Viability and Outcomes with Revascularization or Medical Therapy in Ischemic Ventricular Dysfunction

Subtitle: Prespecified analysis of the REVIVED-BCIS2 randomized clinical trial

Divaka Perera MD[1,2], Matthew Ryan PhD[1], Holly P. Morgan MBBCh[1], John P. Greenwood PhD[3], Mark C. Petrie MD[4], Matthew Dodd MSc[5], Roshan Weerackody PhD[6], Peter D. O'Kane MD[7], Pier Giorgio Masci PhD[8], Muhummad Sohaib Nazir PhD[8,11], Alexandros Papachristidis PhD[1,9], Navtej Chahal PhD[10], Rajdeep Khattar MD[11], Saad M. Ezad MBBCh[1], Stam Kapetanakis PhD[2], Lana J. Dixon MD[12], Kalpa De Silva PhD[2,13], Adam K. McDiarmid PhD[14], Michael Marber PhD[1], Theresa McDonagh MD[1,9], Gerry P. McCann MD[15], Tim Clayton MSc[5], Roxy Senior MD[11] and Amedeo Chiribiri PhD[8], for the REVIVED-BCIS2 Investigators†

1. British Heart Foundation Centre of Research Excellence at the School of Cardiovascular and Metabolic Medicine & Sciences, King's College London, UK
2. Guy's and St Thomas' NHS Foundation Trust, UK
3. Leeds Teaching Hospitals NHS Trust and University of Leeds, UK
4. Institute of Cardiovascular and Medical Sciences, University of Glasgow, UK
5. London School of Hygiene & Tropical Medicine, UK
6. Barts Health NHS Trust, UK
7. University Hospitals Dorset NHS Foundation Trust, UK
8. School of Biomedical Engineering and Imaging Sciences, King's College London, UK
9. King's College Hospital NHS Foundation Trust, London, UK
10. London Northwest Health NHS Trust, UK
11. Royal Brompton Hospital, UK
12. Belfast Health and Social Care NHS Trust, UK
13. University Hospitals Bristol NHS Foundation Trust, UK
14. Newcastle Hospitals NHS Foundation Trust, UK
15. University of Leicester and the NIHR Leicester Biomedical Research Centre, UK

† *Investigators listed in full in the Supplementary Appendix*

Correspondence to Divaka Perera, St Thomas' Hospital, London, SE1 7EH, UK; Divaka.Perera@kcl.ac.uk, +442071881048

Word count: 2669

Date of revision: 08/17/2023

Key points

Question:

Does myocardial viability testing identify patients with ischemic left ventricular dysfunction who benefit from PCI?

Findings:

In the REVIVED-BCIS2 randomized trial, myocardial viability testing with cardiovascular magnetic resonance imaging or stress echocardiography did not identify a population of patients who benefit from PCI. The extent of non-viable myocardium was associated with a higher risk of death or hospitalization for heart failure and a lower chance of improvement in left ventricular function.

Meaning:

In this trial, the extent of dysfunctional-yet-viable myocardium was not associated with revascularization outcomes.

Abstract

Importance

In the REVIVED-BCIS2 trial, percutaneous coronary intervention (PCI) did not improve outcome in patients with ischaemic left ventricular dysfunction. It remained unclear whether myocardial viability testing has prognostic utility in these patients or identify a sub-population who may benefit from PCI.

Objective

To determine the impact of the extent of viable and non-viable myocardium on the effectiveness of PCI, prognosis and improvement in left ventricular function.

Design

Prospective open-label randomized controlled trial recruiting between 2013 and 2020, median follow-up 3.4 years.

Setting

40 secondary and tertiary care centers in the United Kingdom from 2013 to 2020.

Participants

Of 700 randomized patients, 610 participants with left ventricular ejection fraction ≤35%, extensive coronary artery disease and evidence of viability in ≥ 4 segments that were dysfunctional at rest who underwent blinded core laboratory viability characterization.

Intervention

Percutaneous coronary intervention (PCI) in addition to optimal medical therapy (OMT).

