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Long-Term Follow-Up of Complete Versus Lesion-Only Revascularization in STEMI and Multivessel Disease

The CvLPRIT Trial

Anthony H. Gershlick, MBBS,[a] Amerjeet S. Banning, BSc (Hons), MBBS,[a] Emma Parker, RCN,[a] Duolao Wang, PhD,[b] Charley A. Budgeon, PhD,[a] Damian J. Kelly, MB ChB, MD,[c] Peter O. Kane, MBBS, MD,[d] Miles Dalby, MBBS, MD,[e] Simon L. Hetherington, MB ChB, MD,[f] Gerry P. McCann, MB ChB, MD,[a] John P. Greenwood, MB ChB, PhD,[g] Nick Curzen, BM (Hons), PhD[h]

ABSTRACT

BACKGROUND Randomized trials have shown that complete revascularization in patients with ST-segment elevation myocardial infarction (MI) with multivessel disease results in lower major adverse cardiovascular events (MACE) (all-cause death, MI, ischemia-driven revascularization, heart failure).

OBJECTIVES The goal of this study was to determine whether the benefits of complete revascularization are sustained long-term and their impact on hard endpoints.

METHODS CvLPRIT (Complete versus Lesion-only Primary PCI Trial) was a randomized trial of complete inpatient revascularization versus infarct-related artery revascularization only at the index admission. Randomized patients have been followed longer-term. The components of the original primary endpoint were collected from physical and electronic patient records, and from local databases for all readmissions.

RESULTS The median follow-up (achieved in >90% patients) from randomization to first event or last follow-up was 5.6 years (0.0 to 7.3 years). The primary MACE endpoint rate at this time point was 24.0% in the complete revascularization group but 37.7% of the infarct-related artery-only group (hazard ratio: 0.57; 95% confidence interval: 0.37 to 0.87; $p = 0.0079$). The composite endpoint of all-cause death/MI was 10.0% in the complete revascularization group versus 18.5% in the infarct-related artery–only group (hazard ratio: 0.47; 95% confidence interval: 0.25 to 0.89; $p = 0.0175$). In a landmark analysis (from 12 months to final follow-up), there was no significant difference between MACE, death/MI, and individual components of the primary endpoint.

CONCLUSIONS Long-term follow-up of the CvLPRIT trial shows that the significantly lower rate of MACE in the complete revascularization group, previously seen at 12 months, is sustained to a median of 5.6 years. A significant difference in composite all-cause death/MI favoring the complete revascularization was also observed. (Complete versus Lesion-only Primary PCI Trial; ISRCTN70913605) (J Am Coll Cardiol 2019;74:3083–94)

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From the [a]Department of Cardiovascular Sciences, University of Leicester and Cardiovascular Theme, NIHR Leicester Biomedical Research Centre, Glenfield Hospital, Leicester, United Kingdom; [b]Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, United Kingdom; [c]Department of Cardiology, Royal Derby Hospital, Derby, United Kingdom; [d]Department of Cardiology, Royal Bournemouth and Christchurch Hospitals, Bournemouth, United Kingdom; [e]Department of Cardiology, Royal Brompton & Harefield NHS Foundation Trust, Harefield Hospital, Middlesex, London, United Kingdom; [f]Department of Cardiology, Kettering General Hospital, Rothwell Road, Kettering, United Kingdom; [g]Multidisciplinary Cardiovascular Research Centre & The Division of Biomedical Imaging, Leeds Institute of Cardiovascular & Metabolic Medicine, Leeds University, Leeds, United Kingdom; and the [h]Department of Cardiology, University Hospital Southampton, and University of Southampton, Southampton, United Kingdom. The CvLPRIT trial was funded by the British Heart Foundation (SP/10/001) with support from the National Institute for Health Research (NIHR) Comprehensive Local Research Networks, in particular, by the NIHR infrastructure at Leicester Leeds. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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ABBREVIATIONS AND ACRONYMS

CR = complete revascularization

FFR = fractional flow reserve

IDR = ischemia-driven revascularization

IRA = infarct-related artery

MACE = major adverse cardiovascular event

N-IRA = noninfarct-related artery

PCI = percutaneous coronary intervention

P-PCI = primary percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

TLF = target lesion failure

TVR = target-vessel revascularization

How best to manage multivessel disease found during primary-percutaneous coronary intervention (P-PCI) for ST-segment elevation myocardial infarction (STEMI) remains unresolved. Atheromatous disease in the noninfarct-related artery (N-IRA) is seen in 30% to 50% of patients with STEMI (1–4). Those patients with STEMI plus other N-IRA disease have worse outcomes (3,5). Older observational registry data suggested complete revascularization (CR) may not be beneficial (6,7), but 4 recent small- to medium-sized randomized trials all showed similar, highly significant improvements in short-term (12 to 24 month) outcomes for complete versus culprit-only intervention (8–11). In all of the trials, beneficial clinical outcomes were essentially driven by reduction in overall composite major adverse cardiovascular events (MACE) (all-cause death, myocardial infarction [MI], ischemia-driven revascularization [IDR], and heart failure), and although all MACE components fell, lower rates of repeat revascularization were consistently seen.

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Outcome data for all studies extend only to the original reported follow-up time (12 to 24 months). In the trials, the divergence in Kaplan-Meier curves for complete versus culprit-only was seen early and appeared to be being maintained to trials end. Because no long-term follow-up data have previously been published, we believed it is important to determine longer-term patient outcomes.

The aim of this study was, for the first time, to determine if there is a sustained benefit in favor of multivessel percutaneous coronary intervention (PCI) in the longer term.

