.\textsuperscript{7} The assay variation coefficient was <10% for the new MI4a cutoff value.

The long-term follow-up involved initial consultation of the UK National Registry for deaths and then a telephone survey of the surviving subjects who had undergone elective PCI. MACCE was defined as all-cause mortality, stroke or transient ischemic attack, nonfatal MI, acute coronary syndrome (including unstable angina), and left ventricular failure requiring hospital admission. A secondary analysis was performed, which included only cardiovascular deaths in the MACCE definition. Self-reported events were subsequently adjudicated by independent case note review by 2 senior clinicians. When participants had >1 MACCE, the earlier event was recorded. Agreement between the adjudicator’s events was unanimous. Telephone follow-up and final adjudication were performed blinded to the original randomization.

Specific Objectives

The primary objective of the current study was to compare the MACCE rate between RIPC and control groups, 6 years after enrollment. Secondary end point analysis was performed to assess any causal relationship between MACCE and postprocedural cTnI elevation, to determine whether RIPC reduced the new definition of MI4a, and to perform a subgroup analysis of MACCE rate in patients with diabetes mellitus.

The local research ethics committee approved the original and amended study protocol (local research ethics committee references 06/Q0106/20 and 12/SW/0152), and the study conformed to the principles outlined in the Declaration of Helsinki. The study was registered on the UK Clinical Research Network (UKCRN) database (UKCRN 4074).

Statistical Methods and Analysis

The CRISP Stent study was originally powered for a 15% reduction in cTnI post-PCI in the RIPC group, requiring a total sample size of 200, as previously described.\textsuperscript{14} In addition, continuous variables are summarized as mean (SD) or median (quartiles) and compared using Student t test or a Mann–Whitney–Wilcoxon test when appropriate. Categorical data are expressed as numbers (%) using the total number of patients available at follow-up as the denominator and compared using Fisher exact test. Hazard ratios (HRs) were analyzed by log-rank intention to treat and are presented with 95% confidence intervals (CIs). A value of P<0.05 was considered significant. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the article as written.

Results

Two hundred forty-two patients were originally randomized in the CRISP Stent study, of whom 215 had an elective PCI (Figure 1). Six patients in the RIPC group did not receive conditioning before PCI because of alterations in the catheter laboratory schedule. Six-year follow-up was completed in 192 (89.3%) of these patients. The mean time to event or last follow-up was 1579.7±603.6 days. Twenty-three patients were lost to follow-up with a similar incidence in both groups:
RIPC 13.6% versus control 7.6% (P=0.19). Importantly, the lost to follow-up group shared key characteristics with the main cohort: 3 patients had diabetes mellitus (15.0% versus 31.5%; P=0.30) and the post-PCI cTnI levels were not significantly different (1.46±4.34 versus 1.26±3.80; P=0.82).

Both RIPC and control groups were well matched (Table 1). In particular, groups that have previously been reported to be resistant to conditioning (the elderly, patients with diabetes mellitus, and those with prior MI) were equally represented in both groups. Conditioning from other sources, such as angina, balloon inflation, and drugs again, were not different between groups. Finally, the distribution of surrogates for the area of myocardium at risk: percentage left anterior descending artery lesions, proximity of stent implantation by Duke Jeopardy Score, and degree of collateralization to the stented vessel by Rentrop Score, were the same for RIPC and control groups.

Median 24-hour cTnI after PCI had been significantly lower in the RIPC group (0.06 [0.02–0.56] versus 0.16 [0.04–1.04] ng/mL; P=0.04). There were also numerically fewer MI4a (2012 definition) in the RIPC group compared with controls: 40 (38%) versus 47 (48%); P=0.11. A total of 59 (30.7%) MACCE were recorded at long-term follow-up. The mean 24-hour cTnI after PCI was higher in those with MACCE at 6 years (MACCE, 2.07±6.99 versus no MACCE, 0.91±2.07 ng/mL; P=0.05).

