ISRCTN73887615 https://doi.org/10.1186/ISRCTN73887615

Carvedilol versus variceal band ligation in primary prevention of variceal bleeding in liver cirrhosis

Submission date
08/10/2018

Recruitment status
No longer recruiting

Registration date
10/10/2018

Overall study status
Completed

Last Edited
28/04/2025

Condition category
Digestive System

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
People with long-standing liver disease called cirrhosis (scarring of the liver) can develop enlargement of veins in the gullet (food pipe) known as 'oesophageal varices'. Patients with medium to large oesophageal varices have a 1 in 3 chance of these veins bleeding. In very severe cases, this could result in death. It is therefore important to lower the risk of this bleeding. At present, all people with medium to large oesophageal varices are offered one of two treatments to lower the risk of bleeding either beta-blockers or variceal band ligation. Some research studies suggest that banding may be more effective than beta-blockers in lowering the risk of variceal bleeding, but other studies suggest that this is not the case. However, all of these studies have been small and we still do not know which treatment is best. We need to do a study to compare carvedilol with banding in people with cirrhosis who have medium to large varices that have never bled. Therefore the aim of the trial is to see which intervention works better. This will be done by observing which treatment is effective in stopping the bleeding of varices in the first 12 months after randomisation.

Who can participate?
Adults who have been diagnosed with liver cirrhosis who have medium or large varices that have not bled

What does the study involve?
Participants will be randomly allocated to receive either beta-blocker drugs (carvedilol) or variceal banding. Participants will be on the study for 12 months duration and if randomised to the carvedilol arm, they will be prescribed to take carvedilol 12.5 mg for 12 months daily, and they will be seen in clinic at 4 weeks, at 6 and 12 months to see how they progress. Participants will also be asked to take part in two qualitative interviews so that we understand how they feel about being in the trial. This will be after randomisation and the second one from 6-12 months. If participants are randomised to the variceal band ligation arm, they will have up to 5 endoscopy band ligations over the 12 months, and the number of endoscopy visits will depend on how well

the varices are eradicated. Participants will also be asked to take part in two qualitative interviews so that we understand how they feel about being in the trial. This will be after randomisation and the second one from 6-12 months.

What are the possible benefits and risks of participating?
Although there may be no direct benefits to participants for taking part in this study, the results of the trial will lead to the best treatment being offered to prevent bleeding in patients with liver cirrhosis and medium or large oesophageal varices. Variceal banding has been used for nearly 30 years and is generally very safe. As banding is an endoscopic procedure about 1 in 10 patients may experience discomfort and find it difficult to tolerate the procedure. Infrequent complications include bleeding affecting about 1 in 20 patients, and a very small risk of causing narrowing of the gullet making it difficult to swallow or causing a tear in the gullet (perforation). Carvedilol is a medication that was initially developed to treat high blood pressure and some forms of heart disease. As with any drug, there are potential minor side effects that affect around half of patients, but serious complications are very rare. The side effects of carvedilol which can be difficult to tolerate in about 1 in 10 patients include: shortness of breath, low blood pressure causing dizziness, and upset stomach. Other less common side effects include abnormal vision, bradycardia (slow heart rate), asthenia (fatigue), and impotence. We will carefully monitor any side effects and take action where needed. It is important that medium to large varices are treated so if participants are not able to tolerate variceal banding or carvedilol, they will be offered an alternative treatment. All the tests participants will receive and procedures that will be undertaken are part of normal clinical care for patients with oesophageal varices. There will be an independent safety committee that will oversee the trial.

Where is the study run from?
The trial is run from Birmingham Clinical Trials Unit and at least 66 hospitals/ Health boards around the UK will be involved in recruitment.

