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The use of thyroid hormone liothyronine in patients with heart failure

Submission date
12/09/2023

Recruitment status
No longer recruiting

Registration date
29/09/2023

Overall study status
Completed

Last Edited
16/01/2025

Condition category
Nutritional, Metabolic, Endocrine

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Heart failure (HF) is a clinical syndrome in which patients have typical symptoms and signs resulting from an abnormality of cardiac structure and function. In Europe, 15 million individuals are living with HF and, unlike other cardiovascular conditions, the prevalence of HF continues to rise. Management of HF costs healthcare systems between 1 – 2% of all healthcare-related costs. For example, the average costs of HF in the UK are estimated at €26 million per million population; €37 million per million population in Germany; and €39 million per million per million population in France. Furthermore, outcomes of people with HF are poor, and, sometimes, can be worse than certain types of cancer. Despite some significant improvements in survival rates, approximately 1 in 3 patients admitted to hospital with HF die within 12 months. Beyond the risk of death, HF has a considerable, and lasting, impact on a patient's health and well-being. The debilitating and chronic nature of this condition impacts all aspects of life and can increase the patient's dependency on caregivers, leading to social isolation, anxiety and depression. Therefore, newer, safer and cost-effective therapies are required for improving the current management and prognosis of patients with HF. Thyroid hormones (TH) have a number of pleiotropic effects on the cardiovascular system in general and the myocardium in particular. The active TH triiodothyronine (T3) is important for myocardial contractility, acts as a vasodilator and has a direct positive action on myocardial mitochondrial function – processes that are involved in the pathogenesis of HF. Furthermore, ischaemic cardiomyocytes have reduced intra- and extra-cellular T3 levels due to the effects of acute injury on TH-modulating enzymes. The reduction in intracellular T3 has been linked to the development of HF. In rodent models, reduction in tissue T3 levels leads to a state of tissue hypothyroidism, independently of circulating T3 levels. In HF patients on standard therapy, low circulating T3 levels represent a strong independent prognostic predictor of death and major adverse cardiac events. It is therefore possible that T3 therapy in HF patients offers a potentially useful option to improve left ventricular (LV) function as well as morbidity and mortality. Trials of T3 in a small number of patients in other cardiac conditions such as coronary artery bypass grafting surgery have mostly suggested a beneficial impact on LV function. In addition, the safety profile of T3 on heart rate and rhythm has been proven in multiple RCTs in acute as well as chronic cardiac conditions. In the HF setting, there have been three controlled trials to date that have studied a small number of participants with HF and low circulating T3 levels. Of these, two have demonstrated that T3 is effective and safe in improving left ventricular function whereas the third failed to reach

statistical significance. Thus, large adequately powered trials of T3 in HF patients with low serum FT3 levels are required to prove efficacy. This project aims to provide initial evidence regarding the feasibility of recruiting to such a trial and the usefulness of the methodology used and the interventional agent in assessing outcomes. The aims of this feasibility project are to evaluate the number of HFrEF patients with low serum FT3 levels and if a trial designed to normalise serum FT3 therapy in patients with chronic stable HF with reduced ejection fraction (HFrEF) and low circulating T3 levels is acceptable to patients and provides initial data of signal of efficacy.

Who can participate?
Patients aged between 18 – 80 years old with moderate to severe HFrEF (EF <45%), not on any medications affecting thyroid function and who have low serum T3 levels (< 3.5 pmol/L)

What does the study involve?
In part 1 of the study, a blood sample will be taken to see if the participant's blood T3 level is low. If it is low, they will be able to proceed with the rest of the study and an appointment will be made to see the research team for visit 2. If the blood T3 level is normal then they will not be invited for further tests and their health will be followed up through the GP and hospital medical systems.

In part 2, the study team will take consent, check the participant's height, weight, pulse, and blood pressure and go through their past medical history. Using the blood sample provided in part 1, blood markers of your heart and overall health will be checked. The study team will check what medication the participant is currently taking and perform an Electrocardiogram (ECG) which will tell them about the heart's electrical activity and rhythm. They will also be asked to complete some questionnaires and do a walking test to assess their exercise tolerance. They will be prescribed a 3-month supply of Liothyronine (T3) 10 mcg, to be taken orally as tablets twice daily at least 30 minutes before breakfast and evening meal. This will be in addition to their usual medications. An appointment will also be made for them to have a cardiac MRI at Newcastle Magnetic Resonance Centre.

Towards the end of the 3-month period, a repeat blood sample will be taken and their height, weight, pulse, blood pressure and ECG measurements will be undertaken. Participants will be asked to complete some questionnaires and do another walking test, and an appointment will be made for a repeat cardiac MRI at Newcastle Magnetic Resonance Centre. After these investigations are completed, participants will finish taking their prescribed Liothyronine (T3) medication and they will have completed the trial.

