The EVEREST STUDY

A research study to find out whether people with takotsubo cardiomyopathy should be prescribed a drug commonly used to relax blood vessels

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

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Invitation to take part

We would like to invite you to take part in a research study looking at whether people with takotsubo cardiomyopathy should or should not be prescribed a type of drug that is commonly used to relax blood vessels. You have been invited to take part because you have recently had a diagnosis of takotsubo cardiomyopathy.

Before you decide if you would like to take part, it is important for you to understand why the research is being done and what it will involve.

The first part of the Participant Information Leaflet tells you the purpose of the study and what will happen to you if you take part.

Then, in the second part, we will give you more detailed information about how the study is run.

Please take time to read the information carefully. It has been written with the help of patient representatives who have experienced an episode of takotsubo cardiomyopathy. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether you want to take part or not. Contact details for this research study can be found at the end of this leaflet.

Part 1 - the purpose of the study and what will happen if you take part

Takotsubo cardiomyopathy

Takotsubo cardiomyopathy can sometimes be triggered by sudden stress such as bad news, or the physical stress from another illness, or in some cases there is no apparent cause.

The symptoms of takotsubo cardiomyopathy are like a heart attack, but unlike a heart attack they are not caused by a blockage in the heart arteries but by a severe weakening of the heart muscle.

It remains unclear to doctors what causes this muscle weakness. After the acute takotsubo episode, the heart muscle recovers by itself in a matter of a few days to a few weeks. However, in the longer term, there is a higher risk of further health problems including heart attacks, strokes and heart failure as well as a repeat of takotsubo episodes.

This risk is much the same for patients who have had a heart attack. However, unlike heart attacks, there are no proven treatments for takotsubo cardiomyopathy. Although similar medications as those prescribed to patients with heart attacks have been used, we currently do not know if these drugs are effective in treating takotsubo cardiomyopathy. Some studies have suggested possible benefits of these drugs, whereas other studies did not show any benefit. Therefore, there remains uncertainty on whether there is any benefit to patients in taking these drugs. This means there is an absence of any evidence to guide treatment decisions.

Renin Angiotensin System inhibitors (or RAS inhibitors) are a type of drug that helps relax blood vessels. They are commonly used to treat heart attacks, high blood pressure and heart failure and are sometimes prescribed after takotsubo cardiomyopathy.

What is the purpose of the research study?

We are doing the EVEREST study to find out how effective RAS inhibitors are after a takotsubo cardiomyopathy episode.

The EVEREST study will be looking to see if there are any long-term benefits of prescribing RAS inhibitors after an acute takotsubo cardiomyopathy episode and answer the question on whether RAS inhibitors should, or should not, be prescribed to takotsubo cardiomyopathy patients.

This study will run for seven years and aims to recruit 930 participants from hospitals across the UK. The duration of your participation in the study depends on when you join; early participants will be followed for up to six years, all participants will be followed for at least two years.

What would taking part involve?

Before you make a decision about whether or not to take part, a member of your cardiology team will discuss the study with you to make sure you understand everything. If you do decide to take part, we will ask you to complete a consent form confirming that you are happy to take part.

You can complete this consent form while you are in hospital, during a follow-up visit to the hospital, or at home. You can either complete a paper copy of the consent form, or you can complete it online using a computer, tablet or mobile phone. If you would like to take part, please speak to a member of your cardiology team or the study team (details at the end of this leaflet).

Once you have completed the consent form, we will give you a copy to keep.

We will also ask you to complete a questionnaire (which should take about 15 minutes) about your symptoms, quality of life and your recent contact with the NHS. You can complete the questionnaire whilst in hospital or at later date from home. If completed at home you can either post the questionnaire back to us or complete it online.

We will then randomly allocate you to one of the two study groups.

In the EVEREST study, half the people will be prescribed a RAS inhibitor while the other half will not. There are different types of RAS inhibitors, and you can read more about them in the section below.