At 6 months, the MACCE rate had been significantly lower in the RIPC group with 4 events versus 13 in the control group (HR, 0.28; 95% CI, 0.12–0.82; P=0.018). This was predominantly because of fewer admissions with acute coronary syndrome/nonfatal MI in the RIPC group. The MACCE rate continued to be lower in the RIPC group throughout the entire study (30-month interval: 11 versus 21 events [HR, 0.48; 95% CI, 0.24–0.97; P=0.041] and 60-month interval: 21 versus 32 events [HR, 0.58; 95% CI, 0.33–0.99; P=0.049]). The final 6-year follow-up analysis confirmed that the RIPC group had 23 events compared with 36 in the control group (HR, 0.58; 95% CI, 0.35–0.97; P=0.039; absolute risk reduction=0.13 and number needed to treat=8 to prevent the MACCE at 6 years; Figure 2A). There was 1 cardiovascular death in the RIPC group, whereas 5 control subjects died of cardiovascular disease that could have been attributable to MI4a (Table 2). When the MACCE definition included only those with cardiovascular death, rather than all-cause death, the RIPC group fared even better than controls at 6 years (HR, 0.54; 95% CI, 0.31–0.94; P=0.029; Figure 2B). The composition of MACCE at 6 years is shown in Figure 3 and confirms that numerically fewer RIPC events occurred in all the chosen composites, but none were significant.

The mean time between last blood pressure cuff deflation and stent balloon inflation (cuff-to-balloon time) was 66±30 minutes. Cuff-to-balloon time was significantly higher in those who had an MACCE (MACCE: 76.6±34.0 minutes versus MACCE-free: 58.9±23.5 minutes; P=0.024). The MACCE rate was similar between patients with diabetes mellitus (13 [28.2%]) and without diabetes mellitus (46 [31.5%]; P=0.718 although), whereas patients without diabetes mellitus had fewer events after RIPC (17 versus 29 events; HR, 0.55; 95% CI, 0.31–0.99; P=0.045), the patients with diabetes mellitus did not derive any detectable benefit from RIPC (6 versus 7 events; HR, 0.71; 95% CI, 0.24–2.12; P=0.54; Figure 4). In those with diabetes mellitus experiencing events randomized to RIPC, the procedural blood glucose (120.6±9.0 versus 149.4±45.0 mg/dL; P=0.14) and hemoglobin A1c (7.9±1.7 versus 7.9±1.1%; P=0.99) were similar to those who did not experience events.

Discussion

The CRISP Stent study showed that remote ischemic preconditioning before elective PCI resulted in lower PCI-related cTnI release and MACCE at 6 months. This study has confirmed that the initial MACCE reduction observed after RIPC is sustained for 6 years.

RIPC, first demonstrated to provide cardioprotection by Przyklenk et al13 20 years ago, has subsequently been shown to reduce the incidence of procedure-related cTnI release in pediatric cardiac surgery,14 adult bypass surgery,10,11 and abdominal aortic aneurysm repair,12 as well as in the setting of primary PCI.13 Elective PCI produces a predictable ischemia reperfusion injury...
in 30% of patients, and therefore, we anticipated that this would be ideally suited to RIPC cardioprotection, during the early window of protection between 1 and 2 hours after 3 cycles of 5-minute blood pressure cuff inflations. This has previously been confirmed to be sufficient stimulus to confer protection in adult humans.16 We initially showed that RIPC reduced intraprocedural chest discomfort and ECG changes during coronary balloon occlusion and significantly attenuated cTnI release measured 24 hours after stent implantation. MACCE was lower in the RIPC group compared with that in the control group at 6 months.

We now confirm that this early reduction in MACCE is maintained long-term. The MACCE-free survival curves separated early and remained separated for 6 years. It is plausible that the benefit from RIPC occurred at the time of PCI because even the second window of protection from RIPC wanes after 3 to 4 days. The reduction in cTnI we also observed in the RIPC group, compared with that in controls, seems a plausible mediator of the improvements long-term MACCE. Procedure-related troponin release, particularly if >5× the upper reference limit, has been shown to be related to worse prognosis after elective PCI.2–4

We have previously demonstrated that there was a weak correlation between cuff-to-balloon time and post-PCI cTnI level at 24 hours in the RIPC group (\(r=0.28; P=0.006\)). A similar pattern was observed with subsequent MACCE; those with an MACCE had longer delays between the completion of RIPC and their PCI. It is recognized that the early protection from RIPC wanes within an hour or 2 of the initial stimulus.17 Our troponin and MACCE data confirm this and emphasize the importance of expeditious PCI after completion of RIPC.

Table 1. Demographic Data for Control and Patients With RIPC Included in the Long-Term Follow-Up Analysis

<table>
<thead>
<tr>
<th></th>
<th>RIPC (n=95)</th>
<th>Control (n=97)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean±SD)</td>
<td>63.9±10.0</td>
<td>62.6±10.5</td>
<td>0.39</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>77 (81.6)</td>
<td>68 (70.1)</td>
<td>0.09</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>24 (25.3)</td>
<td>22 (22.7)</td>
<td>0.74</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>49 (51.6)</td>
<td>47 (48.5)</td>
<td>1.00</td>
</tr>
<tr>
<td>Active or ex-smoker, n (%)</td>
<td>62 (65.2)</td>
<td>63 (64.9)</td>
<td>1.00</td>
</tr>
<tr>
<td>Previous MI, n (%)</td>
<td>52 (54.7)</td>
<td>47 (48.5)</td>
<td>0.39</td>
</tr>
<tr>
<td>Angina CCS ≥II, n (%)</td>
<td>19 (20.0)</td>
<td>21 (21.6)</td>
<td>0.86</td>
</tr>
<tr>
<td>Statin use, n (%)</td>
<td>83 (87.4)</td>
<td>87 (89.7)</td>
<td>0.66</td>
</tr>
<tr>
<td>eGFR, mL/min, median (IQR)</td>
<td>72.0</td>
<td>75.5</td>
<td>0.15</td>
</tr>
</tbody>
</table>

| Stent length, mm (mean±SD) | 32.8±15.4  | 34.3±18.1      | 0.54    |
| Drug-eluting stent, n (%)  | 66 (69.5)  | 61 (62.9)      | 0.36    |
| Coronary balloon occlusion time, s (mean±SD) | 110.3±48.9 | 112.0±59.7 | 0.84    |

| Coronary balloon inflations, n (mean±SD) | 2.9±1.1 | 2.8±1.2 | 0.75    |
| PCI complication, n (%) | 13 (13.7) | 13 (13.4) | 1.00    |
| Jailed side branch >2 mm, n (%) | 35 (36.8) | 32 (33.0) | 0.65    |
| Type C lesion, n (%) | 35 (36.8) | 27 (27.8) | 0.22    |
| LAD lesion, n (%) | 43 (45.3) | 49 (50.5) | 0.47    |
| Modified Jeopardy score <6, n (%) | 84 (88.4) | 90 (92.7) | 0.24    |
| Modified Rentrop score 0–1, n (%) | 83 (87.4) | 83 (85.6) | 0.60    |
| Intraprocedural RPP, mmHg×bpm (mean±SD) | 8833±2674 | 9136±2478 | 0.43    |
| Chest pain score >1, n (%) | 49 (51.6) | 71 (73.2) | <0.01   |
| ECG ST-segment deviation >1 mm, n (%) | 31 (32.6) | 52 (53.6) | <0.01   |

RIPC indicates remote ischemic preconditioning

Table 2. Cause of Death Data (n=15)

<table>
<thead>
<tr>
<th>Group</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Control</td>
</tr>
<tr>
<td>2</td>
<td>Motor neuron disease</td>
</tr>
<tr>
<td>3</td>
<td>Ischemic heart disease</td>
</tr>
<tr>
<td>4</td>
<td>Pulmonary embolus, metastatic prostate carcinoma</td>
</tr>
<tr>
<td>5</td>
<td>Septicemia, infected total knee replacement</td>
</tr>
<tr>
<td>6</td>
<td>Acute ischemic stroke</td>
</tr>
<tr>
<td>7</td>
<td>Acute ischemic stroke</td>
</tr>
<tr>
<td>8</td>
<td>Metastatic colonic carcinoma</td>
</tr>
<tr>
<td>9</td>
<td>Metastatic carcinoma</td>
</tr>
<tr>
<td>10</td>
<td>Ischemic heart disease</td>
</tr>
<tr>
<td>11</td>
<td>Metastatic breast carcinoma</td>
</tr>
<tr>
<td>12</td>
<td>Cardiac tamponade, acute thoracic aortic dissection</td>
</tr>
<tr>
<td>13</td>
<td>Ischemic heart disease</td>
</tr>
<tr>
<td>14</td>
<td>Bronchopneumonia</td>
</tr>
<tr>
<td>15</td>
<td>Respiratory failure, emphysema</td>
</tr>
</tbody>
</table>

Figure 2. Kaplan–Meier major adverse cardiac and cerebral event (MACCE) rate curves for control and remote ischemic preconditioning (RIPC) groups including all-cause mortality (A) and cardiovascular mortality (B) within the definition of MACCE (P value: log-rank intention-to-treat analysis).