What are the possible benefits and risks of participating?
Participants will receive two cardiac MRI scans which provide accurate and detailed information about the heart and its function and are not usually part of clinical service due to limited availability and cost. Some participants may find this level of detail relating to their heart and its function useful. It is hoped that this trial will provide valuable information about whether people with chronic heart failure may benefit from taking Liothyronine (T3) and will lay the groundwork for a trial on a much larger scale. There is no promise that a study will directly help you but you may benefit from a better understanding of the link between thyroid hormones and heart failure. Participation may benefit other people who have heart failure in the future. The study drug is approved by the UK regulatory authorities for the treatment of underactive thyroid but not for people with heart failure and low blood T3 levels so it is unknown whether T3 treatment will be beneficial. However, the results of this feasibility study will help us in answering this question.

Liothyronine (T3) is a safe tablet and has few side effects because it is a synthetic version of triiodothyronine, a naturally occurring hormone produced by the thyroid gland. The side effects of this medicine usually only occur from excessive dosing. The dose you will receive for this trial is very low. You should contact us immediately in the unlikely event that you experience any side effects of Liothyronine (T3) treatment. Participants will be given a contact card with the contact details of the research team should they have any concerns or problems whilst taking this medication. Possible side effects of overdose could include weight loss, palpitations, tremors, chest pain, diarrhoea, and anxiety.

After blood samples have been taken, participants may get a small bruise, have discomfort or in extremely rare cases get an infection at the needle site. The MRI scan can be noisy. Headphones are usually provided so that you can listen to music during the procedure. Some people may find the MRI scanner to be claustrophobic. Relaxation techniques can be advised if this happens. Any test may detect abnormalities that may be unrelated to your thyroid or your heart condition – termed incidental findings. The study team will inform a participant's GP regarding these findings to be dealt with in the usual manner.

Where is the study run from?
Queen Elizabeth Hospital (UK)

When is the study starting and how long is it expected to run for?
April 2021 to December 2024

Who is funding the study?
1. Merck & Co (USA)
2. National Institute for Health and Care Research (NIHR) (UK)

Who is the main contact?
Dr Salman Razvi, salman.razvi@ncl.ac.uk

Contact information

Type(s)
Principal investigator

Contact name
Dr Salman Razvi

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
309311

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 52501, IRAS 309311

Study information

Scientific Title
Liothyronine to normalise Thyroid Hormones in Heart Failure (T3-HF) - A feasibility study

Acronym
T3-HF

Study objectives
Oral liothyronine (a synthetic version of triiodothyronine [T3], a naturally occurring hormone produced by the thyroid gland) therapy improves cardiac function in patients with chronic stable heart failure who have low serum normal serum free T3 (FT3) levels

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 05/05/2022, South Central – Berkshire B (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, United Kingdom; +44 (0)207 104 8253, (0)207 104 8276, (0)207 104 8256; berkshireb.rec@hra.nhs.uk), ref: 22/PR/0397

Study design
Non-randomised cohort study

Primary study design
Interventional

Study type(s)
Screening, Treatment, Efficacy

Health condition(s) or problem(s) studied
Other forms of heart disease, Disorders of the thyroid gland

Interventions

The study design is a single-centre prospective open-label feasibility interventional before-after trial of T3 therapy for 3 months. There are two parts to the study design.

Part 1
Participants will be identified from the Gateshead HF service database by the Cardiology team. All participants in the Gateshead Heart Failure Service who have moderate to severe HFrEF (EF <45%) and who are not on any medications affecting thyroid function will be invited to have their thyroid function assessed. This will be done by sending out invitation packs (comprising a patient information sheet, invitation letter, GDPR guidance and a reply slip) and giving reasonable time to decide if they wish to participate. Those who express an interest in participating will be invited to a clinic appointment to obtain informed consent (Part 1) and for a blood sample to be taken to check TSH, FT4, FT3, and CRP.

All individuals will have their health monitored for the next 5 years using NHS, GP and hospital records.

Part 2
Participants that have low FT3 levels (<3.5 pmol/L) will be further invited to part 2 of the study. This will involve attending a clinic appointment to obtain informed consent (Part 2) and to undertake the following assessments:
Physical examination: height, weight, blood pressure, pulse.
Clinical History: (Relevant medical history, medication list), admissions to hospital and NYHA classification), ECG (12 lead).
Questionnaires: Health and Quality of life parameters with EQ-5D and Minnesota Living with Heart Failure questionnaires.
Physical assessments: 6-minute walking distance test.
Cardiac MRI.
Using the sample obtained in part 1, the study team will also check NT-pro-BNP to further analyse cardiac function.
Participants will be prescribed a 3-month supply of Liothyronine (T3) 10 mcg at baseline, to be taken orally twice daily.
Participants will be asked to take the 10-mcg tablet of T3 at least 30 minutes before breakfast and evening meal for 3 months. The trial medication will be administered in an open-label manner and prescribed by the principal investigator (PI) or co-investigator using a trial-specific prescription and dispensed according to local pharmacy practice. Participants will be asked to take the 10-mcg tablet of T3 at least 30 minutes before breakfast and evening meal. A contact card will be given to all participants so they can contact the research team should they have any problems or concerns during this treatment phase.