Main Outcomes and Measures

Blinded core laboratory analysis was performed of cardiac magnetic resonance scans and dobutamine stress echocardiograms to quantify the extent of viable and non-viable myocardium, expressed as an absolute percentage of left ventricular mass. The primary outcome was all-cause death or hospitalization for heart failure. Secondary outcomes were all-cause death, cardiovascular death, hospitalization for heart failure and improved left ventricular function at 6-months.

Results

The primary outcome occurred in 107 of 295 participants assigned to PCI and 114 of 315 assigned to OMT alone. There was no interaction between the extent of viable or non-viable myocardium and the effect of PCI on the primary or any secondary outcome. Across the study population, the extent of viable myocardium was not associated with the primary outcome (hazard ratio [HR] 0·98 per 10% increase, 95% confidence interval [CI] 0·93 to 1·04) or any secondary outcome. The extent of non-viable myocardium was associated with the primary outcome (HR 1·07, CI 1·00 to 1·15), all-cause death, cardiovascular death and improvement in left ventricular function.

Conclusions and Relevance

Viability testing does not identify patients with ischemic cardiomyopathy who benefit from PCI. The extent of non-viability, but not the extent of viable myocardium, is associated with event-free survival and likelihood of improvement of left ventricular function.

Trial Registration

ClinicalTrials.gov number, NCT01920048.

Introduction

Myocardial viability tests are thought to identify patients with ischemic cardiomyopathy who may benefit from revascularization. These tests typically characterize myocardial tissue into three distinct states; healthy myocardium contracting normally at rest, viable or hibernating myocardium which contracts abnormally at rest where improvement in function is predicted, and non-viable, scarred myocardium which contracts abnormally at rest but where improvement is not predicted. Historically, viability has been regarded in a binary manner and when classified in this way, observational, non-randomized data suggest that patients with extensive hibernation might experience left ventricular recovery and improved survival following revascularization.[1] However, when the treatment was by random allocation in the Surgical Treatment for Ischemic Heart Failure (STICH) trial, no interaction was found between viability status and the effect of coronary artery bypass surgery.[2] Other observational studies that regarded viability as a continuum have suggested an incremental benefit of revascularization above medical therapy alone, although interpretation of these data is limited by their retrospective nature and non-randomized treatment allocation.[3] Hence it remains unclear whether myocardial viability testing predicts event-free survival or left ventricular recovery and which viability characteristics are associated with the effect of revascularization on these outcomes.[4]

We recently completed the Revascularization for Ischemic Ventricular Dysfunction (REVIVED-BCIS2) trial, a randomized comparison of percutaneous coronary intervention (PCI) versus optimal medical therapy (OMT) alone in patients with ischemic cardiomyopathy who had undergone mandatory viability testing. We now report the prespecified analysis of clinical and left ventricular outcomes in relation to the extent of viable myocardium and

non-viable myocardium, to determine their relationships with prognosis and functional recovery and the interaction with revascularization.

Design and Methods

REVIVED was a prospective, multicentre, open-label randomized controlled trial the design and preliminary results of which have been published previously[5,6] The trial was funded by the National Institute for Health and Care Research (UK) Health Technology Assessment Program and the viability analysis by the British Heart Foundation. It was sponsored by King's College London and coordinated by the London School of Hygiene and Tropical Medicine Clinical Trials Unit. Participants were recruited from 40 sites in the UK. The trial protocol received ethical approved from the UK Health Research Authority, was registered prior to enrolment of the first participant (NCT01920048) and is available online at https://revived.lshtm.ac.uk/protocol/. All participants provided informed written consent. The manuscript conforms with the CONSORT guidelines for reporting of randomised clinical trials. The authors had access to the trial data and vouch for the completeness and accuracy of this analysis.

