

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

ScienceDirect

journal homepage: [www.elsevier.com/locate/jval](http://www.elsevier.com/locate/jval)

# Economic Evaluation of Complete Revascularization for Patients with Multivessel Disease Undergoing Primary Percutaneous Coronary Intervention

Garry R. Barton, BA, MSc, PhD<sup>1,\*</sup>, Lisa Irvine, BA, MSc<sup>1</sup>, Marcus Flather, MB, BS<sup>1</sup>,  
Gerry P. McCann, MB, ChB, MD<sup>2,3</sup>, Nick Curzen, BM, PhD<sup>4,5</sup>,  
Anthony H. Gershlick, MBBS<sup>2,3</sup>, on behalf of the CvLPRIT Investigators

<sup>1</sup>Norwich Medical School, University of East Anglia, Norwich, UK; <sup>2</sup>Department of Cardiovascular Sciences, University of Leicester, Leicester, UK; <sup>3</sup>NIHR Leicester Cardiovascular Biomedical Research Unit, University Hospitals of Leicester NHS Trust, Glenfield Hospital, Leicester, UK; <sup>4</sup>University Hospital Southampton NHS Foundation Trust, Southampton, UK; <sup>5</sup>Faculty of Medicine, University of Southampton, Southampton, UK

## ABSTRACT

**Objectives:** To determine the cost-effectiveness of complete revascularization at index admission compared with infarct-related artery (IRA) treatment only, in patients with multivessel disease undergoing primary percutaneous coronary intervention (P-PCI) for ST-segment elevation myocardial infarction. **Methods:** An economic evaluation of a multicenter randomized trial was conducted, comparing complete revascularization at index admission to IRA-only P-PCI in patients with multivessel disease (12-month follow-up). Overall hospital costs (costs for P-PCI procedure(s), hospital length of stay, and any subsequent re-admissions) were estimated. Outcomes were major adverse cardiac events (MACEs, a composite of all-cause death, recurrent myocardial infarction, heart failure, and ischemia-driven revascularization) and quality-adjusted life-years (QALYs) derived from the three-level EuroQol five-dimensional questionnaire. Multiple imputation was undertaken. The mean incremental cost and effect, with associated 95% confidence intervals, the incremental cost-effectiveness ratio, and the cost-effectiveness acceptability curve were estimated. **Results:** On the basis of 296 patients, the mean

incremental overall hospital cost for complete revascularization was estimated to be –£215.96 (–£1390.20 to £958.29), compared with IRA-only, with a per-patient mean reduction in MACEs of 0.170 (0.044 to 0.296) and a QALY gain of 0.011 (–0.019 to 0.041). According to the cost-effectiveness acceptability curve, the probability of complete revascularization being cost-effective was estimated to be 72.0% at a willingness-to-pay threshold value of £20,000 per QALY. **Conclusions:** Complete revascularization at index admission was estimated to be more effective (in terms of MACEs and QALYs) and cost-effective (overall costs were estimated to be lower and complete revascularization thereby dominated IRA-only). There was, however, some uncertainty associated with this decision.

**Keywords:** economic evaluation, myocardial infarction, percutaneous coronary intervention, revascularization.

Copyright © 2017, International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

Cardiovascular disease is a leading cause of mortality in the United Kingdom, with more than 150,000 deaths each year and annual costs of more than £15 billion [1]. Primary percutaneous coronary intervention (P-PCI) is the standard treatment for patients presenting with ST-segment elevation myocardial infarction (STEMI), with more than 90,000 such procedures undertaken in the United Kingdom each year [2]. P-PCI involves inserting a catheter via the groin or arm. A small balloon is then inflated in the narrowed artery to move the obstructing fatty tissue/clot and to widen the artery. Usually, at least one stent is then permanently implanted to hold the artery open and improve blood flow to the heart [2]. Of patients presenting with STEMI,

40% to 65% are estimated to have bystander stenosis in non-infarct-related arteries (N-IRAs) (multivessel disease) [3]. Until recently, treatment of the IRA alone was the internationally recommended strategy [4–6]. There is, however, growing trial evidence [7–9] that the additional treatment of N-IRAs (complete revascularization) is associated with fewer adverse cardiac events, and the previous “do-not-do” guidance by the American College of Cardiology has now been withdrawn [10]. Although these results need to be confirmed in larger trials, the emerging clinical evidence presents the opportunity to examine the cost-effectiveness of complete versus infarct-only revascularization. Revascularization may be associated with increased initial procedure costs, but it is important to also assess whether these costs are offset by reduced future hospital admissions and fewer

\* Address correspondence to: Garry R. Barton, Norwich Medical School, University of East Anglia, Norwich NR4 7TJ, UK.

E-mail: [g.barton@uea.ac.uk](mailto:g.barton@uea.ac.uk).

1098-3015/\$36.00 – see front matter Copyright © 2017, International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<http://dx.doi.org/10.1016/j.jval.2017.02.002>

adverse events. Here, we report an economic evaluation [11,12], which was conducted alongside the Complete versus Lesion-only Primary PCI Trial (CvLPRIT) [8], to assess whether complete revascularization constitutes a cost-effective use of health care resources. We are not aware of any previous economic evaluations of complete revascularization in this patient group.

## Methods

### Participants

As previously described [8], the CvLPRIT was a multicenter randomized trial comparing complete revascularization with IRA-only P-PCI for patients with bystander multivessel coronary artery disease. Patients were eligible if, after angiography, at least one other artery had a significant (70%) stenosis in addition to the occluded IRA. Inclusion and exclusion criteria are listed in the [Appendix Table in Supplemental Materials](http://dx.doi.org/10.1016/j.jval.2017.02.002) found at <http://dx.doi.org/10.1016/j.jval.2017.02.002>. Patients were randomized to either the IRA-only strategy or to complete revascularization, undertaken either at the time of P-PCI or during that index admission. Randomization was via an automated 24-hour telephone randomization system and stratified by infarct location (anterior/nonanterior) and symptom onset ( $\leq 3$  hours or  $> 3$  hours). Patients were followed up for 12 months postrandomization. The study was approved by the National Research Ethics Service (NRES) Committee East Midlands Derby (reference number: 11/H0405/4).

### Costs

Costs were estimated from the perspective of the UK National Health Service (NHS). Specifically, index admission P-PCI procedure(s) costs (based on procedure time, consumables, and equipment [e.g., catheter, balloon, and stents] used for both IRA and any N-IRA interventions performed, for both the initial procedure and any staged procedure), hospital length of stay costs (including time in critical care/high dependency and/or intensive care), and the costs of any hospital re-admissions were estimated. All centers were asked to prospectively collect detailed information on the PCI procedure and admission on study-specific case record forms. Follow-up data (including hospital re-admissions) were subsequently collected via telephone (6-month postrandomization) and face-to-face appointment (12-month postrandomization). Unit costs (in Great Britain pound [£] for the 2012–2013 financial year) were assigned to all items of resource use. When national unit cost data [13–15] were not available, for example, for stents and other P-PCI devices, we conducted a survey of participating centers to estimate the average cost for each item. Index admission (P-PCI procedure(s) and hospital length of stay) and re-admission costs were combined to estimate overall hospital costs.

In a subsample of sites (three out of the seven centers), all patients were asked to complete an additional resource use questionnaire at the 12-month visit. They were asked to report (1) all postdischarge health professional visits in the previous 12 months, (2) whether they were in paid employment at the point of randomization, and (3) whether they had returned to work at the 12-month follow-up point. Only the first three enrolled sites were asked to complete the additional resource use questionnaire because of the associated burden for staff and patients. Other sites that came on board later to boost recruitment were not asked to complete the additional resource use questionnaire. Health professional visits (including general practitioner visits, outpatient attendances, and therapist contacts) were costed as mentioned earlier and added to overall hospital

costs to estimate overall NHS and personal social services (PSS) costs.

### Outcomes

The primary outcome measure was a major adverse cardiac event (MACE) occurring within 12 months of randomization (a composite of all-cause mortality, recurrent myocardial infarction, heart failure, and need for repeat revascularization [PCI or coronary artery bypass grafting]), as defined in [Appendix 2](#) of the main trial article [8]. Hospitals recorded MACE data, informed by telephone contact with the patients at 6 months postrandomization and hospital visits at approximately 12 months. Clinicians blinded to the randomization group adjudicated all MACEs. All MACEs across the 12-month follow-up period were included in the cost-effectiveness analyses (the primary end point in the clinical article was time to first MACE [8]). In line with the National Institute for Health and Care Excellence methods guide [12], quality of life was measured using the three-level EuroQol five-dimensional questionnaire (EQ-5D) [16] at initial discharge (baseline) and at 12 months postintervention. Utility scores (a scale in which 0 is equal to death and 1 is full health) [11] were derived from the UK York A1 tariff [17] and converted into quality-adjusted life-years (QALYs) using the area under the curve approach, with linear interpolation between the baseline EQ-5D and the 12-month follow-up point [18]. For patients who died during follow-up, an EQ-5D score of 0 was assigned at their date of death [19].

