The PREFECTUS Study: Heart Failure with Preserved Ejection Fraction Treated by Cardiac Resynchronisation Therapy Versus Rate Responsive Pacing: A Mechanistic Study

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Abbreviations

6MWT	6-minute walk test
AAIR	Atrial inhibited mode with rate response
APMHR	Age-predicted maximum heart rate
Ar	Duration of pulmonary venous A-wave reversal
AV	Atrio-ventricular
CI	Chronotropic incompetence
CPEX	Cardiopulmonary exercise
CRT	Cardiac resynchronisation therapy
DDDR	Dual chamber, dual response mode with rate response
DT	Deceleration time
ECG	Electrocardiogram
EF	Ejection Fraction
FEV1	Forced expiratory volume over 1 second
GLS	Global longitudinal strain
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
IVCT	Isovolumic contraction time
IVRT	Isovolumic relaxation time
LVOT VTI	Left ventricular outflow tract velocity time integral (a measure of the volume of blood ejected from the heart with each heart beat)
MEDIA	Metabolic road to diastolic heart failure (study)
MLHFQ	Minnesota living with heart failure questionnaire
MVI	Myocardial velocity imaging
NYHA	New York Heart Association
RER	Respiratory exchange ratio
RRP	Rate responsive pacing
SAE	Serious adverse event
VE-VCO_2	Rate of increase of minute ventilation per unit of carbon dioxide production
VO_2 max	Peak oxygen consumption
Vp	Peak diastolic suction velocity

1.0 Project Summary

Half of patients with heart failure have normal heart pumping function (Heart failure with Preserved Ejection Fraction, HFpEF), most commonly characterised by breathlessness on exercise. A number of mechanisms are responsible, but frequently patients are unable to raise their heart rate on exercise. This can be treated by a 'rate-responsive pacemaker' (RRP), which detects exercise and increases the heart rate accordingly. Some beneficial effects on echocardiographic parameters have been reported with exercise programmes. However, evidence based treatment options are limited in this group and therapy mainly relies on water tablets and treatment of blood pressure.

Cardiac resynchronisation therapy (CRT) is a technique using specialised 'biventricular' pacemakers that is well established in heart failure with reduced pump function. Patients who respond to this treatment have lower risk of death and hospitalisation and usually feel better. CRT is not currently used in HFpEF. The PROSPECT trial showed that some patients with relatively preserved heart function exhibited similar benefits to those with poor pump function, but this has not been formally tested. CRT aims to make the heart beat in a more synchronised way. Patients with HFpEF commonly have evidence of reduced heart synchronisation.

We plan to investigate the feasibility of using a prospective crossover study to assess the incremental benefit of CRT over and above RRP in patients with HFpEF. We will recruit 10 patients with HFpEF and insufficient heart rate and perform exercise testing, heart scanning and symptom questionnaires. A biventricular pacemaker will be implanted the patients will be randomised in a 1:1 ratio to receive either CRT or RRP for 12 weeks and the functional tests will be repeated. The groups will then be swapped so that each patient receives the alternative programming function for the next 12 weeks and the assessments performed again. If incremental benefit is shown with CRT we will study the echocardiograms to determine the mechanism of change. We will then invite study participants to participate in a study extension. This will involve non-invasively programming the pacemakers to optimise their function guided by the results of the echocardiograms in the first two phases of the study. After a further 12 weeks, the functional assessments will be repeated. If no benefit is seen with CRT after initial analysis, the participant involvement will end.

1.1 Background and Rationale

Half of patients with the clinical syndrome of heart failure have normal ejection fraction. Their cardiovascular mortality is similar to those with reduced ejection fraction (including 26% sudden cardiac death, 14% heart failure and 5% myocardial infarction). [1]

The hallmark of Heart Failure with Preserved Ejection Fraction (HFpEF) is exercise intolerance. The mechanisms for this include impaired left ventricular active relaxation, impaired untwisting and torsion, reduced left ventricular suction, increased passive stiffness, dyssynchrony, impaired systolic and diastolic reserve, increased arterial stiffness and impaired peripheral oxygen utilisation, among others. Chronotropic incompetence is a contributor to this, affecting up to 63% of patients.[2] Despite the prevalence of impaired chronotropy, it is little recognised in clinical practice.

Exercise endurance training has been shown to increase peak heart rate in patients with chronotropic incompetence and heart failure by an average of 12 beats per minute.[3] Additionally, such training programmes improved peak oxygen utilisation on exercise testing

by 38% and self-reported physical functioning score by 50% in HFpEF.[4] However, in practice exercise programmes are difficult to coordinate and maintain. Use of rate-responsive pacing improved peak oxygen consumption by 18% in heart failure patients with proven chronotropic incompetence undergoing cardiac resynchronisation therapy (with reduced ejection fraction).[5] The RESET trial is currently recruiting and aims to evaluate the effect of rate responsive pacing on patients with HFpEF; [6] currently, chronotropic incompetence is a Class IIb indication for dual-chamber pacing.