METHODS

The CvLPRIT (Complete versus Lesion-only Primary PCI Trial) (9) was undertaken in 7 sites in the United Kingdom. The sample size was based on data published by Politi et al. (12). Study rationale, design, and power calculation have been previously published (13). The first patient was randomized in May 2011, recruitment was for 2 years, and so the last recruited patient was randomized in May 2013; 12-month follow-up was completed in May 2014. The primary outcome analysis for the trial was published in 2015 (9). The primary outcome measure was MACE (composite of death, recurrent MI, heart failure, and IDR). The definitions of the primary endpoint and its components have been published in the Online Appendix of the main trial paper (9).

For this long-term follow-up, patient-level data were collected from the individual centers over the time period extending from the 12-month original follow-up (range May 2012 to 2014) until August 2018. This latter date was arbitrarily chosen as it exceeded 5-year follow-up of the last patient randomized to the CvLPRIT trial. Consent for long-term patient data collection was covered under the original ethics committee application and original consent.

Each center was contacted and provided with an individual list of their patients' trial ID numbers and a list of events for any of these patients that had occurred in the 12 months (and so reported in the main trial paper). Hospital electronic databases and case notes were interrogated to identify any new incidence of the original trial MACE event occurring since trial completion at 12 months. If the patient was flagged as having had a MACE event after 12 months, then a case report form (based on those from the original trial) was generated by the center.

The primary outcome was the occurrence of MACE event, and secondary outcomes included composite of death/MI and the individual components of MACE.

STATISTICAL ANALYSES. Time-to-event data were plotted using Kaplan-Meier method and compared between groups using log-rank test.

Kaplan-Meier curves were generated to represent the following:

1. MACE events from randomization to final patient long-term follow-up date (time-to-first-event analysis including all patients, intention-to-treat population).
2. Landmark analyses of MACE events from 12 months to final follow-up.

Event tables were generated for the following:

1. Time-to-first-event analysis of all MACE and its component endpoints for all patients from randomization until follow-up.
2. IDR in all patients from 12 months post-randomization until end of follow-up, including those who had a nonfatal MACE event in the first 12 months.
3. Additional, subsequent MACE events in patients who had had a nonfatal event in the first 12 months (first event per patient).

Cox proportional hazard models were used to derive hazard ratios (HR) and 2-sided 95% confidence intervals (CIs). Landmark analysis was from

12 months. Continuous data were expressed as mean ± SD or median (interquartile range) and compared using the Student's *t*-test or Wilcoxon test, as appropriate. Binary event outcomes were expressed as number (%) of patients and comparisons done using the chi-square or Fisher exact test.

RESULTS

The original trial recruited 296 patients, with 150 randomized to CR and 146 randomized to IRA-only PCI. The original demographic data for the 2 groups are shown in Online Table 1. Secondary prevention medication at time of discharge, important in the context of longer-term follow-up, is shown in Online Table 2. The 12-month MACE and its components from the original paper are shown in Online Table 3 (9).

At 12 months of follow-up, 288 patients were still alive (2 deaths in the CR group and 6 deaths in the IRA-only revascularization). The original CONSORT diagram showed that there were 11 patients lost to follow-up in the CR group and 8 patients lost to follow-up in the IRA-only group. After the completion of the original CvLPRIT trial, further follow-up data beyond 12 months could not be obtained for 1 patient from the CR group and 4 patients from the IRA-only group despite multiple contact attempts. Thus, long-term follow-up data were available for 272 patients (91.9% of original randomized cohort; 91.8% of patients undergoing CR and 92.0% of IRA-only PCI patients) (**Figure 1**). From the time of initial randomization to the end of longer-term follow-up, the number of patients with complete follow-up for MACE was 138 for the CR group and 134 patients for the IRA-only group. The median time of follow-up from randomization to final follow-up was 5.6 years (range 0 to 7.3 years).

INTENTION-TO-TREAT ANALYSIS FROM RANDOMIZATION TO LONG-TERM FOLLOW-UP. The time-to-first event analysis of all patients included in the long-term follow-up is shown in **Figure 2**. At a median time of 5.6 years, the composite MACE rate was 24.0% in the CR group and 37.7% in the IRA-only group (HR: 0.57; 95% CI: 0.37 to 0.87; p = 0.0079).

The individual components of the primary endpoint are shown in **Table 1**. Although no individual component drove the primary endpoint, the composite endpoint demonstrated a significant difference in favor of CR.

When the secondary composite of "death/MI" was analyzed, this showed a significantly lower rate in the CR group; 10.0% compared with 18.5% in the IRA-only group (HR: 0.47; 95% CI: 0.25 to 0.89; p = 0.0175).

Rates of IDR were not significantly different between groups (CR = 11.3%; IRA-only = 13.0%; HR: 0.76; 95% CI: 0.40 to 1.49; p = 0.4447) in this long-term analysis (as compared with differences at 12 months in the original analysis).

LANDMARK ANALYSIS OF THE INTENTION-TO-TREAT POPULATION FROM 12 MONTHS TO END OF FOLLOW-UP. We found that beyond 12 months there remains a nonsignificant trend toward a lower event rate for the primary composite endpoint of MACE in the CR group. The MACE rate from 12 months to end of long-term follow-up in the intention-to-treat population was 17.1% in the CR group and 23.3% in the IRA-only group (HR: 0.72; 95% CI: 0.40 to 1.27; p = 0.248) (**Figure 3, Table 2**).

As shown in **Table 2**, the individual components of the primary endpoint are similar between the CR and the IRA-only groups. The secondary composite endpoint of death/MI was also similar between both groups (CR = 8.9%; IRA-only = 16.5%; HR: 0.53; 95% CI: 0.25 to 1.12; p = 0.0905) but trending toward CR.