### Analyses

The problem of missing data is common in randomized trials and can lead to bias and lack of precision [20]. As recommended for within-trial analysis of cost-effectiveness [20], patterns of missing data were examined to infer the assumed missing data mechanism, and complete case analysis [21] did not constitute the base-case analysis. Health professional visit costs were requested for only three of the centers and these costs constituted only a small component of the total cost (see Results section). Pragmatically, it was therefore considered inappropriate to undertake either complete case analysis or imputation for this variable and no further analysis was thereby undertaken for health professional visit costs or overall NHS and PSS costs. To impute missing data, multiple imputation was undertaken [20], where the “mi impute” command (Stata 12.1 [StataCorp LP, College Station, TX] [22]) was used to create 20 data sets (a rule of thumb is that the number of data sets should equal the percentage of missing data [23]), which were then pooled using Rubin rules [24]. In addition to the costs (procedure time, consumables and equipment, hospital length of stay, and re-admissions) and outcomes (baseline and 12-month EQ-5D scores), the multiple imputation model included variables ( $P < 0.10$ ) associated with missing data, costs, or outcomes (time since symptom onset at randomization [ $\leq 3$  hours or  $> 3$  hours], infarct location [anterior/nonanterior], medical history of treated hypercholesterolemia, medical history of treated diabetes, age, death, center, sex, and treatment allocation). Baseline and 12-month EQ-5D scores were included, rather than individual dimension scores, because if EQ-5D data were missing, then it would generally be for the whole questionnaire. Nevertheless, disaggregated costs were used (and then combined to estimate overall hospital costs) because different resource items had different levels of missing data.

Cost and outcome data were analyzed simultaneously using bivariate regression, which is generally robust for skewed data and allows for any correlation between costs and effects [25]. We followed the intention-to-treat approach, in which patients were analyzed according to the group to which they were allocated (regardless of treatment received). All the regressions included

age and sex as covariates. The QALY regression also included the baseline EQ-5D as a covariate [18]. This enabled the mean incremental cost between the two groups (mean difference in cost) and the mean incremental effect (the mean difference in both the total number of MACEs/QALYs) to be estimated.

The incremental cost-effectiveness ratio (ICER), defined as mean incremental cost/mean incremental effect [12], for complete revascularization, compared with IRA-only, was subsequently estimated. If one intervention was both less costly and more effective, it was not necessary as that intervention would be categorized as dominant [11]. The ICER can be used to assess whether the extra cost of the intervention (in this case, complete revascularization) constitutes value for money. In the United Kingdom, the National Institute for Health and Care Excellence refers to a cost-effectiveness threshold ( $\lambda$ ) value of £20,000 to £30,000 per QALY [12]. As such, if complete revascularization had an ICER (incremental cost per QALY) lower than this level, then we would consider it to be cost-effective.

To estimate the level of uncertainty associated with the decision regarding cost-effectiveness, bootstrap resampling [26] (with 250 replications drawn from each of the 20 imputed data sets [20]) was used to depict results on the cost-effectiveness plane and the cost-effectiveness acceptability curve (CEAC). The cost-effectiveness plane depicts estimates of the mean incremental cost and the mean incremental effect [27], whereas the CEAC depicts the probability of the intervention being cost-effective at various “willingness-to-pay” thresholds compared with standard care [28]. In addition, the expected value of perfect information (EVPI), which provides a guide to the upper limit of the value of further research [29], was also calculated at a  $\lambda$  value of £20,000 per QALY.

Finally, sensitivity analyses were performed to assess the robustness of the aforementioned base-case analysis conclusions to changes in key assumptions [11]. First, a *per protocol* analysis (SA1) was conducted, excluding patients who did not receive the intervention to which they were allocated (crossovers). Next, a complete case analysis (SA2) [21] was conducted for comparison, in which patients were included only if they had available data for all costs and outcomes. All analyses were performed in Stata version 12.1 [22] and because of the 12-month follow-up period, no discounting [11] was undertaken.

## Results

### Participants

Recruitment took place between May 2011 and May 2013 at seven participating UK centers. In total, 296 patients were randomized. Baseline demographic and clinical characteristics were similar in both arms; 85.3% of complete revascularization patients were male and the mean age was 64.6 years compared with 76.7% males and a mean age of 65.3 years for IRA-only patients. In the 12-month follow-up period, 14 died and 19 were lost to follow-up. A national database search indicated none of these lost to follow-up patients died during the study period [8].

### Costs

Table 1 presents the levels of resource use for both groups on the basis of available data. Mean P-PCI procedure(s) time (including any staged procedures) was higher in the complete revascularization arm (76.6 minutes compared with 45.2 minutes for the IRA-only arm;  $P < 0.001$ ), as were the number of stents (2.84 per patient vs. 1.45 per patient;  $P < 0.001$ ). Other resource item use was broadly similar between arms (see Table 1).

The unit costs attached to each item of resource use are detailed in Table 2. Total costs were subsequently estimated (see Table 3), when mean P-PCI procedure(s) costs were lower for IRA-only patients, although mean index admission length of stay costs and MACE re-admission costs were both slightly higher for IRA-only patients (see Table 3). Mean overall hospital costs were estimated to be higher for complete revascularization patients (£5552 complete [ $n = 121$ ]; £4919 IRA-only [ $n = 116$ ]), although there was no statistically significant difference between the two groups.

In relation to the additional resource use questionnaire, health professional visit data were provided by 48 (54.5%) of the 88 complete revascularization patients from whom details were requested, compared with 48 (52.2%) of the 92 IRA-only patients. In addition, because they would have had no (postdischarge) health professional visits, these costs were set to 0 for the patients who died within their index admission ( $n = 5$  IRA-only).