If you decide to take part, you will be randomly allocated (using a computer) to one of the two study groups. Being randomised means that neither you nor your healthcare team will decide which group you are in. Once you have been randomly selected for a group, you and your healthcare team will then know which group you are in. You will either:

- **Be in the group who are prescribed a RAS inhibitor**

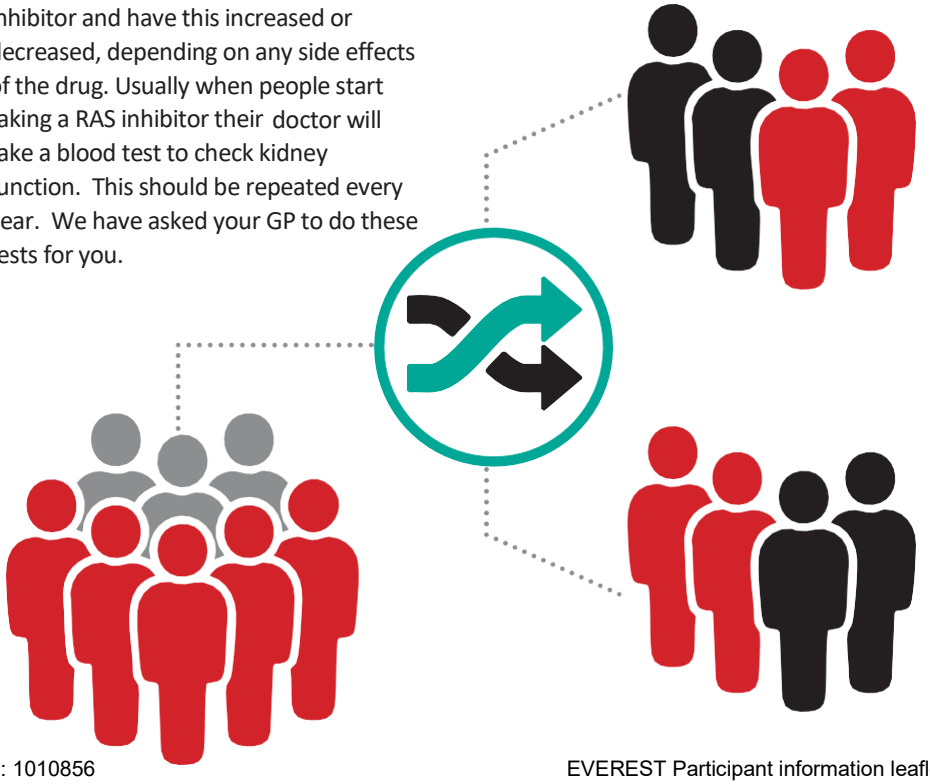
or

- **Be in the group who are not prescribed a RAS inhibitor**

There is an equal chance that you will be placed in either group. This helps make sure that the research study compares similar groups of individuals where the only difference is the RAS inhibitor prescribing.

If you are allocated to the group who will be prescribed a RAS inhibitor, we will arrange for you to have a regular prescription for RAS inhibitor from your doctor, for the duration of the study. If there is a chance that you could be pregnant, we will ask you to take a pregnancy test before you start taking the RAS inhibitor. There are a number of different RAS inhibitors that your doctors can try until they find one that best suits you – you can read more about this in the section on RAS inhibitors later in this leaflet. The doctors will also prescribe the dose to best suit you – this might mean that you start on one dose of a RAS inhibitor and have this increased or decreased, depending on any side effects of the drug. Usually when people start taking a RAS inhibitor their doctor will take a blood test to check kidney function. This should be repeated every year. We have asked your GP to do these tests for you.

We will either arrange for the prescription to be issued in hospital by your cardiology team or by your GP/doctor. You will be able to pick up the RAS inhibitor from your local pharmacy, as you would do with any other prescription. If you usually pay for your prescriptions, we will give you a prescription pre-payment certificate which you can show to the pharmacist, and this means that you will NOT have to pay for any of your prescriptions during your time in the EVEREST Study.



We will ask that you take the RAS inhibitor every day while you are part of the study. If you want, or have to stop taking the RAS inhibitor, please contact your local study team (details at the end of this leaflet). You can continue to take part in the EVEREST study even after you stop taking the RAS inhibitor.