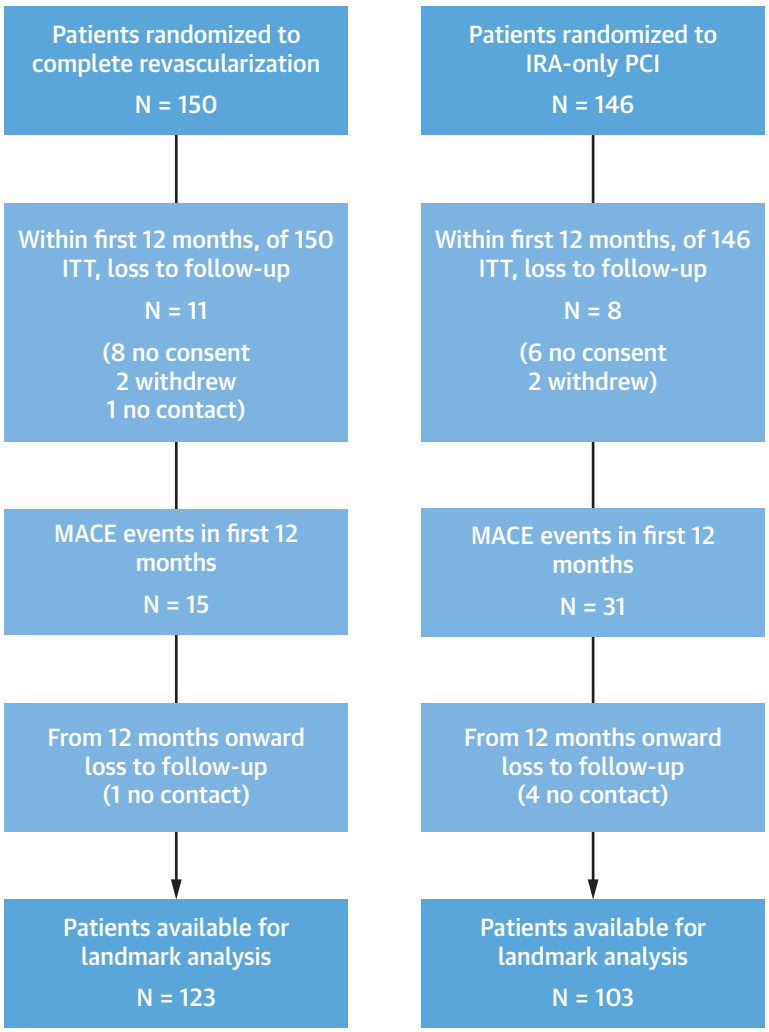
REVASCULARIZATION IN PATIENTS FOLLOWING 12-MONTH FOLLOW-UP. From the 12-month landmark analysis, the rates of ischemia-driven revascularization (IDR) were similar between the CR and the IRA-only group after the initially reported 12-month follow-up period (**Table 2**). Specifically, in the CR group, this was 8.1% and in the IRA group 6.8% (HR: 1.12; 95% CI: 0.44 to 3.04; p = 0.7694).

In terms of total number of IDRs (e.g., if a patient initially presented with MI and went on to revascularization as a result) after 12 months, rates were also similar between IRA-only and CR groups (CR group 13 of 148 [8.8%]; IRA-only group 14 of 140 [10.0%]; p = 0.736) (**Table 3**).

Of these 27 IDR cases, only 3 cases used coronary artery bypass grafting as a means of revascularization. The proportion of PCI for IDR in long-term follow-up was 12 of 14 (85.7%) cases for the IRA-only group and 12 of 13 (92.3%) for the CR group (p = 0.586). The proportion of IDR cases after 12 months in the context of MI was 4 of 13 (30.8%) for the CR group and 7 of 14 (50.0%) for the IRA-only group (p = 0.31).

Figure 4 shows IDR rates in each treatment group both before and after 12-month post-randomization. We observed that there continues to be a requirement for IDR in those patients who received CR. This is equally distributed between IRA and N-IRA lesions.

FIGURE 1 Flow Diagram for Long-Term Follow-Up and Landmark Analyses of CvLPRIT



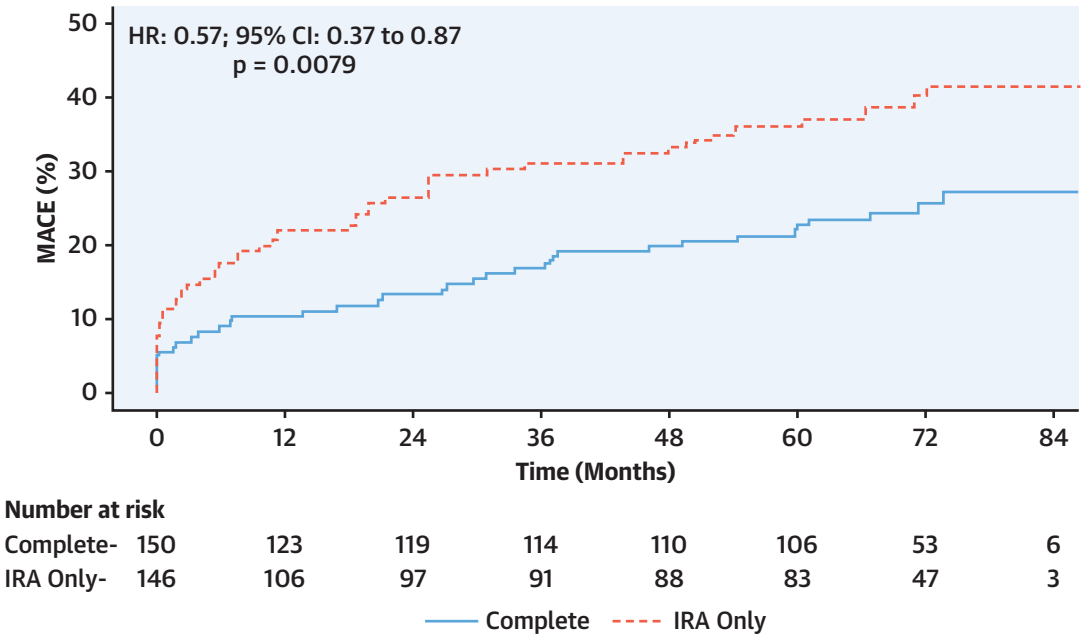
Flow diagram illustrating the longer-term follow-up of patients randomized to complete revascularization or IRA-only PCI, and the number of patients in each group available for landmark analysis beyond 12 months of initial randomization. CvLPRIT = Complete versus Lesion-only Primary PCI Trial; IRA = infarct-related artery; ITT = intention to treat; MACE = major adverse cardiovascular events; PCI = percutaneous coronary intervention.