Participants were eligible for enrolment if they had a left ventricular ejection fraction less than or equal to 35%, extensive coronary artery disease (British Cardiovascular Intervention Society (BCIS) jeopardy score greater than or equal to 6)[7] and evidence of myocardial viability. The qualifying threshold for viability was defined as at least 4 segments that were dysfunctional at rest, judged by recruiting centres to be viable and supplied by coronary arteries that were severely diseased but amenable to revascularization by PCI. Key exclusion criteria were myocardial infarction less than four weeks prior to randomization, decompensated heart failure, sustained ventricular tachycardia or ventricular fibrillation less than 72 hours prior to randomization. Participants were randomized in a 1:1 ratio to a strategy of either PCI plus optimal medical therapy (PCI group) or optimal medical therapy

alone (OMT group) using and online randomization system (Sealed Envelope). All clinical outcomes were adjudicated by an independent clinical events committee and left ventricular ejection fraction was measured by an independent echocardiography core laboratory blinded to treatment assignment, outcome data and the temporal sequence of scans.[6]

Viability assessment could be obtained by cardiovascular magnetic resonance (CMR) imaging, dobutamine stress echocardiography (DSE), single photon emission computed tomography (SPECT) or positron emission tomography (PET). For this analysis, participants who had viability assessed with CMR or DSE were included, with CMR data used where both were available. Given the small number of participants assessed only by SPECT or PET these participants were excluded as the results would not be generalizable to nuclear imaging techniques. Any participants for whom viability studies could not be obtained or were unsuitable for core laboratory analysis were also excluded.

All available CMR and DSE studies were analyzed by independent core laboratories (CMR core laboratory at King's College London, UK and DSE core laboratory at King's Health Partners, UK). The left ventricle was described using a 17-segment American Heart Association model.[8] Segmental wall motion was classed as normal or dysfunctional, with dysfunctional segments classified as viable or non-viable based on a 25% late gadolinium enhancement (LGE) transmurality threshold by CMR or the presence of contractile reserve by DSE (Table 1).[9,10] Per participant viability status was described by the extent of viable and non-viable myocardium; segments with non-ischemic scar were excluded from the analysis.

A sensitivity analysis was performed with segmental viability and non-viability adjudicated using a 50% LGE transmurality threshold.

In the CMR cohort, per participant ischemic scar burden was determined semi-quantitatively by visual consensus of two expert readers and expressed as a percentage of total LV myocardial volume (Table 1). This included all segments regardless of resting wall motion, though segments with clearly non-ischemic LGE were excluded.

The primary outcome was a composite of death from any cause or hospitalization for heart failure over a minimum follow-up period of 24 months. Secondary outcomes were all-cause death, cardiovascular death, hospitalization for heart failure and improvement in left ventricular function at 6 months, defined as a greater than the median absolute change in left ventricular ejection fraction on echocardiography measured by a blinded core laboratory at Guy's and St Thomas' NHS Foundation Trust.

Statistical analysis

The statistical analysis plan was finalized prior to unblinding of viability data. A formal power calculation was not performed for this secondary analysis. A Cox proportional hazards model was used to assess the relationship between the extent of viable myocardium, non-viable myocardium, scar burden and the primary outcome across the whole population, adjusted for baseline factors, including age, sex, previous heart failure hospitalization, presence of diabetes, chronic renal failure, left ventricular ejection fraction, extent of coronary disease and the modality of viability testing. The interaction between randomized assignment, independent variables (the extent of viable myocardium, non-viable

myocardium, scar burden) and major outcomes was assessed using a Cox proportional hazards model containing the following covariates: viability characteristics (treated as a linear effect), assigned treatment, their interaction, and baseline risk factors. The results were calculated by considering each viability characteristic as a continuous variable (expressed as hazard ratios and 95% confidence intervals) but for illustrative purposes, Kaplan-Meier curves and forest plots were stratified by tertiles of these parameters. Logistic regression models were also created as above to explore the relationship between viability characteristics and improvement in left ventricular function, defined dichotomously by the median change in left ventricular ejection fraction (with a linear mixed effect model for repeated measures) adjusting for baseline variables.

Finally, a landmark analysis was performed, of participants who survived at least 6 months from randomization, to test the relationship between improvement in left ventricular function and the primary outcome, using Cox proportional models. Missing values of left ventricular ejection fraction were imputed using a multiple imputation model with chained equations which included randomized treatment, age, sex, and baseline, 6-month and 12-month left ventricular ejection fraction. A sensitivity analysis was performed restricted to observed values, without imputation. All analyses were conducted using Stata software, version 17·0 (StataCorp).