You should continue to take all of your other medication(s) as usual.

Women who are taking RAS inhibitors should avoid becoming pregnant. If relevant for you, we will give you an additional leaflet about avoiding pregnancy while taking RAS inhibitor.

If you decide that you want to try for a baby, please stop taking the RAS inhibitor and contact your GP and let the local study team know. If you are taking a RAS inhibitor and think you might be pregnant, please stop taking the RAS inhibitor, contact your GP and let the local study team know.

If you do become pregnant while taking RAS inhibitor, we will ask you to provide details of the pregnancy and the pregnancy outcome, and in some circumstances, it may be necessary to monitor the development of the newborn post-delivery up to the first 6 weeks of the baby's life.

If you are allocated to the group who are NOT prescribed a RAS inhibitor, you should continue taking any other medication (if applicable) as normal.

If you usually pay for your prescriptions, we will give you a prescription pre-payment certificate which you can show to the pharmacist. This means that you will NOT have to pay for any other prescriptions for as long as you continue in the study.

If your doctor needs to prescribe a RAS inhibitor for any reason while you are taking part in the study, they can do this – if this is the case, please let your local study team know (details at the end of this leaflet).

Whichever group you are in, you will be in the EVEREST study for a minimum period of two years, but you do not need to return in person for study visits, unless you specifically want to.

We will ask you to complete a questionnaire 30 days after you join the study, and again after 3 and 6 months. We will then ask you to complete a questionnaire each year that you are in the study (up to a maximum of 6 years). These questionnaires are widely used in clinical care and will be used to assess your symptoms, general and heart health, and quality of life. They will also ask you about the visits to your GP and about any medication you are taking. Each questionnaire will take about 15 minutes to complete.

When you join the study, we will ask how you would prefer to complete these questionnaires – either by post, or online. If you would like help completing the questionnaires, either over the telephone or by coming in to complete them with the local study team, please let us know.

We will also contact you at 3 months and each year by phone to find out how you are and if you have had any health problems.

We will collect relevant information from your medical records (e.g. any cardiovascular or subsequent admissions that may be relevant to takotsubo cardiomyopathy) via NHS central registers: in England this is NHS England; in Wales it is NHS Wales Informatics Service; in Northern Ireland it is Administrative Data Research Northern Ireland and in Scotland it is Public Heath Scotland. The reason for this is to make sure that we have the correct information about everyone who is taking part in the EVEREST study and ensure that the results are as accurate as possible. In order to do this, we will securely send the NHS central registers some information about you (e.g. date of birth, name, address and/or NHS hospital number). They will then match this information to their records and return this information to us using only your study number (de-identified).

Those who take part in the EVEREST study will be followed up for between 2 and 6 years – with the last follow-up being in 2031. We hope to be able to follow up EVEREST study participants for longer than this by using routine data from NHS central registers. We do not have the funding for this longer-term follow-up yet, but we will ask for your permission to do this when you join the study. You can take part in EVEREST without agreeing to this long-term follow-up.

We will also ask for your permission to keep your contact details to allow us to contact you about participating in future research, again, you do not have to agree to this to be part of the EVEREST study.

We will ask for your permission to collect a small saliva sample. You do not have to agree to this, but if you do, we will send you a saliva test kit by post. This is very easy to use and can be returned in a prepaid envelope which we will provide.

Your saliva sample will be stored securely at the University of Aberdeen in a container labelled with a number that will identify you within the study, but will not include your name, date of birth or any other personal information.

Only the study team will have access to the saliva samples. We plan to look for extra funding to extract the DNA from your sample to look for genes that are related to takotsubo cardiomyopathy. Once DNA is extracted and processed there will be no saliva sample or DNA left. We will not be able to share the results of genetic tests with individual participants. Anonymised genetic data may be shared with other researchers to use in future ethically approved studies. There is more information about we might share data with other researchers on page 20 of this leaflet. If we cannot get extra funds for the DNA extraction and analysis, we will destroy the saliva samples after 25 years.

As a token of our appreciation, we would like to send you a £20 shopping voucher with your second annual study questionnaire, and a £20 shopping voucher with your final questionnaire at the end of the study. Please tell us if you do not want to receive these.

What are RAS inhibitors?

RAS inhibitors are generally used to treat hypertension (high blood pressure), heart failure or heart attacks. There are two main types of RAS inhibitors:

1. **Angiotensin converting enzyme (ACE) inhibitors**, which include drugs like Ramipril, Lisinopril, Enalapril, Perindopril, Fosinopril and Captopril. These are what is called "first line therapy" which means that they are the first treatment tried.

In the EVEREST study, the RAS inhibitor Ramipril, is our preferred choice for the first line medicine to be used. This is because it has the most evidence in all other heart conditions, but, in discussion with you, the study team or your GP may decide to use another medicine such as Lisinopril, Enalapril, Perindopril, Fosinopril or Captopril instead.

2. **Angiotensin II receptor blockers (ARB),** which include drugs like Valsartan, Candesartan, Losartan, Irbesartan, Telmisartan and a combination called Entresto (Sacubitril-Valsartan). These are what is called "second line therapy" which means that they can be tried if the first line therapy causes unwanted side effects.

In the EVEREST study, Valsartan is the preferred choice for the second line medicine to be used, but, in discussion with you, the study team or your GP may decide to use another medicine such as Candesartan, Losartan or Irbesartan, Telmisartan or Entresto instead.

If you are allocated to the group who will be prescribed a RAS inhibitor, you will only take one RAS inhibitor as part of the study. Usually, this will be Ramipril or Valsartan but may be one of the other drugs named above.

What are the possible benefits of taking part?

By taking part, you 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. We expect the results of this study to feed directly into the NHS guidelines and, for the first time, provide evidence for the treatment of takotsubo cardiomyopathy.

As with any research, you may not benefit personally from taking part.

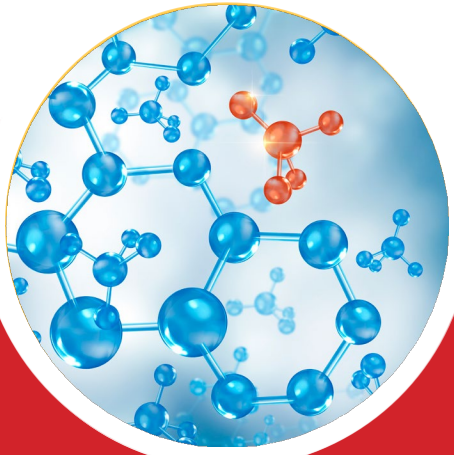
What are possible disadvantages, risks and side effects when taking part?

We do not think there are any major disadvantages to you.

For those prescribed a RAS inhibitor, the risks and side effects of the drug are few and will be explained to you by the study team. Before you agree to take part in the study, you can and should discuss any concerns that you may have with your doctor.

If you feel unwell at any point, please seek medical help as you would do usually. Do not delay in seeking urgent medical care in an emergency.

If you are concerned that you may have developed side effects, you should contact your local study team, or your GP and they will provide help and advice.



Below, we have listed the most common side effects of Ramipril (**an ACE inhibitor**). affecting between 1 in 10 to 1 in 100 people.

The side effects of the other **ACE inhibitors** that might be used in EVEREST (Lisinopril, Enalapril, Perindopril, Fosinopril and Captopril) are similar. Whichever drug you are prescribed, there will be more information about the side effects in the box.

- *headache, dizziness, tickling cough, bronchitis, sinusitis, dyspnoea (breathlessness), gastrointestinal side effects (such as diarrhoea, nausea or vomiting), rash, low blood pressure which can make some people feel lightheaded especially when standing up suddenly, fatigue*

A rare side effect (1 in 1000) is angioedema (swelling of the lips and tongue, or possibly of other organs).

If you experience side effects, please contact the local study team or your GP. They may suggest switching to an ARB, and this usually resolves some of the side-effects, especially any cough

Below, we have listed the most common side effects of Valsartan (an ARB) affecting between 1 in 10 to 1 in 100 people.

