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Percutaneous Revascularisation for Ischemic Left Ventricular Dysfunction: Cost-Effectiveness Analysis of the REVIVED-BCIS2 Trial

Running Title: *Chivardi et al.; Cost-Effectiveness of REVIVED-BCIS2 Trial*

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Abstract

Background: Percutaneous coronary intervention (PCI) is frequently undertaken in patients with ischemic left ventricular systolic dysfunction (ILVD). The REVIVED-BCIS2 trial concluded that PCI did not reduce the incidence of all-cause death or heart failure (HF) hospitalization, however patients assigned to PCI reported better initial health-related quality of life than those assigned to optimal medical therapy (OMT) alone. The aim of this study was to assess the cost-effectiveness of PCI+OMT compared with OMT alone.
Methods: REVIVED-BCIS2 was a prospective, multi-centre UK trial, which randomized patients with severe ILVD to either PCI+OMT or OMT alone. Healthcare resource use (including planned and unplanned revascularizations, medication, device implantation and HF hospitalizations) and health outcomes data (EQ-5D-5L questionnaire) on each patient were collected at baseline and up to 8 years post-randomization. Resource use was costed using publicly available national unit costs. Within trial mean total costs and quality-adjusted life years (QALYs) were estimated from the perspective of the UK health system. Cost-effectiveness was evaluated using estimated mean costs and QALYs in both groups. Regression analysis was used to adjust for clinically relevant predictors.
Results: Between 2013 and 2020, 700 patients were recruited (mean age: PCI+OMT=70, OMT=68; male (%): PCI+OMT=87, OMT=88); median follow up was 3.4 years. Over all follow-up, patients undergoing PCI yielded similar health benefits at higher costs compared to OMT alone (PCI+OMT: 4.14 QALYs, £22,352; OMT alone: 4.16 QALYs; £15,569; Difference: -0.015; £6,782). For both groups most health resource consumption occurred in the first 2 years post-randomization. Probabilistic results showed that the probability of PCI being cost-effective was 0.
Conclusions: Minimal difference in total QALYs was identified between arms and PCI+OMT was not cost-effective compared to OMT, given its additional cost. A strategy of routine PCI to treat ILVD does not appear to be a justifiable use of healthcare resource in the UK.
Clinical Trial Registration: URL: https://clinicaltrials.gov/ Unique Identifier: NCT01920048

Key Words: Cost-effectiveness analysis implantable devices, heart failure, myocardial revascularization, percutaneous coronary intervention

Nonstandard Abbreviations and Acronyms:
AIC/BIC: Akaike's information criteria / Bayesian information criteria
BCIS: British Cardiovascular Intervention Society
CABG: Coronary artery bypass grafting
CRF: Case report form
EQ-5D-5L: EuroQol 5-Dimension 5-Level
GLMs: Generalised linear models
ILVD: Left ventricular systolic dysfunction
KCCQ: Kansas City Cardiomyopathy Questionnaire
MICE: Multiple Imputation by Chained Equations
NICE: National Institute for Health and Care Excellence
NYHA: New York Heart Association
OMT: Optimal medical therapy
PCI: Percutaneous coronary intervention
PSA: Probabilistic sensitivity analysis
QALY: Quality adjusted life year

REVIVED: Revascularisation for Ischemic Ventricular Dysfunction
STICH: Surgical Treatment for Ischemic Heart Failure

What is Known

- Percutaneous coronary intervention (PCI) is frequently utilized in patients with ischemic left ventricular systolic dysfunction (ILVD).
- The REVIVED-BCIS2 trial demonstrated that PCI did not decrease all-cause death or heart failure hospitalization rates, although patients undergoing PCI initially reported an improved health-related quality of life compared to optimal medical therapy (OMT) alone.
- The economic and health consequences of a PCI strategy for ILVD remain unknown.

What the Study Adds

- This study evaluates the economic implications associated with PCI in ILVD patients, filling a crucial knowledge gap.
- Results indicate that although PCI provides similar health benefits, it comes at a higher cost when compared to OMT alone.
- Most health resource utilisation occurred in the first 6 months post-randomization, related to the PCI procedures.
- Study findings indicate that routine PCI as a treatment strategy for ILVD is not cost-effective, which has implications for healthcare resource allocation.

Introduction

Heart failure (HF) is an increasing worldwide health problem, with coronary artery disease the most common cause[1]. Over the last few decades, advances in medical and device therapy have been central to improving the prognosis of patients with ischemic heart failure. Coronary revascularization is frequently used as an adjunct to medical therapy in these patients, the benefits of coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) having been evaluated in the Surgical Treatment for Ischemic Heart Failure (STICH) and the Revascularisation for Ischaemic Ventricular Dysfunction (REVIVED) trials, respectively[2,3].

In the REVIVED trial, it was hypothesized that revascularization with PCI in addition to optimal medical therapy (OMT) compared to OMT alone could improve event-free survival in patients with severe ILVD [4]. There was no difference between groups in the occurrence of the primary outcome at a median of 3.4 years. Early health related quality of life was better in patients assigned to have PCI, and although this difference was not sustained this has led some to conclude PCI is still a beneficial strategy.[5]

The aim of our current analysis was to assess the cost-effectiveness of PCI for patients with severe stable ILVD by using patient-level resource use and patient-reported outcome data collected in the REVIVED trial.