When is the study starting and how long is it expected to run for?
March 2018 to May 2024

Who is funding the study?
National Institute for Health Research Health Technology Assessment Programme (UK)

Who is the main contact?
Lisa Holden
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Contact information

Type(s)
Scientific

Contact name
Dr Lisa Holden

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Additional identifiers

Clinical Trials Information System (CTIS)
2018-002488-24

Integrated Research Application System (IRAS)
248487

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
RG_17-229

Study information

Scientific Title
CArvediloL versus varIceal Band ligation in primary pREvention of variceal bleeding in liver cirrhosis

Acronym
CALIBRE

Study objectives
To compare carvedilol versus variceal band ligation in preventing any variceal bleeding within 1 year of randomisation in patients with cirrhosis and medium to large oesophageal varices that have never bled.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 19/10/2018 NHS HRA North East - York REC, (Priory Street Centre, Priory Street, York, YO1 6ET; 0207 104 8079; nrescommittee.northeast-york@nhs.net), ref: 18/NE/0296.
CTA MHRA approval granted 20/09/2018.

Study design
Interventional prospective multicentre pragmatic open-label two-arm randomized controlled parallel group trial with internal pilot

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Variceal bleeding in liver cirrhosis

Interventions
After participant eligibility has been confirmed and informed consent has been received, the participant can be randomised into the trial. A Randomisation Form will be provided to investigators and will be used to collate the necessary information prior to randomisation. All questions and data items on the Randomisation Form must be answered before a Trial Number can be given. If data items are missing, randomisation will be stopped, but can be restarted once the information is available. Only when all eligibility criteria and baseline data items have been provided will a Trial Number be allocated. Participants will be randomised at the level of the individual in a 1:1 ratio to either treatment with 12.5 mg carvedilol once daily for 12 months or variceal band ligation. Both of these treatments will start on the same day as randomisation, or as soon as possible after. Patients randomised in clinic after the diagnostic endoscopy will be started on carvedilol 12.5 mg once daily for 12 months or variceal band ligation within two weeks of randomisation. A minimisation algorithm will be used within the online randomisation system to ensure balance in the treatment allocation over the following variables: presence or absence of hepatic decompensation (ascites or encephalopathy), size of the largest varix (Grade II, or Grade III), age of patient at randomisation (18-50, 51-70, >70), and presence or absence of alcohol related liver disease. A 'random element' will be included in the minimisation algorithm, so that each patient has a probability (unspecified here), of being randomised to the opposite treatment that they would have otherwise received. Full details of the randomisation specification will be stored in a confidential document at BCTU.
Participants will be in the study for a total duration of 12 months from the point of randomisation.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Carvedilol

Primary outcome(s)
Any variceal bleeding within 12 months of randomisation, assessed through endoscopy for the variceal band ligation (VBL) and through observation for the carvedilol arm at 4 weeks and after 6 and 12 months

Key secondary outcome(s))
1. Time to first variceal bleed in days from randomisation, assessed through endoscopy for the variceal band ligation (VBL) and through observation for the carvedilol arm at 4 weeks and after 6 and 12 months
2. Mortality at 12 months from randomisation, assessed using medical records and staff notification after 6 and 12 months:
2.1. All-cause mortality

2.2. Liver-related mortality
2.3. Cardiovascular mortality
3. Transplant-free survival at 12 months after randomisation, assessed using medical records and staff notification after 6 and 12 months
4. Adverse events related to treatment up to 12 months after randomisation, assessed using follow-up case report forms (CRFs), medical records and staff notification after 6 and 12 months:
4.1. Dysphagia
4.2. Symptomatic hypotension
4.3. Dyspnoea
4.4. Gastrointestinal upset
5. Other complications of cirrhosis, assessed using follow-up case report forms (CRFs), medical records and staff notification after 6 and 12 months:
5.1. New onset ascites
5.2. New onset encephalopathy
5.3. Spontaneous bacterial peritonitis
5.4. Hepatocellular carcinoma
5.5. Any renal dysfunction
6. Health-related quality of life, assessed using the EQ-5D-5L at the baseline and after 6 and 12 months
7. Use of healthcare resources, cost and cost-effectiveness, based on:
7.1. Cost per variceal bleeding avoided within 12 months of randomisation, assessed using a follow-up CRF
7.2. Cost per Quality-Adjusted Life Year (QALY) estimated using the EQ-5D-5L
7.3. Cost per death avoided at 12 months, assessed using a follow-up CRF
8. Patient preferences, assessed using qualitative interviews that explore patients' experience of and preferences related to treatment (carvedilol or VBL), providing the basis to describe qualitatively patients' experience of the trial interventions. The first interview will be just after randomisation (ideally wuthin 2 weeks) and the second will be 6-12 months after randomisation.
9. Use of alternative therapies, assessed using a follow-up CRF after 6 and 12 months
10. Crossover therapies, assessed using a follow-up CRF after 6 and 12 months