Table 3 shows whether in each group the IDR was to the target or nontarget vessel, indicating likely in-stent restenosis or stent thrombosis, or a de novo lesion. In the IRA group, target-vessel revascularization (TVR) indicates need for revascularization in the treated IRA lesion/vessel, whereas in the CR group TVR can include any vessel that was stented, and thus distinction is made between TVR and de novo lesion (i.e., non-TVR).

There was an even split within the CR group, with 6 of 13 cases of IDR due to TVR, and the other 7 non-TVR/de novo lesions. Within the IRA-only group, predominantly ischemia-driven revascularization was performed, that is, in a nonculprit lesion (11 of 14 IDR cases non-TVR, with 2 of these lesions being identified as a de novo lesion and not an originally identified N-IRA lesion and 9 of the 140 [6.4%] underwent PCI to the originally identified N-IRA lesion).

Within the reported IDR events, there was only 1 report of stent thrombosis in the longer-term follow-up period. This occurred in a patient randomized to the CR group, with stent thrombosis occurring in the treated culprit lesion.

FIGURE 2 MACE for Randomization to Long-Term Follow-Up (First Event, Intention-to-Treat Analysis)



Kaplan-Meier curves indicating composite MACE (all-cause death, myocardial infarction, heart failure, and ischemia-driven revascularization) in the complete revascularization **(blue line)** and IRA-only **(red line)** groups, from randomization until end of longer-term follow-up. There is a significant reduction in MACE with the complete revascularization group compared with IRA-only PCI group (HR: 0.57; 95% CI: 0.37 to 0.87; p = 0.0079, log-rank test). CI = confidence interval; HR = hazard ratio; other abbreviations as in Figure 1.

SUBSEQUENT MACE EVENTS IN PATIENTS WITH A PRIOR NONFATAL EVENT IN THE FIRST 12 MONTHS. Of the 38 patients who had a nonfatal event in the first 12 months, 11 patients had a subsequent event from 12 months until the end of follow-up. Table 4 shows these events. In total, there were 3 events in the CR group (23.1%) and 8 events in the IRA-only group (32%). Within the CR group, there were 2 deaths and 1 MI (that was fatal). Similar rates of death and MI were observed between the 2 groups. In the IRA-only group, there were 2 patients who required IDR in a non-MI setting.

DISCUSSION

The major and novel findings of this long-term follow-up of the CvLPRIT trial are as follows:

1. The MACE event rate curves remain separated to a median time point of 5.6 years (maximum 7.3 years).
2. A highly significant difference in MACE rates between the CR undertaken at the time of the primary PCI and IRA-only group revascularization persist at longer-term follow-up.
3. There was no in-group difference in MACE between 12 months post-randomization and long-term follow-up.
4. Although individual components of the MACE were not significantly different individually, all were numerically lower in the favor CR group.
5. Rate of combined hard endpoint of death/MI was significantly different between the 2 groups (favoring CR) at longer-term follow-up. This finding (albeit at shorter follow-up median of 3 years) has now been supported by the recently published

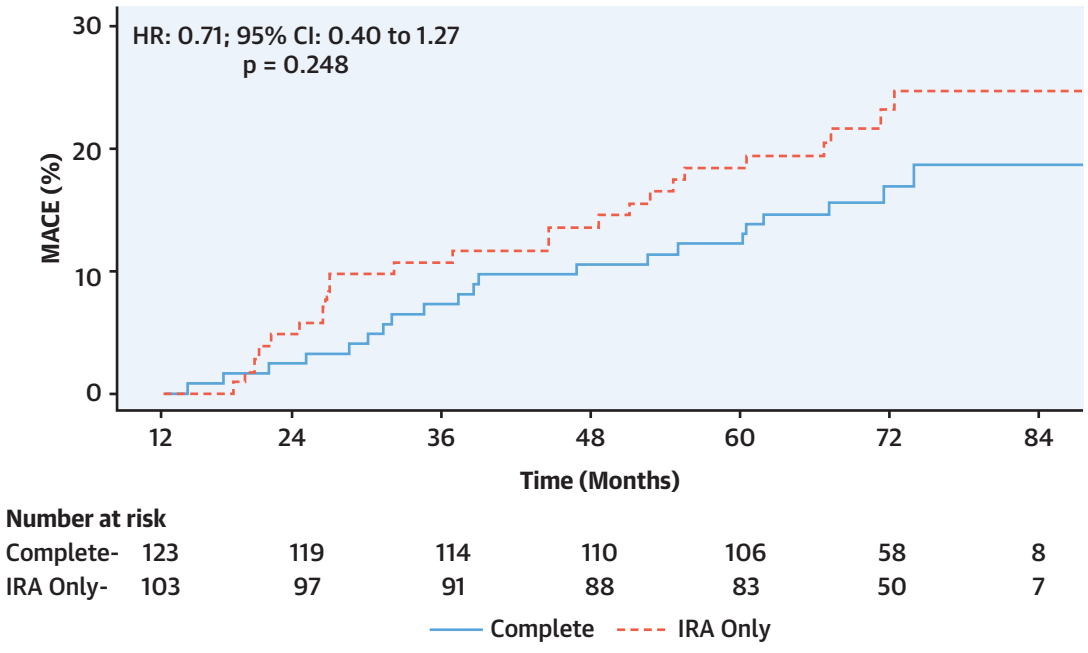
TABLE 1 Individual Components of MACE: Randomization to End of Long-Term Follow-Up

	Complete (n = 150)	IRA-Only (n = 146)	HR (95% CI)	p Value
Total MACE	36 (24.0)	55 (37.7)	0.57 (0.37–0.87)	0.0079
Death (all-cause)	9 (6.0)	15 (10.3)	0.51 (0.22–1.16)	0.1001
Recurrent MI	6 (4.0)	12 (8.2)	0.43 (0.16–1.15)	0.0837
Heart failure	4 (2.7)	9 (6.2)	0.42 (0.13–1.37)	0.1383
Ischemia-driven revascularization	17 (11.3)	19 (13.0)	0.76 (0.40–1.49)	0.4447
Death/MI	15 (10.0)	27 (18.5)	0.47 (0.25–0.89)	0.0175

Values are n (%) unless otherwise indicated.