Methods

Trial design and patient population

REVIVED was a prospective, multicentre, randomized, open-label trial involving 700 patients with ILVD [3]; randomization was to either PCI+OMT or OMT alone. Participants were enrolled between 2013 and 2020; full patient eligibility criteria have been published previously[4]. The trial protocol was registered before enrollment of the first patient

(NCT01920048) and was approved by the UK Health Research Authority. All patients provided written informed consent. The data that support the findings of this study and the analytic methods will be made available 1 year from completion of the trial on reasonable request to the corresponding author.

The patients enrolled had a median age of 69 years, 12% were female, the median British Cardiovascular Intervention Society (BCIS) jeopardy score was 10, mean baseline LVEF was 27% ±6.8 and 26% had New York Heart Association (NYHA) class III or IV functional status (Table S1). The baseline Kansas City Cardiomyopathy Questionnaire (KCCQ) mean overall score was 60.9 and EuroQol 5-Dimension 5-Level (EQ-5D-5L) mean utility score was 0.67.

Economic Analysis

The analysis follows the preferred methods of the UK National Institute for Health and Care Excellence (NICE)[6] and took a UK NHS and Personal Social Services perspective. A time horizon of up to eight years was used based on trial follow-up, with costs and consequences discounted at 3.5% annual rate[6]. Economic evaluation results were expressed using differences in costs and quality-adjusted life years (QALYs) between the treatment options.

Estimation of Costs

Healthcare resources used by each participant in the trial were obtained from the trial Case Report Forms (CRF) completed by trial investigators. The CRF captured the health resource consumption at baseline, 6 months, 12 months and then on a yearly basis, with only post-randomization consumption included for analysis. Relevant health resources included revascularization, prescribed medications, heart failure (HF) hospital admissions and related treatments, implantable cardiac device implantation or upgrade, outpatient visits and clinical investigations (e.g. echocardiogram) during the first 2 years following randomization. HF hospitalizations, unplanned revascularizations and implantable device information were

collected yearly from 2 to 8 years. Unit costs for the health resources were obtained from National NHS Reference Costs databases[7] (Table S2) and medication prices obtained from the British National Formulary[8].

Healthcare resource use was combined with relevant unit costs and aggregated to produce a total cost for each trial participant. Six distinct cost categories were defined: planned and unplanned revascularization procedures, medications, hospitalization, implanted devices and clinical investigations (including: haemoglobin, creatinine, cholesterol, LDL, HDL, triglyceride, BNP, HbA1C, echocardiogram, etc). Within the intervention arm, planned revascularization procedures encompassed the costs associated with the initial planned percutaneous coronary procedures and its subsequent stages. Unplanned revascularization related to any subsequent unplanned PCIs or CABG procedures throughout trial follow up. Medication costs related to cardiac medication at randomization, at hospital discharge and at relevant assessment points of follow-up, in both arms of the trial. The cost of medication was estimated according to the dosage and duration of each drug consumed. Heart failure hospitalization costs include costs related to inpatient stays, as well as any associated diagnostic tests, procedures, and medication required within that admission. Implantable device costs encompassed the device itself (CRT, CRT-D, or ICD only) as well as all costs associated with its implantation or upgrade. Finally, clinical investigation costs were related to the diagnosis and management of coronary artery disease and HF, including costs associated with tests such as blood tests and echocardiograms (pre-randomization eligibility testing was not considered).

By estimating the costs associated with each of these categories, we aimed to provide a comprehensive understanding of the cost burden associated with treating patients with ILVD. Costs were expressed as total per participant costs over the follow up period.

Health-Related Quality of Life

In the REVIVED trial health-related quality-of-life was assessed using the KCCQ and the EQ-5D-5L questionnaires.[9] Health-related quality-of-life data were collected at baseline, 6 months, 12 months and annually thereafter until trial end. The current analysis used the EQ-5D-5L, a standardised instrument for measuring health-related quality-of-life that consists of five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each domain is scored on a 5-point scale (no problems, slight problems, moderate problems, severe problems and unable) and the response of each trial participant is converted into a single 'utility' score, ranging from 0 (representing death) to 1 (representing perfect health). Utilities are based on the preferences of a sample of the UK population[10,11]. For each individual participant QALYs were derived from the utilities for each year of follow-up, considering zero QALYs for deceased patients.

Multiple Imputation

Missing responses to the EQ-5D instrument were imputed using MICE (Multiple Imputation by Chained Equations)[12]. Two types of missing values were imputed: 1) missing values resulting from questionnaires that were not completed during follow-up were and intended to have been collected via the CRF; 2) values beyond the last date of follow-up, up to a hypothetical follow-up duration of 8 years, where the actual patient follow-up duration was shorter. The overall missing rate in the OMT group was 5.0 % and 4.6% for the PCI group. Results from imputed datasets were combined using Rubin's rules to obtain joint regression model estimates[12]. Further detail on the multiple imputation approach can be found in the supplementary materials and Table S3.