No trial of drug therapy in HFpEF has yet shown symptomatic or outcome benefit, although there is some evidence of improved diastolic and longitudinal function with valsartan (VALIDD),[7] amlodipine (ASCOT),[8] nebivolol (ENESYS)[9] and spironolactone (TOPCAT);[10] all except the latter were conducted in hypertensive patients rather than HFpEF.

Analyses of patients with HFpEF have suggested that mechanical dyssynchrony is present in up to 60% of patients with HFpEF and that it may also play a significant pathophysiological role in the disease process. [11, 12] A PARAMOUNT sub-study found that dyssynchrony was significantly more common than in age-matched healthy controls, even in patients with narrow QRS complexes and ejection fraction >55%.[13] This relationship persisted when corrected for age, left ventricular mass, gender and blood pressure and was associated with reduced global longitudinal strain and markers of diastolic dysfunction such as e', a marker of early diastolic relaxation. However, some trials have suggested that dyssynchrony in HFpEF is relatively uncommon, as low as 18% for systolic dyssynchrony, unless the QRS duration is prolonged.[14, 15]

Another notable abnormality in HFpEF is that of twisting and untwisting. The left ventricle does not simply squeeze inwards during systole; rather, the complex arrangement of myofibrils in three separate layers of differing orientation means that the heart demonstrates a wringing motion during contraction with untwisting during diastole. This twist can be measured using speckle tracking, an echocardiographic method by which individual acoustic 'speckles' within the myocardium can be traced between frames and therefore throughout the cardiac cycle. This technique can be performed in short and long-axis imaging planes, allowing the precise motion of the myocardium to be approximated. Prior studies in HFpEF have found that systolic torsion and diastolic untwisting rate are significantly reduced in patients compared to healthy controls.[16] The overall untwisting was not significantly reduced at rest, but became so on exercise in these patients; however, early diastolic untwisting was markedly reduced at rest. Reduction in systolic twisting was noted at rest compared with controls, but was more marked on exercise.

Cardiac Resynchronisation Therapy (CRT) is a well-established therapy in Heart Failure with reduced Ejection Fraction (HFrEF), but there is little evidence regarding its use in HFpEF. A PROSPECT sub-study demonstrated benefit with CRT for patients with ejection fraction >35%.[17] In this group, functional class and 6-minute walk test times appeared to predict response to CRT rather than ejection fraction, and CRT was associated with a significant reduction in end-systolic volumes. These findings were confirmed by a second study examining CRT in pure diastolic dysfunction using pressure-volume loops and echocardiography to demonstrate a reduction in dyssynchrony, although markers of symptomatic and physiological improvement were not examined.[18]

Several studies have looked at markers of diastolic dysfunction and dyssynchrony in patients with broad QRS undergoing CRT implantation. [19-24] Diastolic dyssynchrony has been found to be more prevalent in prospective CRT candidates than systolic dyssynchrony (74% vs 49%), but the two often occur together and both appear to predict response to CRT.[24]

Additionally, there is evidence that dyssynchrony is present in a significant number of patients with QRS duration <120 ms, and one study suggested that diastolic dyssynchrony is more prevalent than systolic (44% diastolic, 33% systolic dyssynchrony). [23, 24]

Patients undergoing CRT for classical indications typically exhibit an improvement in diastolic parameters such as peak mitral E wave velocity, E/A ratio and diastolic filling time, left ventricular filling pressure and overall grade of diastolic dysfunction. [20-24] Moreover, relatively load-insensitive markers of diastolic function such as peak lateral and septal e' velocity, and E/e' have also been seen to improve in some studies. [20-22] Propagation velocity (Vp), a marker of diastolic suction, improved in one study,[20] but was unchanged in another.[23] In another study, deactivation of CRT in patients with HFrEF resulted in delayed early diastolic vortex development and immature vortex at aortic valve opening. These vortices are thought to reduce left ventricular shear stress and improve energy conservation by allowing channelling of blood towards the left ventricular outflow tract. These findings reversed on reactivation of CRT.[25] Improvements in left ventricular torsion have been demonstrated following CRT implantation and torsion is increasingly recognised as a marker of overall left ventricular systolic function.[26, 27] Little work has been done looking at left ventricular diastolic untwisting in this patient population. However, given the continuum of myocardial function that involves sequential contraction and relaxation, it is likely that CRT involves improvements in untwisting as well as twisting. More research is required in this area.

Furthermore, improvement in diastolic parameters is seen in some patients who experience clinical response to CRT without demonstrating echocardiographic response (i.e. reduction in left ventricular end-systolic volume or increase in ejection fraction).[22, 24]

To our knowledge, there has been no previous comparison of rate-responsive pacing (RRP) and cardiac resynchronisation therapy in HFpEF. We therefore propose to compare these treatments in a population of HFpEF patients with proven chronotropic incompetence.

