ISRCTN60045220 https://doi.org/10.1186/ISRCTN60045220

A randomised trial investigating therapies needed to maintain remission in dilated cardiomyopathy

Submission date	**Recruitment status**	[X] Prospectively registered
09/12/2022	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
18/08/2023	Ongoing	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
08/04/2024	Circulatory System	[ ] Record updated in last year

Plain English summary of protocol

Background and study aims

Dilated cardiomyopathy is a common disease of the heart muscle, where it becomes stretched and weak. After treatment with 4 medications, many patients experience resolution of symptoms and improvement in heart function. This is heart failure remission. Patients with heart failure remission often wish to reduce the number of medications they take to alleviate side effects and improve quality of life.

In a previous trial, we showed that 2 out of 5 patients will experience a reduction in heart function if all medications are stopped. Our research suggested that one medication, beta-blockers, may be the most important to maintain remission. It is possible that some others are no longer required. Our research and focus groups conducted with patients and a patient charity have emphasised the importance of further studies investigating the feasibility of reducing the number of medications taken by patients with heart failure remission. This led to the design of this study.

Who can participate?

We will study 50 patients with remission of dilated cardiomyopathy who are taking 3-4 medications.

What does the study involve?

Remission will be defined by 1) an improvement in left ventricular ejection fraction (a measure of heart function) to >50%, 2) an N-terminal propeptide of B-type natriuretic peptide (NT-pro-BNP; a blood test measuring heart stress) of <250ng/L and 3) resolution of heart failure symptoms. A computer will randomly select 25 patients to stop 1-2 medications (mineralocorticoid receptor antagonists and sodium glucose co-transporter 2 inhibitors) whilst continuing beta-blockers and medications that inhibit the renin-angiotensin system. The other 25 patients will continue all medications. We will perform heart MRI scans and blood tests and compare heart function between the groups over 4 months. Patients that continued therapy for the first half of the study will have the opportunity to stop the same 1-2 medications in the same fashion between 4-8 months.

What are the possible benefits and risks of participating?
Benefits:
Not provided at time of registration
Risks:
It is possible that patients will experience a deterioration in cardiac function during therapy de-escalation. To mitigate the risk of this, patients will be monitored closely with frequent cardiac imaging, biomarkers and clinical assessment. We previously demonstrated the safety of this strategy in the TRED-HF trial - only one patient developed mild signs of heart failure that resolved with re-introduction of therapy, there were no unplanned heart failure hospitalisations and all those who had a reduction in cardiac function following therapy withdrawal, had a subsequent improvement in function with re-introduction of therapy. We will use a significantly more conservative strategy in this study by only withdrawing a maximum of 2 out of 4 medications for heart failure. We anticipate the risks to be much lower.
Trial participants will be closely monitored by doctors and specialist nurses, experienced in the management of heart failure to identify early markers of deteriorating cardiac function. If there is any suggestion of deterioration, we will ask patients to attend clinic for an earlier review.
The results and progress of patients will be reviewed on a regular basis by an adjudication panel led by a Consultant Cardiologist. Strict criteria have been set to identify patients with early adverse effects from reducing their medications. The panel will make prompt decisions to re-establish therapy in patients meeting these criteria. Patients will be educated on the signs and symptoms of heart failure and will be instructed to weigh themselves daily. They will be asked to contact the research team if they develop signs and symptoms of heart failure or their weight increases by 2kg from baseline. A contact telephone number and email will be provided to enable patients to contact the research team with any concerns between 9am-5pm. Out of hours, they will be given the contact number for the Duty Cardiology doctor on call at the Royal Brompton Hospital and they will be asked to contact a member of the research team at the earliest possibility during office hours.
An independent data monitor will review interim trial data and will be informed of all SAEs. They will be able to recommend termination of the study to the Chief Investigator. Our patient information leaflet will inform participants that there is a risk of developing symptoms of heart failure or that their cardiac function will deteriorate as a result of medication withdrawal.
As part of the study, participants will undergo Cardiovascular Magnetic Resonance (CMR). This involves lying in a large magnetic tube for 30-45 minutes. It is not painful, involves no radiation and has no side effects. Participants will hear a noise from the machine. This will be reduced by ear defenders. If participants suffer from claustrophobia, the researchers will discuss the risk that the scan may exacerbate this.
Participants will be given intravenous gadolinium contrast as part of the baseline scan. This is part of routine clinical care and allows the detection of fibrosis which may be an important predictor of response to treatment. Gadolinium is well tolerated by the vast majority of patients. There is small risk of minor allergic reactions. Occasionally this requires treatment with anti-histamines which are available at all scanning locations. Anaphylaxis is very rare. All scanning sessions will supervised by a doctor trained to deal with this. Anaphylactic medication packs are available at all scanning locations. An allergy history will be taken prior to contrast administration. There is an extremely small risk of nephrogenic systemic fibrosis associated with gadolinium in patients with kidney impairment. For this reason, patients with renal impairment (eGFR <45ml/min) will be excluded from the study.
Current guidelines on the use of CMR in clinical settings recommend that MRI studies be delayed until after pregnancy when possible. SGLT2 inhibitors and MRAs are generally contraindicated in pregnancy. We have therefore included pregnancy or planned pregnancy as an exclusion criteria. Women of child-bearing age will be required to use contraception during the study and have a negative pregnancy test before each CMR scan.
Patients with MR-conditional implantable devices will have scans as per department protocols.