At the end of the 3-month period, participants will be asked to attend a final clinic visit to undertake the following assessments:
Physical examination: height, weight, blood pressure, pulse.
Venepuncture: 10mls blood to check TSH, Free T4, Free T3, TPO, CRP and NT-pro BNP.
Clinical History: (Relevant medical history, medication list), admissions to hospital and NYHA classification.
Questionnaires: Health and Quality of life parameters with EQ-5D and Minnesota Living with Heart Failure questionnaires.
Physical assessments: 6-minute walking distance test.
Cardiac MRI.
Safety reporting.

The study team will ask participants to return all empty medication blister packs/ bottles and any surplus supply in the original packaging to the study team who will verify and document compliance.

Intervention Type
Other

Phase
Not Specified

Primary outcome(s)
1. Acceptability of trial design measured using the number of participants recruited /number of participants approached at baseline; the information is obtained from the study recruitment log
2. Retention of trial participants measured using the number of participants completing the study/number of participants recruited; the information is obtained from study records and recruitment log
3. Rate of recruitment: calculated as the number of participants recruited per month; the information is obtained from the study recruitment log

Key secondary outcome(s))
1. Proportion of patients with chronic and stable HFrEF with low serum FT3 levels at baseline; information obtained from study case report form
2. Change in LVEF at 3 months compared to baseline using cardiac MRI
3. Change in left ventricular systolic and diastolic diameters at 3 months compared to baseline – assessed by cardiac MRI
4. Change in N-terminal-pro brain natriuretic peptide (NT-pro BNP) and markers of inflammation (hsCRP) at 3 months from baseline
5. Change in thyroid function tests at 3 months from baseline
6. Health and Quality of life parameters measured using the EQ-5D and Minnesota Living with Heart Failure questionnaires assessed at baseline and at 3 months
7. Exercise capacity measured using the 6-minute walking distance at baseline and at 3 months
8. Pulse rate and rhythm (new-onset atrial fibrillation), admissions to hospital, and NYHA classification at baseline and at 3 months
9. Compliance with study medication measured using tablet counting at 3 months

Completion date
31/12/2024

Eligibility

Key inclusion criteria
1. Men and women aged between 18 – 80 years
2. Stable HFrEF (no admission to hospital with HF exacerbations in the previous 3 months)
3. Chronic HFrEF (diagnosed more than 3 months prior to recruitment)
4. Moderate – severe systolic left ventricular dysfunction (LVEF < 45% on cardiac echocardiogram within last 6 months)
5. On standard HFrEF therapy
6. With low serum T3 levels (< 3.5 pmol/L)

Participant type(s)

Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit
80 years

Sex
All

Total final enrolment
65

Key exclusion criteria
1. Those on medications affecting thyroid function (such as levothyroxine, antithyroid drugs, amiodarone, lithium and sodium valproate)
2. Patients admitted to hospital with acute exacerbation of HF in the preceding 3 months
3. Claustrophobia precluding cardiac magnetic resonance (MR) assessment
4. Cardiac devices (such as implantable cardioverter defibrillators) that are incompatible with MR scanning
5. Untreated valvular heart disease as the main cause of the HFrEF
6. With severely abnormal serum TSH (< 0.1 or > 10.0 mIU/L) or thyroxine (FT4) levels (< 9.0 or > 23.0 pmol/L)
7. Participants who are unable to provide written informed consent
8. Individuals who are pregnant or trying to conceive

Date of first enrolment
17/08/2022

Date of final enrolment
30/09/2024

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Queen Elizabeth Hospital
Sheriff Hill

Gateshead
United Kingdom
NE9 6SX

Sponsor information

Organisation
Gateshead Health NHS Foundation Trust

ROR
https://ror.org/01aye5y64

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Merck

Alternative Name(s)
Merck & Co., Inc., Merck & Co.

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Dr Salman Razvi, salman.razvi@ncl.ac.uk. From 1st July 2025. Data will be shared with bona fide researchers upon reasonable request for scientific reasons. The criteria for deciding what is reasonable and with whom data should be shared will be decided by the PI and the sponsor's representative. Data will be provided for meta-analyses and will be shared in a password-protected file. No individually identifiable data will be shared and only group-level data shared.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes