REVASCULARISATION FOR
ISCHAEMIC
VENTRICULAR
DYSFUNCTION

Summary

Protocol

ISRCTN45979711 / NCT01920048

Background:

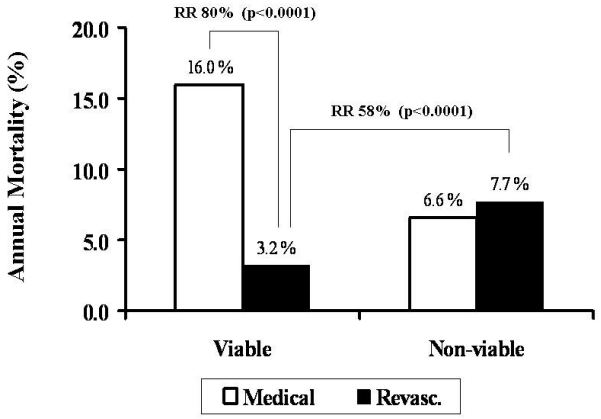
Epidemiology

In 2002, it was estimated that approximately 900,000 individuals in the United Kingdom had a diagnosis of heart failure and at least 5% of all deaths in the country were related to this condition. At that time, one million in-hospital bed-days per year were estimated to be due to heart failure, with an annual cost to the NHS in excess of £625 million. Furthermore, there is evidence of a rising prevalence of heart failure in the population, with the number of associated hospital admissions expected to increase by around 50% in the next 25 years. This emerging epidemic is the likely consequence of a progressively aging population and improved survival from acute coronary syndromes, partly due to more efficient and timely revascularisation techniques. The Framingham Heart Study suggests that the most common cause of chronic heart failure is no longer hypertension or valvular heart disease, as it was in previous decades, but rather coronary artery disease. Recent meta-analyses of heart failure trials and large registries have shown that coronary disease is the underlying cause of heart failure in 65% of cases, although this may have been an underestimation, given that few of these studies mandated systematic exploration of aetiology.

Hibernating Myocardium

The concept of viable but dysfunctional myocardium emerged approximately three decades ago, when it was observed that patients undergoing coronary artery bypass surgery for chronic stable angina had improvement or normalisation of left ventricular function following revascularisation. The energy utilized during myocyte contraction far exceeds the requirement for sustaining viability and as such, myocardial tissue may survive in a hypocontractile state in the presence of reduced coronary blood flow or decreased coronary flow reserve, known as hibernation. Improvement of blood flow by revascularisation of hibernating myocardium can lead to restoration of regional and global left ventricular function and reversal of adverse remodelling, provided this is achieved before the onset of irreversible cellular and ultrastructural alterations. Potentially reversible, dysfunctional myocardium is characterised by preserved cellular integrity and a degree of contractile reserve, whereas scarring and absence of inducible contraction tend to reflect irreversible myocardial damage. Each of these distinguishing features can be used to predict myocardial viability or the likelihood of functional recovery following revascularisation. The parameter most widely used to determine viability is contractile reserve, which is assessed by measuring the augmentation of function of hypocontractile myocardium, in response to inotropic stimulation. The most commonly used agent is Dobutamine (at doses up to 20µg/kg/min) while the change in regional and global contractility could be imaged by echocardiography (DSE) or cine-MRI. While MRI allows scar imaging as well as assessment of contractile reserve, at present it is contra-indicated in patients with implantable cardioverter defibrillators or pacemakers in situ, which can limit its use in a heart failure population.

Despite variation in the sensitivity and specificity of MRI, DSE, positron emission tomography (PET) and Nuclear Medicine techniques, patients found to have viable myocardium (by any modality) have been shown to have a strong survival advantage following revascularisation compared to medical therapy alone. A meta-analysis of more than 3000 patients in 24 randomised studies (in which viability was assessed by single photon emission computed tomography (SPECT), PET or DSE) showed an impressive 80% relative reduction (and 12.8% absolute reduction) in mortality with revascularisation compared to medical therapy in patients found to have significant viable myocardium. In contrast, no survival benefit was seen in the absence of viability and even a trend to worse outcome with revascularisation. These data also argue against a strategy of revascularising all patients with heart failure and coronary disease, regardless of viability; mortality following CABG surgery in patients without viability was more than double that observed in those who did have viable myocardium.



A more recent analysis of 14 non-randomised studies suggests that the findings of the Allman meta-analysis have not changed despite changes in revascularisation techniques and medical therapy. It has traditionally been held that completeness of revascularisation (in relation to the angiographic findings) is a major determinant of outcome in ischaemic cardiomyopathy; whether regional viability can be used to guide the extent (and hence the mode) of revascularisation in a given patient, remains untested to date.

Notwithstanding the compelling nature of these small studies, there is a lack of consensus on the role of revascularisation in patients with heart failure owing to the absence of adequately powered randomised controlled studies in this field. Furthermore, there have been major advances in medical therapy for heart failure during the last decade and the incremental benefit of revascularisation in contemporary practice is unknown. REVIVED-BCIS2 will be the largest contemporary randomised comparison of percutaneous revascularisation (with optimal medical therapy) versus optimal medical therapy alone in patients with heart failure and viable myocardium, and is expected to definitively resolve the role of this treatment.

Aim: To evaluate the efficacy and safety of percutaneous coronary intervention (PCI) combined with optimal medical therapy (OMT) compared to OMT alone for ischaemic left ventricular dysfunction.

Hypothesis: Compared to OMT alone, PCI+OMT improves event free survival in patients with ischaemic cardiomyopathy and viable myocardium.

PATIENT ELIGIBILITY

Inclusion Criteria

ALL of the following:

1. Poor left ventricular function (EF≤35%)
2. Extensive coronary disease
3. Viability in at least 4 dysfunctional myocardial segments, that can be revascularised by PCI

Exclusion Criteria

1. Myocardial infarction < 4 weeks previously (clinical definition)
2. Decompensated heart failure requiring inotropic support, invasive or non-invasive ventilation or IABP/left ventricular assist device (LVAD) therapy <72 hours prior to randomisation
3. Sustained VT/VF or appropriate ICD discharges <72 hours prior to randomisation
4. Valve disease requiring intervention
5. Contraindications to PCI
6. Age <18 years
7. eGFR <25 ml/min, unless established on dialysis
8. Women who are pregnant
9. Previously enrolled in REVIVED-BCIS2 or current enrolment in other study that may affect REVIVED-BCIS2 outcome data
10. Life expectancy <1 year due to non-cardiac pathology

Sample size: 700 patients across 30-35 sites in the UK.

Primary Endpoint: All-cause death or hospitalisation due to heart failure. This composite endpoint will be collected over the entire duration of follow-up in the trial (follow up a minimum of 2 years up to 5 ½ years).

Major Secondary Endpoints: Quality of life (Kansas City Cardiomyopathy Questionnaire and EuroQol EQ-5D-5L), New York Heart Association (NYHA) functional class and Left ventricular ejection fraction.

Treatment:

Percutaneous Coronary Intervention

Routine stent placement is required where feasible and drug-eluting stents are strongly recommended. The use of IABP therapy is at the discretion of the operator; routine elective placement of an IABP is not recommended.

It is strongly recommended that PCI is considered and, if feasible, attempted on all significant coronary lesions in major proximal coronary vessels (or side branches > 2.5mm in diameter) subtending viable myocardium.

A single stage strategy should be employed where possible. However, provisional staging could be considered in patients with renal dysfunction, complex coronary disease (including chronic total occlusions) or if it is felt during PCI that deferring intervention to one or more vessels is in the patient's best interests.

There is no time limit from randomisation to PCI.

Optimal Medical Therapy

A Medical Therapy Committee will review available evidence annually from the start of recruitment (or in the event of relevant new data/guidelines becoming available in the interim) to ensure that drug and device therapy given to all patients in the study (including randomised arms and registry) remains optimal and contemporary. At present, optimal medical therapy for patients with ischaemic cardiomopathy includes ACE-inhibitor (or Angiotensin Receptor Blocker in the event of side effects to ACE-inhibitors or as an adjunct to an ACE inhibitor), Betablocker, Aldosterone Antagonist, anti-platelet drug and statin. Formal anticoagulation for severe left ventricular dysfunction/ dyskinesis is at the discretion of the treating physician. It is recommended that aggressive rate control or rhythm control strategies are used in patients with Atrial Fibrillation, all of whom should be considered for formal anticoagulation.

Initiation of the above treatments, dose-titration and relevant monitoring will be as per local heart failure protocols and will be supervised by a designated heart failure lead at each centre. It is recommended that patients are initiated on medical therapy prior to randomisation, however the doses do not need to have been optimised before a patient can be randomised.

OUTCOME MEASURES

Primary

1. All cause death or hospitalisation for heart failure up to end of the follow-up period (minimum f/u 2 years, maximum f/u 5 ½ years)

Secondary

2. Quality of life score up to the end of the follow-up period
3. NYHA functional class up to 2 years
4. Left ventricular ejection fraction up to 1 year
5. Cardiovascular death up to the end of the follow-up period
6. All cause death up to the end of the follow-up period
7. Hospitalisation for heart failure up to the end of the follow-up period
8. Acute Myocardial Infarction up to the end of the follow-up period
9. Appropriate ICD therapy up to the end of the follow-up period
10. Unplanned further revascularisation up to the end of the follow-up period
11. Canadian Cardiovascular Society (CCS) class up to 2 years
12. NHS resource use
13. Brain natriuretic peptide (BNP or NT-Pro BNP) level up to 2 years
14. Major bleeding
15. AKI up to 48 hours post-PCI
16. Creatinine and HbA1C up to 1 year

Please refer to the full protocol for details of any references mentioned in this summary. The full protocol is available online at http://revived.lshtm.ac.uk/protocol/ or by emailing revived@LSHTM.ac.uk to request a copy