The randomised Complete versus Lesion-only PRimary percutaneous coronary Intervention Trial: Cardiovascular Magnetic Resonance imaging substudy (CvLPRIT-CMR)

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Scientific summary

CvLPRIT-CMR study

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Scientific summary

Background

Multivessel coronary artery disease is seen in approximately 30–50% of patients presenting with ST-segment elevation myocardial infarction (STEMI) who are treated with the primary percutaneous coronary intervention (PPCI). Clinical guidelines recommend percutaneous coronary intervention (PCI) to the infarct-related artery (IRA) only, largely based on registry data that have suggested increased risk of adverse events with complete revascularisation in those patients selected to receive complete revascularisation. However, two recent prospective randomised controlled trials [PReventative Angioplasty in Myocardial Infarction (PRAMI) trial and Complete versus Lesion-only PPCI Trial (CvLPRIT)], which compared a strategy of complete versus IRA-only revascularisation in the PPCI patients with multivessel disease, found a reduction in major adverse cardiovascular events with complete revascularisation. However, there is concern that PCI to non-IRAs may be associated with additional procedural-related myocardial infarction (MI) that cannot be detected by conventional enzymatic markers at the time of the PPCI.

Objectives

The primary aim of the current prespecified substudy of the CvLPRIT was to assess whether or not a complete revascularisation strategy, because it causes additional infarcts in the non-IRA territories, was associated with greater infarct size (IS) than an IRA-only strategy. Secondary objectives were to assess whether or not myocardial salvage, microvascular obstruction (MVO), myocardial ischaemia, left ventricular (LV) volumes and ejection fraction, and final IS at follow-up were different in the two treatment groups.

Design

Pragmatic, prospective, multicentre, randomised, open-label trial with blinded end-point analysis.

Methods

Study population

Patients presenting within 12 hours of symptom onset and being treated by the PPCI for STEMI at hospitals in seven centres (Leicester, Leeds, Southampton, Harefield, Royal Derby, Kettering and Bournemouth) were potentially eligible.

Participants

Patients aged $\geq$ 18 years with multivessel coronary artery disease (angiographic stenosis $>$ 70% in one view or $>$ 50% in orthogonal views) on baseline angiography were eligible for inclusion. Exclusion criteria were (1) any contraindication to the PPCI (presentation timing, inadequate arterial access, etc.); (2) age $<$ 18 years; (3) contraindication to multivessel PPCI, according to operator judgement (with documentation of reasons); (4) previous Q-wave MI; (5) cardiogenic shock; (6) ventral septal defect or moderate/severe mitral regurgitation; (7) known severe chronic renal disease (i.e. stage 4 or 5); (8) patients with previous coronary artery bypass graft; (9) suspected or confirmed thrombosis of a previously stented artery; (10) only significant non-IRA lesion is a chronic total occlusion; and (11) contraindications to cardiac magnetic resonance (CMR) imaging (e.g. pacemaker, implantable cardiac defibrillator, implanted stimulators or other devices and severe claustrophobia) were exclusions.

Consent and randomisation

Prior to coronary angiography, patients were asked to provide verbal assent for the study, after being read a short information sheet. Patients who were still eligible after coronary angiography were asked to confirm their assent. Randomisation was undertaken while the PPCI was being undertaken via a 24-hour automated voice-activated central system with concealment of treatment allocation. Randomisation was stratified by infarct location (anterior/non-anterior) and symptom onset ($\leq$ or $>$ 3 hours). When patients were clinically stable they were given the patient information leaflet to read and those agreeing to continue participation provided written informed consent.

Interventions

Patients were randomised to one of two groups in a 1 : 1 ratio: complete revascularisation (including all non-IRAs) or IRA-only treatment. The PPCI was undertaken in accordance with current guideline recommendations and operators' routine practice, and could include aspiration thrombectomy, heparin, bivalirudin or a glycoprotein IIb/IIIa inhibitor. Drug-eluting stents were recommended for both IRA and non-IRA lesions unless clinically contraindicated, to reduce risk of in-stent restenosis. It was mandated that if randomised to complete revascularisation, then the IRA be treated first. If there were no clinical contraindications complete revascularisation was recommended at the same sitting to reduce multiple vascular punctures, to avoid prolonged hospitalisation and attenuate potential patient drop-out. If the operator decided for clinical reasons that the procedure be staged, it was mandated that the non-IRA be treated during index admission.