The scanning of MR-conditional devices using such protocols is safe and supported by the Royal College of Radiologists.
Incidental findings will be communicated to the participants and usual doctors. The latter will be asked to consider further investigation if necessary.

Where is the study run from?
Imperial College London (UK)

When is the study starting and how long is it expected to run for?
December 2022 to September 2026

Who is funding the study?
British Heart Foundation

Who is the main contact?
Dr Brian Halliday, b.halliday@imperial.ac.uk

Contact information

Type(s)
Scientific

Contact name
Dr Keith Boland

Contact details
Joint Research and Compliance Office
Room 221, Medical School Blding
St Mary's Campus
Norfolk Pl
London
United Kingdom
W2 1PG
-
rgit.ctimp.team@imperial.ac.uk

Type(s)
Principal Investigator

Contact name
Dr Brian Halliday

Contact details
CMR Unit
Royal Brompton Hospital
Sydney St
London
United Kingdom
SW3 6NP
+44 2073528121 ext 2928
b.halliday@imperial.ac.uk

Additional identifiers

EudraCT/CTIS number
2022-003734-39

IRAS number
1006543

ClinicalTrials.gov number
NCT06091475

Secondary identifying numbers
22HH8010, IRAS 1006543, CPMS 58108

Study information

Scientific Title
A randomised trial examining therapy to maintain remission in dilated cardiomyopathy

Acronym
TRED-HF2

Study objectives
Primary objective:
To determine whether it is safe and feasible to stop mineralocorticoid receptor antagonits and sodium glucose co-transporter 2 inhibitors in asymptomatic patients with dilated cardiomyopathy and improved cardiac function who are taking beta-blockers and renin-angiotensin system inhibitors.

Secondary objectives:
1. To determine the relapse rate following withdrawal of mineralocorticoid receptor antagonits and sodium glucose co-transporter 2 inhibitors in asymptomatic patients with dilated cardiomyopathy and improved cardiac function who are taking beta-blockers and renin-angiotensin system inhibitors.
2. To determine if patients with dilated cardiomyopathy and improved cardiac function have specific imaging and genetic phenotypes that predict the occurrence of relapse following the withdrawal of mineralocorticoid receptor antagonits and sodium glucose co-transporter 2 inhibitors.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 17/08/2023, London Dulwich Research Ethics Committee (Health Research Authority, 2nd Floor, 2 Redman Place, Stratford, London, E20 1JO, United Kingdom; +44 207 104 8286; dulwich.rec@hra.nhs.uk), ref: 23/LO/0052

Study design
Interventional randomized cross over controlled trial

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet.

Health condition(s) or problem(s) studied
Patients with a previous diagnosis of dilated cardiomyopathy who have improved cardiac function and who are asymptomatic

Interventions
We will do a randomised controlled trial of SGLT2i and MRA withdrawal between the point of randomisation and 16 weeks, with a follow-on phase between 16-32 weeks that will include a single-arm cross-over for those initially randomised to the control arm. Patients will be randomised using an online tool to two arms in a 1:1 ratio using random permuted blocks, stratified by three groups of NT-pro-BNP: 1) <50ng/l, 2) 50-125ng/l, 3) >125ng/L.
Patients randomised to Arm B will stop SGLT2i at baseline, followed by MRA at 8 weeks. In the follow-on phase, they will continue follow-up off these medications between 16-32 weeks.
Patients randomised to Arm A will continue current therapy between baseline and 16 weeks. After 16 weeks, patients who have continued therapy in Arm A will have the opportunity to enter a single arm cross-over phase and stop MRA followed by SGLT2i at 24 weeks (the reverse order to Arm B in the randomised phase).

