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Percutaneous Revascularization for Ischemic Ventricular Dysfunction: rationale and design of the REVIVED-BCIS2 trial

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Commonly used abbreviations

BNP:	Brain-type natriuretic peptide
BCIS-JS:	British Cardiovascular Intervention Society jeopardy score
CABG:	Coronary artery bypass graft surgery
EF:	Ejection fraction
HF:	Heart failure
ICD:	Implantable cardioverter defibrillator
ICM:	Ischemic cardiomyopathy
LV:	Left ventricular
MRI:	Magnetic resonance imaging
MI:	Myocardial infarction
OMT:	Optimal medical therapy
PCI:	Percutaneous coronary intervention

Condensed Abstract

Heart failure (HF) due to coronary artery disease is associated with significant mortality and morbidity. REVIVED-BCIS2 is a prospective, multi-center, open-label, randomized controlled trial that addresses the hypothesis that PCI in combination with optimal medical therapy (OMT) will reduce all-cause death and hospitalization for HF compared to a strategy of OMT alone in patients with a left ventricular ejection fraction (LVEF) ≤35%, extensive coronary disease and demonstrable myocardial viability. Change in LVEF is a major secondary endpoint. Follow-up will be for at least 2 years from randomization. 400 of 700 patients have been enrolled to date.

Abstract

Background: Ischemic cardiomyopathy (ICM) is the commonest cause of heart failure (HF) and is associated with significant mortality and morbidity. Surgical revascularization has been shown to improve long-term outcomes in some patients, but surgery itself carries a major early hazard. Percutaneous coronary intervention (PCI) may allow a better balance between risk and benefit.

Objectives: Evaluate whether PCI in combination with optimal medical therapy (OMT) will reduce all-cause death and hospitalization for HF compared to a strategy of OMT alone.

Methods: REVIVED-BCIS2 is a prospective, multi-center, open- label, randomized controlled trial, funded by the National Institute for Health Research in the United Kingdom. Follow-up will be for at least 2 years from randomization. Secondary outcomes include left ventricular (LV) ejection fraction (EF), quality of life scores, appropriate Implantable Cardioverter Defibrillator therapy and acute myocardial infarction. Patients with LVEF ≤35%, extensive coronary disease and demonstrable myocardial viability are eligible for inclusion and those with a myocardial infarction within 4 weeks, decompensated HF or sustained ventricular arrhythmias within 72 hours are excluded. A trial of 700 patients has more than 85% power to detect a 30% relative reduction in hazard.

Results: 400 patients have been enrolled to date.

Conclusion: International guidelines do not provide firm recommendations on the role of PCI in managing severe ICM, due to lack of robust evidence. REVIVED-BCIS2 will provide the first randomized data on the efficacy and safety of PCI in ICM and has the potential to inform guidelines pertaining to both revascularization and HF.

Introduction

The prevalence of heart failure (HF) due to left ventricular (LV) systolic dysfunction is increasing (1) and ischemic cardiomyopathy (ICM) accounts for approximately 60% of all HF cases(2, 3). Pathophysiologically, ICM encompasses a spectrum of sequelae of coronary disease, including myocardial infarction (MI) (which leads to irreversible fibrosis) and hibernation (a potentially reversible adaptation to repetitive ischemia), which often co-exist in a given patient and can both lead to adverse remodeling and LV dysfunction. Hibernation was a term coined nearly 40 years ago to describe the reversal of remodeling and augmentation of systolic function following surgical coronary artery bypass grafting (CABG), noted in patients with chronic stable angina and severe LV dysfunction(4). While subsequent observational studies of surgical revascularization appeared to confirm the existence of hibernation(5, 6), until recently, this had not been adequately assessed in a randomized study.

The seminal Surgical Treatment for Ischemic Heart Failure (STICH) trial, the only randomized evaluation of CABG for ICM to date, enrolled patients with a LV ejection fraction (EF) ≤35%. At a median of 4.6 years, the primary outcome, all-cause mortality, was not significantly different between patients treated with optimal medical therapy (OMT) alone compared to those assigned to CABG surgery (41% vs. 36%, hazard ratio (HR) 0.86, 95% confidence interval (CI) 0.72 to 1.04, p=0.12)(7). Mortality in the first 30 days was significantly higher in the surgical group (4% vs. 1%, HR 3.12, 95% CI 1.33 – 7.32, p=0.009). This finding is in keeping with the known association between mortality and LV dysfunction following CABG surgery(8). The early hazard of CABG may have negated the benefits of revascularization, which become gradually manifest in those who survive the complications of surgery. The Surgical Treatment for Ischemic Heart Failure Extension Study (STICHES) reported longer-term mortality data from the STICH trial. At median follow up of approximately 10 years, 59% of patients assigned to CABG died versus 66% in the medical therapy group (HR 0.84; 95% CI 0.73-0.97; p=0.02)(9). Death from cardiovascular causes and several pre-specified composite secondary endpoints also occurred less often in the CABG group. The critical balance between safety and efficacy is also borne out when

examining the impact of age on treatment effect in STICH. Long-term survival benefit was most apparent in the youngest patients enrolled in the trial (in whom the risks of peri-procedural mortality and morbidity are lowest) and this benefit diminished with increasing age(10).