Cardiac magnetic resonance assessments

The CMR imaging protocols were standardised at hospitals and performed acutely (days 1–4 post PPCI) on 1.5-T scanners and at 9 months' follow-up. Patients from Derby and Kettering were scanned at Leicester. The acute CMR scan was recommended on days 2 or 3 post STEMI but always after complete revascularisation had been performed, if applicable. The baseline scan incorporated functional oedema (T2-weighted images) and infarct assessment with late gadolinium enhancement (LGE) following 0.2 mmol of gadolinium diethylenetriaminepentaacetate (Magnevist, Bayer, Faversham, UK) covering the entire left ventricle. The follow-up scan was similar to the baseline scan with the omission of oedema imaging and the addition of adenosine stress and rest myocardial perfusion to assess myocardial ischaemia. CMR scans were analysed at the University of Leicester core laboratory, which was blinded to all patient details and treatment allocation.

Outcome measures

Primary

Cardiac magnetic resonance imaging measured total IS on LGE images (as a percentage of LV mass) on the acute CMR scan.

Secondary

Myocardial salvage index (acute and final), the extent of MVO, LV volumes and ejection fraction (acute and follow-up), ischaemic burden and new (post-index MI) myocardial injury (follow-up) were secondary outcome measures. Clinical major adverse cardiovascular events (MACEs) were also measured at 12 months.

One hundred patients in each arm had 81% power to detect a 4% absolute difference in IS, assuming a mean of 20% of LV mass and standard deviation (SD) of 10%, using a two-tailed test with $\alpha = 0.05$.

Results

Of the 296 patients randomised in the main CvLPRIT, 205 consented to participate in the CMR imaging substudy. Of these, two patients were excluded: one patient did not complete the early CMR imaging and in one patient the LGE images for the primary end point were not analysable. The IRA-only ($n = 105$) and complete revascularisation ($n = 98$) groups were well matched for baseline characteristics {age, 64.1 ± 10.8 vs. 63.1 ± 11.3 years; male sex, 89% vs. 79%; time from symptom onset to the PPCI, median 172 minutes [interquartile range (IQR) 127–268 minutes] vs. median 192 minutes (IQR 131–302 minutes); anterior MI, 36% vs. 35%; respectively}, with no statistically significant differences between groups.

Acute cardiac magnetic resonance

Acute CMR imaging was undertaken at a median of 3 days post PPCI in both treatment arms. There was no statistical difference in the primary end point of total IS between the IRA-only (13.5%, IQR 6.2–21.9%) and complete revascularisation groups (12.6%, IQR 7.2–22.6%) of the LV mass [95% confidence interval (CI) –4.09% to 31.17%; $p = 0.57$]. The prevalence of multiple territory infarcts in the complete revascularisation group was double that in the IRA-only group (22/98 vs. 11/105; $p = 0.02$) and the number of acute non-IRA infarcts was increased threefold in those undergoing complete revascularisation (17/98 vs. 5/105; $p = 0.004$). Acute non-IRA infarcts were generally small, with only 6 of 17 patients in the complete revascularisation group (median 2.5%, IQR 0.54–4.5%) and two out of five patients in the IRA-only group (median 2.1%, IQR 0.81–4.5%) having infarcts greater than 4% of LV mass. MVO was present in more than half of all patients, although quantitatively the amount was very low (median < 0.2% of the LV mass) and there was no significant difference between groups. In 52 patients (26%), oedema images were non-diagnostic [no artefact but no oedema discernible ($n = 33$), not performed owing to arrhythmia or suboptimal breath-holding ($n = 14$) or severe artefact ($n = 5$)]. Area at risk [mean 32.2% (SD 11.8%) vs. mean 36.0% (SD 12.9%) LV mass; $p = 0.06$] and the myocardial salvage index (median 58.5%, IQR 32.8–74.9% vs. median 60.5%, IQR 40.6–81.9%) were lower, but not significantly, in the complete revascularisation group. LV volumes, mass and ejection fraction were similar in both groups.

Follow-up cardiac magnetic resonance imaging

Follow-up CMR imaging was completed in 84 patients in the complete revascularisation group and 80 patients in the IRA-only group. Thirty-nine patients did not undergo repeat CMR: 29 patients declined, three had died, two cited claustrophobia, one had an implantable cardioverter defibrillator and one had a severe non-cardiovascular illness; logistical reason accounted for failure to repeat CMR in three patients. Three patients were unable to undertake adenosine stress perfusion because of obstructive airways disease (one in the complete revascularisation group and two in the IRA-only group) and perfusion imaging was not analysable in two patients owing to severe persisting dark-rim artefacts (one in each group). LV volumes and function were similar between groups [ejection fraction: mean 50.8% (SD 8.7%) vs. mean 49.7% (SD 9.4%); $p = 0.42$]. The prevalence of infarct and multiple infarcts was greater in the complete revascularisation group than in the IRA-only group (9/80 vs. 20/84, respectively; $p = 0.035$). However, there was no significant difference in total IS between the complete revascularisation group and the IRA-only group [median 7.3% of LV mass (IQR 3.0–14.4%) vs. median 7.6% (IQR 3.2–15.1%), respectively] or in final myocardial salvage index. Reversible perfusion defects were seen in 21% of patients in both groups and overall ischaemic burden was small [complete revascularisation group: mean 3.4% of LV mass (SD 8.9%); IRA-only group: mean 4.3% of LV mass (SD 11.3%)]. When the extent of ischaemia was assessed only in patients with defects, the ischaemic burden was not statistically different between the complete revascularisation and IRA-only groups.

Clinical outcomes

Median follow-up was 372 days (IRA group: 377 days; complete revascularisation group: 366 days; $p = 0.38$). A total of 198 (98%) patients attended the 12-month clinical follow-up (three patients died before this time point and two patients withdrew consent). The length of inpatient stay and incidence of in-hospital clinical events were similar in the two treatment arms. There was a borderline significant reduction in MACEs in patients undergoing complete revascularisation (8/103, 8%) versus IRA only (18/95, 17.1%), and the corresponding events rates and hazard ratio (0.43, 95% CI 0.18 to 1.04; $p = 0.055$) were similar to that seen in the main trial.

Limitations

The CMR substudy population may not be a true representation of the overall study population and the study was not powered to detect differences in clinical outcomes. The mean IS was slightly lower than expected and the power of the study was reduced to detect a 4% difference in IS. The optimal timing of CMR imaging to measure IS post PPCI is uncertain. Myocardial salvage was assessable in only 70% of the patients.

Conclusions

The CvLPRIT-CMR is the first detailed substudy of acute and follow-up CMR imaging outcomes in a randomised study of IRA only versus complete revascularisation in patients presenting with STEMI who have multivessel coronary disease at the PPCI. The data showed that non-IRA PCI is associated with additional infarction. However, these additional infarcts were relatively infrequent, generally small, and did not lead to an increase in total IS or a reduction in myocardial salvage index. There is mounting evidence from randomised trials that treating multivessel disease with complete revascularisation leads to a reduction in MACEs after the PPCI compared with an IRA-only strategy. The current results provide reassurance that complete revascularisation does not lead to increased total IS and adds to the evidence base suggesting in-hospital non-IRA PCI can be undertaken after the PPCI.

Recommendations for research

Larger clinical trials in patients with multivessel disease presenting for the PPCI are required to assess (1) whether or not death and MI are reduced by a complete revascularisation strategy; (2) whether or not functional assessment of non-IRA lesions results in similar outcomes to a pragmatic angiographic-based revascularisation strategy; (3) the optimal timing of in-hospital versus staged outpatient complete revascularisation; and (4) the cost-effectiveness of various complete revascularisation strategies versus an IRA-only strategy. In addition, long-term follow-up of patients in the CvLPRIT-CMR imaging substudy should be undertaken to ascertain whether or not the increase in non-IRA MI associated with adverse clinical outcomes.

Trial registration

This trial is registered as ISRCTN70913605.

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