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Dapagliflozin, empagliflozin, spironolactone, eplerenone

Primary outcome measure
Relapse of DCM defined by any one of the following:
1. A reduction in LVEF>10% and to below 50%
2. A two-fold rise in NT-pro-BNP and to >400ng/L or
3. Clinical features of heart failure as determined by the research team.
This is a composite of prognostically important variables supported by the findings of TRED-HF,

taking into account changes in markers of cardiac function and congestion. The primary analysis will take place after 16 weeks of the randomised phase. There will also be a follow-on phase. The incidence of the primary end-point will also be assessed between 16-32 weeks.

Secondary outcome measures
At baseline, 16 weeks and 32 weeks:
1. Left ventricular ejection fraction (%) (cardiovascular magnetic resonance [CMR])
2. Left ventricular end-diastolic volume indexed to body surface area (ml/m²) (CMR)
3. Left ventricular global longitudinal strain (LV GLS) (CMR)
4. Left ventricular mass index (LVMi; g/m²) (CMR)
5. Left atrial volume index (LAVi; ml/m²) (CMR)
6. Left atrial strain (LAS) (CMR)
7. Right ventricular ejection fraction (RVEF; %) (CMR)
8. NT-pro-BNP (ng/L) (plasma concentration from peripheral blood sampling)
9. Quality of life: EQ-5D-5L score
10. Treatment Burden Questionnaire score

Overall study start date
06/12/2022

Completion date
01/09/2026

Eligibility

Key inclusion criteria
1. A diagnosis of DCM
2. Previous LVEF <40% (on echocardiography or cardiovascular magnetic resonance [CMR])
3. Current LVEF >50% for at least 6 months duration with normal left ventricular end-diastolic volume (LVEDV) at inclusion
4. Plasma NT-pro-BNP<250ng/L
5. New York Heart Association (NYHA) class I
6. Sinus rhythm
7. Taking a beta-blocker and an ACEi, ARB or sacubitril-valsartan, along with at least one of an MRA or SGLT2i.

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
50

Key exclusion criteria

1. Current atrial fibrillation
2. Prior sustained ventricular tachycardia or fibrillation
3. A known likely pathogenic or pathogenic variant in LMNA/DSP/FLNC/RBM20
4. Sudden cardiac or heart failure death in a first degree relative <50 years
5. Contraindication to CMR
6. Estimated glomerular filtration rate (eGFR) <45mls/min
7. Current or planned pregnancy
8. Known active myocardial inflammation
9. Another indication for an SGLT2i (diabetes mellitus or CKD)
10. Previous relapse of symptomatic heart failure following initial recovery in function
11. Current participation in another CTIMP
12. Ongoing need for other heart failure therapies including loop diuretics, ivabradine or digoxin

Date of first enrolment
21/10/2023

Date of final enrolment
01/08/2024

Locations

Countries of recruitment
United Kingdom

Study participating centre
Royal Brompton & Harefield NHS Foundation Trust
Royal Brompton Hospital
Sydney Street
London
United Kingdom
SW3 6NP

Sponsor information

Organisation
Imperial College London

Sponsor details
Joint Research and Compliance Office
Room 221, Medical School Blding
St Mary's Campus
Norfolk Pl
London
England
United Kingdom

SW3 6NP
-
rgit.ctimp.team@imperial.ac.uk

Sponsor type
University/education

Website
http://www.imperial.ac.uk/

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Charity

Funder Name
British Heart Foundation

Alternative Name(s)
the_bhf, The British Heart Foundation, BHF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Peer reviewed scientific journals
Internal report
Conference presentation
Where consent is provided by the participants, data will be shared with collaborators for appropriate and ethically approved research. Any data shared will be anonymised wherever possible. Any linked identifiers will be kept strictly confidential by the research team.

Intention to publish date
01/04/2027

Individual participant data (IPD) sharing plan

The current data sharing plans for this study are unknown and will be available at a later date

IPD sharing plan summary

Data sharing statement to be made available at a later date