Results

Of the 700 participants randomized in the REVIVED trial, 610 were included in this pre-specified analysis, 295 assigned to the PCI group and 315 to the OMT group (Figure 1). The groups were balanced in relation to baseline clinical, demographic and viability characteristics (Table 2). The median extent of viable and non-viable myocardium was 29% (interquartile range, 12% to 53%) and 29% (12% to 41%) respectively, across the whole trial population. The characteristics of those undergoing CMR, DSE and who were not included in this analysis were similar (Table S1).

A primary outcome event occurred in 107 participants in the PCI group and 114 participants in the OMT group (36·9% vs. 36·2%, difference between groups 0.7%, hazard ratio [HR], 0·99; 95% confidence interval [CI], 0·76 to 1·29; p = 0·93), at a median of 3·4 (2·3 to 5·0) years, consistent with the results in the whole trial population (Table S2).

There was no evidence of an interaction between the extent of viable myocardium and the effect of assignment to PCI versus OMT on occurrence of the primary outcome (p for interaction = 0·33) or any of the secondary outcomes (Figures 2, S1-S2 and Table S3). Similarly, there was no evidence of an interaction between the extent of non-viable myocardium and the effect of assignment to PCI versus OMT on occurrence of the primary outcome (p for interaction = 0·11) or any of the secondary outcomes (Figures S1-S2 and Table S3).

Across the trial population, no association was observed between the extent of viable myocardium and occurrence of the primary outcome (HR per 10% absolute increase in viable myocardium, 0·98; 95% CI, 0·93 to 1·04; p = 0.56, Figure 3 and Table S4) or any of the secondary outcomes . In contrast, an increasing volume of non-viable myocardium was associated with a greater likelihood of the primary outcome (HR per 10% absolute increase in non-viable myocardium, 1·07; 95% CI, 1·00 to 1·15; p = 0·048, Figure 3 and Table S4). Results were consistent for all-cause death and cardiovascular death, whilst no effect was observed on hospitalization for heart failure (Table S4).

Sensitivity analyses based on a LGE transmurality threshold less than or equal to 50% also showed no association between the extent of viability and primary outcome, as well as no interaction with assignment to PCI versus OMT (Table S5).

In the 479 participants assessed with CMR, scar burden did not interact with the effect of assignment to PCI versus OMT on the risk of the primary outcome or any secondary outcomes (Figures S1-S2 and Table S3). A greater scar burden was associated with an increased incidence of the primary outcome (HR per 10% absolute increase in scar burden, 1·18; 95% CI, 1·04 to 1·33; p = 0·009), all-cause death and cardiovascular death across the whole trial population (Figure 3 and Table S4).

The median change in left ventricular ejection fraction was +4·7 (-2·2 to +12·5) percent at 6 months (Table S6). None of the viability characteristics influenced the effect of assignment to PCI versus OMT on the likelihood of improvement in left ventricular function (Figure S3 and Table S7). In the whole trial population, the extent of viable myocardium was not

associated with improvement in left ventricular function at 6 months (odds ratio (OR), 1·01; 95% CI, 0·93 to 1·11; p = 0·78) but increasing volumes of non-viable myocardium and scar were associated with a lower likelihood of improvement in left ventricular function (OR, 0·82; 95% CI, 0·73 to 0·93; p = 0·002 and OR, 0·69; 95% CI 0·56 to 0·84; p = 0·0003, respectively; Table S4). The determinants of improvement in left ventricular function at 12 months were the same as at 6 months (Figure S4 and Table S7).

In the landmark analysis of participants surviving more than 6 months, improvement in left ventricular function by at least 4·7% was associated with a 38% relative risk reduction for the primary outcome when compared to those who did not have an improvement (OR, 0·62; 95% CI 0·41 to 0·95; Figure S5). The relationship was maintained when improvement in left ventricular function at 6 months was regarded as a continuous variable (HR per 5% absolute improvement in ejection fraction, 0·87; 95% CI, 0·79 to 0·95; p = 0·003).

Discussion

The REVIVED trial showed that, compared to medical therapy alone, PCI neither reduced the occurrence of death or hospitalization for heart failure nor influenced the degree of left ventricular recovery in patients with severe ischemic cardiomyopathy. In this pre-specified sub-study, in which we carried out blinded core laboratory analysis of CMR and DSE viability tests performed before randomization, we did not find any of the viability characteristics to influence the effect of PCI on either prognosis or likelihood of improvement in left ventricular function. Our findings do not support the use of myocardial viability testing to select patients with severe left ventricular systolic dysfunction for revascularization.

The traditional concept of myocardial hibernation, an adaptive state of decreased contractility which can be reversed by relieving the ischemic substrate through medical therapy and revascularization appears at odds with our findings.[11-13] Furthermore, whilst an increasing amount of hibernating myocardium has previously been linked to a worse prognosis we did not find any association with all-cause or cardiovascular mortality.[3,14] Several potential explanations need to be considered. It may be because contemporary viability testing merely demonstrates the absence of appreciable myonecrosis in regions that are dysfunctional but does not specifically detect myocardial hibernation.[15] Alternatively, it is possible that the hibernation paradigm itself may need modification. While ischemia may trigger the process of hibernation, revascularization may not be sufficient to effectively reverse it.[16] The time taken to reverse hibernation has also been reported to be very variable[13] but given that the associations with 12-month left ventricular

remodeling were similar to those at 6-months in our study and that clinical follow-up was continued for a median of 3·4 years, length of follow-up is unlikely to have affected our findings.

In contrast, the extent of non-viable myocardium was associated with an increased likelihood of the primary outcome, independent of whether participants were assigned to have revascularization or not. This effect was driven by increased mortality, rather than more heart failure hospitalization, with a clear relationship between non-viable myocardial mass and cardiovascular death. When scar burden was semi-quantitatively assessed on CMR, agnostic to resting wall motion, the prognostic association was stronger. Whether the negative association between scar and event-free survival is mediated by an increased incidence of fatal ventricular arrhythmia, and whether scar burden and morphology could be used to stratify risk and guide management warrants further investigation. Given that current international guidelines recommend that arrhythmic risk stratification be primarily based on left ventricular ejection fraction[17], it is notable that scar burden remained strongly associated with the incidence of the primary outcome after adjusting for baseline left ventricular ejection fraction.

Finally, our results demonstrate that patients who experience improvement in left ventricular function by 6-months have markedly better event-free survival than those who do not. While this association has been reported in non-ischemic left ventricular dysfunction[18], the STICH trial investigators did not find that improvement in left ventricular function affected survival.[19] The discordance may be due to differences in trial methodology, as assessment of left ventricular function was protocol-mandated in all

participants in REVIVED and continued out to twelve months (rather than 4 months in STICH), as well as the observation that mean change in ejection fraction was lower in STICH (2% versus 5% in REVIVED), which may in turn reflect improvements in optimal medical and device therapy between the trials.

Apart from mandated viability testing, randomized assignment to revascularization and high rates of guideline-directed medical and device therapy, our study has two key strengths compared to previous observational data. Firstly, we characterized participants in terms of viable and non-viable myocardium, each of which relates to a distinct pathophysiological determinant of outcome in ischemic cardiomyopathy. Secondly, all these viability characteristics were analyzed as continuous rather than binary variables, which better captures biological heterogeneity and enhances our ability to detect potential interactions.