Given the lower procedural risks associated with percutaneous coronary intervention (PCI), it has the potential to allow the benefits of revascularization to be realized with fewer complications than CABG surgery, but this assertion is yet to be tested in a randomized trial. Table 1 summarizes randomized and observational studies of revascularization versus medical therapy published in the past 15 years and includes the proportion of patients treated by PCI. It should be noted that the risk of longer-term complications, such as restenosis and late stent thrombosis, in this population who tend to have complex coronary disease and multiple comorbidities, is largely unknown. While numerous comparisons have been made between PCI and CABG in patients with symptomatic coronary disease, most of the large randomised trials excluded patients with impaired LV function. Less than 2% of all patients included in the largest randomised controlled trial comparing PCI with CABG, SYNTAX, had significant LV impairment (EF<30%) at baseline(11). We reported outcomes of PCI in 301 patients with severe ICM (mean EF 24%), showing 30-day, 6-month and 4 year mortality rates of 1.3%, 6% and 33%, respectively(12, 13). These results appear to compare favourably with the surgical data, but as these are not matched cohorts, further comparison is not possible. On the other hand, the degree of LV impairment is a known determinant of adverse outcome even in patients undergoing PCI(14) and whether this modality of revascularization would offer incremental prognostic benefit, over and above contemporary HF medication and device therapy, is unclear. A recent meta-analysis of observational data suggests that CABG may offer superior outcomes compared to PCI, with either modality being preferable to medial therapy alone(15). The 2014 ESC guidelines for revascularisation make a class IIb recommendation (with a level of evidence C) for PCI, in the presence of viable myocardium, where surgery is not indicated(16). REVIVED-BCIS2 is the first randomised comparison of

percutaneous revascularisation (with OMT) versus OMT alone in patients with LV dysfunction and viable myocardium.

Trial hypotheses and outcome measures

The principle hypothesis of REVIVED_BCIS2 is that PCI in combination with OMT will improve event-free survival in patients with ICM and viable myocardium, compared to a strategy of OMT alone. The main secondary hypothesis is that PCI will improve LV systolic function in this cohort compared to OMT alone. The primary outcome is a composite endpoint of all-cause death or hospitalization due to HF, over the entire duration of the trial. Patients will be followed up for at least 2 years from randomization (expected range 2 to 8.5 years). The major secondary outcome is LVEF, assessed by echocardiography, 6 and 12 months from randomization. Other outcome measures include cardiovascular death, all-cause death, hospitalization due to HF, acute MI, appropriate Implantable Cardioverter Defibrillator (ICD) therapy, quality of life scores (Kansas City Cardiomyopathy Questionnaire and EuroQol EQ-5D-5L), New York Heart Association (NYHA) functional class, unplanned further revascularization, Canadian Cardiovascular Society (CCS) angina class, health resource use, serial Troponin T or I levels, serial Brain-type Natriuretic Peptide (BNP or NT-proBNP) levels and the incidence of major bleeding. Definitions of outcome measures are detailed in table 2.

Study Population

Individuals with all of the following characteristics will be eligible for inclusion: severe LV dysfunction (EF≤35%), extensive coronary disease and demonstrable viability in at least 4 dysfunctional myocardial segments(17) that can be revascularized by PCI. As this is a trial assessing the prognosis of patients with LV dysfunction, those with a spectrum of HF symptoms (NHYA I to IV) will be enrolled.

LVEF is assessed by the biplane Simpson's Rule/3D echocardiography or by Magnetic Resonance Imaging (MRI). If there has been a recent clinical diagnosis of MI (MI), the imaging study is performed at least 4 weeks after the MI.

Extensive coronary disease is defined as a British Cardiovascular Intervention Society myocardial jeopardy score (BCIS-JS)(18) of at least 6 (the maximum possible score is 12; a calculation tool is included in the supplementary appendix). The BCIS-JS can be applied to patients with or without previous bypass grafts; for illustration, patients who do not have bypass grafts will have a BCIS-JS ≥6 if they have significant left main, proximal LAD or at least proximal two-vessel disease. Myocardial viability is characterized using the AHA 17-segment model and can be assessed using any recognised modality, including MRI, Dobutamine Stress Echocardiography (DSE), Single Photon Emission Computerised Tomography (SPECT) or Positron Emission Tomography (PET).

Trial exclusion criteria are a MI within 4 weeks of randomization (this is a clinical definition as adjudicated by recruiting centres); acutely decompensated HF requiring treatment with inotropes/ ventilation/MCS within 72 hours of randomization; sustained ventricular tachycardia/fibrillation (VT/VF) or appropriate ICD discharges within 72 hours of randomisation; valve disease deemed by the local heart team to require imminent intervention; any contraindications to PCI; age <18 yrs (there is no upper age limit); estimated glomerular filtration rate < 25 ml/min/1.73m^2, unless established on dialysis; pregnancy; previous enrolment in REVIVED-BCIS2 or current enrolment in other trial that may affect REVIVED-BCIS2 outcome data and life expectancy < 1 year due to non-cardiac pathology.