Regression Analysis

Generalised linear models (GLMs) were used to estimate independently predicted total costs and QALYs over the follow-up period. Adjustment for clinically relevant and validated

covariates was performed, consistent with the primary outcome analysis[4,12]. Covariable adjustment included the following baseline characteristics: age centred (continuous), sex (binary: F/M), New York Heart Association (NYHA) scale (categorical: I (reference), II, III and IV), BMI (continuous), ethnicity (categorical: Caucasian (reference), Asian, Afro-Caribbean and Other), BCIS jeopardy score (categorical: Mild = 2-4; Moderate = 6-8; Severe = 10-12), smoking status (categorical: Never (reference), Current and Ex-smoker), previous HF hospitalisation (binary: Y/N), previous PCI and/or CABG (binary: Y/N), previous MI (binary: Y/N), hypertension (binary: Y/N) and diabetes (binary: Y/N). The modelling of total QALYs also considered patients' baseline EQ-5D utilities (continuous) as covariable. Different distributional assumptions (log-normal; gen gamma; gaussian) and link functions (identity and log) were tested for the total costs and QALY models. The model selection process was based on the distributional properties of the dependent variables, their statistical fit as assessed by AIC/BIC statistics [13], and, notably, considering the suitability and reasonableness of the estimated or predicted outcomes generated by the selected statistical model.

To consider the potential interdependence and/or correlation between costs and outcomes, a Seemingly Unrelated Regression (SUR) model was performed as a modelling alternative[14]. SUR is considered particularly useful when analysing complex systems or datasets where multiple dependent variables, such as costs and QALYs here, are expected to have shared underlying factors.[14]

Cost-Effectiveness Analysis

Incremental cost-effectiveness analysis was conducted based on differences in mean costs and QALYs between the two randomized groups. In the context of one group having higher mean costs and QALYs, an incremental cost-effectiveness was estimated as the relevant intervention's incremental cost per additional QALY. Judgements on the cost-effectiveness

of interventions was performed by comparing the incremental cost-effectiveness ratio to the NICE cost-effectiveness threshold range of £20,000-£30,000 per QALY gained.

Sensitivity analyses were performed to assess the robustness of results. The analyses were conducted to evaluate the impact of key assumptions and uncertainties on the estimated incremental cost-effectiveness ratio and to test the validity of findings. A probabilistic sensitivity analysis was considered to account for the joint uncertainty in all parameters simultaneously based on 1,000 random samples from the parameter distributions, enabling the estimation of the probability of each intervention being cost-effective at a range of cost-effectiveness thresholds. A scenario analysis was also considered by varying the unit cost of implantable devices (CRT, CRT-D and ICD only), covering values reported in two different sources (Table S2).

Results

Between 2013 and 2020, 347 patients were randomized to PCI+OMT and 353 to OMT alone. A total of 225 patients (32%) died during the median trial follow up of 41 months. The KCCQ overall summary score at 6 months increased by 6.5 points more in the PCI+OMT arm (+11.2 vs +4.7). However, by 24 months the difference was not significant (70.6 vs 68.1, difference of 2.6); the same trend was also seen in EQ-5D-5L[3]. By the end of trial follow up, 53.1% of patients had a cardiac device in situ, with 93 patients in the PCI+OMT and 120 patients in the OMT arm having a device inserted or upgraded after randomization[15]. Regarding unplanned revascularizations, there were 10 (2.9%) and 37 (10.5%) procedures in the PCI+OMT and OMT arms, respectively.

Resource Use and Costs

In the OMT group, the unadjusted mean total cost per patient during all follow-up was £15,882 (95% CI £13,958 - £17,806), while for the PCI+OMT group it was £21,674 (95% CI

£19,722 - £23,626). The mean difference between the groups was £5,791 (95% CI £3,056 - £8,528)(Table 1). Figure 1 displays the distribution of unadjusted mean costs by category over the follow-up period for each treatment group. The higher unadjusted mean costs for PCI+OMT were driven by the assigned treatment (planned revascularization mean cost: £7,752) performed during the first 6 months post-randomization (n=325, 94%, patients received a planned PCI). A total of 417 PCI procedures were performed on 334 patients; 80 patients had at least one staged procedure (Table 1). All other costs were broadly similar between the groups across the whole duration of follow-up, with implantable devices, medication and HF-related hospitalisations having a substantial impact on total costs in both groups. More patients in the OMT group received implantable devices following randomization than the PCI+OMT group, although this difference was not statistically significant (34% versus 27%). Although the frequency of hospitalisations for heart failure was similar (PCI+OMT, n=103, 29%; OMT alone, n=108, 31%), patients hospitalised in the OMT group spent on average, more days in hospital (mean 3.14 days (95% CI: -2.88 – 9.49) due to HF than the PCI+OMT group.