CI = confidence interval; HR = hazard ratio; IRA = infarct-related artery; MACE = major adverse cardiovascular events; MI = myocardial infarction.

FIGURE 3 Landmark Analysis in Patients From 12 Months to Follow-Up (Intention-to-Treat Analysis)



Kaplan-Meier curves indicating composite MACE (all-cause death, myocardial infarction, heart failure, and ischemia-driven revascularization) in the complete revascularization **(blue line)** and IRA-only **(red dotted line)** groups, from 12 months post-randomization until end of longer-term follow-up. There is no significant difference in MACE rate within the complete revascularization group compared with IRA-only PCI group (HR: 0.71; 95% CI: 0.40 to 1.27; p = 0.248, log-rank test), indicating sustained initial reduction in MACE with complete revascularization over the longer-term follow-up period. Abbreviations as in Figures 1 and 2.

COMPLETE (Complete vs Culprit-Only Revascularization Strategies to Treat Multivessel Disease after Early PCI for STEMI) trial (14).

6. Ischemia-driven revascularization rates were low during extended follow-up, with no difference between groups beyond 12 months. In the complete group, repeat intervention was equally split between culprit- and nonculprit-treated vessels, whereas in the incomplete group, repeat revascularization was due mostly to ischemia-driven intervention to nonculprit vessels.

TABLE 2 Components of MACE in Landmark Analysis: From 12 Months to End of Follow-Up

	Complete (n = 123)	IRA-Only (n = 103)	HR (95% CI)	p Value
Total MACE	21 (17.1)	24 (23.3)	0.71 (0.40–1.27)	0.248
Death (all-cause)	7 (5.7)	9 (8.7)	0.63 (0.23–1.68)	0.3478
Recurrent MI	4 (3.3)	8 (7.8)	0.41 (0.12–1.36)	0.1333
Heart failure	0 (0.0)	0 (0.0)	NA	NA
Ischemia-driven revascularization	10 (8.1)	7 (6.8)	1.12 (0.44–3.04)	0.7694
Death/MI	11 (8.9)	17 (16.5)	0.53 (0.25–1.12)	0.0905

Values are n (%) unless otherwise indicated. Twenty-four individuals were excluded, as they withdrew consent at 12 months (12 from each treatment group; 8 IRA and 11 complete from initial trial; additional 4 IRA and 1 complete who did not consent beyond 12 months). p from log-rank test.

NA = not applicable; other abbreviations as in Table 1.

These long-term data are novel and thought-provoking. Until now there have been no published longer-term follow-up data in patients randomized at the time of P-PCI to either complete or IRA-only intervention. To date, unpublished data presented at EURO-PCR 2018 by the COMPARE ACUTE (Comparison Between Fractional Flow Reserve Guided Revascularization Versus Conventional Strategy in Acute ST-segment Elevation Myocardial Infarction Patients With Multivessel Disease) (11) study group suggest that the difference in outcomes seen at 12 months is maintained to 2 years. It is interesting that the curves both in that study and in our current extended follow-up study remain separated over a longer period. Similarly, the median follow-up of DANAMI-3 (Third Danish Trial in Acute Myocardial Infarction)-PRIMULTI (Primary PCI in Patients With ST-Elevation Myocardial Infarction and Multivessel Disease: Treatment of Culprit Lesion Only or Complete Revascularization) trial was 27 months, with longest follow-up of 4 years, and this also showed a sustained lower rate of MACE following CR (10), but

this was not planned long-term follow-up as such. All of these data suggest that lower rates of events seen within 12 months do translate into longer-term benefit, predominantly through nonattenuation of benefit. Our data, showing a highly significant difference in the longer term without safety concerns, supports the current European Society of Cardiology Guidelines, and the focused update of the American College of Cardiology guidelines, which indicate that CR within the hospital admission should be at least considered in this patient group (Class IIa A and Class IIb, respectively) (15,16).

It remains unclear exactly how early CR could lead to longer-term benefit. We postulate that early CR benefits in patients with STEMI with multivessel disease may be due to both improvement in collateral flow to the peri-infarct ischemic territory, and to the proactive management of N-IRA lesions, in the context of a pan-inflammatory paradigm.

Certainly, given that both the MRI and nuclear medicine substudies of CvLPRIT (17,18) showed no difference between the groups in infarct size (at 1 week) and no difference in ischemic burden at 6 weeks, the benefit we have demonstrated does not appear to be explained simply in terms of ischemic burden being dealt with prophylactically in the complete group. It is important to state that the groups in CvLPRIT were evenly matched so an excess of events could be only due to the randomized treatments. Stenting has become a robust procedure with low stent-associated complications, reducing degradation of event benefit in the CR arm.