It is anticipated that some eligible candidates (such as those with severe limiting angina) will be considered for revascularization on clinical grounds, at the discretion of the responsible clinician and in accordance with the wishes of the patients. Similarly, in some cases, eligible patients may be offered coronary artery bypass surgery, including those thought to benefit from adjunctive surgical procedures (like valve repair/replacement or left ventricular reconstruction) or those whose coronary anatomy is considered by the local team to be more amenable to surgical rather than percutaneous revascularization. These patients will not be enrolled in the trial but the screening log (see below) will capture such exclusions.

Trial design, conduct and organization

REVIVED-BCIS2 is a prospective randomized controlled trial, conducted across 30-35 centers in the United Kingdom. Once the principal investigator at each site confirms the eligibility of a patient and written informed consent is obtained, randomization is carried out via an online web-based system. Randomization of the treatment assignment is stratified by center using randomly permuted blocks of varying size, with 1:1 allocation between the PCI and OMT arms. Given the nature of PCI, this is an open-label trial, but researchers adjudicating and analysing trial outcomes will be blinded to treatment assignment. Figure 1 summarizes recruitment and study flow.

The trial is sponsored by King's College London, UK and funded by the UK Department of Health via the National Institute for Health Research (NIHR) (Health Technology Assessment project 10/57/67) with oversight by a Trial Steering Committee (TSC) that meets pre-specified independence criteria (Figure 3). A Data and Safety Monitoring Committee (DSMC) has been convened and a DSMC charter developed, which includes details of the meeting schedule and stopping guidelines. The DSMC are independent of the trial team and report directly to the TSC. The Clinical Trials Unit (CTU) at the London School of Hygiene and Tropical Medicine coordinate and monitor all aspects of the trial. The trial is officially endorsed by the British Cardiovascular Intervention Society (BCIS) and hence is referred to as REVIVED-BCIS2.

The protocol and amendments have been reviewed and approved by the UK National Research Ethics Service (London - Westminster committee; REC reference 10/H0802/46). The trial is carried out in accordance with the declaration of Helsinki and in keeping with Good Clinical Practice Guidelines. Registration was completed before recruitment commenced (NCT01920048) and ISRCTN45979711). The first patient was randomized on 28th August 2013 and at the time of this publication, 400 patients have been randomized. Figure 2 summarizes the study timeline. There has been one major amendment to the protocol, implemented in July 2014, when the first inclusion criterion was

modified from "LVEF ≤30%" to "LVEF≤35%" to facilitate comparison with relevant literature and guidelines. At this stage, "≥CCS class 3 angina" was removed from the list of exclusion criteria, due to the difficulty in distinguishing angina from breathlessness in this particular population.

Assessment of LV function and viability

Suitability of patients on the basis of EF will be adjudicated by the participating centers, on the basis of recent echocardiography or MRI studies. All patients will also have echocardiography performed at randomization (if the qualifying EF was based on a recent echocardiogram, this can be submitted as the baseline study) as well as 6 and 12 months later. Baseline, 6 month and 12 month echocardiograms will be anonymized and submitted to an independent echocardiography core laboratory (at Guy's and St Thomas' Hospital, London, UK), which will determine LV volumes and EF using a biplane Simpson's method, for evaluation of the major secondary outcome. The core laboratory will be blinded to treatment assignment as well as to the timing of the studies in relation to randomization. Core laboratory analysis will also include the degree of mitral regurgitation and segmental wall motion.

Myocardial viability testing is used to prospectively predict hibernation by identifying the extent of fibrosis, contractile reserve, membrane integrity or metabolic activity(19). There has never been a randomized evaluation of the value of viability testing in the management of ICM and observational series have reported seemingly conflicting results. A meta-analysis of over 3000 patients with ICM from 24 studies showed that mortality was lower following revascularization in patients with viable myocardium but that this benefit was not seen in the absence of viability(20). A more recent observational series of patients with ICM assessed by PET showed that revascularization was associated with lower mortality compared to OMT when the extent of viability exceeded more than 10% of the whole myocardium(21). However, analysis of a subgroup of patients in the STICH trial who underwent discretionary viability testing, did not demonstrate an interaction between the response to revascularization and their viability classification(22). A pertinent consideration is the fact that the

STICH substudy classified patients dichotomously as having viable hearts or not. However, an individual with ICM usually has some regions that are clearly viable and others that are not and with PCI, it is possible to target revascularization to myocardial territories selected on this basis. Notwithstanding differences in sensitivity and specificity between imaging modalities, in order to ensure widespread applicability of trial results, segmental viability will be determined by any recognized modality in REVIVED. Imaging and intervention specialists at each participating center assess segmental viability and the feasibility of revascularizing the relevant segments, to determine whether an individual patient will be eligible for randomization.

Percutaneous coronary intervention arm

PCI will be performed according to local protocols. Dual antiplatelet therapy should be given in all cases, with pre-loading, and the post-PCI duration based on the individual's bleeding risk and local/national guidelines. In general, drug-eluting stents are recommended, but in patients who have an indication for long-term formal anticoagulation (e.g. for concurrent atrial fibrillation, LV thrombus or venous thromboembolic disease), the choice of stent type should be based on their suitability for medium-term combined antiplatelet and anticoagulation therapy.