Our study does have some limitations. We have only used data from 87% of the trial population, although the baseline characteristics and clinical outcomes were very similar to the overall trial population, so this loss of data is unlikely to have affected the results. Enrolment in the REVIVED-BCIS2 trial required participants to have at least four segments of viable myocardium, according to local adjudication and consequently the exclusion of patients without viability means the results cannot be generalised to the entire viability continuum; however given the consistency of our results with the STICH trial it is unlikely that the headline findings would be affected. Participants in whom viability was assessed with PET or SPECT were excluded and we cannot extrapolate the results to these modalities. The accuracy of CMR-based scar measurement might be improved by quantitative analysis, but automated methods are not yet in widespread clinical use and our method best reflects

the current way in which CMR studies are interpreted in this patient population. As we did not mandate paired ischemia testing, it is not possible to link clinical outcomes and improvement left ventricular function to change in ischemic burden (with medical therapy and/or PCI) and hence any comments on the mechanisms of hibernation remain speculative. Finally, differentiating ischemic left ventricular dysfunction from nonischemic cardiomyopathy with bystander coronary artery disease can be challenging in the absence of a definitive test. This might influence the results, although the REVIVED-BCIS2 population was phenotyped with advanced cardiac imaging during viability testing and a threshold BCIS jeopardy score that is highly specific for ischaemic left ventricular dysfunction.[20]

In conclusion, in our randomized trial of PCI versus OMT alone, viability testing did not identify participants in whom PCI would confer a prognostic benefit or improve left ventricular function. In this ischemic left ventricular dysfunction population, the extent of viability, as estimated by CMR or DSE, did not correlate with event-free survival or the likelihood of improvement in left ventricular function of 5% or greater, although the extent of non-viable myocardium (by CMR or DSE) and the total left ventricular scar burden (by CMR) were associated with both outcomes.

Table 1 – Characterization of myocardial viability

Viability Definitions			
Segmental classification – by CMR or DSE			
	Wall motion*	**CMR - Transmurality of late enhancement**	**DSE - Contractile reserve†**
Normal	Normal	N/A	N/A
Viable	Dysfunctional	≤ 25%‡	Present
Non-viable	Dysfunctional	> 25%‡	Absent
Participant-level classification – by CMR or DSE			
	Numerator	**CMR denominator**	**DSE denominator**
Extent of viability (% LV)	Number of viable segments	All segments, excluding those with non-ischemic scar	All segments
Extent of non-viable myocardium (% LV)	Number of non-viable segments	All segments, excluding those with non-ischemic scar	All segments
Participant-level classification – CMR only			
Scar burden (% LV)	Transmural extent of late gadolinium enhancement (LGE) in each segment was classified by visual consensus of two expert readers according to the following ranges: 0, 1-25%, 26-50%, 51-75% or 76-100%.[9] Segmental LGE was calculated as the mid-point in each range (for instance, 13% for the range 1-25%). LGE was then summed across all segments and expressed as a proportion of the left ventricle.		

* Myocardial wall motion was graded on a 5-point scale as normal, hypokinetic, akinetic, dyskinetic or aneurysmal.

†Contractile reserve was defined as an improvement in wall motion score ≥ 1, or ≥ 2 if the segment was dyskinetic at rest.

‡ Sensitivity analyses were performed for an LGE threshold of ≤ 50%.

Table 2. Demographic and clinical characteristics of the participants at baseline[1]

	PCI (N=295)	OMT (N=315)
Ag, mean (SD), years	69·8±9·1	68·8±8·9
Male sex (%)	258 (88)	277 (88)
Diabetes (%)	116 (39)	134 (43)
Race (%)[1]		
Asian	26 (9)	13 (4)
Black	3 (1)	3 (1)
Mixed, other or not reported	5 (2)	3 (1)
White	261 (89)	296 (94)
History of myocardial infarction (%)	146 (50)	175 (56)
Hospitalization for heart failure in prior 2 years (%)	104 (35)	102 (32)
Cardiac medication (%)		
RAAS inhibitor	258 (88)	282 (90)
Beta blocker	266 (90)	285 (91)
Mineralocorticoid receptor antagonist	153 (52)	151 (48)
BCIS jeopardy score, median (IQR)[3]	10 (8–12)	10 (8–12)
ICD +/- CRT at randomization (%)	65 (22)	58 (18)
Left main coronary artery disease (%)	46 (16)	40 (13)
Left ventricular ejection fraction, mean (SD), %[4]	32±10	32+10
Viability test (%)[5]		
CMR	236 (80)	243 (77)
DSE	59 (20)	72 (23)
Extent of viable myocardium, median (IQR), %	29 (18-53)	29 (12-47)
Extent of non-viable myocardium, median (IQR), %	29 (12-41)	29 (12-41)
Scar burden, median (IQR), %	19 (9-28)	18 (9-28)