The side effects of the ARBs that might be used in EVEREST (Candesartan, Losartan, Irbesartan, Telmisartan or Entresto) are similar. Whichever drug you are prescribed, there will be more information about the side effects in the box.

- *low blood pressure which can make some people feel lightheaded especially when standing up suddenly, dizziness.*

Do I have to take part?

No. It is entirely up to you whether or not to take part. Please take as much time as you need to make this decision. You can read this information as many times as you wish and ask your GP, the cardiology team, or the local study team as many questions as you like.

You can decide at any time to withdraw from the study without giving a reason by contacting your local site team This decision will not affect the standard of care you are receiving now or in the future. If you make this decision, you should continue attending appointments with your consultant and/or GP as part of your standard care

If you decide to withdraw from this study, we will keep and continue to use all your previously collected data. We would also like to continue collecting information about your health from central NHS records. If you do not want this to happen, tell us and we will stop. This information will remain confidential. To safeguard your rights, we will use the minimum personally identifiable information possible.

Before taking part, check if any insurance you have may be affected by your participation. Get advice if you need it.

Part 2 - More information about how the study is run

What happens when the research study stops?

If the study is stopped earlier than expected for any reason, we will tell you and arrange continuing care for you – either from the cardiology team or from your GP.

At the end of the study, we will analyse the study data. There will be a few months between the end of the study until the results are available. After the results of EVEREST are available, we expect there will be clear guidance for both doctors and patients on whether there is any benefit or not in prescribing RAS inhibitors after takotsubo cardiomyopathy.

At the end of the study, and before the study results are available, the continued prescribing of any RAS inhibitor will remain at the discretion of your cardiology team or GP. This means that, if you have been taking a RAS inhibitor as part of the study, you can discuss with your cardiology team or GP if you would like to keep taking it.

What if relevant new information becomes available?

Sometimes during a research project, new information becomes available about the treatment that is being studied.

If this happens, the local study team will contact you to let you know about the choices available to you. However, we are not aware that any new, relevant information is likely to become available before the end of this study.

What if there is a problem?

If you have a question or concern about the study, you can speak with your doctor who will do their best to answer your questions. Contact details for your local study team and the Study Office can be found on the last page of this information leaflet. If you wish to make a formal complaint or have any concerns about any aspects of the way you have been approached or treated during this study, you can do this through the normal NHS Complaints Procedure. Contact details can be found at the end of this leaflet

We do not expect any harm to come to you by taking part in this study. If something does go wrong, and you believe that you have been harmed by taking part in this study, you have the right to pursue a complaint and seek compensation through the research sponsors of this study. Contact details can be obtained from the EVEREST study Office.

If you are harmed due to someone's negligence, as a patient of the NHS you have the right to take legal action. You may have to pay for your legal costs yourself (as you would in standard NHS care).

We will provide compensation for any injury caused by taking part in this study in accordance with the guidelines of the Association of the British Pharmaceutical Industry (ABPI).
We will pay compensation where the injury probably resulted from:
- A drug being tested or administered as part of the trial protocol;
- Any test or procedure you received as part of the trial.

Any payment would be without legal commitment. (Please ask if you wish more information on this). We would not be bound by these guidelines to pay compensation where the injury resulted from a drug or procedure outside the trial protocol or where the protocol wasn't followed.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information which is collected about you for the purpose of this research study will be handled in strict confidence and securely stored by the University of Aberdeen. With your permission, we will tell your GP that you are taking part in the study.

How will we use information about you?

We will use information from you and your medical records for this research project. This information will include your name, contact details, date of birth and NHS number (England, Wales and Northern Ireland only) or CHI number (Scotland only). People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. The University of Aberdeen are a co-sponsor of this research and are responsible for looking after your information. The University of Aberdeen will be the data controller for this research. We will keep all information about you safe and secure by:

- Handling it confidentially
- Storing it securely with access restricted to authorised individuals directly involved in the study or data analysis. We will store any information recorded on paper in locked cabinets. Any information held electronically will be protected with passwords.