RIPC indicates remote ischemic preconditioning.
The failure of RIPC to protect patients with diabetes mellitus from long-term MACCE is interesting, particularly because none of the patients with diabetes mellitus were taking glibenclamide, an ATP-dependent potassium channel blocker, which has been shown to attenuate the effect of conditioning during coronary angioplasty. Diabetic resistance to conditioning has been previously described and may be attributable to hyperglycemia, exacerbating the ischemia reperfusion injury. However, we did not demonstrate a link between glycemic control and MACCE rate in RIPC-treated patients with diabetes mellitus. Others have reported that the conditioning threshold required to protect diabetic myocardium is higher because of alterations in diabetic mitochondrial ATP-sensitive potassium channels. Cardioprotection can be restored with further cycles of the ischemic conditioning stimulus, although our study was not designed to confirm this.

Clinical Implications
Patients undergoing elective PCI should be considered for RIPC before the procedure, in an attempt to reduce postprocedural troponin release and thus abrogate MACCE at both short- and long-term follow-up. Delays between the conditioning stimulus and subsequent PCI should be minimized to maximize the full beneficial effect of RIPC in this clinical setting.

Study Limitations
Despite every effort, ≈10% of the original cohort of patients was lost to follow-up and, therefore, unavailable for inclusion in our analysis. However, key characteristics of these patients were not significantly different to the main cohort. MACCE was self-reported, and therefore, this may have resulted in underreporting of events, particularly if they were not recent. The study was not powered to assess the effect of RIPC on clinical end points, particularly in any subgroups, and therefore definitive conclusions regarding the efficacy of RIPC on MACCE is not possible. However, our observations provide useful guidance and highlight that the study of this therapy is merited. The CRISP Stent study had broad inclusion criteria to enable enrollment of patients that reflected a real-world PCI practice. As a result, patients resistant to conditioning and those who had their PCI outside the window of protection of RIPC because of unforeseen delays were included in the study. In addition, patients in both RIPC and control groups may have inevitably been exposed to exogenous conditioners. We used a RIPC protocol previously shown to offer protection, but accept that in patients with diabetes mellitus, this may have been below the threshold of protection. Despite these limitations, we still perceived a durable clinical benefit.
of RIPC-treated patients undergoing elective PCI. We think this was attributable to RIPC limiting PCI-induced myonecrosis, but acknowledge that protection of other organs and specifically renoprotection may have also contributed. However, our findings need to be confirmed in a large, multicenter, randomized, control trial adequately powered for clinical events.

Conclusions

RIPC reduces the incidence of myocardial necrosis post-PCI and improves event-free survival at long-term follow-up.

Acknowledgments

The authors thank all the patients and staff of Papworth Hospital National Health Service Foundation Trust who took part in this study.

Sources of Funding

This study was funded, in part, by the British Heart Foundation and National Institute for Health Research Cambridge Biomedical Research Center.

Disclosures

None.

References

Remote Ischemic Preconditioning Improves Outcome at 6 Years After Elective Percutaneous Coronary Intervention: The CRISP Stent Trial Long-term Follow-up
William R. Davies, Adam J. Brown, William Watson, Liam M. McCormick, Nick E.J. West, David P. Dutka and Stephen P. Hoole

Circ Cardiovasc Interv. 2013;6:246-251; originally published online May 21, 2013;
doi: 10.1161/CIRCINTERVENTIONS.112.000184
Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-7640. Online ISSN: 1941-7632

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circinterventions.ahajournals.org/content/6/3/246

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Interventions can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Interventions is online at:
http://circinterventions.ahajournals.org//subscriptions/