**Table 1 – Levels of resource use.**

Resource use	Complete (n = 150)	IRA-only (n = 146)
IRA-only, N	11 (crossover) (n = 150)	139 (n = 146)
N-IRA completed in same sitting, N	97 (n = 150)	7 (crossover) (n = 146)
N-IRA completed in separate (staged) sitting, N	42 (n = 150)	0 (n = 146)
P-PCI procedure time (min), mean $\pm$ SD	59.92 $\pm$ 29.37 (n = 140)	45.19 $\pm$ 17.60 (n = 132)
Staged N-IRA procedure time (min), mean $\pm$ SD	53.89 $\pm$ 29.10 (n = 36 of 42)	–
P-PCI and any staged N-IRA procedure time (min), mean $\pm$ SD	76.65 $\pm$ 41.20 (n = 135)	45.19 $\pm$ 17.60 (n = 132)
Glycoprotein IIb/IIIa inhibitors, N	46 (n = 145)	44 (n = 134)
Bivalirudin, N	78 (n = 139)	63 (n = 128)
Bare metal stents, N	9 (n = 147)	13 (n = 140)
Drug-eluting stents, N	141 (n = 147)	127 (n = 140)
Total number of stents (used per patient), mean $\pm$ SD	2.84 $\pm$ 1.26 (n = 147)	1.45 $\pm$ 0.90 (n = 140)
Thrombus aspiration, N	93 (n = 145)	102 (n = 140)
Radial access, N	112 (n = 146)	99 (n = 140)
Initial hospital length of stay per patient (d), mean $\pm$ SD	3.89 $\pm$ 4.26 (n = 148)	5.10 $\pm$ 10.33* (n = 140)
Re-admissions (all), length of stay per patient (d), mean $\pm$ SD	1.47 $\pm$ 3.70 (n = 139)	1.66 $\pm$ 4.08 (n = 138)

IRA, infarct-related artery; n, number of patients for whom data were available; N, number of patients in receipt; N-IRA, non-IRA; P-PCI, primary percutaneous coronary intervention.

\* One IRA patient had an index admission length of stay of 65 d and another 104 d; if these data are removed, then the IRA mean is 3.96 d and the median value in both arms is 3 d.

**Table 2 – Unit costs.**

Resource use	Unit cost (£)
<i>Index admission costs</i>	
P-PCI procedure time cost (per minute)	5.94*
Glycoprotein IIb/IIIa inhibitor: abciximab	710.15*† [15]
Bivalirudin	426.25*† [15]
Bare metal stent	97.50
Drug-eluting stents	301.88
Femoral access	46.86
Radial access	26.50
Thrombus aspiration catheter	160.00
Disposables <sup>§</sup> (cost per sitting)	154.50
Bed day	
Standard care	379.40 [13]
High dependency	851.89 [13]
Intensive care	1236.48 [13]
<i>Re-admission costs (up to 12-mo follow-up)</i>	
Bed day (non-MACE)	265.06 [13]
Myocardial infarction	1710.18 + 224.15 per day if > 5 d [13]
Heart failure	2168.19 + 280.56 per day if > 5 d [13]
Revascularization	
PCI	2016.59 + 379.40 per day if > 5 d [13]
CABG	9002.01 + 388.82 per day if > 5 d [13]
<i>Health professional visits (most commonly reported)</i>	
Cardiologist	125.89 [13]
Hospital nurse	45.00 [14]
General practitioner	25.00 [14]
CABG, coronary artery bypass grafting; MACE, major adverse cardiac event; P-PCI, primary percutaneous coronary intervention.	
* On the basis of a survey of the participating centers.	
† 2.8 vials per sitting.	
‡ 1.38 vials per sitting.	
§ Balloon, sheath, and catheter.	

The mean number of health professional visits in the 12-month follow-up period was 8.7 in the complete revascularization arm, compared with 10.6 in the IRA-only arm. The associated mean costs were £422 (n = 48) and £480 (n = 53), respectively. When health professional visit costs were added to overall hospital costs to estimate overall NHS and PSS costs, these were

estimated to be £5814 (n = 41) for complete revascularization and £5089 (n = 42) for IRA-only (see Table 3).

The two employment questions in the additional resource use questionnaire were completed by 48 (54.5%) of the 88 complete revascularization patients and 48 (52.2%) of the 92 IRA-only patients at the 12-month follow-up point. Of the 25 complete revascularization patients who reported that they were in employment at the time of their heart attack, 20 reported they had returned to work at the 12-month follow-up point. In the IRA-only arm 15 out of 23, who reported that they were in employment at the time of their heart attack, reported that they had returned to work.

### Outcomes

Table 4 presents clinical outcomes for both groups on the basis of available data. Over the 12-month follow-up period, the mean number of MACEs in the complete revascularization arm was significantly lower (0.14 per patient, 19 events in total) than that in the IRA-only arm (0.30 per patient, 41 events in total). In terms of health-related quality of life, the three-level EQ-5D scores were slightly, nonsignificantly higher for complete revascularization patients both at baseline and at 12-month follow-up.