Completeness of revascularization: it is strongly recommended that PCI be attempted on all significant coronary lesions in major proximal coronary vessels (or side branches >2.5mm in diameter) subtending viable myocardium. Lesion significance is defined as >70% diameter stenosis on angiography or for lesions between 50 and 70% diameter stenosis, when accompanied by demonstrable reversible ischemia on invasive or non-invasive testing. Planned target lesions will need to be identified by the operator and recorded by the trial coordinator before the procedure. Patients who meet inclusion criteria and have chronic total occlusion (CTO) of coronary arteries subtending viable myocardial segments should be considered for REVIVED, provided that the PCI operators predict a high likelihood of successfully reopening these vessels. It is recommended that dedicated CTO operators, in units that have this degree of

specialization, undertake such cases. The coronary disease burden at baseline and the completeness of final revascularization will be characterized by the BCIS-JS and Revascularization Index (RI), where RI = $(JS_{pre} - JS_{post})/JS_{pre}$(18). The interaction between treatment effect and RI as well as the presence of a CTO will be the subject of a separate substudy.

Staged PCI: a single stage strategy should be employed where possible. However, provisional staging could be considered in patients with renal dysfunction, complex coronary disease (including CTO) or if it is felt during PCI that deferring intervention to one or more vessels is in the patient's best interests (e.g. due to unexpected high contrast volumes or procedural complications during PCI to the first vessel). Staging must be prespecified at the index procedure. Urgent revascularization before the planned second stage procedure will be considered a secondary endpoint.

Optimal medical therapy in both arms

In order to ensure that patients in both arms of the trial receive optimal medical and device therapy, there is a nominated heart failure lead at each participating centre who is actively involved in patient selection and monitoring of therapy during the course of the trial. Furthermore, a trial Medical Therapy Committee has been established, that will review available evidence and guidelines at least annually and refine recommendations to ensure that drug and device therapy given to all patients in the trial remains optimal and contemporary. Each site is provided with a standard operating procedure for delivering and monitoring OMT, which sets out classes of drugs appropriate for trial patients, including HF therapies (such as angiotensin converting enzyme inhibitor or angiotensin receptor blocker +/- neprilysin inhibitor, betablocker and mineralocorticoid receptor antagonist (23)) and secondary prevention for atherosclerosis (including statin and antiplatelet agent) as well as recommended treatment targets (including lipid profile, HbA1c, resting heart rate). Formal anticoagulation for LV thrombus detected on imaging or as prophylaxis for severe LV dysfunction/ dyskinesis is at the discretion of the treating physician.

Initiation of the above treatments, dose-titration and relevant monitoring is per local HF protocols.

Eligible patients are initiated on medical therapy prior to randomization and, in patients presenting with de novo HF, assessment of LV EF is deferred if they are not on appropriate medical therapy at presentation. Optimization of medical and device therapy will continue in both groups even after randomization, throughout the course of the trial.

ICD implantation is not mandatory for inclusion in REVIVED, although many patients who fulfill trial eligibility criteria may also be candidates for primary prevention ICDs. Participating sites are encouraged to follow international guidelines(23) when deciding on ICD or resynchronization device therapy and to make and document the decision to implant (or not implant) a device, before randomization.

Statistical considerations

Power Calculation: In the STICH trial, the rate of all cause death or hospitalization for HF at 5 years was 54% in the medical therapy group, with approximately 50% of events occurring in the first year and a steady rate thereafter(7). These data are similar to the 1 year rates of death or HF hospitalization reported in registries of Western European populations(24). On this basis, the predicted occurrence of death or hospitalization for HF at two years is 36% in the OMT group. The primary outcome will be measured over the entire trial duration, with a minimum follow-up duration of two years. A trial of 700 (350 in each group), with 300 patients experiencing a primary outcome, would have over 85% power to detect a hazard ratio of 0.7 (a 30% relative reduction in the hazard) at 5% significance, allowing for up to 5% losses by the end of follow-up. The hazard ratio of 0.7 is considered clinically meaningful and in line with the magnitude of benefit observed across other treatment modalities in this population. For the major secondary endpoint, even half this sample size will provide 90% power to detect a minimum difference in EF of 4%, assuming a standard deviation of 11%.

This trial will be a comparison of initial strategy, rather than technique; the projected event rates and hazard ratio allow for the fact that OMT patients may undergo subsequent revascularization. As such, no additional adjustments have been made to the power calculation to account for unplanned revascularization in the OMT arm. In patients assigned to receive OMT, revascularization by PCI or CABG during the trial would only be recommended in one of the following circumstances: readmission with an acute coronary syndrome (diagnosed on the basis of typical ischemic symptoms as well as a rise in cardiac biomarker levels or dynamic ST-segment deviation on ECG), deterioration in exertional angina to ≥CCS class 3 symptoms or the occurrence of resistant ventricular arrhythmias considered to be ischemic in etiology.