Most of the within-trial costs were incurred during the first two years of randomization in both groups. The average cost per patient during the first two years was £13,366 for the OMT group and £19,905 for the PCI+OMT group. Apart from the cost of the randomized intervention, the two groups had similar resource consumption (equivalent medication and clinical investigation usage up to 2 years) and costs (cost difference: £6,539, 95% CI: 5,214 - £8,071) as the OMT group (Table S4-S7).

Health-Related Quality-of-Life

Table 2 presents observed EQ-5D-5L utilities for the two treatment groups, PCI and OMT, across the follow-up. A higher mean utility for PCI+OMT than for OMT was observed up to one year with minimal difference thereafter. Over the course of the study, observed mean

utility for PCI+OMT was the same or higher than for OMT. Figure 2 provides a time trend of imputed EQ-5D index scores by treatment group, which reinforces these findings. Patients in the PCI+OMT group accrued, on average, 0.527 unadjusted EQ5D score, while patients randomized to the OMT alone group gained on average, 0.509 unadjusted EQ5D score. Table S8 presents the observed total QALYs.

Regression Analysis

Table S9 highlights the baseline characteristics which were identified to have influenced total costs and QALYs. Randomized treatment group was important in explaining the variation in total costs but not in total QALYs, with PCI+OMT associated with a higher cost (Figure 1). Findings suggested older age was associated with lower QALYs ($p<0.05$), though having non-significant impact on costs ($p = 0.27$). BMI was found to be relevant to explain variation in total costs but not total QALYs. A comparison of the baseline characteristics of patients with higher predicted costs (≥£20,000) with the overall sample revealed that patients with higher consumption of health resources have higher prevalence of diabetes (76% vs. 41%) and previous PCI (35% vs. 20%) and a greater proportion of classes 3/4 NYHA classification (53% vs. 26%).

Cost-Effectiveness

The predicted average cost for OMT alone, adjusted for differences in baseline covariables, was £15,569 (95% CI: £15,302 - £15,835) compared to £22,352 (95% CI: £21,969 - £22,734) for a strategy of PCI+OMT (Table 3). The predicted mean cost difference between the two strategies was £6,782 (95% CI: £6,666 - £6,899), indicating a substantial cost difference between strategies, in favour of OMT alone. The OMT group accrued 4.16 (95% CI: 4.02 – 4.30) QALY over the follow-up period, adjusted for differences in baseline covariables, compared to 4.14 (95%CI: 4.02 – 4.27) in the PCI+OMT group, which results in an incremental predicted QALY difference of -0.015 (95% CI: -0.385 – 0.355) for a strategy of

PCI+OMT. Thus, PCI+OMT is estimated to have a higher mean cost with lower mean QALYs when compared to OMT alone, which means it is dominated by OMT alone and not cost-effective. Table S8 presents the observed incremental costs and QALYs, which are aligned with the adjusted outcomes.

The probabilistic sensitivity analysis revealed that none of the simulations implemented resulted in a different outcome to the deterministic one (Figure 3). That is, even when accounting for parameter uncertainty, OMT alone continues to be less costly with slightly higher QALYs when compared to PCI+OMT. Thus, the probability of PCI+OMT being cost-effective at the NICE cost-effectiveness threshold (£20k to £30k per QALY gained) was 0. Results of the SUR model were found to be consistent with the outcomes of the main regression analysis, as no significant difference was identified between estimated QALYs for the control and the treatment group (Table S10). The scenario analysis examined the potential impact of changes in implant costs on treatment expenses and found that such variations did not result in significant cost fluctuations.

Discussion

In this prospective within-trial cost-effectiveness analysis of the REVIVED trial, no appreciable difference in total QALYs was identified between arms, but PCI+OMT strategy was substantially more expensive than OMT alone, largely due to the upfront cost of PCI. Consequently, PCI+OMT was economically dominated and not cost-effective compared to OMT. When parameter uncertainty is allowed for there was a no probability of PCI+OMT being cost-effective at a threshold of £20,000/QALY or higher. The clinical results of REVIVED were neutral for the comparison of strategies, with no safety concerns raised with PCI, in contrast the STICH trial where CABG was associated with a 3-4-fold excess in mortality within the first two years following randomization[2]. Hence, the REVIVED clinical

result for PCI has been interpreted as showing neither a clinical benefit nor any clinical downside to performing PCI in these patients. In REVIVED the short-term impact of PCI on health-related quality-of-life captured in the KCCQ (overall score) and EQ-5D-5L (utility score) suggested a possible benefit relative to OMT and justified this economic evaluation. However, our economic findings are notable in showing that routine performance of PCI in these patients has a negative economic impact on health care systems. Given the high prevalence of HF patients with severe ILVD, and the expectation of an increased incidence over the medium to longer-term in the context of an aging population, substantial healthcare system savings are anticipated.

No prior study of has reported on the incremental costs of the PCI against relevant comparators for patients with ILVD. Our findings are in contrast to the economic analysis performed on the STICH trial data[2]. The STICH trial compared CABG plus medical therapy (MT) to MT alone in patients with ILVD and showed no overall difference in survival at 5 years, although improved survival was demonstrated in the CABG arm at 10 years of follow-up[16]. An economic analysis of the STICH trial concluded that CABG increased the quality-adjusted life expectancy compared with medical therapy alone at an increased cost ($63,989), although the latter was within the pre-specified benchmark for good value within the US health care system ($100,000)[2]. The authors found that patients randomized to CABG+OMT gained 0.45 QALYs compared to OMT alone over a 10-year follow-up whereas the REVIVED trial has identified no difference in QALYs between groups, albeit over a slightly shorter time horizon (median follow up 3.4 years). The difference in QALY in turn is driven primarily by a differential treatment effect in relation to all-cause mortality. Whilst it remains possible that this may relate to fundamental differences between CABG and PCI, direct study-level comparison of STICH and REVIVED is hampered by substantial differences between trial populations[17] (as exemplified by the difference in age with patients enrolled in

REVIVED being 10 years older than those in STICH) and major differences in use of device and medical therapy in the two trials.

Economic analyses of revascularization by PCI have also been performed for the COURAGE and ORBITA trials in patients with stable coronary artery disease, although these studies specifically excluded patients with severe LV systolic dysfunction and multivessel disease. Notwithstanding the important differences in target populations, different settings (US and UK), modelling assumptions (within-trial and model-based) and comparators (best medical therapy and placebo), the results of the aforementioned analyses support the view of some disparity in the economic value of PCI.[18,19]

The clinical results of REVIVED were neutral for the comparison of strategies, with no safety concerns raised with PCI, in contrast the STICH trial where CABG was associated with a 3-4-fold excess in mortality within the first two years following randomization[2]. Hence, the REVIVED clinical result for PCI has been interpreted as showing neither a clinical benefit nor any clinical downside to performing PCI in these patients. In REVIVED the short-term impact of PCI on health-related quality-of-life captured in the KCCQ (overall score) and EQ-5D-5L (utility score) suggested a possible benefit relative to OMT and justified this economic evaluation. However, our economic findings are notable in showing that routine performance of PCI in these patients has a negative economic impact on health care systems. Given the high prevalence of HF patients with severe ILVD, and the expectation of an increased incidence over the medium to longer-term in the context of an aging population, substantial healthcare system savings are anticipated.

A strength of this economic analysis was the relatively long study follow-up period (up to 8 years, median 3.4 years). This offers a good understanding of the medium to long-term costs and benefits of the strategies being evaluated. Whilst a life-time analysis could have been conducted, the results of this 8-year analysis indicated this was unnecessary. Given

the clinical, cost and health-related quality-of-life results we have reported, there seems to be very unlikely a scenario in which longer-term costs and outcomes would make PCI a cost-effective treatment, and we believe that it is reasonable to conclude that estimated cost-effectiveness over an 8-year time horizon is generalisable to the patient's lifetime. For this reason, no modelling to extrapolate evidence from the trial to the long-term was considered necessary.

By employing regression analyses in our study, we aimed to provide an unbiased estimate of the expected costs and health outcomes associated with each treatment, as should be the objectives of any cost-effectiveness analysis. By describing the relationship between the outcome of interest, and treatment assignment, it helped us identify the expected costs and outcomes associated with the comparator treatment. The regression framework also enabled a characterization of the decision uncertainty from which an assessment of the need for any additional research could be made. A note that the uncertainty expressed in the cost-effectiveness estimates presented relate to second-order uncertainty (uncertainty around the mean, for the average severe ILVD patient) and are subject to structural uncertainty (uncertainty relating to the form of regression model implemented). On the latter, model specification may hinder an appropriate reflection of parameter uncertainty, which may be reflected in the relatively narrow confidence intervals of the predicted total costs. With its advantages and disadvantages, alternative modelling has been implemented through a SUR model.

The study has some limitations. The resource use collected within the REVIVED trial are believed to be comprehensive, though the aim of our study was not to estimate the total cost burden of ILVD but capture cost and QALY differences between therapies here under scrutiny. Nevertheless, and as with many trial analyses, there are practical limits to what has been collected. For example, the total number of clinical tests performed on trial patients are

likely to exceed what was captured in the CRF as only mandated tests to inform the specified clinical outcomes were captured. The total cost of managing these patients is likely to be appreciably higher than we have estimated, however, these uncaptured costs are likely to be distributed evenly between groups. Another potential limitation of our work is that medication data were collected only for the initial 2-years of follow-up. These limitations apply to both study arms and are unlikely to impact on the overall conclusions of the analysis. A sensitivity analysis using alternative unit costs from NHS Reference costs 2020/21 [20] showed that the cost-effectiveness results were robust to changes to these costs.

Health-related quality-of-life collected via the EQ-5D-5L questionnaire contained a proportion of missing data. This was due to a small proportion of patients being lost to follow-up, being too unwell to complete the questionnaires as well as limitations in face-to-face visits due to the COVID-19 pandemic. It was assumed that systematic differences between the missing and observed EQ-5D index scores existed, but that these could be entirely explained by other observed variables. Thus, multiple imputation was used to address missingness and generate multiple imputed datasets and achieve a similar timeframe of analysis, providing a fuller understanding of the health-related quality-of-life data. This approach allowed us to account for any gaps or missing values in the per patient QALY calculations and ensure a comprehensive evaluation of the health outcomes for both the OMT and PCI+OMT arms.