The FULL REVASC (Ffr-gUidance for compLete Non-cuLprit REVASCularization) trial (NCT02862119) is currently suspended according to the original trial design following publication of the COMPLETE trial (14). The FLOWER-MI (FLOW Evaluation to Guide Revascularization in Multi-vessel ST-elevation Myocardial Infarction) trial (NCT02943954) is another larger randomized controlled trial that will determine if cardiovascular outcomes are improved with fractional flow reserve (FFR)-guided revascularization of nonculprit lesions compared with angiographically driven PCI of these lesions. Meta-analyses of the recent smaller trials do, however, confirm significant benefit in terms of hard endpoints (19,20). In this context, our new finding of significant benefit from a combined death/MI endpoint at longer-term follow-up suggests that the original trial was indeed underpowered for hard endpoints and that in the longer-term hard endpoint combinations may become important. This is a novel observation supporting a CR strategy, and is the first time that a benefit, judged by hard endpoints, has been seen in a single trial. Although this is clearly the combination of 0 to 12 months (NS) and 12 months to follow-up (nonsignificant in landmark 0.0819) (**Table 2**), and despite the small numbers, these are not small differences (approximately 50% reduction). The contribution to this reduction in combined hard endpoint is shared between death and MI with the greater impact perhaps from MI (**Tables 1 and 2**).

TABLE 3 Ischemia-Driven Revascularization Beyond 12 Months in All Patients Surviving Beyond 12 Months

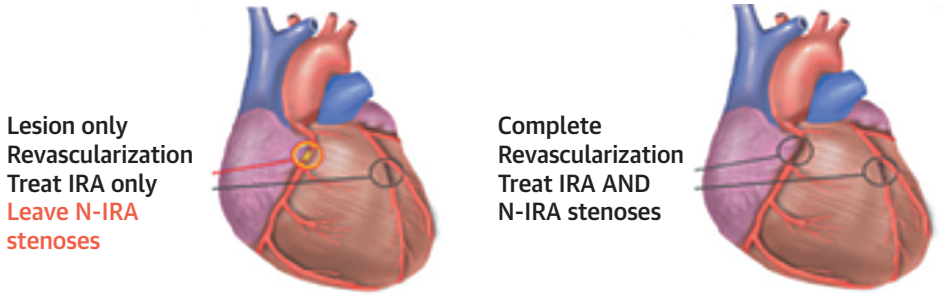
	Complete Revascularization (n = 148)	IRA-Only PCI (n = 140)	p Value
TVR	6 (4.1)	3 (2.1)	0.346
Non-TVR	7 (4.7)	11 (7.9)	0.279
Total IDR	13 (8.8)	14 (10.0)	0.736

Values are n (%). For IRA-only group, TVR refers to revascularization required in the culprit-only artery. For complete revascularization group, TVR refers to revascularization required in any vessel that was treated with PCI during index admission.

IDR = ischemia-driven revascularization; IRA = infarct-related artery; PCI = percutaneous coronary intervention; TVR = target-vessel revascularization.

The IDR seen within the CvLPRIT trial was based on angiographic assessment of lesion severity in the context of either acute coronary syndrome or stable angina. There was no systematic noninvasive testing during follow-up after 12 months, and before 12 months only those included in the cardiac magnetic resonance or nuclear substudies underwent systematic assessment. The decision for further revascularization during long-term follow-up (>12 months) was based on clinical evidence of ischemia or presentation with repeat MI. Information pertaining to whether non-MI-driven repeat revascularization was performed in the context of noninvasive testing or based on clinical judgment in the longer-term follow-up was not available for all patients. It was the patient presentation and clinical decision making that directed management. Some will of course have had noninvasive testing in the clinical context, but it was not systemically recorded. Although FFR was not used in this study at initial presentation, the PRIMULTI study did use FFR-guided revascularization and demonstrated similar findings to CvLPRIT with reduction of MACE in CR driven by reduction in IDR in the CR group (10). The CvLPRIT CMR substudy showed no difference in the infarct size or ischemic burden between the IRA-only and CR groups at follow-up MRI (17). Similarly, the CvLPRIT nuclear substudy showed that the extent of inducible ischemia was small and again similar between both groups (inducible hypoperfusion as percentage of LV; IRA-only = 1.5% [range: 0 to 4.4], CR = 1.5% [range: 0 to 5.9], p = 0.70) (18). These substudies and lack of hard endpoint reduction with

FIGURE 4 Revascularization During Follow-Up According to Randomization Group and Artery Treated (IRA or N-IRA) During 2 Periods of Follow-Up (Randomization Until 12 Months and 12 Months Until Last Follow-Up)



IRA only treatment	X	√		Complete revascularization	√	√
	N-IRA 255	IRA 146			N-IRA 251	IRA 150
IDR Rand – 12 mo	11	1		IDR Rand – 12 mo	5	2
IDR 12 mo follow-up	11	3		IDR 12 mo follow-up	7	6
TOTAL	22	4		TOTAL	12	8

The table shows the number of lesions in the IRA and N-IRA and the number of lesions treated. IDR = ischemia-driven revascularization; IRA = infarct-related artery; N-IRA = noninfarct-related artery; Rand = randomized.

FFR-guided revascularization seen with PRIMULTI would indicate that ischemia may play less of a role in the benefits seen with CR. In this instance, vulnerable plaque may play an important role; however, this would have to be assessed with prospective studies.

It should be noted that although there appear to be no cases of heart failure during follow-up, in fact the 3 cases that did occur were not counted in the analyses, as these were not hierarchical first events. In addition, the robust diagnosis of heart failure can be challenging.