Statistical Analysis: A detailed statistical analysis plan will be finalized before any data are analyzed by treatment assignment. Analysis of outcomes will be by treatment assignment, on an intention-to-treat basis. An unadjusted time-to-event analysis will be performed on the primary outcome using data across all follow-up, with time to the first event (or censoring) times measured from randomization. Hazard ratios together with associated confidence intervals will be calculated from the Cox proportional hazards model. Cumulative event rates will be calculated and presented using Kaplan-Meier time-to-event curves. As a measure of absolute treatment difference, cumulative event rates will be compared at 2 years. Each individual component of the primary composite outcome as well as other secondary time to event outcomes will be analyzed using the above methods. Losses to follow-up are expected to be minimal and patients will be included up until the time they experience the event or are censored. Any categorical outcome measures compared at specific time points will be examined using risk ratios and risk differences, confidence intervals and significance tests. Continuous variables will be analyzed and presented as mean treatment differences, confidence intervals and p-values derived from analysis of co-variance models or unpaired t-tests as appropriate (with appropriate transformation if necessary).

Interim analyses by treatment assignment are not planned. A limited number of subgroups analyses will be performed, which will be detailed in the analysis plan. A risk model will be developed, based on interactions between variables and treatment in the Cox model, and used to examine whether the impact of treatment depends on a person's underlying risk.

Health Economic Analysis

The Centre for Health Economics at the University of York, UK will perform a formal health economic analysis. Data will be collected on health service resource use including length of inpatient stays, outpatient visits, use of primary care resources, use of cardiovascular medication and devices and subsequent cardiovascular procedures. Resource use will be valued in monetary terms using routine unit cost data relevant to the UK National Health Service (NHS). These will include NHS Reference Costs, British National Formulary drug prices and the Personal Social Services Research Unit (PSSRU) survey of unit costs.

A formal cost effectiveness of PCI in this population will be undertaken using a decision analytic framework, which will be a cohort model with states representing death and different levels of HF symptoms. Key features will include the quantification of health benefits in terms of quality-adjusted life years (QALYs) and the use of an NHS cost perspective. Standard decision rules will be used to assess cost effectiveness and extensive sensitivity analysis will be undertaken (probabilistic and deterministic) to assess the implications of uncertainty in the available evidence for cost-effectiveness. Heterogeneity in cost effectiveness between different sub-groups of patients will be assessed using methods consistent with those applied to clinical outcomes.

Data Collection and Monitoring

Each patient's demographic details, medical history, electrocardiogram, routine blood results, cardiac medication, LVEF, viability assessment, ICD interrogation result (if applicable) and the BCIS-JS are recorded at baseline. LVEF will be reassessed at 6 and 12 months as detailed above. ICD interrogation, quality of life scores, BNP (or NT-Pro BNP) level, Troponin (T or I) level and cardiac medication are recorded at 6, 12 and 24 months post-randomization. All major

outcomes and Serious Adverse Events are collected at 6, 12 and 24 months for all patients and yearly thereafter for patients who have been randomized more than 2 years before the end of the trial. Additionally, patients who undergo revascularization (by treatment assignment or as an unplanned procedure) have Troponin levels checked before and after the procedure. Hospitalization and mortality will be tracked using national databases to ensure that any unreported major outcome events are identified. The DMSC will review serious adverse events and any other trial safety issues. The Clinical Trial Unit collects a snapshot of screening, from each center, twice a year. Recruiting centers capture details of all patients with extensive CAD and EF ≤35% during this representative period. These data will be used to generate a Consort-style flowchart, describing the total population screened as well as the frequency and causes of patients excluded from the trial.

Conclusion

Ischemic cardiomyopathy is the commonest cause of HF and is associated with significant mortality and morbidity. Surgical revascularization has recently been shown to improve long-term outcomes in some patients, but surgery itself carries a major early hazard in this group. PCI is an appealing alternative to surgery, which may allow a better balance between risk and benefit, but this assertion has never been formally tested. REVIVED is the first randomized controlled trial of PCI for severe ischemic LV dysfunction and will provide important data that will inform guidelines on revascularization in ICM.