Completion date
31/05/2024

Eligibility

Key inclusion criteria
1. Liver cirrhosis as defined clinically, radiologically (USS and transient elastography), or on histology
2. Medium varices (Grade II varices that do not flatten on air insufflation and do not occlude the lumen) and large varices (Grade III varices which are larger than Grade II varices and occupy the whole lumen) that have never bled as defined in the BSG guidelines
3. Aged 18 years or older

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group

Adult

Lower age limit
18 years

Sex
All

Total final enrolment
266

Key exclusion criteria
Current exclusion criteria as of 24/11/2021:
1. Age <18 years
2. Pregnant or lactating women
3. Known intolerance or contraindications to beta-blockers including asthma
4. Current or past history of non-selective beta-blocker use (such as carvedilol, nadolol or propranolol)
5. Current or history of variceal band ligation
6. Presence of malignancy or systemic disease that significantly affects 1-year survival
7. Unable to give informed consent
8. Diagnosed with acute alcoholic hepatitis at the point of randomisation
9. Patients with surgical or radiological portosystemic shunts such as transjugular portosystemic stent-shunt (TIPSS)
10. Previous organ transplantation

Previous exclusion criteria:
1. Pregnant or lactating women
2. Known allergy to carvedilol
3. Already on non-selective beta-blockers that could not be discontinued
4. Presence of malignancy or systemic disease that significantly affects 1-year survival
5. Unable to give informed consent
6. Contraindications to beta-blockers including asthma
7. Acute alcoholic hepatitis

Date of first enrolment
22/01/2019

Date of final enrolment
31/08/2022

Locations

Countries of recruitment
United Kingdom

England

Northern Ireland

Scotland

Wales

Study participating centre
Basildon and Thurrock University Hospital NHS Foundation Trust
Nethermayne
Basildon
United Kingdom
SS16 5NL

Study participating centre
Bradford Royal Infirmary
Duckworth Lane
Bradford
United Kingdom
BD9 6RJ

Study participating centre
University Hospital Coventry & Warwickshire NHS Trust
Clifford Bridge Road
Coventry
United Kingdom
CV2 2DX

Study participating centre
County Durham and Darlington NHS Foundation Trust
University Hospital of North Durham
North Road
Durham
United Kingdom
DH1 5TW

Study participating centre
The Newcastle upon Tyne Hospitals NHS Foundation Trust
Freeman Hospital
Newcastle
United Kingdom
NE7 7DN

Study participating centre

Gateshead Health NHS Foundation Trust
Queen Elizabeth Hospital
Sheriff Hill
Gateshead
United Kingdom
NE9 6SX

Study participating centre
Greater Glasgow and Clyde Health Board
GI Offices
4th Floor Walton Building
Glasgow Royal Infirmary
Castle Street
Glasgow
United Kingdom
G4 0SF

Study participating centre
Gloucestershire Hospitals NHS Foundation
Department of Hepatology
Orchard Centre
Gloucestershire Royal Hospital
Gloucester
United Kingdom
GL1 3NN

