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A randomised controlled trial to find out whether people with takotsubo cardiomyopathy should be prescribed a drug commonly used to relax blood vessels (renin angiotensin system inhibitors)

Submission date 15/04/2025	**Recruitment status** Recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 01/07/2025	**Overall study status** Ongoing	
Last Edited 01/08/2025	**Condition category** Circulatory System	

Plain English summary of protocol

Background and study aims

Takotsubo cardiomyopathy affects 5,000 people annually in the UK, mostly middle-aged women, and one in ten dies from it. A takotsubo attack is usually caused by experiencing sudden stress, such as bereavement or illness, although the cause can be unknown. Takotsubo cardiomyopathy isn't caused by a blockage in the heart arteries but a severe weakening of the heart muscle. In those who survive an attack, the heart muscle recovers, but they face higher risks of death, heart attacks, strokes, heart failure, and repeated takotsubo episodes compared to the general population. This long-term risk after a takotsubo attack is similar to patients who have a heart attack due to a blocked heart artery. Despite this, there are no proven treatments for takotsubo. Research suggests that renin-angiotensin system (RAS) inhibitors used to treat heart attacks due to heart artery blockage or heart failure might help takotsubo patients. These drugs have been shown to be safe and easy to take in other heart conditions. The Everest Study aims to determine if RAS inhibitors can prevent deaths, heart attacks, strokes, heart failure and repeated takotsubo attacks in people who suffer a takotsubo attack.

Who can participate?

Adult participants who have experienced a takotsubo attack in the previous 6 months from 40 hospitals across the UK

What does the study involve?

Participants will be randomly allocated to receive the drug or not, for a minimum of 2 years. Information will be collected on patients' symptoms, subsequent illnesses and deaths from centrally held NHS electronic health records and patient questionnaires. The number of deaths, heart attacks, strokes, heart failure or repeated takotsubo attacks will be compared between the two groups to report whether or not these drugs are effective at preventing repeated health problems, improving symptoms and quality of life, and reducing health care costs in

patients after a takotsubo attack.
Side effects of RASi therapy may be considered a risk, however, it is anticipated that the side effect profile for RASi in those with takotsubo cardiomyopathy will reflect that for use in people with myocardial infarction, heart failure, hypertension and albuminuria in diabetes. The trial protocol does not fix the dose of RASi – clinicians will start the dose that they would routinely use in their clinical practice and can titrate to maximum tolerated dose with monitoring blood pressure and renal function as appropriate (in line with standard practice when starting any patient on a RASi). If there are side effects associated with first-line RASi therapy (angiotensin-converting enzyme inhibitor), second-line RASi therapy (angiotensin II receptor blocker) can be tried. If there is intolerance to this second-line RASi therapy, the study drug can be stopped.

What are the possible benefits and risks of participating?
By taking part, participants will be directly helping to inform the treatment of future patients with takotsubo cardiomyopathy. The results of this study will help plan effective services offered by the NHS in the future. The results of this study are expected to feed directly into the NHS guidelines and, for the first time, provide evidence for the treatment of takotsubo cardiomyopathy.
The main risks to participants taking RASi are (i) hypotension, which can be managed by monitoring blood pressure, with a dose reduction or change of RASi if indicated and (ii) renal function decline, which can be monitored via annual u&e as in routine clinical practice. If participants in the RASi arm experience side effects, an alternative RASi can be offered. If they do not tolerate RASi, they can remain in the study, but not take further RASi.
Participants will be asked to complete questionnaires at 30 days, 3 months, 6 months, and then annually. Each questionnaire should take about 15 minutes to complete. If participants find the questionnaires too burdensome, they can opt out of questionnaire completion.

Where is the study run from?
University of Aberdeen (UK)

When is the study starting and how long is it expected to run for?
January 2025 to December 2031

Who is funding the study?
National Institute for Health and Care Research (NIHR) (UK)

Who is the main contact?
everest@abdn.ac.uk

Study website
https://w3.abdn.ac.uk/hsru/EVEREST/Public/Public/index.cshtml

Contact information

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Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1010856

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
3-067-24

Study information

Scientific Title
A randomised controlled trial of renin-angiotensin system inhibition for the reduction of cardiovascular events after takotsubo cardiomyopathy

Acronym
EVEREST

Study objectives

To compare the clinical effectiveness of RAS inhibition or no RAS inhibition on the primary composite endpoint of all-cause death or hospitalisation for heart failure, myocardial infarction, stroke, or recurrent takotsubo cardiomyopathy.

Establish if RAS inhibition (ACEi/ARB):
1. Reduces the incidence of the individual components of the primary composite endpoint
2. Improves patient-reported outcomes

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 20/06/2025, East of England -Essex Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 1048106, +44 (0)207 1048151, +44 (0) 2071048177; Essex.REC@hra.nhs.uk), ref: 25/EE/0100

Study design
Randomized controlled open-label parallel group study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital, Medical and other records

Study type(s)
Treatment

Participant information sheet
See study outputs table

Health condition(s) or problem(s) studied
Takotsubo cardiomyopathy

Interventions
An online tool will randomly assign participants in the EVEREST Trial to either receive RAS inhibition (oral angiotensin-converting enzyme inhibitor (ACEi) or oral angiotensin II receptor blocker (ARB))alongside local or individual clinician practice as standard care or the comparator, local or individual clinician practice as standard care without prescription of a RAS inhibition (ACEi/ARB).

For the purposes of this trial, RAS inhibition is defined as any angiotensin converting enzyme inhibitor (ACEi) or any angiotensin receptor blocker (ARB), inclusive of angiotensin receptor blocker-neprilysin inhibitor. The RAS inhibition (ACEi/ARB) will not be specifically manufactured or labelled for use within the EVEREST trial. The trial will use routine stocks prescribed by the clinical team or their GP and dispensed by the hospital or local pharmacy.

Medication will be started by the clinician at the dose they routinely use in their clinical practice and titrated to the maximum tolerated dose with monitoring blood pressure and renal function as appropriate (in line with standard practice when starting any patient on a RAS inhibition (ACEi /ARB).

In most cases, the participant will be started on an angiotensin-converting enzyme inhibitor by the clinician (first-line therapy), and in case of intolerance (1 in 10 patients), can be switched to an angiotensin II receptor blocker (second-line therapy). However, in certain circumstances (e.g. known intolerance to angiotensin-converting enzyme inhibitors), the participant may be started on an angiotensin II receptor blocker. Ramipril is the preferred first-line therapy, but other angiotensin-converting enzyme inhibitors are acceptable. Valsartan is the preferred second-line therapy, but other angiotensin II receptor blockers are acceptable.

Intervention Type
Drug

Pharmaceutical study type(s)
Therapy

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Ramipril, lisinopril, perindopril, fosinopril, captopril, valsartan, candesartan, losartan, irbesartan, telmisartan, sacubitril-valsartan, enalapril

Primary outcome measure
The primary composite outcome (endpoint) is the time-to-first event from randomisation to a composite of all-cause death or hospitalisation for either heart failure, myocardial infarction, stroke or recurrent takotsubo cardiomyopathy.

The primary endpoint will be collected via routine healthcare electronically linked data (NHS England (Digital), NHS Wales Informatics Service, Public Health Scotland, Health and Social Care (HSC) Business Services Organisation Information Technology Services (ITS) Northern Ireland) of specific codes as detailed in the Statistical Analysis Plan, routine data collection will be completed at the end of the study. Clinical outcomes will also be recorded by local study teams at 3 months and 1 year after randomisation and annually thereafter, via case note review.

Secondary outcome measures
1. Time-to-first event of the individual components of the primary composite endpoint measured using data collected from routine healthcare electronically linked data and local study teams at one timepoint
2. Symptoms and quality of life measured using the Kansas City Cardiomyopathy Questionnaire (KCCQ-12), health status using the EQ-5D-5L, and anxiety, depression, fatigue and treatment measured using acceptability questionnaires; health care use will be collected by participant completed questionnaires at baseline, 30 days, 3months, 6 months, 12 months, and annually from the date of participant randomisation

Overall study start date
01/01/2025

Completion date
31/12/2031

Eligibility

Key inclusion criteria
1. Acute takotsubo cardiomyopathy within 6 months (either first episode or a recurrent episode)
2. Age ≥18 years
3. Able and willing to give informed consent and to participate in study procedures
4. Willing to have a pregnancy test for those of childbearing potential

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
930

Key exclusion criteria
1. Current pregnancy or current breastfeeding, or female actively trying to become pregnant
2. Any significant disease/disorder which, in the investigator’s opinion, either puts the patient at risk because of study participation or may influence the results of the study or the patient's ability to participate in the study.
3. Mandated clinical indication for RASi (ACE/ARB) therapy (any class 1A ESC guideline recommendation)
4. Known intolerance to RASi (ACE/ARB)
5. Previous allocation of a randomisation code in the current study
6. People without capacity

Date of first enrolment
01/07/2025

Date of final enrolment
30/09/2029

Locations

Countries of recruitment
Scotland

United Kingdom

Study participating centre
NHS Grampian
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Sponsor type
University/education

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ROR
https://ror.org/016476m91

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

Results and Publications

Publication and dissemination plan
1. Peer reviewed scientific journals
2. Conference presentation
3. Publication on website
4. Other publication

Intention to publish date
31/12/2032

Individual participant data (IPD) sharing plan
The datasets generated during the current study will be available upon reasonable request upon completion of the study. A request to access the datasets generated during the study should be directed in the first instance to dana.dawson@abdn.ac.uk. The dataset will be available in fully anonymised electronic form, at an individual level, and in accordance with participant consent. Applicants will be asked to complete a data request form, which will be reviewed by a Data Sharing Committee which includes the Chief Investigator. Applications will be assessed on a case-by-case basis by bona fide researchers. We are obligated to ensure that optimal use is made of the data that is collected for research, and we recognise the value of sharing individual-level data. The interests of research participants, researchers and other stakeholders will be considered when considering each application.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 2	15/05/2025	15/07/2025	No	Yes