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Figure 1: STUDY FLOW

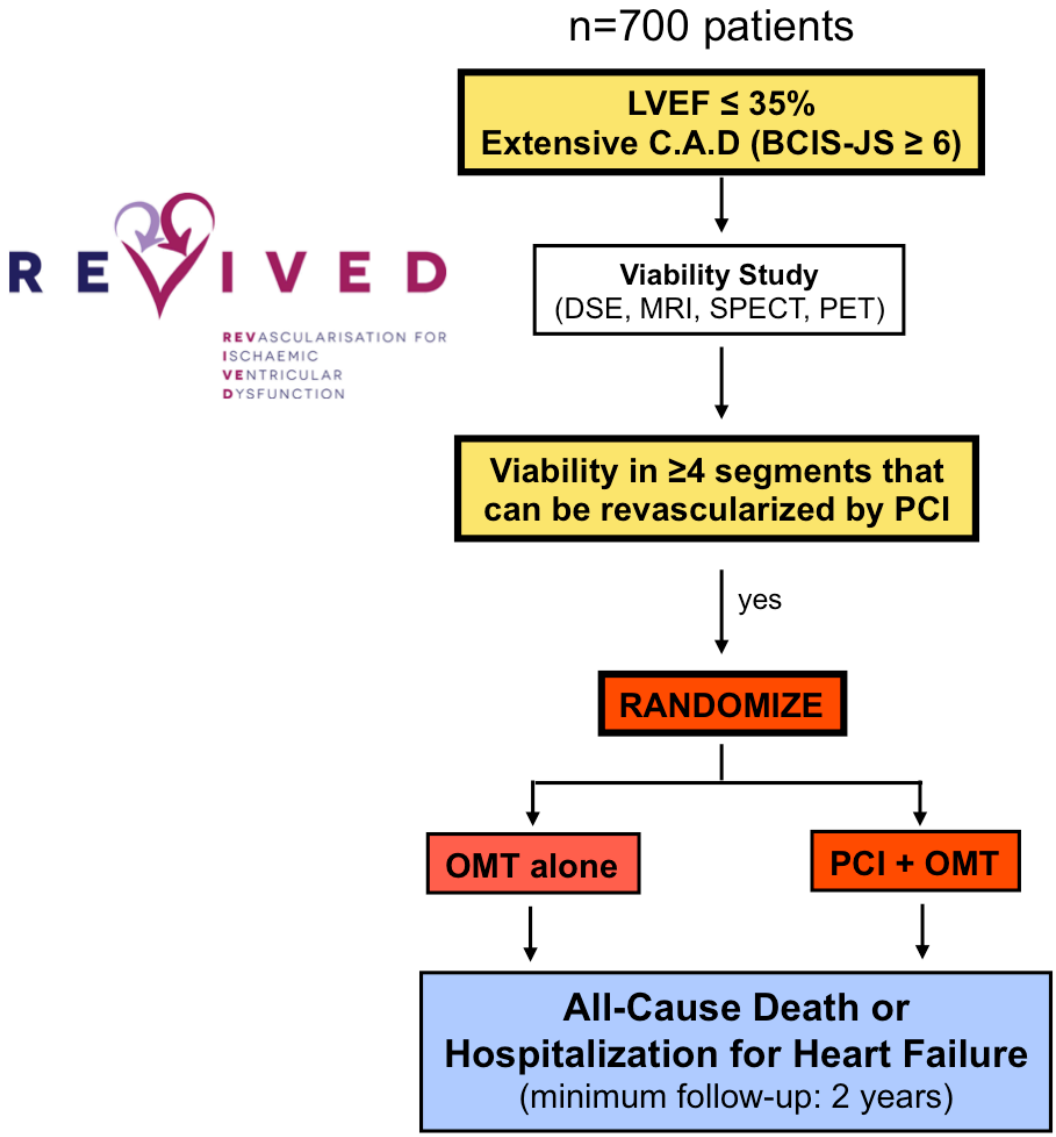

Figure 2: STUDY TIMELINE

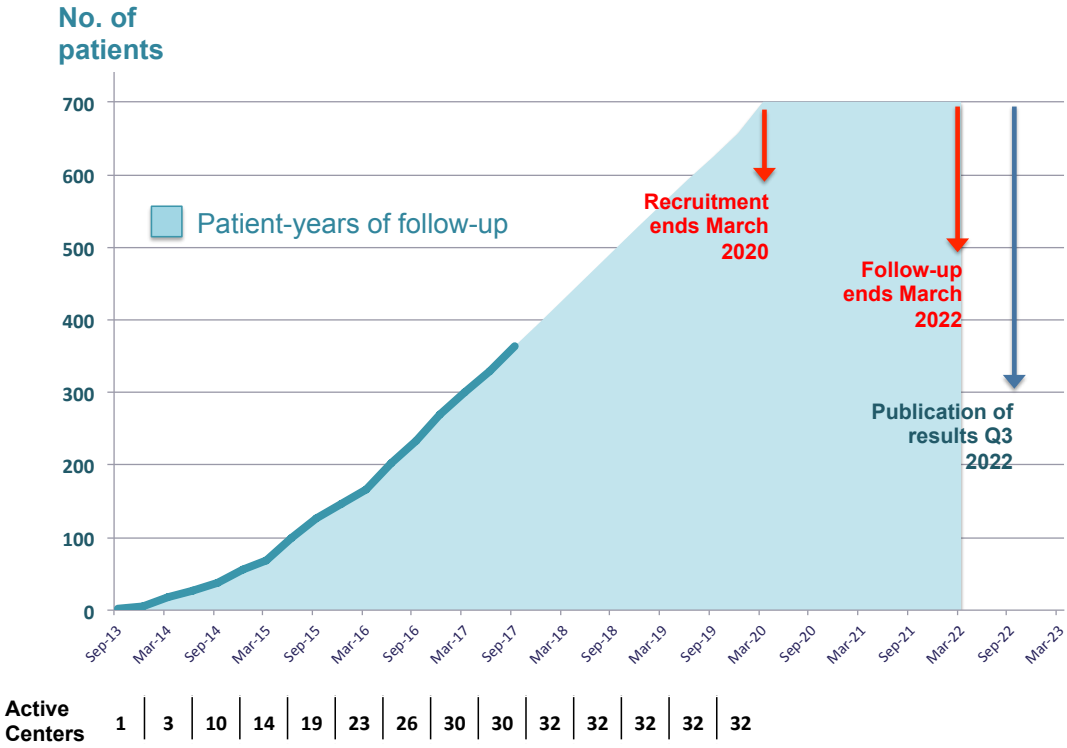

Figure 3: Trial Organization

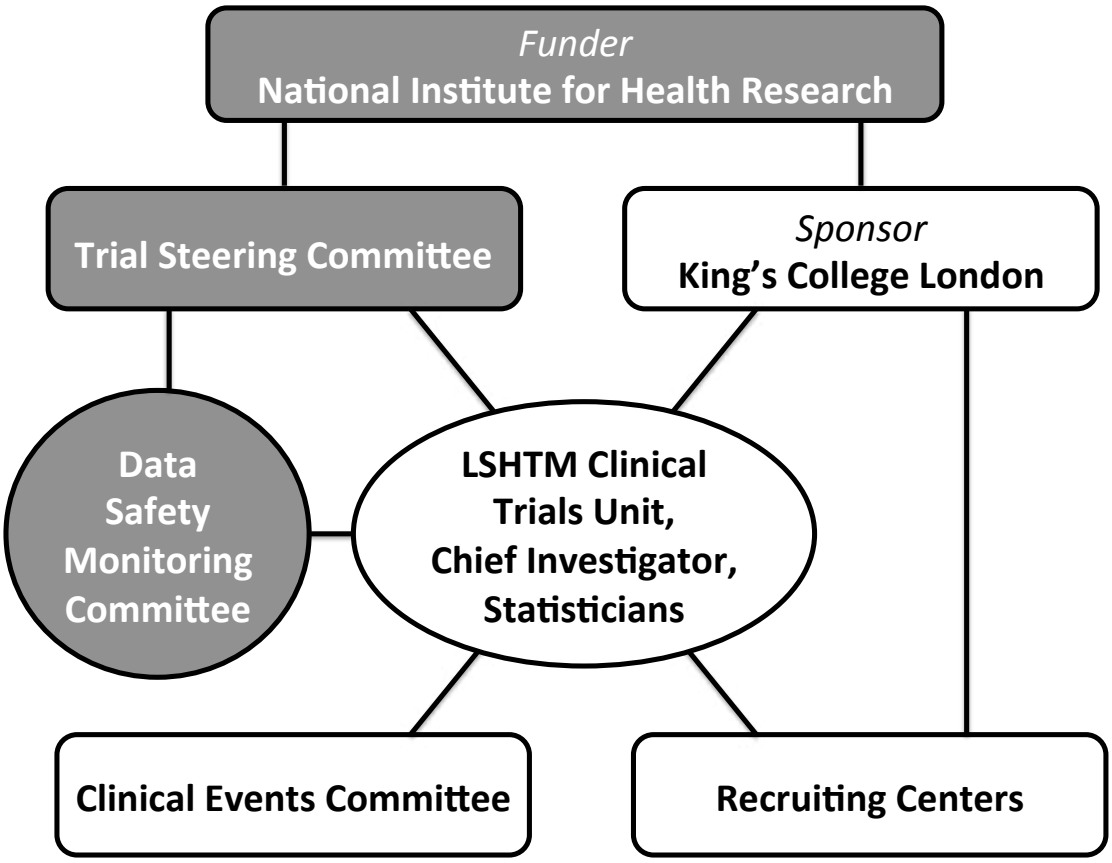

Table 1. Studies of revascularization versus medical therapy published between 2002 and 2017

Study	Publication Year	All patients (n)	Revascularized (n)	% revascularized by PCI	Follow up duration (months)	Deaths in Medical Therapy Group	Deaths in Revascularization Group
Velazquez†	2016	1212	610	0	118 (109-132)	5yr: 244 (41%); 10yr: 398 (66%)	5yr: 218 (36%); 10yr 359 (59%)
Ling	2013	648	199	NR	34 ±14	122 (30.4%)	43 (21.6%)
Gerber	2012	144	86	8	36 (IQR NR)	HR 2.5 (95% CI: 1.1 to 6.1)‡	
Aljaroudi	2012	486	96	0	23 ±17	97 (25%)	11 (11%)
Velazquez	2012	763	139	0	120	5yr: 43%; 10yr: 72%‡	5yr: 29%; 10yr: 58%‡
Cleland†	2011	138	45	33	59 (33-63)	25 (36%)	26 (38%)
Sawada	2010	274	130	7	54±44.4	69 (48%)	45 (35%)
Desideri	2005	261	94	0	25 (IQR NR)	40 (24%)	12 (13%)
Liao	2004	107	63	17	27 ±19	21 (48%)	17 (27%)
Meluzin	2003	113	62	13	27 ±23	17 (33%)	10 (16%)
Sicari	2003	425	188	37	37.2 (IQR NR)	85 (36%)	41 (21%)
Sawada	2002	139	65	5	23±13	28 (38%)	13 (20%)
Shah	2002	439	141	NR	NR	5yr: 53%‡	5yr: 27%‡
O'Connor	2002	1391	339	0	NR	5yr: 63%; 10yr: 87%‡	5yr: 39%; 10yr: 58%‡