2. Study Design

This is an exploratory single-centre, prospective, single-blinded, randomised crossover study comparing rate responsive pacing (RRP) with CRT in patients with confirmed HFpEF and chronotropic incompetence.

2.1 Objectives

The Primary Objective of this study is:

- To evaluate the feasibility and acceptability of using a randomised crossover trial design to assess efficacy of CRT versus rate-responsive pacing in patients with HFpEF

The Secondary Objectives of this study are:

- To evaluate the use of diastolic and systolic reserve index as end-points in a trial design comparing CRT with RRP in patients with HFpEF
- To establish appropriate secondary end-points for future studies into the effect of CRT on:
    i. Longitudinal and global longitudinal strain, torsion and untwisting, and diastolic dyssynchrony at rest and on exercise echocardiography,
    ii. Exercise duration and oxygen carrying capacity measured by cardiopulmonary exercise (CPEX) testing,
    iii. Distance walked in a 6-minute walk test,
    iv. New York Heart Association (NYHA) functional class,
    v. Quality of life using the Minnesota Living with Heart Failure Questionnaire (MLHFQ)
- To establish the likely drop-out rate following recruitment for the trial in terms of failed implantation and patient disengagement
- To establish the number of participants required to appropriately power a further randomised trial of CRT versus RRP in patients with HFpEF
- To identify possible confounders and covariates to inform sample size calculations for future studies

2.2 Setting and Participants

2.2.1 Setting:

The study will be conducted in Cardiff and Vale University Health Board, with patients drawn from Cardiology clinics and inpatient wards. Follow-up assessments will be conducted at Cardiff School of Sport, a research facility at a university campus close to the main hospital.

2.2.2 Number of subjects planned:

10 patients. This will be sufficient to establish estimates of variability in the diastolic reserve index (see below), allow estimation of treatment difference and gauge acceptability.

2.2.3 Target population:

Subjects with HFpEF and chronotropic incompetence

2.3 Endpoints:

Systolic and diastolic longitudinal reserve index are calculated by the following formulae:

Systolic reserve = $\Delta s' \times [1-(1/s'_{rest})]$
Diastolic reserve = $\Delta e' \times [1-(1/e'_{rest})]$

These are known to be impaired in patients with HFpEF and are a marker of adaptation to exercise in terms of filling pressures and left ventricular relaxation. Tan et al report a significant difference between the results seen with 56 patients with HFpEF and 27 control subjects on exercise echocardiography with semi-supine bicycle.[16] Patient characteristics were similar to those of our proposed study group (EF >50%, NYHA II, HFpEF according to Vasan and Levy criteria).[28]

We will therefore investigate diastolic and systolic reserve index as possible endpoints of a future study into the efficacy of CRT versus RRP in HFpEF patients.

2.4 Planned interventions:

Visit 1 – Baseline Assessments: Patients will undergo initial assessment of baseline characteristics by echocardiography, cardiopulmonary exercise testing, 6MWT and MLHFQ. (Visit length: approx. 4 hours)

Visit 2 - Device Implantation (≤ 7 days after baseline assessments completed):
Eligible subjects will undergo implantation of a biventricular pacemaker under normal laboratory conditions. Patients will be randomised in a 1:1 ratio to receive either rate-responsive pacing (DDDR) or CRT. Patients will be blinded to their treatment allocation. They will return to pacing clinic a week later for a programming check; during this visit, they will also undergo a chest x-ray according to local protocol to ensure correct lead placement (Visit length: 1 day + 2 hours)

Visit 3 – Assessments and Device Reprogramming
After 12 weeks, the baseline parameters will be reassessed and patients will then have their device non-invasively reprogrammed to the remaining treatment allocation. (Visit length: approx. 4 hours)

Visit 4 – Assessments
After a further 12 weeks, the baseline assessments will be repeated. The pacemaker will be non-invasively reprogrammed to DDDR mode and the patient will go home. (Visit length: approx. 4 hours)

Optional extension (pending analysis of results)
Visit 5 – Reprogramming
If incremental benefit has been demonstrated with CRT above the benefit of RRP, the echocardiograms will be examined to establish the mechanism of improvement. Subjects will be invited to participate in a study extension using multisite technology. The device will be non-invasively reprogrammed to optimise the CRT settings targeted specifically for the mechanism identified. (Visit length: approx. 3 hour)

Visit 6 – Assessments
12 weeks after the final reprogramming, patients will attend for a final set of assessments as per baseline. Participant involvement will then cease. (Visit length: approx. 4 hours)

Total contact time with research team: Approximately 27 hours (22 hours without extension)

2.5 Rationale for use of crossover design

HFPEF subjects are known to have similar mortality rates to HFREF subjects. However, they tend to be clinically stable for fairly long periods of time. A crossover design has been employed in preference to a cohort study to minimise the effects of natural disease progression on the measurement of each treatment effect. The period length is designed to allow effects of the pacing modes to be well-established without a high likelihood of significant change in the subject's overall wellbeing, cardiac function or functional status.

Previous studies using similar pacing protocols have found no carry-over effects in haemodynamic parameters such as e' (and therefore diastolic and systolic reserve index), which demonstrate beat-to-beat change; however, end-systolic and end-diastolic volumes are more slow to change.[6, 29, 30] Previous studies, most notably the MUSTIC trial, have employed similar 3-month blocks as in our study design with no washout period.[31] The study involved 48 patients and found no carry-over effect for the stated haemodynamic parameters.

Covariates and confounders may include the subject's baseline demographic, echocardiographic and functional parameters. Full characterisation of each subject will be undertaken at baseline with respect to possible confounders such as comorbidity, baseline diastolic function and baseline exercise ability. In this exploratory study, we are aiming to identify possible confounders and will not make statistical corrections for them due to the small sample size.

2.6 Device Characteristics:

The device implanted will be a St Jude Quadra Allure MP™ CRT device with St Jude Quartet™ quadripolar left ventricular lead, and standard compatible right ventricular and right atrial leads. These components comprise a standard CRT device implanted at University Hospital of Wales (UHW). Quadripolar leads have 4 sites along the lead from which pacing can be performed, including in combination or sequence. This is called multisite pacing. In comparison to the traditional style leads, which pace only from the lead tip, this offers a far greater array of options for optimising pacing. For example, where the lead is stimulating the phrenic nerve (resulting in uncomfortable hiccups for the patient) or where the pacing lead is placed over a patch of scar on the heart, a different site can be selected on the lead, allowing the clinician or physiologist to pace around these issues.

All CRT devices are able to deliver conventional pacing as well as biventricular pacing and this will be utilised for the first stage of the study, where RRP only is needed.

2.7 Pacing Modes:

Whilst programmed to DDDR mode, the pacemakers will be programmed to a base rate of 30 min^{-1} with a prolonged atrio-ventricular delay of 350 ms. This will mean that the patient's own intrinsic atrio-ventricular (AV) conduction is favoured over pacing. The purpose of this is to avoid right ventricular pacing, which can be detrimental. Abbott pacemakers include technology known as VIP (ventricular

intrinsic preference) which will also be switched on with the same aim. DDDR mode allows for rate response, meaning that if the pacemaker detects the onset of exercise, it will increase the atrial rate in order to maintain an adequate heart rate. This is a treatment for chronotropic incompetence and has been shown to be beneficial in HFrEF with CI.[5]

CRT will be programmed to maximise biventricular pacing as close to 100% of the time as possible. A short AV delay will therefore be selected, with a ventricular base rate of 30 min^{-1} to favour intrinsic atrial rate and AV conduction. The AV delay will be tailored to the individual patient according to the interval that gives greatest left ventricular outflow tract velocity time integral (LVOT VTI) as measured on echocardiography. Ventriculo-ventricular delay (VV delay, the time difference between the stimulation of the left and right ventricles) will be programmed to optimise cardiac output according to LVOT VTI once optimal AV delay has been determined. Maximum tracking rate will be programmed according to heart rate achieved on exercise testing, but nominally at 120 min^{-1}. Atrial mode switching algorithms will be included as despite atrial arrythmias being an exclusion criterion in this group, they have multiple risk factors for developing atrial fibrillation.

These settings have an evidence base when programmed in HFREF. Although cardiac output is not significantly impaired at rest in HFPEF, settings which reduce cardiac output would potentially have a deleterious effect on patient symptoms and therefore this has been selected as the target of device programming.

2.8 Duration of Treatment:

12 weeks in each period followed by full symptomatic and physiological evaluation. Total study participation will be up to 40 weeks from baseline visit. We will gain written consent from the participants to contact them by telephone up to study completion in order to gain outcome information.

2.9 Diagnosis of HFpEF:

All subjects will be recruited according to the criteria recommended by the European Society of Cardiology consensus statement for the diagnosis of HFpEF.[32]

Previously defined criteria included symptoms of heart failure in the absence of reduced ejection fraction, and no evidence of cardiac (valvular disease, coronary artery disease or significant arrhythmia) or non-cardiac (chronic lung disease, central causes of breathlessness or haematological abnormality) cause, with parameters consistent with HFpEF on echocardiographic and biomarker profiling.

2.10 Diagnosis of Chronotropic incompetence:

Chronotropic incompetence (CI) is a Class IIb recommendation for pacemaker implantation. CI is defined by failure to achieve 80% of expected heart rate reserve on maximal exercise testing, according to the following formula:

$$\frac{\text{Heart rate reserve}}{\text{APMHR} - \text{Rest HR}} \times 100$$

(APMHR = age-predicted maximum heart rate; heart rate reserve = change in heart rate from rest to peak exercise; APMHR will be defined by 208 – 0.7 x age [Tanaka et al],[33] or for patients on beta blockers 164-0.7(age) [Brawner et al][34])

2.11 Cardiopulmonary exercise testing

Cardiopulmonary exercise testing on an upright bicycle will be used to assess the presence of CI. This initial test will also serve as a familiarisation test for the subsequent study assessments. The exercise will be performed according to standard hospital protocol. Expired gas analysis will be conducted to assess the Respiratory Exchange Ratio (RER). Maximal exercise will be deemed to have occurred if this is greater than 1.05. Data regarding ventilator efficiency will be gathered to explore whether a cardiac cause for breathlessness exists. 12-lead electrocardiogram monitoring will be performed throughout the test until at least 3 minutes after exercise completion.