### Analyses

Table 5 presents estimates of the mean incremental cost and incremental effect (MACE or QALY), generated from bivariate regression, along with ICER and CEAC estimates. For the base case (intention to treat) and SA1 (per protocol), complete revascularization was estimated to dominate the IRA-only arm, in terms of both MACEs and QALYs, because it had both lower mean costs and higher mean effects. Significantly fewer MACEs occurred in the complete revascularization arm, and there was no significant difference between groups with regard to either overall hospital costs or QALYs.

In terms of uncertainty, 49.0% of the cost-effect pairs on the cost-effectiveness plane were located in the southeast quadrant, where complete revascularization would be estimated to have both lower mean costs and higher mean effects. Nevertheless, there was wide variation in the bootstrap estimates of both the mean incremental cost and the mean incremental QALY gain (see Fig. 1). Similarly, according to the CEAC, at £20,000 per QALY, the probability that complete revascularization was more cost-effective than IRA-only was approximately 70%, indicating that there was some uncertainty associated with this decision (see Appendix Figure in Supplemental Materials found at <http://dx.doi.org/10.1016/j.jval.2017.02.002>). In addition, the EVPI (per patient) was estimated to be £82.73. On the assumption that about one-third of the 90,000 annual P-PCI procedures for STEMI would be eligible for

**Table 3 – Summary of total costs.**

Cost component	Complete, mean ± SD	IRA-only, mean ± SD	P value
P-PCI procedure(s) time	£455.37 ± £244.77 (n = 135)	£268.46 ± £104.55 (n = 132)	<0.001
P-PCI procedure(s) consumables and equipment	£1695.95 ± £583.41 (n = 137)	£1183.98 ± £467.88 (n = 128)	<0.001
Index admission—hospital length of stay	£2830.98 ± £2091.97 (n = 148)	£3605.11 ± £6231.66 (n = 140)	0.164
Total index admission cost	£4890.12 ± £2097.54 (n = 129)	£4668.21 ± £5048.39 (n = 121)	0.654
MACE re-admissions	£277.92 ± £1264.14 (n = 139)	£400.88 ± £1232.14 (n = 138)	0.413
Other hospital re-admissions	£310.83 ± £935.73 (n = 139)	£251.62 ± £668.20 (n = 138)	0.545
Overall hospital costs	£5551.70 ± £2974.40 (n = 121)	£4918.60 ± £2449.29 (n = 116)	0.074
Health professional visits	£422.07 ± £385.47 (n = 48)	£480.43 ± £368.74 (n = 53)	0.440
Overall NHS and PSS costs	£5814.25 ± £3041.03 (n = 41)	£5089.17 ± £2101.78 (n = 42)	0.212

n, number of patients for whom data were available; MACE, major adverse cardiac event; NHS, National Health Service; P-PCI, primary percutaneous coronary intervention; PSS, personal social services.



**Table 4 – Outcomes.**

Item	Complete (n = 150)	IRA-only (n = 146)	P value
Baseline EQ-5D-3L score, mean ± SD	0.824 ± 0.216 (n = 116)	0.791 ± 0.295 (n = 116)	0.287
12-mo EQ-5D-3L score, mean ± SD	0.837 ± 0.256 (n = 122)	0.798 ± 0.311 (n = 115)	0.295
QALY score, mean ± SD	0.833 ± 0.204 (n = 103)	0.801 ± 0.258 (n = 100)	0.339
MACE, N	19 (n = 139)	41 (n = 138)	0.016*
Death, N	4 (n = 150)	10 (n = 146)	0.098
Heart failure, N	6 (n = 139)	11 (n = 138)	0.259
Myocardial infarction, N	1 (n = 139)	3 (n = 138)	0.312
Revascularization, N	8 (n = 139)	17 (n = 138)	0.079

EQ-5D-3L, three-level EuroQol five-dimensional questionnaire; MACE, major adverse cardiac event; n, number of patients for whom data were available; N, number of events; QALYs, quality-adjusted life-years truncated at 12 mo.

\* Statistically significant  $P < 0.05$ .

complete revascularization [8], over 10 years the population EVPI would be estimated to be approximately £25 million (at a willingness-to-pay threshold value of £20,000 per QALY).

As in base-case analyses, all sensitivity analyses estimated that there was a nonsignificant difference in mean costs and QALYs, but a significant reduction in MACEs in patients undergoing complete revascularization compared with IRA-only PCI (see Table 5). For base case and SA1, costs were higher in the IRA-only group; in SA2 (complete case) however, costs were higher in the intervention arm. This was largely due to two participants in the IRA-only group with very high costs (>£50,000). These participants were excluded from SA2 because some cost components were missing; their known costs were, however, used to estimate the imputation models, and they were included in base-case and SA1 analyses.