We may share data about you outside the UK for research related purposes to:

- Allow future analysis of data in other ethically approved projects
- Provide data to be included in reviews of existing data sets

If this happens, we will only share the data that is needed. We will also make sure you can't be identified from the data that is shared where possible. This may not be possible under certain circumstances-for instance, if you have a rare illness, it may still be possible to identify you if your data is shared outside the UK, it will be with the following sorts of organisations:

- Academic institutions
- Academic researchers

We will make sure your data is protected. Anyone who accesses your data outside the UK must do what we tell them so that your data has a similar level of protection as it does under UK law. We will make sure your data is safe outside the UK by doing the following:

- making sure that you cannot be identified from it.
- we do not allow those who access your data outside the UK to use it for anything other than what our written contract with them says
- we need other organisations to have appropriate security measures to protect your data which are consistent with the data security and confidentiality obligations we have. This includes having appropriate measures to protect your data against accidental loss and unauthorised access, use, changes or sharing
- we have procedures in place to deal with any suspected personal data breach. We will tell you and applicable regulators when there has been a breach of your personal data when we legally have to. For further details about UK breach reporting rules visit the Information Commissioner's Office (ICO) website

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

We will keep your study data for a maximum of 25 years. The study data will then be fully anonymised and securely archived or destroyed.

What are your choices about how your information is used?

- You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have
- If you choose to stop taking part in the study, we would like to continue collecting information about your health from central NHS records / your hospital. If you do not want this to happen, tell us and we will stop
- You have the right to ask us to remove, change or delete data we hold about you for the purposes of the study. We might not always be able to do this if it means we cannot use your data to do the research. If so, we will tell you why we cannot do this
- If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study.

Where can you find out more about how your information is used?

You can find out more about how we use your information, including the specific mechanism used by us when transferring your personal data out of the UK.

- at www.hra.nhs.uk/patientdataandresearch
- by asking one of the research team
- by sending an email to dpa@abdn.ac.uk, or
- by ringing us on 01224 272585.
- at www.abdn.ac.uk/about/privacy/

What will happen to the results of the study?

We will use results of the study to make recommendations to the NHS in the UK (and possibly world-wide) on treatments for patients with takotsubo cardiomyopathy. We will publish the results of this study in scientific journals and present the information at appropriate meetings.

You will not be identified in any publication of the results of the study.

We will write to you to let you know the results of the study when it is finished unless you tell us that you do not wish to know.

Who is organising and funding the study?

The study is co-sponsored by the University of Aberdeen and NHS Grampian who have overall responsibility for the management of the study. The study is funded by the Health Technology Assessment branch of the National Institute for Health and Care Research in the UK.

The research is being carried out by experienced cardiologists from across the UK, in collaboration with researchers from the Centre for Healthcare Randomised Trials (CHaRT) a UKCRC registered Clinical Trials Unit at the University of Aberdeen.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee (REC), to protect your interests. This study has been reviewed and given a favourable opinion by the East of England -Essex Research Ethics Committee.

In addition, the study has also been reviewed and approved by the Medicines and Healthcare Products Regulatory Agency. The Research and Development Department of your local hospital has also reviewed and approved the study.

Thank you for reading this.

Thank you for taking the time to read this information leaflet. We hope that it has been helpful in enabling you to decide if you would like to participate in the EVEREST study. Please ask us if you have any questions or would like more information about the study.

Further information and contact details

If you have any questions or would like any more information, please

Everest Study Team
Centre for Healthcare Randomised Trials (CHaRT), Aberdeen Centre for Evaluation, University of Aberdeen Health Sciences Building, Foresterhill, Aberdeen AB25 2ZD
Tel: 01224 437421
Email: everest@abdn.ac.uk

Local Study Team contact details

For free, confidential advice and support in regard to your healthcare you can also contact the following:

<< insert local contact details for your Patient Advice and Liaison Service (England), Community Health Council (Wales), Patient and Client Council (Northern Ireland) or Patient Advice and Support Service (Scotland)>>

Further information can be found at the following websites:

British Heart Foundation: https://www.bhf.org.uk/

Cardiomyopathy UK: https://www.cardiomyopathy.org/

Chest Heart and Stroke Scotland: https://www.chss.org.uk/

Notes

The EVEREST Study

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