Patients with a Class I indication for beta blocker therapy will continue the treatment (namely prior history of ventricular tachyarrhythmia or myocardial infarction; those with significant angina or recent arrhythmia will be excluded).

Inclusion Criteria:

1. Confirmed HFpEF as described above
2. Chronotropic incompetence as described above
3. Ongoing exertional breathlessness of NYHA Grade II or worse
4. Ability to understand and sign written consent form
5. Males and females, age >18 years
6. Ability to participate in follow-up appointments at 3 and 6 months post-implantation
7. Ability to complete a cardiopulmonary exercise test

Exclusion criteria

1. Any contraindication to implantation of permanent pacemaker, namely unresolved infective process or sepsis, vascular access difficulties, advanced neoplastic process, expected lifespan less than 1 year or patient choice
2. Ejection fraction <50%
3. Known valvular disease graded severe or moderate-to-severe
4. Cardiac arrhythmia (paroxysmal or persistent) within 1 year of recruitment
5. Exertional chest pain suggestive of angina or personal history of coronary artery disease without subsequent revascularisation, or coronary angiogram within the past 5 years demonstrating >50% stenosis in ≥ 1 epicardial coronary artery
6. Significant chronic lung disease (FEV1 <80%)
7. Inability to complete follow-up process for any reason not defined above

3. Study Procedures

At baseline, the following assessments will be undertaken:

- NYHA functional class assessment
- 6-minute walk test (6MWT)
- MLHFQ
- Echocardiographic assessment of systolic and diastolic parameters at rest, followed by exercise echocardiography on semi-supine bicycle ergometer of the same parameters. (Appendix).
- Cardiopulmonary exercise testing on an upright bicycle according to standard local protocol (see above).

Study subjects will then undergo implantation of a biventricular pacemaker with leads in the right ventricular apex, coronary sinus (aiming for posterolateral or lateral wall position where anatomically possible), and right atrium.

Following successful device placement, subjects will be randomised in a 1:1 ratio (using online computer randomisation software, https://www.randomizer.org/) to receive either RRP (in DDDR mode) or CRT as described above. This will be performed whilst the subject is still in the pacing laboratory and the device programmed by the attending physiologist according to the parameters described above, tailored to the subject's individual heart rate. Patients will be blinded to the treatment allocation, but investigators will not as the pacing mode will be evident on ECG traces.

3.1 Assessments and Reprogramming:

After 12 weeks, patients will be recalled for repeat assessment of the same modalities (rest and exercise echocardiography, CPEX, 6MWT, NYHA functional class assessment, MLHFQ). The pacemakers will be non-invasively reprogrammed (using a magnet placed over the chest) to switch the treatment period so that subjects experience whichever mode they have not yet received. After a further 12 weeks, the same assessments will be repeated. The pacemaker will then be non-invasively programmed back to RRP.

3.2 Study Extension: Targeted Multipoint Pacing

Once all subjects have completed 12 weeks of RRP and 12 weeks of CRT (in either order), provisional analysis of the data will be performed. If an incremental benefit is shown for CRT above the benefit of RRP, analysis of echocardiograms before and after CRT will be performed to elucidate the mechanisms. Subjects will be invited to participate in a study extension. The pacemakers will then be non-invasively programmed using multisite optimisation to administer optimised CRT targeted to the specific mechanism of action. Final assessments will occur after 12 weeks, following which the participant involvement will end.

If no incremental benefit is shown for CRT at the initial analysis, the study will end at this point (after 24 weeks).

Incremental benefit for CRT will be defined as a statistically significant difference between average values for RRP and for CRT in paired t-tests in one or more of the following parameters: a) echocardiographic: diastolic reserve index; systolic reserve index; left ventricular end-systolic volume; left ventricular end-diastolic volume; tricuspid regurgitant peak velocity; torsion and untwisting on strain imaging; global longitudinal strain; b) cardiopulmonary exercise testing: peak oxygen consumption; exercise duration; VE-VCO_2 slope; c) distance walked on 6-minute walk test.

Ongoing pacemaker function will be a clinical decision based on patient preference and objective markers such as 6MWT. Long-term pacemaker follow-up will take place at Professor Yousef's CRT clinic at University Hospital of Wales. All medications can be continued as prescribed for the duration of the study, but medication changes should be noted during follow-up.

4. Criteria for Evaluation

At each 12-week stage, the following will be assessed:

1. Change in end-diastolic volume
2. Change in end-systolic volume
3. Change in ejection fraction (Simpson's Biplane method)
4. Change in left ventricular filling by pulsed-wave Doppler of mitral inflow (peak E and A wave velocities, E wave deceleration time, A wave duration, diastolic filling time (DFT))
5. Change in pulmonary venous Ar (Atrial reversal) duration.
6. Change in left and right ventricular isovolumic relaxation time (IVRT) and isovolumic contraction time (IVCT)
7. Change in peak diastolic suction velocity (Vp)
8. Change in peak systolic twist (torsion) and in untwisting rate on speckle tracking
9. Myocardial velocity imaging (MVI) in basal anterior, inferior, septal and lateral walls to assess:
    a. Change in peak systolic velocity (s')
    b. Change in peak early diastolic wave velocity (e')
    c. Change in time from onset of QRS to onset of s' wave
    d. Change in time from onset of QRS to peak e' wave
10. Change in duration of pulmonary venous *a* wave
11. Change in peak longitudinal strain in 12 wall segments, and peak global longitudinal strain (GLS) in 12-segment model
12. Change in pulmonary pressures as measured by tricuspid regurgitant jet peak velocity
13. Change in above parameters on exercise echocardiography where feasible due to image quality
14. Change in peak oxygen consumption (VO_2 max) and slope of ventilation to carbon dioxide production (VE-VCO_2 slope) on exercise
15. Change in exercise capacity as defined by duration of exertion and work-level achieved on cardiopulmonary exercise testing
16. Change in blood pressure response to exercise
17. Change in distance walked on 6-minute walk test
18. Change in New York Heart Association Functional Class
19. Change in Minnesota Living with Heart Failure Questionnaire score

5. Statistical Analysis Plan

Enrolled subjects will be analysed in a per protocol fashion. Estimates of period effects will be made by performing an unpaired t-test on the mean difference between the two treatment orders. Carryover effects will be estimated by performing a t-test comparing the mean within patient score (the mean of the two period means for each patient) with the mean between the treatment arms. If significant period or carry-over effects exist, then only the first period will be analysed.

The change in exercise, echocardiographic, functional class and wellbeing parameters will be evaluated using paired sample t-tests. A Wilcoxon signed rank test will be employed as a test of robustness.

The settings in the study extension will be compared with the CRT programming during the initial crossover period for each patient using paired sample t-tests (this may have taken place in period 1 or period 2).

Where normality of distribution is not found, attempts will be made to transform the data using a suitable mathematical function. Where this is not possible, the Mann-Whitney U test will be employed. Analysis of categorical data will be by Chi-squared tests. Normality will be evaluated using visual assessment histograms and Q-Q plots. Significance will be tested at the 95% confidence level for all analyses, including calculation of period and carry-over effects.

An intention to treat analysis will be reported if the drop-out rate exceeds 10%. Corrections for multiplicity will not be made due to the exploratory nature of this data. No subgroup analysis is planned. Where data is missing, analysis will only be completed if 80% or more of data is present. For each analysis performed, subjects with data missing will be excluded from the individual parameter analysis, but will be included where data is present. Interim analysis will not be performed, except in the event of study discontinuation. Study discontinuation will occur only in the event of safety concerns, as detailed below, or in the event of failure to recruit within the planned timeframe.

Drop-out rates and reasons will be recorded at each stage. This will be presented as a CONSORT diagram in the publication of study results.

All statistical analysis will be double-checked by a statistician prior to dissemination of study results.

6. Study Administration

6.1 Resources

The study will be carried out principally by Dr Freya Lodge, the principal investigator, who is employed by the health board and funded by St Jude Medical (now Abbott). Eligibility assessments required for the study are part of the usual care for patients with heart failure and will therefore be conducted at University Hospital of Wales under the NHS.

Baseline assessments, follow-up appointments, echocardiography, cardiopulmonary exercise testing, questionnaires and functional tests will be carried out by Dr Lodge and research staff from the School of Sport, Cyncoed Campus, Cardiff Metropolitan University. This will be overseen by prior agreement with Professor Robert Shave. Device implantation will be conducted by Prof Yousef in the Pacing Theatre at University Hospital of Wales on normal clinical lists, usually on a Tuesday. Abbott will pay for the difference in device cost between a dual chamber and a biventricular device. A member of nursing staff from the coronary care unit will be required to assist in these procedures and this will be arranged prior to implantation. Patients recruited to the study will be under a consultant at the hospital and will have a Class IIb indication for pacing.

6.2 Ethical Considerations

Patients recruited to this study will have an indication for a dual chamber pacemaker and significant symptoms of breathlessness. Full written consent will be obtained prior to study entry. Patients will be exposed to a small increase in risk due to implantation of a biventricular rather than dual chamber pacemaker. This equates to an increase from 1% to 2% of serious complications requiring further hospital treatment. This risk is felt to be acceptable in patients with reduced ejection fraction undergoing biventricular pacemaker implantation. Additionally, there will be extra radiation exposure due to longer procedure

time associated with CRT implantation compared with standard pacemakers. These risks have been reviewed by experts in clinical radiology and nuclear physics. The overall exposure to radiation is equivalent to 21 months of background radiation in the UK and confers a low cancer risk of 1 in 5100. Exercise tests are low risk procedures conferring overall risk of 1 in 10 000 of serious complication. Subjects will be counselled regarding these procedures prior to recruitment.

6.3 Safety

Local procedures will apply to tests carried out at University Hospital of Wales, and to pacemaker implantation. A local anticoagulant policy is in place. Patients will receive intra-venous antibiotics prior to pacemaker implantation according to local policy (usually Teicoplanin).

All investigations at Cardiff Metropolitan University will take place in the presence of an experienced clinician. Other members of staff will be available who have been trained in Intermediate Life Support. A cardiac defibrillator, supplemental oxygen and intravenous adrenaline will be available. Additionally, there will be equipment for cannulation and airway support that will be kept in an easily accessible bag within the department. These products and medications will be checked on a monthly basis by study staff.

6.3.1 Adverse Events

Early termination will occur in the case of serious adverse events (SAE) related to study interventions. If a SAE occurs (death or hospitalisation of study subject for heart failure or related conditions, device related complications), the study team will meet at the earliest possible juncture. A decision as to whether adverse events are related to study procedures will be made according to clinical judgement by the study group, which includes several experienced clinicians.

If the SAE is deemed to be due to the study intervention, the trial will be immediately suspended pending further investigation and terminated if evidence emerges of causality. In the event of study suspension, all participants will be contacted to explain the situation and will be asked to attend for reprogramming of their pacemaker as appropriate.

In the event of early study termination, all participants will be contacted by telephone and asked to attend for device reprogramming. Devices will be programmed to RRP on study termination unless safety issues arise with this programming mode.

6.4 Data Handling

Case record forms will be created for each participant in the study; these will be stored in the clinical research area of Cardiff Metropolitan University School of Sport. This is a secure building protected by swipe-card access available only for approved university staff.

Data will be stored on personal computer databases (Excel, SPSS) in anonymised form. Access to all computers is password-protected.

Echocardiographic images will be stored on a secure server in Cardiff Metropolitan University and will be coded by the patient's record number but not by name.

No patient-identifiable data will be stored in data logs. After recruitment, patients will be issued with a study number which will be used thereafter in place of identifiable details. Only date of birth will be stored alongside the study number. Each patient will be assigned a

folder with all study paperwork, investigations and data in. This will be kept in a swipe card-accessed office within Cardiff Metropolitan University. All data collected will be stored by study number only on computer databases on a locked computer. This computer will remain in the possession of the Principal Investigator; however, no sensitive data or personal data will be stored on this computer.

6.5 Dissemination of Results

The results from the study will be published in one or more articles in peer-reviewed journals, and/or be presented at international cardiovascular meetings, either as abstracts or oral presentations. Patients will be notified of the study findings by post following the termination of the study. This study will form part of a Medical Doctorate project for the Principal Investigator, Dr Freya Lodge and as such will be published as a thesis.

6.6 Arrangements for supervision

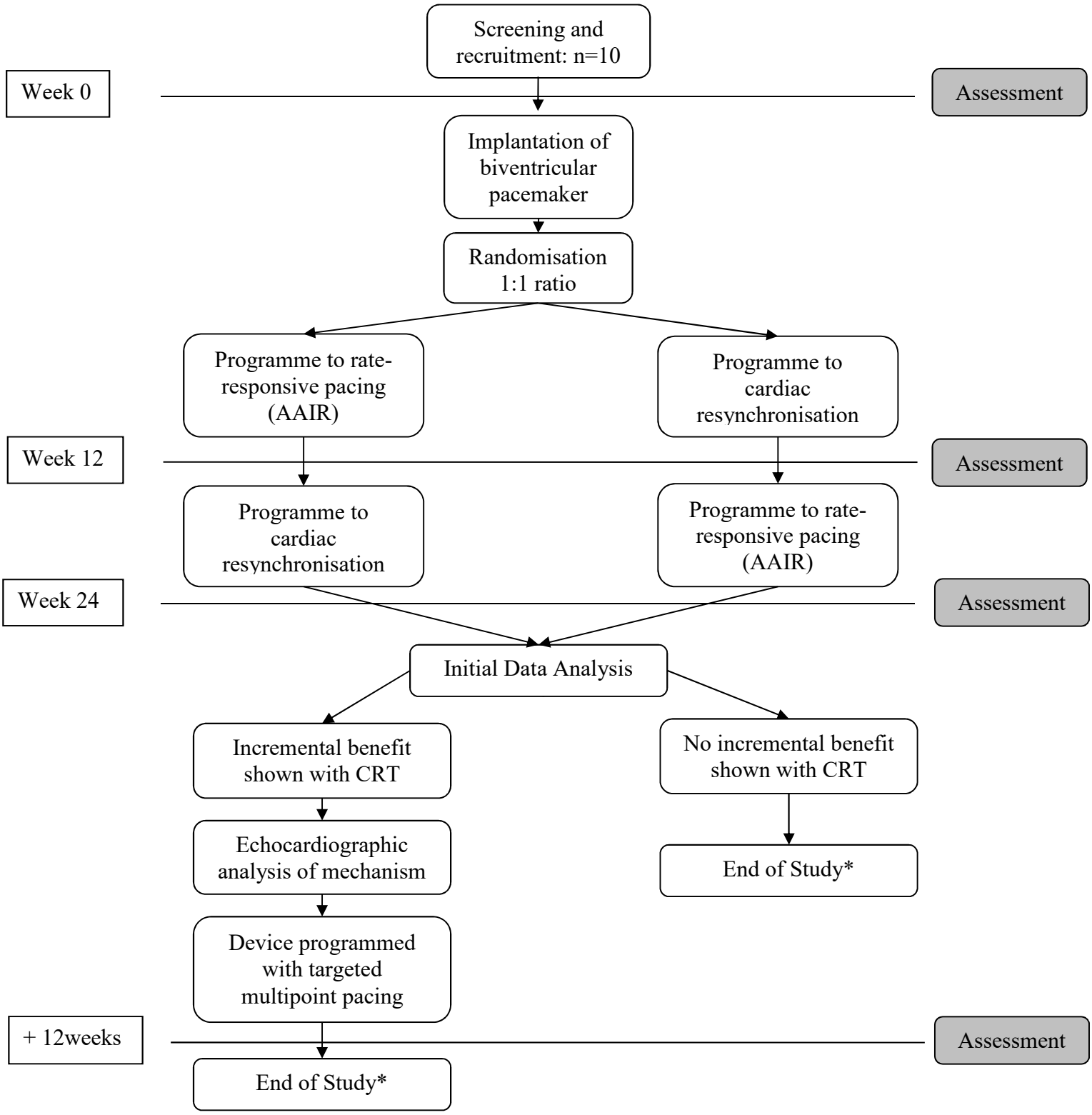
The project is being overseen by Prof Yousef. Frequent meetings are arranged to review protocols and progress with both Prof Yousef and the other project collaborators. This protocol has undergone review by scientific staff at Cardiff and Vale University Health Board, as well as by the scientific committee at Abbott. After recruitment begins, all study personnel will meet every 6 months to review progress until termination of the study.

Appendix: Exercise Echocardiography Protocol

Exercise:

- Workload at anaerobic threshold will be calculated using results from the introductory cardiopulmonary exercise test.
- For echocardiography, a ramped stress protocol, aiming to achieve image acquisition at baseline, and at 50% and 100% of anaerobic threshold (AT, also known as ventilatory threshold) will be used.
- A pedalling rate of 55–65 r.p.m. will be aimed for.
- Ramp to 50% of AT workload will occur over one minute, with a further minute for stabilisation of heart rate and vasculature.
- Images will then be obtained over the following three minutes.
- Once images have been obtained, a further ramp will occur to AT workload over one minute with a further minute for stabilisation.
- Images will be obtained at AT over three minutes.
- Following image acquisition, the test will cease.
- Should the subject be unable to maintain pedalling rate or exercise at AT, the workload will be reduced by 25% to enable continued scanning until image acquisition is complete.
- Total exercise time for this test will be 10 minutes.
- Workload at each stage will be kept the same for each test that a participant performs.

Study Diagram



* Pacemaker settings at end of study to be determined clinically based on patient preference and objective measures such as 6MWT

Schedule of Evaluations

Visit	Screening	Visit 1	Visit 2	Visit 3	Visit 4 [c]	Provisional Analysis: once data obtained from all subjects	Visit 5	Visit 6[c]
Day/Week/Month	**≤ -12 Weeks [a]**	**Day 0**	**Day 1 +/- 7 days**	**Week 12 [b]**	**Week 24 [b]**		**+0 weeks**	**+ 12 weeks**
Informed consent	X							
Demographic data	X							
Medical history	X							
Medical examination	X	X		X	X			X
Medication history	X	X		X	X			X
Height & weight		X						
Inclusion and exclusion criteria	X	X						
12-lead ECG	X	X		X	X			X
NYHA Functional Assessment	X	X		X	X			X
6-minute walk test		X		X	X			X
MLHFQ		X		X	X			X
Echocardiogram		X		X	X			X
Cardiopulmonary exercise test		X		X	X			X
Implant CRT device			X					
Randomisation [a]			X					
Reprogram device				X	X		X	

Abbreviations: CRT = cardiac resynchronisation therapy, NYHA = New York Heart Association, MLHFQ = Minnesota Living with Heart Failure Questionnaire, ECG = Electrocardiogram

a Randomisation must occur within 12 weeks of screening visit; https://www.randomizer.org/

b ±7 days permissible for follow-up visit

c Study termination occurs after Visit 4 if no incremental benefit for CRT seen and after Visit 6 if benefit seen

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