## Discussion

### Main Findings

On the basis of evidence provided from the CvLPRIT [8], because complete revascularization had both lower mean costs and higher mean effects compared with IRA-only, we would estimate complete revascularization to be cost-effective. There is, however, some uncertainty associated with this decision. For example, according to the CEAC it was estimated that there was approximately a 30% chance (at a willingness-to-pay threshold value of £20,000 per QALY) of making the wrong decision by

implementing complete revascularization, and the population EVPI was estimated to be approximately £25 million.

### Comparisons with Other Studies

We are not aware of any previous economic evaluations that have compared complete revascularization with IRA-only for patients with STEMI with multivessel disease. The findings of this study are, however, consistent with previous clinical evidence, which suggests that complete revascularization reduces future MACEs [7,9,30,31] (with associated reduced hospital re-admission costs) and also improves quality of life (according to the Seattle Angina Questionnaire) [32]. There are few well-conducted economic analyses of P-PCI, especially in the context of randomized trials. When compared with thrombolysis, P-PCI has higher initial costs that are offset by reduced downstream costs and complications [33,34]. In the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications trial, P-PCI with stenting was shown to be cost-effective compared with plain balloon angioplasty [35]. Although they are based on different treatment comparisons, and the results may not be generalizable to the population in our study, these previous studies indicate that better revascularization in the context of STEMI can be cost-effective, in spite of higher initial costs.

### Study Limitations

In line with good practice recommendations for cost-effectiveness analyses [36], we concentrated on large cost drivers

**Table 5 – Estimates of incremental cost, incremental effect, and cost-effectiveness of complete revascularization in the base-case and sensitivity analyses.**

Analysis (N <sub>c</sub> , N <sub>i</sub> )	Incremental cost (£) (95% CI)	Incremental effect (95% CI)	ICER	CEAC <sup>†</sup>
		MACE		
Base case: imputed (150, 146)	–215.96 (–1,390.20 to 958.29)	–0.170 (–0.044 to –0.296)	Dominant <sup>‡</sup>	
SA1 <sup>§</sup> : imputed per protocol (139, 139)	–534.89 (–1,730.65 to 660.88)	–0.201 (–0.070 to –0.331)	Dominant <sup>‡</sup>	
SA2 <sup>§</sup> : complete case (121, 116)	590.63 (–91.02 to 1272.27)	–0.156 (–0.023 to –0.290)	£3,776.87	
		QALYs (truncated at 12 months)		
Base-case: imputed (150, 146)	–215.96 (–1,390.20 to 958.29)	0.011 (–0.019 to 0.041)	Dominant <sup>‡</sup>	72.0%
SA1: imputed per protocol (139, 139)	–534.89 (–1,730.65 to 660.88)	0.012 (–0.019 to 0.043)	Dominant <sup>‡</sup>	84.4%
SA2: complete case (89, 86)	446.65 (–151.55 to 1,044.86)	0.021 (–0.018 to 0.060)	£21,495.69	45.3%

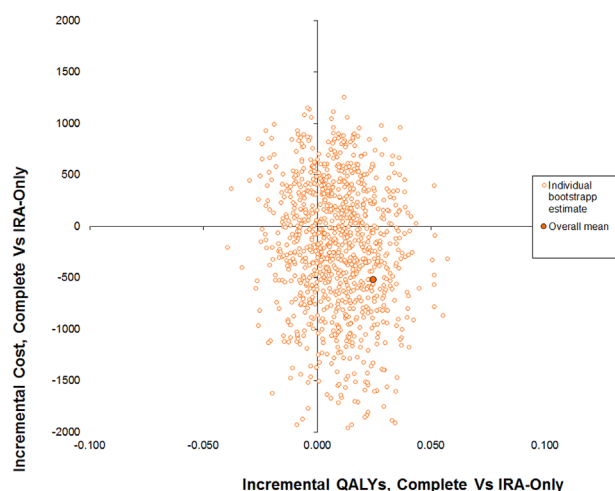
CEAC, cost-effectiveness acceptability curve; CI, confidence interval; ICER, incremental cost-effectiveness ratio; MACE, major adverse cardiac event; QALYs, quality-adjusted life-years truncated at 12 mo.

\* N<sub>c</sub> (N<sub>i</sub>) is the number of patients randomized to complete revascularization (IRA-only) who were included in the analysis.

<sup>†</sup> Probability of being cost-effective on the CEAC at the threshold (λ) of “£20,000 per QALY.”

<sup>‡</sup> “Dominant” refers to lower mean costs and higher mean effect.

<sup>§</sup> SA1 and SA2 refer to the first and second sensitivity analyses described in the Methods section.