Follow-up duration is quoted as mean ± SD or median (IQR).
† RCTs, ‡ adjusted mortality/propensity matched data; NR: not reported
(6, 7, 9, 21, 25-35)

Table 2. Definitions of outcome measures

Acute Myocardial Infarction (MI)	1. Spontaneous MI (≥48 hrs after PCI/CABG) Detection of a rise and/or fall of cardiac Troponin T or I levels, with at least one value higher than the 99th percentile upper reference limit (URL) AND symptoms consistent with ischaemia OR dynamic ECG changes (including >1mm ST elevation, new Left Bundle Branch Block (LBBB) >1mm ST depression, >3mm T wave inversion) 2. Peri-procedural MI (<48 hrs after PCI/CABG)* **Following PCI,** Troponin (T or I) > 5 x the 99th percentile URL) (or 5 x the baseline value if this is higher than the URL) in combination with any of (a) evidence of prolonged ischaemia (>20 min) as demonstrated by prolonged chest pain and/or ischaemic ST changes or (b) new pathological Q waves or (c) angiographic evidence of a flow limiting complication, such as of loss of patency of a side branch, persistent slow-flow or no-reflow, embolisation, or (d) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. **Following CABG**, Troponin (T or I) > 10 x 99th percentile URL (or 10 x the baseline value if this is higher than the URL) in combination with any of the following: (i) new pathological Q waves or (ii) angiographically documented new graft or new native coronary artery occlusion or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, 3. Sudden death Cardiac arrest accompanied by new ST elevation/LBBB on ECG and/or evidence of fresh coronary thrombus at autopsy/angiography * *In addition to classifying patients dichotomously, as having suffered a periprocedural MI or not on the basis of the 2012 Universal Definition of a type 4 MI*(36)*, baseline and peak Troponin levels measured within 24 hours of a procedure will be recorded. This will provide a continuous outcome measure of periprocedural myocardial injury and will also allow subsequent reclassification in the event of further revisions to definitions of periprocedural MI that may occur during the course of the trial..*
Appropriate ICD therapy	At least one ICD shock or episode of anti-tachycardia pacing for documented ventricular tachycardia (VT) or ventricular fibrillation (VF)

Cardiovascular death	All deaths where there is no clinical or post-mortem evidence of a non cardiovascular aetiology
Hospitalization for heart failure (HF)(37).	Hospital admission (lasting at least 24 hours) for deteriorating symptoms or signs of HF, where there is a documented diagnosis of HF and the patient receives initiation or intensification of treatment for HF. Initiation or intensification of treatment includes at least one of the following: increase in oral diuretic dose or addition of another oral diuretic, intravenous diuretic therapy, intravenous vasoactive therapy (vasodilator, inotrope or vasopressor), mechanical circulatory support (MCS) (including intra-aortic balloon pump, Impella, extra-corporeal membrane oxygenation) or cardiac transplantation. HF during or after the assigned PCI procedure itself is defined as prolongation of the planned admission by at least 24 hours due to acute heart failure requiring initiation or intensification of treatment as defined above. Prolongation of hospital admission in patients who have prophylactic pre-PCI insertion of a MCS should not be recorded as having a HF hospitalization unless there are features of HF requiring initiation or intensification of treatment as defined above. Elective admission for implantation or revision of ICD/cardiac resynchronization therapy (CRT) devices will not constitute a HF hospitalization endpoint.
Major Bleeding	Major bleeding will be defined using the Bleeding Academic Research Consortium (BARC) categories(38) below: Type 3a • Overt bleeding plus haemoglobin drop of ≥30 to <50g/L (provided haemoglobin drop is related to bleed) • Any transfusion with overt bleeding Type 3b • Overt bleeding plus haemoglobin drop ≥50g/L (provided haemoglobin drop is related to bleed) • Cardiac tamponade • Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid) • Bleeding requiring intravenous vasoactive drugs Type 3c • Intracranial haemorrhage (does not include microbleeds or haemorrhagic transformation; does include intraspinal)

	• Subcategories; confirmed by autopsy or imaging or lumbar puncture • Intra-ocular bleed compromising vision Type 4: CABG-related bleeding • Perioperative intracranial bleeding within 48 hours • Reoperation following closure of sternotomy for the purpose of controlling bleeding • Transfusion of ≥ 5 units of whole blood or packed red blood cells within a 48 period • Chest tube output ≥ 2 L within a 24 h period • If a CABG-related bleed is not adjudicated as at least a Type 3 severity event, it will be classified as 'not a bleeding event' Type 5: fatal bleeding Type 5a • Probable fatal bleeding: no autopsy or imaging confirmation, but clinically suspicious Type 5b • Definite fatal bleeding: overt bleeding or autopsy or imaging confirmation
Unplanned revascularisation	PCI group: any unplanned target vessel or non-target vessel revascularisation by PCI or CABG following index PCI, excluding provisional staged PCI (with plan documented at the index procedure). OMT group: any revascularisation by PCI or CABG