Lastly, our analysis is based specifically on costs relating to the UK NHS and cannot therefore be directly transferable to other health systems. The costs of PCI are relatively low in the publicly funded NHS by comparison with privately funded healthcare systems, such as the US. If similar health resource consumption and health-related quality-of-life are assumed, a higher cost for PCI would augment overall costs further and further increase its negative economic impact.

In summary, our results have identified that for patients with severe ILVD in the UK, revascularization using PCI in addition to OMT is not considered to be cost-effective when compared to OMT alone, given its additional cost. These conclusions were robust to different modelling assumptions and unit costs. Routine use of PCI for the treatment of severe ILVD does not appear to be a justifiable use of the UK NHS resources.

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Disclosures

None.

Supplemental Material

Supplemental Methods

Supplemental Tables

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References

1. British Heart Foundation. UK Factsheet. 2023:1–21. Available at: https://www.bhf.org.uk/-/media/files/for-professionals/research/heart-statistics/bhf-cvd-statistics-uk-factsheet.pdf [Accessed: 20 Sept 2023]
2. Chew DS, Cowper PA, Al-Khalidi H, Anstrom KJ, Daniels MR, Davidson-Ray L, Li Y, Michler RE, Panza JA, Piña IL, et. al. Cost-Effectiveness of Coronary Artery Bypass Surgery Versus Medicine in Ischemic Cardiomyopathy: The STICH Randomized Clinical Trial. *Circulation*. 2022;145(11):819–828.
3. Perera D, Clayton T, Petrie MC, Greenwood JP, O'Kane PD, Evans R, Sculpher M, Mcdonagh T, Gershlick A, de Belder M, et. al. Percutaneous Revascularization for Ischemic Ventricular Dysfunction: Rationale and Design of the REVIVED-BCIS2 Trial. *JACC: Heart Failure*. 2018;6(6):517–526.
4. Perera D, Clayton T, O'Kane PD, Greenwood JP, Weerackody R, Ryan M, Morgan HP, Dodd M, Evans R, Canter R, et al. Percutaneous Revascularization for Ischemic Left Ventricular Dysfunction. *New England Journal of Medicine*. 2022;387(15):1351–1360.
5. Pathak S, Lai FY, Miksza J, Petrie MC, Roman M, Murray S, Dearling J, Perera D, Murphy GJ. Surgical or percutaneous coronary revascularization for heart failure: an *in silico* model using routinely collected health data to emulate a clinical trial. *European Heart Journal*. 2023;44(5):351–364.
6. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual. 2022. Available at: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation [Accessed: 20 Sept 2023]
7. National Health Service England. National Cost Collection for the NHS. 2022. Available at: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/ [Accessed: 20 Sept 2023]
8. Joint Formulary Committee. British National Formulary. 2023. Available at: https://bnf.nice.org.uk/drugs [Accessed: 20 Sept 2023]..
9. Brooks. R., Rabin R, de Charro F eds. *The Measurement and Valuation of Health Status Using EQ-5D: A European Perspective: Evidence from the EuroQol BIOMED Research Programme*. Springer Science & Business Media; 2013.
10. Dolan P. Modeling Valuations for EuroQol Health States. *Medical Care*. 1997;35(11):1095–1108.
11. Hernández Alava M, Pudney S, Wailoo A. Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results from a UK Population Study. *PharmacoEconomics*. 2023;41(2):199–207.
12. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. John Wiley & Sons; 2004.
13. Sakamoto Y, Ishiguro M, Kitagawa G. *Akaike Information Criterion Statistics*. Springer; 1986.
14. Srivastava VK, Giles DEA. *Seemingly Unrelated Regression Equations Models: Estimation and Inference*. CRC Press; 2020.
15. Perera D, Morgan HP, Ryan M, Dodd M, Clayton T, O'Kane PD, Greenwood JP, Walsh SJ, Weerackody R, McDiarmid A, et. al. Arrhythmia and Death Following Percutaneous Revascularization in Ischemic Left Ventricular Dysfunction: Prespecified Analyses From the REVIVED-BCIS2 Trial. *Circulation*. 2023;148(11):862–871.

16. Graber CJ, Lauring AS, Chin-Hong P V. Clinical problem-solving. A stitch in time--a 64-year-old man with a history of coronary artery disease and peripheral vascular disease was admitted to the hospital with a several-month history of fevers, chills, and fatigue. *The New England Journal of Medicine*. 2007;357:1029–1034.
17. Wa MELK, Assar SZ, Kirtane AJ, Perera D. Revascularisation for Ischaemic Cardiomyopathy. *Interventional Cardiology: Reviews, Research, Resources*. 2023;18, e24.
18. Weintraub WS, Boden WE, Zhang Z, Kolm P, Zhang Z, Spertus JA, Hartigan P, Veledar E, Jurkovitz C, Bowen J, et al. Cost-Effectiveness of Percutaneous Coronary Intervention in Optimally Treated Stable Coronary Patients. *Circulation: Cardiovascular Quality and Outcomes*. 2008;1(1):12–20.
19. McCreanor V, Nowbar A, Rajkumar C, Barnett AG, Francis D, Graves N, Boden WE, Weintraub WS, Al-Lamee R, Parsonage WA. Cost-effectiveness analysis of percutaneous coronary intervention for single-vessel coronary artery disease: an economic evaluation of the ORBITA trial. *BMJ Open*. 2021;11(2):e044054.
20. Briggs A, Sculpher M, Buxton M. Uncertainty in the economic evaluation of health care technologies: The role of sensitivity analysis. *Health Economics*. 1994;3(2):95–104.
21. Carpenter J, Kenward M. Multiple Imputation and its Application. John Wiley & Sons; 2012.
22. Kleinke K, Reinecke J, Salfrán D, Spiess M. Applied Multiple Imputation: Advantages, Pitfalls, New Developments and Applications in R. Springer Nature; 2020
23. Legendre B, Cerasuolo D, Dejardin O, Boyer A. [How to deal with missing data? Multiple imputation by chained equations: recommendations and explanations for clinical practice]. Nephrol Ther. 2023;19: 171–179.
24. Mealing, Stuart, Beth Woods, Neil Hawkins, Martin R. Cowie, Christopher J. Plummer, William T. Abraham, John F. Beshai, Helmut Klein, and Mark Sculpher. "Cost-effectiveness of implantable cardiac devices in patients with systolic heart failure." Heart 102, no. 21 (2016): 1742-1749.

Table 1. Breakdown of Total Cost Per Visit

		Percutaneous coronary intervention + optimal medical therapy (n = 347)				*Optimal medical therapy (n = 353)*				
Visit	***Category***	***n***	***% usage***	***mean***	***SD***	***n***	***% usage***	***mean***	***SD***	***Mean difference***
BL to 6M	Planned PCI	325	0.94	£8,277.00	£3,130.85	0	0	0	0	£8,277.00
	Unplanned revasc	4	0.01	£7,497.25	£5,617.30	10	0.03	£4,299.20	£1,868.27	£3,198.05
	Medication	347	1	£995.39	£3,026.07	353	1	£1,325.35	£3,567.67	-£329.96
	Hospitalisations	99	0.29	£3,084.85	£12,543.05	92	0.26	£2,685.32	£4,201.25	£399.53
	Devices	55	0.18	£18,933.30	£1,976.24	70	0.2	£18,713.00	£1,832.00	£220.30
	Clinical tests	283	0.82	£105.21	£11.46	287	0.81	£104.41	£16.40	£0.80
6 M to 1Y	Planned PCI	12	0.03	£12,793.75	£4,462.62	0	0	0	0	£12,793.75
	Unplanned revasc	2	0.01	£3,413.00	£0.00	9	0.03	£7,002.73	£6,128.51	-£3,589.73
	Medication	328	0.95	£1,142.63	£3,215.77	334	0.95	£1,273.76	£3,406.07	-£131.13
	Hospitalisations	81	0.23	£3,750.39	£7,875.72	72	0.2	£2,225.03	£3,828.42	£1,525.36
	Devices	14	0.04	£18,786.00	£1,501.94	22	0.06	£17,614.27	£1,994.23	£1,171.73
	Clinical tests	264	0.76	£92.26	£12.64	261	0.74	£91.97	£11.53	£0.29
1Y to 2Y	Planned PCI	1	0	£20,025.00	£0.00	0	0	0	0	£20,025.00
	Unplanned revasc	1	0	£3,413.00	£0.00	14	0.04	£9,096.22	£6,933.43	-£5,683.22
	Medication	317	0.91	£2,390.87	£6,662.65	317	0.9	£2,134.35	£6,225.97	£256.52
	Hospitalisations	95	0.27	£3,429.44	£6,572.97	106	0.3	£3,492.85	£8,095.82	-£63.41
	Devices	12	0.03	£19,217.71	£1,577.42	21	0.06	£18,329.01	£2,461.83	£888.70
	Clinical tests	162	0.47	£7.40	£0.00	162	0.46	£7.40	£0.00	£0.00
2Y to 3Y	Unplanned revasc	1	0	£3,413.00	£0.00	3	0.01	£3,413.00	£0.00	£0.00
	Hospitalisations	61	0.18	£3,590.96	£6,682.08	60	0.17	£3,185.32	£5,554.48	£405.64
	Devices	7	0.02	£15,395.80	£3,947.88	6	0.02	£16,862.40	£3,749.64	-£1,466.60
3Y to 4Y	Unplanned revasc	1	0	£3,413.00	£0.00	1	0	£3,413.00	£0.00	£0.00
	Hospitalisations	37	0.11	£2,780.10	£4,672.02	44	0.12	£6,707.42	£23,112.20	-£3,927.32
	Devices	2	0.01	£9,616.69	£0.00	0	0	0	0	£9,616.69

4Y to 5Y	Unplanned revasc	0	0	0	0	0	0	0	0	£0.00
	Hospitalisations	24	0.07	£1,852.61	£3,253.33	26	0.07	£6,834.22	£15,170.17	-£4,981.61
	Devices	2	0.01	£17,707.44	£0.00	0	0	0	0	£17,707.44
5Y to 6Y	Unplanned revasc	1	0	£3,413.00	£0.00	0	0	0	0	£3,413.00
	Hospitalisations	9	0.03	£3,847.36	£4,922.57	13	0.04	£6,493.66	£11,312.54	-£2,646.30
	Devices	1	0	£20,727.97	£0.00	1	0	£17,707.44	£0.00	£3,020.53
6Y to 7Y	Unplanned revasc	0	0	0	0	0	0	0	0	£0.00
	Hospitalisations	6	0.02	£3,247.24	£3,913.35	6	0.02	£1,202.16	£946.46	£2,045.08
	Devices	0	0	0	0	0	0	0	0	£0.00
Average cost over time		347	1	£21,674.00	£18,485.42	353	1	£15,882.12	£18,379.44	£5,791.88

Note: BL = baseline, M = months, Y = years; unplanned revasc = unplanned revascularization; Mean diff = mean difference.

Table 2. Observed EQ5D Index Scores

EQ-5D-5L utility scores	Percutaneous coronary intervention + optimal medical therapy (N=347)			Optimal medical therapy (N=353)			Difference	p-value
	N	N miss	mean (95% CI)	N	N miss	mean (95% CI)	mean (95% CI)	
Baseline	340	7	0.68 (0.65 to 0.70)	341	12	0.66 (0.63 to 0.69)	-	-
6 months	297	29	0.73 (0.70 to 0.75)	306	30	0.68 (0.65 to 0.71)	0.05 (0.00 to 0.09)	0.033
1 year	291	26	0.73 (0.70 to 0.76)	287	28	0.67 (0.64 to 0.70)	0.06 (0.01 to 0.10)	0.012
2 years	254	38	0.71 (0.67 to 0.74)	253	45	0.69 (0.66 to 0.73)	0.01 (-0.04 to 0.06)	0.671
3 years	174	28	0.69 (0.65 to 0.74)	183	23	0.69 (0.64 to 0.73)	0.01 (-0.05 to 0.07)	0.854
4 years	130	14	0.70 (0.65 to 0.75)	133	21	0.67 (0.62 to 0.72)	0.03 (-0.04 to 0.10)	0.398
5 years	84	8	0.66 (0.58 to 0.74)	87	7	0.66 (0.59 to 0.73)	0.00 (-0.10 to 0.11)	0.937
6 years	33	5	0.70 (0.59 to 0.80)	30	7	0.69 (0.57 to 0.81)	0.01 (-0.15 to 0.16)	0.941
7 years	12	2	0.84 (0.75 to 0.93)	9	1	0.76 (0.54 to 0.98)	0.08 (-0.11 to 0.28)	0.389
8 years	0	3	-- (-- to --)	1	2	0.99	-- (-- to --)	--

Note: Mean utility scores for each group are reported alongside corresponding 95% confidence intervals (CI). EQ-5D-5L = EuroQol 5-Dimension 5-Level; N Miss = Number of missing values. CI = Confidence intervals.

Table 3. Cost-Effectiveness Results

Cost-effectiveness outcomes – Mean [95% CI]	Percutaneous coronary intervention + optimal medical therapy	Optimal medical therapy
Predicted total costs (£)	22,352 [21,969 – 22,734]	15,569 [15,302 – 15,835]
Predicted total QALYs	4.14 [4.02 – 4.27]	4.16 [4.02 – 4.30]
Incremental predicted total costs (£)	6,782 [6,666 – 6,899]	
Incremental predicted total QALYs	-0.015 [-0.385 – 0.355]	

Note: QALYs: quality adjusted life years; CI = confidence interval
Due to the negative incremental total QALYs value (north west quadrant of cost effectiveness plane; percutaneous coronary intervention + optimal medical therapy is dominated by optimal medical therapy) an ICER cannot be calculated.

Figure Legends

Figure 1. Breakdown mean total costs by treatment group over all years.

Note: Planned revascularizations, medication and clinical test information was not collected from 2 years onwards. HF = Heart failure, BL = baseline, M = months, Y= years, OMT = optimal medical therapy, PCI = percutaneous coronary intervention

Figure 2. Post imputation EQ5D score time trend by treatment group across follow-up (excluding those who have died). Note: Shaded areas represent 95% confidence intervals. OMT = optimal medical therapy, PCI = percutaneous coronary intervention; EQ-5D-5L = EuroQol 5-Dimension 5-Level

Figure 3. Cost-effectiveness plane with probabilistic sensitivity analysis results.

Note: £20,000 = UK threshold and £ 82,000 is US threshold using the current official exchange rate of £0.81. QALYs: quality adjusted life years