**Fig. 1 – Bootstrap estimates (and overall mean) of the incremental cost and effect of complete revascularization compared with IRA-only, depicted on the cost-effectiveness plane. IRA, infarct-related artery; QALYs, quality-adjusted life-years.**

and excluded resources that were not expected to differ between the two treatment arms (e.g., routine monitoring scans or tests). That said, a potential limitation is that a narrow health sector cost perspective was taken, particularly because patients in only three centers were asked to complete the additional self-report questionnaire (reporting health professional visits and employment status). These costs were excluded from subsequent analyses. The results presented in Table 3 indicate that these were not the main cost drivers for responding patients. With regard to health-related quality of life, QALY scores were available for approximately 70% of participants only (see Table 4). Some of the missing EQ-5D baseline data may be due to the patient being discharged at short notice or at the weekend when a research nurse was not available.

A further potential limitation is that our analysis is based on the evidence generated by one trial [8] and therefore may not incorporate all relevant evidence [37]. That said, a recent meta-analysis [31] shows that our trial results are in keeping with the few trials that have been conducted in this area. Similarly, it could be argued that the conclusions might differ if results were estimated over a longer follow-up period. Nevertheless, if the treatment effect was maintained beyond 12 months, the conclusions would be unchanged because extrapolation would increase the QALY gain, improving the estimated level of cost-effectiveness. The main strength of this economic analysis is that it is based on a randomized study [8], an advance on observational studies that may not control for confounding factors [30].

## Conclusions

On the basis of an economic evaluation of the CvLPRIT [8], we have shown that in a population of patients with STEMI with multi-vessel disease, complete revascularization undertaken during the index admission was more effective in terms of fewer MACEs, and had an incremental QALY gain, compared with IRA-only revascularization. Because higher procedure costs are broadly offset by lower re-admission rates, such that overall costs are similar, these data suggest that complete revascularization constitutes a cost-effective treatment option for patients with STEMI with multi-vessel disease. That said, the CEAC and EVPI values suggest that there is some uncertainty associated with this decision.

## Acknowledgments

CvLPRIT Investigators: Anthony H. Gershlick, Gerry P. McCann, Jamal N. Khan (Department of Cardiovascular Sciences, University of Leicester, and the NIHR Leicester Cardiovascular Biomedical Research Unit, University Hospitals of Leicester NHS Trust), Garry R. Barton, Lisa Irvine, Marcus Flather, Helen L. Risebro (Norwich Medical School, University of East Anglia), John P. Greenwood, Daniel J. Blackman (Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds), Miles Dalby (Royal Brompton and Harefield Foundation Trust, Harefield Hospital), Nick Curzen (University Hospital Southampton NHS Foundation Trust, and Faculty of Medicine, University of Southampton), Simon Hetherington (Kettering General Hospital), Damian J. Kelly (Royal Derby Hospital), Duolao Wang (London School of Tropical Medicine), Thiagarajah Sasikaran (Clinical Trials and Evaluation Unit, Royal Brompton and Harefield NHS Foundation Trust, and Imperial Clinical Trials Unit, Imperial College London), and Howard Swanton (The Heart Hospital, University College London Hospitals). Conflicts of interest: M. Flather reports grants and personal fees from Astra Zeneca and grants from Novartis. N. Curzen reports grants and personal fees from Boston Scientific, Haemonetics, HeartFlow, and St Jude Medical; nonfinancial support from Volcano; and personal fees and nonfinancial support from Abbott Vascular. No other author declared any conflicts of interest.

*Source of financial support:* This independent research was funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit Programme (grant reference no. PB-PG-0711-25003). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health. The main CvLPRIT was funded by the British Heart Foundation [1].

## Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at <http://dx.doi.org/10.1016/j.jval.2017.02.002> or, if a hard copy of article, at [www.valueinhealthjournal.com/issues](http://www.valueinhealthjournal.com/issues) (select volume, issue, and article).

## REFERENCES

- [1] British Heart Foundation. Cardiovascular disease statistics UK factsheet 2015. Available from: <https://www.bhf.org.uk/research/heart-statistics>. [Accessed April 12, 2016].
- [2] British Cardiovascular Intervention Society. National Audit of Percutaneous Coronary Intervention Public Report, Annual Public Report January 2012–December 2012. London: National Institute for Cardiovascular Outcomes Research (NICOR), Institute of Cardiovascular Science, University College London, 2012.
- [3] Harries I, Ramcharitar S. Total revascularization of coronary disease at the time of primary percutaneous coronary intervention. *Future Cardiol* 2014;10:451–5.
- [4] Steg PG, James SK, Atar D, et al. Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the ESC. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012;33:2569–619.
- [5] Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation* 2011;124:e574–651.
- [6] Sethi A, Bahekar A, Bhuriya R, et al. Complete versus culprit only revascularization in acute ST elevation myocardial infarction: a meta-analysis. *Cathet Cardiovasc Diagn* 2011;77:163–70.

- [7] Wald DS, Morris JK, Wald NJ, et al. PRAMI Investigators. Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med* 2013;269:1115–23.
- [8] Gershlick AH, Khan JN, Kelly DJ, et al. Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. *J Am Coll Cardiol* 2015;65:963–72.
- [9] Engström T, Kelbæk H, Helqvist S, et al. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3—PRIMULTI): an open-label, randomised controlled trial. *Lancet* 2015;386:665–71.
- [10] American College of Cardiology. American College of Cardiology updates heart attack recommendations 2014: Available from: <http://www.choosingwisely.org/clinician-lists/american-college-cardiology-stenting-of-non-culprit-lesions-during-pci/>. [Accessed April 12, 2016].
- [11] Drummond MF, Sculpher MJ, Claxton K, et al. *Methods for the Economic Evaluation of Health Care Programmes* (4th ed.). New York, NY: Oxford University Press, 2015.
- [12] National Institute of Health and Care Excellence. *Guide to the Methods of Technology Appraisal* 2013. London: National Institute of Health and Care Excellence, 2013.
- [13] Department of Health. *National Schedule of Reference Costs 2012–13*. London: Department of Health, 2014.
- [14] Curtis L. *Unit Costs of Health and Social Care*. Kent, UK: The University of Kent, 2013.
- [15] Health and Social Care Information Centre (Prescribing and Primary Care Team). *Prescription Cost Analysis, England—2013*. Leeds, UK: Health and Social Care Information Centre, 2014.
- [16] Brooks R. EuroQol: the current state of play. *Health Policy* 1996;37:53–72.
- [17] Dolan P. Modelling valuations for EuroQol health states. *Med Care* 1997;35:1095–108.
- [18] Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. *Health Econ* 2005;14:487–96.
- [19] Longworth L, Bryan S. An empirical comparison of EQ-5D and SF-6D in liver transplant patients. *Health Econ* 2003;12:1061–7.
- [20] Faria R, Gomes M, Epstein D, White IR. A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials. *Pharmacoeconomics* 2014;32:1157–70.
- [21] Noble SM, Hollingworth W, Tilling K. Missing data in trial-based cost-effectiveness analysis: the current state of play. *Health Econ* 2012;21:187–200.
- [22] StataCorp LP. STATA statistical software [program]. Stata/SE 12.1 version. College Station, TX: StataCorp LP, 2011.
- [23] White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med* 2011;30:377–99.
- [24] Little RJA, Rubin DB. *Statistical Analysis with Missing Data* (2nd ed.). Hoboken, NJ: Wiley, 2002.
- [25] Willan AR, Briggs AH, Hoch JS. Regression methods for covariate adjustment and subgroup analysis for non-censored cost-effectiveness data. *Health Econ* 2004;14:461–75.
- [26] Briggs AH, O'Brien BJ, Blackhouse G. Thinking outside the box: recent advances in the analysis and presentation of uncertainty in cost-effectiveness studies. *Annu Rev Public Health* 2002;23:377–401.
- [27] Black WC. The CE plane: a graphic representation of cost-effectiveness. *Med Decis Making* 1990;10:212–4.
- [28] Fenwick E, O'Brien BJ, Briggs AH. Cost-effectiveness acceptability curves—facts, fallacies and frequently asked questions. *Health Econ* 2004;13:405–15.
- [29] Wilson EC. A practical guide to value of information analysis. *Pharmacoeconomics* 2015;33:105–21.
- [30] Politi L, Sgura F, Rossi R, et al. A randomised trial of target-vessel versus multi-vessel revascularisation in ST-elevation myocardial infarction: major adverse cardiac events during long-term follow-up. *Heart* 2010;96:662–7.
- [31] El-Hayek GE, Gershlick AH, Hong MK, et al. Meta-analysis of randomized controlled trials comparing multivessel versus culprit-only revascularization for patients with ST-segment elevation myocardial infarction and multivessel disease undergoing primary percutaneous coronary intervention. *Am J Cardiol* 2015;115:1481–6.
- [32] Henry TD, Gershlick A. Going beyond the hard endpoints: "quality of life" may be dependent on quality of available data. *J Am Coll Cardiol* 2015;66:2114–5.
- [33] Aasa M, Henriksson M, Dellborg M, et al. Cost and health outcome of primary percutaneous coronary intervention versus thrombolysis in acute ST-segment elevation myocardial infarction—results of the Swedish Early Decision reperfusion Study (SWEDES) trial. *Am Heart J* 2010;160:322–8.
- [34] Selmer R, Halvorsen S, Myhre KI, et al. Cost-effectiveness of primary percutaneous coronary intervention versus thrombolytic therapy for acute myocardial infarction. *Scand Cardiovasc J* 2005;39: 276–85.
- [35] Bakhai A, Stone GW, Grines CL, et al. Cost-effectiveness of coronary stenting and abciximab for patients with acute myocardial infarction: results from the CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trial. *Circulation* 2003;108:2857–63.
- [36] Ramsey SD, Willke RJ, Glick H, et al. Cost-effectiveness analysis alongside clinical trials II—an ISPOR Good Research Practices Task Force report. *Value Health* 2015;18:161–72.
- [37] Sculpher M. Clinical trials provide essential evidence, but rarely offer a vehicle for cost-effectiveness analysis. *Value Health* 2015;18:141–2.