Study participating centre
Hull University Teaching Hospitals
Gastroenterology and Hepatology Research Department
Level 8 Alderson House
Hull Royal Infirmary
Anlaby Road
Hull
United Kingdom
HU3 2JZ

Study participating centre
Imperial College Healthcare NHS Trust
Hepatology Clinical Research Facility
Liver & Anti-Viral Unit
Imperial College Healthcare NHS Trust
10th Floor
QEQM

St Mary's
South Wharf Road
London
United Kingdom
W2 1NY

Study participating centre
King's College Hospital
Denmark Hill
Brixton
London
United Kingdom
SE5 9RS

Study participating centre
University Hospitals of Leicester NHS Trust
Leicester Royal Infirmary,
Infirmary Square
Leicester
United Kingdom
LE1 5WW

Study participating centre
The Royal Wolverhampton Trust
New Cross Hospital
Wolverhampton
United Kingdom
WV10 0QP

Study participating centre
NHS Tayside
Ninewells Hospital
Dundee
United Kingdom
DD1 9SY

Study participating centre
Nottingham University Hospitals NHS Trust
Queen's Medical Centre
Derby Road
Nottingham

United Kingdom
NG7 2UH

Study participating centre
Portsmouth Hospitals NHS Trust
Queen Alexandra Hospital
Portsmouth
United Kingdom
PO6 3LY

Study participating centre
Royal Devon and Exeter NHS Foundation Trust
Department of Gastroenterology and Hepatology
Barrack Road
Exeter
United Kingdom
EX2 5DW

Study participating centre
Royal Free London
Institute of Liver and Digestive Health
Upper Third Floor
UCL Medical School Royal Free Campus
London
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NW3 2PF

Study participating centre
York Teaching Hospital NHS Foundation Trust
Scarborough Hospital
Woodlands Drive
Scarborough
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YO12 6QL

Study participating centre
South Tyneside District Hospital
Harton Lane
South Shields
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NE34 0PL

Study participating centre
York Teaching Hospital NHS Foundation Trust
York Hospital
Wigginton Road
York
United Kingdom
YO31 8HE

Study participating centre
Birmingham Heartlands Hospital
Bordesley Green E
Birmingham
United Kingdom
B9 5SS

Study participating centre
University Hospitals Birmingham
Liver Unit
Mindelsohn Way
Edgbaston
Birmingham
United Kingdom
B15 2TH

Study participating centre
NHS Lothian
Liver Unit
Royal Infirmary of Edinburgh
Little France
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EH6 4SA

Study participating centre
Leeds Teaching Hospitals NHS Trust
Merville Building
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Beckett Street

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LS9 7TF

Study participating centre
Aintree University Hospital NHS Foundation Trust
Lower Lane
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L9 7AL

Study participating centre
Belfast HSC Trust
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Royal Victoria Hospital
Grosvenor Road
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Study participating centre
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G51 4TF

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L7 8XP

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University Hospital Southampton NHS Foundation Trust
Tremona Road
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SO16 6YD

Study participating centre
Cwm Taf University Health Board
Singleton Hospital
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Swansea
United Kingdom
SA2 8QA

Study participating centre
The Mid Yorks NHS Trust
Pinderfields Hospital
Aberford Road
Wakefield
United Kingdom
WF1 4DG

Study participating centre
Cambridge University Hospitals NHS Foundation Trust
Liver Unit
Addenbrookes Hospital
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
South Tees Hospital NHS Foundation Trust
Endoscopy Centre
James Cook University Hospital

Marton Road
Middlesbrough
United Kingdom
TS4 3BW

Study participating centre
University Hospitals Plymouth NHS Trust
Derriford Hospital
Crownhill Road
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PL6 8DH

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Oxford University Hospitals NHS Foundation Trust
John Radcliffe Hospital
Headley Way
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OX3 9DU

Study participating centre
University Hospitals of Derby and Burton NHS Foundation Trust
Royal Derby Hospital
Uttoxeter Road
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DE22 3NE