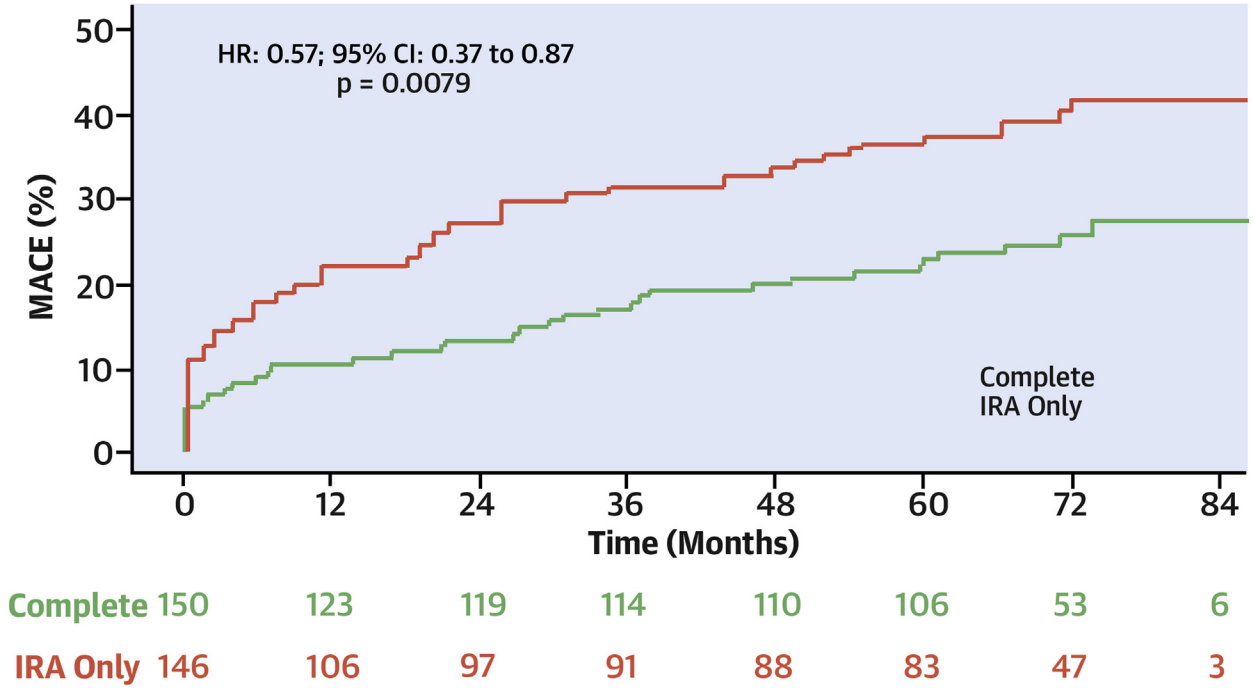
TABLE 4 Subsequent Events During Long-Term Follow-Up in Those Patients With a Nonfatal Event in the First 12 Months After Randomization (First Event Only Per Patient)

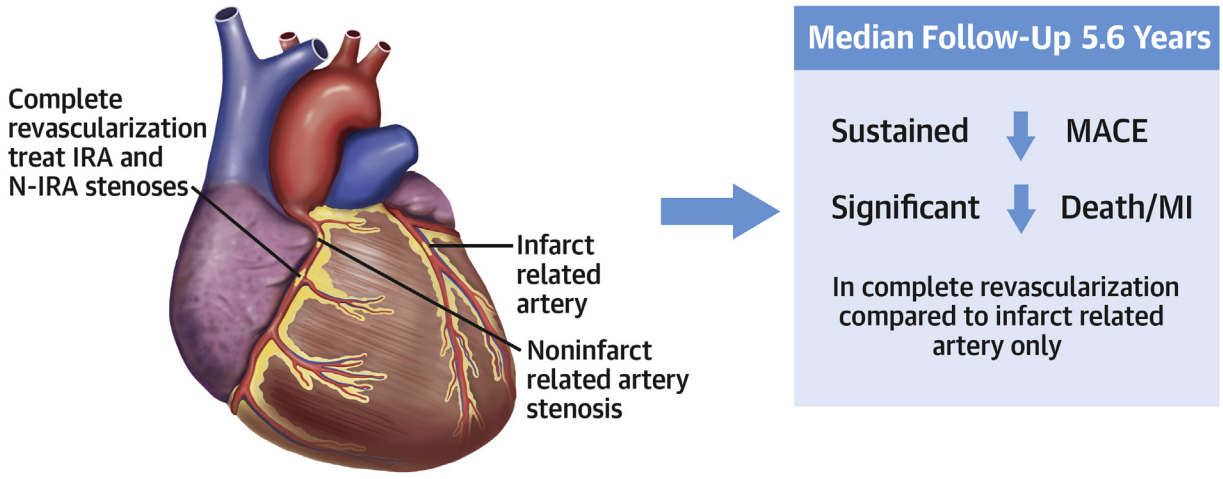
	Complete Revascularization (n = 13)	IRA-Only PCI (n = 25)
Death	2 (15.4)	5 (20.0)
Myocardial infarction	1 (7.7)	1 (4.0)
Ischemia-driven revascularization	0 (0.0)	2 (8.0)
Heart failure	0 (0.0)	0 (0.0)
MACE events from 12 months until end of follow-up	3 (23.1)	8 (32.0)

Values are n (%).
Abbreviations as in Tables 1 and 3.

Revascularization rates are low in both groups in our study and remain low over extended follow-up. From 12 months onward, the rates of revascularization are similar between the IRA-only and CR groups. In the IRA-only group, revascularization after 12 months is mainly N-IRA PCI; by contrast, in the CR group, it is split between de novo intervention and repeat revascularization to the originally treated vessels. The overall numbers remain low, however, and do not indicate that there is risk of excess requirement for repeat PCI in the CR group: contemporary stenting is a robust procedure. For example, it is established that current restenosis rates for third-generation drug-eluting stents are very low at <5% (e.g., real-world follow-up of patients treated with the Everolimus-Eluting Synergy Stent from the Swedish Coronary Angiography Angioplasty Registry showed restenosis rate at 1 year of 1.1% and stent thrombosis 0.4% [21]). Longer-term rates of restenosis in second-generation drug-eluting stents are also very low. The NOBORI-2 study demonstrates 5-year rates of target lesion failure of 7.3% in

CENTRAL ILLUSTRATION **Longer-Term Follow-Up of Complete Versus Infarct-Related-Artery-Only Revascularization in Patients Presenting With ST-Segment Elevation Myocardial Infarction and Multivessel Disease**





Gershlick, A.H. et al. J Am Coll Cardiol. 2019;74(25):3083-94.

Patients in the CvLPRIT (Complete versus Lesion-only Primary PCI Trial) presenting with STEMI and multivessel disease demonstrated lower rates of MACE (all-cause death, myocardial infarction, heart failure admissions, and ischemia-driven revascularization) following complete revascularization compared with IRA-only PCI (Kaplan-Meier curve, HR: 0.57; 95% CI: 0.37 to 0.87; p = 0.0079, log-rank test). There is also reduction in composite of all-cause death and myocardial infarction at longer-term follow-up (HR: 0.47; 95% CI: 0.25 to 0.89; p = 0.0175, log-rank test). The reduction in longer-term MACE following complete revascularization reflects the sustained reduction in this group beyond 12 months of initial randomization. CI = confidence interval; HR = hazard ratio; IRA = infarct-related artery; MACE = major adverse cardiovascular events; MI = myocardial infarction; MVD = multivessel disease; N-IRA = noninfarct-related artery; STEMI = ST-segment elevation myocardial infarction.

nondiabetic patients and 12.4% in diabetic patients (22). Similarly, the DUTCH PEERS (TWENTE II) study (DUrable polymer-based sTent CHallenge of Promus ElemEnt versus ReSolute integrity: TWENTE II) showed low rates of TVR and stent thrombosis at 5 years with Promus Element and Resolute Integrity drug-eluting stents (23). The 5-year results of the EXAMINATION (Everolimus-Eluting Stents Versus Bare-Metal Stents in ST-Segment Elevation Myocardial Infarction) trial demonstrated that definite stent thrombosis at 5 years in patients with STEMI treated with Everolimus-Eluting Synergy Stents was 2%, with target-lesion revascularization of 4% and overall revascularization rate of 12% (24). The findings are commensurate with the current presented analysis of the CvLPRIT study, in which the minimum follow-up was 5.6 years. Hence, this analysis confirms the robust outcome and longer-term safety of performing PCI to nonculprit lesions. Trials of prophylactic interventional treatment of coronary lesions must be predicated on demonstrable good outcomes. If a trial such as CvLPRIT had been undertaken 10 years earlier, the outcomes (with the then high rates of stent thrombosis and in-stent restenosis) might well have looked very different, with early benefits offset by high stent event rates.

It should be highlighted that in the original paper, the rate of IDR in the IRA-only group mostly drove the primary endpoint difference, which is not the case in this timeframe.

Our data suggest that total revascularization, known to have benefits in various cohorts with coronary artery disease (25), should now probably be considered the standard of care in suitable patients with STEMI with multivessel disease. Although the individual trials were small, the meta-analyses with their low I^2 statistic are compelling, especially because they show a lack of significant harm (no contrast-induced nephropathy, no excess bleeding), and the novel data in this report should add to the evidence base that CR appears better for the patient in the longer term as well as previously shown short-term.

STUDY LIMITATIONS. The essential limitations in this study include all those published in the original trial (9). Specifically, the numbers remain small and therefore need to be interpreted cautiously despite the high significance and low HRs. For this study, there is always the chance that, despite methodological rigor, some events may have been missed, especially as the follow-up after 1 year was reliant on retrospective center-reported clinical events completed on a proforma rather than systematic consultation or telephone-based follow-up of patients. However, this was mitigated by achieving patient-level data from the original recruiting centers by the local investigators and original trial research nurses. The forms used were based on trial event capture forms to ensure cross checking and that event details (such as repeat revascularization) were cross checked, although it is possible that some events were not reported, through some patients having presented to another center with a MACE event. However, these were large regional centers, and patient data review at formal follow-up also would include questions about any procedures/MACE events for which the patients were treated in another center. Furthermore, follow-up was >90%. Thus, although there may have been some missed MACE events, we anticipate this to be a low level, and as the trial was randomized, will have affected both groups equally.

In addition, we have reported in this article the patient-oriented endpoints, and as such these will likely be (from the patient perspective) equally distributed between groups, especially because the length of follow-up is long (i.e., the impact of the patient's perception of "benefit" will have been attenuated). Also, the new finding of the increase in death/MI is a hard endpoint.

As with any longer-term follow-up study, the use of all-cause mortality as opposed to cardiovascular mortality may affect interpretation of the results. However, full data could not be obtained on the cause of death and hence cardiovascular mortality could not be reported in this study.

The assessment of repeat revascularization procedures was limited to angiographic and PCI procedural descriptions from case note-based angiography reports, as was the assessment as to whether there was target-lesion revascularization/TVR/non-TVR or stent thrombosis. Hence, event adjudication could not be formally conducted.

Finally, although high levels of secondary prevention were administered at discharge, we have not adjudicated this at long-term follow-up.

CONCLUSIONS

Long-term follow-up of the CvLPRIT trial shows that the significantly lower rate of MACE in the CR group, previously seen at 12 months, is sustained to a median of 5.6 years (**Central Illustration**). A significant difference in composite all-cause death/MI favoring the CR also was observed. These data support the longer-term safety and efficacy of CR in patients with multivessel STEMI.

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ADDRESS FOR CORRESPONDENCE: Dr. Anthony H. Gershlick, Department of Cardiovascular Sciences, University of Leicester and Cardiovascular Theme, NIHR Leicester Biomedical Research Centre, Glenfield Hospital, Groby Road, Leicester, LE3 9QP, United Kingdom. E-mail: agershlick@aol.com. Twitter: @UoLCVS.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

In patients with STEMI and multivessel coronary disease, CR is associated with lower rates of MACE, including MI and death, during long-term follow-up, than revascularization of the IRA alone.

TRANSLATIONAL OUTLOOK:

Further studies are required to determine the optimal timing of revascularization of N-IRAs.

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KEY WORDS complete revascularization, multivessel disease, myocardial infarction, noninfarct-related lesion, primary percutaneous coronary intervention, ST-elevation

APPENDIX For supplemental tables, please see the online version of this paper.