[1] Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. BCIS denotes British Cardiovascular Intervention Society, CMR cardiovascular magnetic resonance imaging, CRT cardiac resynchronization therapy, DSE dobutamine stress echocardiography, ICD implantable cardioverter defibrillator, IQR interquartile range, RAAS renin angiotensin aldosterone system.

[2] Race as self-reported by participants using options defined by the investigators.

[3] The British Cardiovascular Intervention Society (BCIS) jeopardy score is a quantification of the extent of myocardial jeopardy relating to clinically significant coronary artery stenoses. The score ranges from 0 (no significant coronary disease) to 12 (disease jeopardising the whole left ventricular myocardium).

[4] Baseline left ventricular ejection fraction measured by the blinded echocardiography core laboratory.

[5] 16 (5·4%) participants in the PCI group and 19 (6·0%) participants in the OMT group had non-ischemic scar. The median (IQR) number of segments with non-ischemic scar in these participants was 2 (1 to 3) segments the PCI group and 2 (1 to 3) in the OMT group.

Figure Legends

Figure 1. Consort diagram

Consort diagram showing flow of participants through the study. CMR denotes cardiovascular magnetic resonance imaging, DSE dobutamine stress echocardiography, OMT optimal medical therapy, PCI percutaneous coronary intervention.

Figure 2. All-cause death or hospitalization for heart failure in participants assigned to PCI or OMT, stratified by viability tertile

Kaplan-Meier estimates of the cumulative incidence of death from any cause of hospitalization for heart failure in a time-to-first event analysis, stratified by tertiles of the extent of myocardial viability. Panel A shows the lower tertile (extent of viability less than or equal to 18%). Panel B shows the middle tertile (greater than 18% to less than or equal to 41%). Panel C shows the upper tertile (greater than 41%). CI denotes confidence interval, HR hazard ratio, OMT optimal medical therapy, PCI percutaneous coronary intervention.

Figure 3. Relationship between viability characteristics and trial outcomes

Forest plot of the hazard ratio (for clinical outcomes) or odds ratio (*for improvement in left ventricular function) for the primary and secondary outcomes according to the extent of viable myocardium, extent of non-viable myocardium and scar burden. Data relate to the whole trial population. Ratios are expressed per 10% absolute increase in the characteristic, relative to overall left ventricular mass. The values relating to this graph are reported in table S5.

Contributors

DP was Chief Investigator for REVIVED-BCIS2, conceptualized the analysis and wrote the first draft of the manuscript with assistance from MR, HPM and AC. MCP, JPG, RW, PO'K, KDS and LJD were site principal investigators and assisted with the design of this analysis. MD performed all statistical analyses under supervision of TC, the trial statistician. PGM, MSN, AP, NC and RK performed blinded analysis of viability studies. HPM co-ordinated the cardiovascular magnetic resonance core laboratory and SE co-ordinated the stress echocardiography core laboratory. SK was director of the echocardiography core laboratory, RS was director of the stress echocardiography core laboratory and AC was director of the cardiovascular magnetic resonance core laboratory. MM and TMcD assisted with trial design. MCP, JPG, AKM, GPM, RW and AC were members of the viability sub-study steering committee.

Declarations of interest

We declare no competing interests

Data sharing

De-identified data will be made available one year from the end of the trial on submission of a structured request to the corresponding author and completion of a signed data sharing agreement.

Acknowledgements

The trial was funded by the National Institute for Health and Care Research (UK) Health Technology Assessment Program (10/57/67) and the viability analysis by the British Heart Foundation (FS/CRTF/21/24190). The authors had full access to all the data in the study and the lead author (Divaka Perera) takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Allman KC, Shaw LJ, Hachamovitch R, Udelson JE. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. *J Am Coll Cardiol.* 2002;**39**:1151-8.

2. Bonow RO, Maurer G, Lee KL et al. Myocardial viability and survival in ischemic left ventricular dysfunction. *N Engl J Med*. 2011;**364**:1617-25.

3. Ling LF, Marwick TH, Flores DR et al. Identification of therapeutic benefit from revascularization in patients with left ventricular systolic dysfunction: inducible ischemia versus hibernating myocardium. *Circ Cardiovasc Imaging*. 2013;**6**:363-72.

4. Ryan M, Morgan H, Chiribiri A, Nagel E, Cleland J, Perera D. Myocardial viability testing: all STICHed up, or about to be REVIVED? *Eur Heart J*. 2022;**43**:118-26.

5. Perera D, Clayton T, Petrie MC et al. Percutaneous revascularization for ischemic ventricular dysfunction: rationale and design of the REVIVED-BCIS2 Trial. *JACC Heart Fail.* 2018;**6**:517-26.

6. Perera D, Clayton T, O'Kane PD et al. Percutaneous revascularization for ischemic left ventricular dysfunction. *N Engl J Med*. 2022;**387**:1351-60.

7. De Silva K, Morton G, Sicard P et al. Prognostic utility of BCIS myocardial jeopardy score for classification of coronary disease burden and completeness of revascularization. *Am J Cardiol*. 2013;**111**:172-7.

8. Cerqueira MD, Weissman NJ, Dilsizian V et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation*. 2002;**105**:539-42.

9. Kim RJ, Wu E, Rafael A et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med*. 2000;**343**:1445-53.

10. Cigarroa CG, deFilippi CR, Brickner ME, Alvarez LG, Wait MA, Grayburn PA. Dobutamine stress echocardiography identifies hibernating myocardium and predicts recovery of left ventricular function after coronary revascularization. *Circulation*. 1993;**88**:430-6.

11. Rahimtoola SH. The hibernating myocardium. *Am Heart J*. 1989;**117**:211-21.

12. Selvanayagam JB, Kardos A, Francis JM et al. Value of delayed-enhancement cardiovascular magnetic resonance imaging in predicting myocardial viability after surgical revascularization. *Circulation*. 2004;**110**:1535-41.

13. Bax JJ, Visser FC, Poldermans D et al. Time course of functional recovery of stunned and hibernating segments after surgical revascularization. *Circulation*. 2001;**104**:I314-8.

14. Pasquet A, Robert A, D'Hondt AM, Dion R, Melin JA, Vanoverschelde JL. Prognostic value of myocardial ischemia and viability in patients with chronic left ventricular ischemic dysfunction. *Circulation*. 1999;**100**:141-8.

15. Bax JJ, Poldermans D, Elhendy A, Boersma E, Rahimtoola SH. Sensitivity, specificity, and predictive accuracies of various noninvasive techniques for detecting hibernating myocardium. *Curr Probl Cardiol*. 2001;**26**:147-86.

16. Gunning MG, Kaprielian RR, Pepper J et al. The histology of viable and hibernating myocardium in relation to imaging characteristics. *J Am Coll Cardiol*. 2002;**39**:428-35.

17. Zeppenfeld K, Tfelt-Hansen J, de Riva M et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J.* 2022;**43**:3997-4126.

18. Schliamser JE, Kadish AH, Subacius H et al. Significance of follow-up left ventricular ejection fraction measurements in the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation trial (DEFINITE). *Heart Rhythm*. 2013;**10**:838-46.

19. Panza JA, Ellis AM, Al-Khalidi HR et al. Myocardial Viability and Long-term Outcomes in Ischemic Cardiomyopathy. *N Engl J Med*. 2019;**381**:739-748

20. Morgan HP, Ryan M, Briceno N, Modi B, Rahman H, Arnold S, Villa A, Chiribiri A, Perera D. Coronary jeopardy score predicts ischemic etiology in patients with left ventricular systolic dysfunction. *J Invasive Cardiol*. 2022;34:E683-E685.