Study participating centre
Cardiff and Vale University Health Board
Department of Gastroenterology and Hepatology
Ward A7
University Hospital of Wales
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Cardiff
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CF14 4XN

Study participating centre

Torbay and South Devon NHS Foundation Trust
Torbay Hospital
Lowes Bridge
Torquay
United Kingdom
TQ2 7AA

Study participating centre
Royal Cornwall Hospital Trust
Department of Gastroenterology and Hepatology
Royal Cornwall Hospital
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Sandwell & West Birmingham Hospital NHS Trust
Dudley Road
Birmingham
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B18 7QH

Study participating centre
Sheffield Teaching Hospitals NHS Foundation Trust
Robert Hadfield Level 2
Northern General Hospital
Herries Road
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S5 7AU

Study participating centre
North Bristol NHS Trust
Southmead Hospital
Bristol
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BS10 5NB

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NHS Fife
Victoria Hospital
Hayfield Road
Kirkcaldy
United Kingdom
KY2 5AH

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St. George's University Hospitals NHS Foundation Trust
Blackshaw Road
London
United Kingdom
SW17 0QT

Study participating centre
Northumbria Healthcare Trust
North Tyneside Hospital
Rake Lane
South Shields
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NE29 8NH

Study participating centre
South Tyneside and Sunderland NHS Foundation Trust
South Tyneside Hospital
Harton Lane
South Shields
United Kingdom
NE34 0PL

Study participating centre

Wrightington, Wigan and Leigh NHS Foundation Trust
Royal Albert Edward Infirmary
Wigan lane
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WN1 2NN

Study participating centre
Shrewsbury and Telford Hospitals NHS Trust
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Mytton Oak Road
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SY3 8XQ

Study participating centre
Guy's and St. Thomas NHS Foundation Trust
Guy's and St. Thomas Hospital
Westminster Bridge Road
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United Kingdom
SE1 7EH

Study participating centre
Dudley Group of NHS Hospitals Foundation Trust
Russells Hall Hospital
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DY1 2HQ

Study participating centre
Chelsea and Westminster Hospital Foundation Trust
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369 Fulham Road
Chelsea
London
United Kingdom
SW10 9NH

Study participating centre

Hampshire Hospitals NHS Foundation Trust
Aldermaston Road
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RG24 9NA

Study participating centre
The Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust
The Royal Bournemouth Hospital
Castle Lane East
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BH7 7DW

Study participating centre
Cwm Taf Morgannwg University Health Board
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Study participating centre
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Study participating centre
South Tyneside and Sunderland NHS Foundation Trust
Kayll Road
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SR4 7TP

Study participating centre
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Marlborough Road
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SN3 6BB

Study participating centre
Walsall Healthcare NHS Trust
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WS2 9PS

Sponsor information

Organisation
University of Birmingham

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Government

Funder Name
Health Technology Assessment Programme

Alternative Name(s)
NIHR Health Technology Assessment Programme, Health Technology Assessment (HTA), HTA

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

This trial will include optional consent to allow linkage to patient data available in NHS routine clinical datasets, including primary care data (e.g. Clinical Practice Research Datalink; CPRD, The Health Improvement Network; THIN, QResearch), secondary care data (Hospital Episode Statistics; HES) and mortality data from the Office of National Statistics (ONS) through NHS Digital and other central UK NHS bodies. The consent will also allow access to other new central UK NHS databases that may appear in the future. This will allow us to double check the main outcomes against routine data sources, and extend the follow-up of patients in the trial and collect long-term outcome and health resource usage data without needing further contact with the trial participants. This is important, as it will link a trial of treatments that may become a clinical standard of care to long-term outcomes that are routinely collected in clinical data, but which may not be collected during the period of the trial.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		16/04/2025	17/04/2025	Yes	No
Protocol article	protocol	01/04/2019	24/05/2019	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol file	version 4.0	03/05/2023	28/04/2025	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes