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Beta-blockers or placebo for primary prophylaxis of oesophageal varices trial

Submission date
02/11/2018

Recruitment status
No longer recruiting

Registration date
04/12/2018

Overall study status
Ongoing

Last Edited
27/04/2026

Condition category
Digestive System

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

Plain English summary of protocol

Background and study aims
Cirrhosis or liver scarring is an important problem in healthcare in the United Kingdom. 60,000 patients are living with this disease and about 11,000 people every year will die because of it. There are several ways in which patients with this severe form of liver disease become unwell or die and bleeding from the oesophagus or stomach is one. Cirrhosis causes pressure changes inside the abdomen and swelling of veins in the oesophagus (called varices) which can bleed catastrophically. When varices are large they need to be treated with medication called beta-blockers to reduce the pressure in the varices. If the varices are small, it is not certain if they need to be treated with beta-blockers and this study aims to address this uncertainty.

Who can participate?
Patients aged over 18 with cirrhosis and small varices without evidence of previous bleeding

What does the study involve?
Patients are randomly allocated to be treated with either beta-blockers or a placebo (dummy drug). They are observed closely for 3 years for bleeding from their varices or other complications of cirrhosis or side effects of taking medication. This is the amount of time needed to observe for bleeding when the varices are small. The patients are reviewed every 6 months including assessing the varices by a camera test called an endoscopy at the beginning and each year until the study is finished. The study also assesses the barriers and facilitators of doctors in primary care (such as General Practitioners) in adjusting the dose of the tablets to improve treatment effects, and assesses patients' views on taking part in the study, and whether the side effects justify the potential benefits of reducing the risk of bleeding. The impact of beta-blockers on the overall costs to the NHS of caring for people with cirrhosis during the study is measured. The impact of treatment on costs, mortality and quality of life over a patient's lifetime is estimated, to assess whether any increased costs are justified by better outcomes for patients and represent good value for money for the NHS budget.

What are the possible benefits and risks of participating?
When the study is complete, the results could help advance the use of beta blockers in patients with damaged livers and small oesophageal varices. This would mean that beta-blocker use could be extended to a wider patient population to which there is currently no agreed treatment

available. At a patient level, should the patient be allocated to the beta blocker, there is the potential that worsening of varices and progression to variceal bleeding may be prevented or slowed down. This study is relatively non-invasive and uses a well-established drug, therefore few potential risks are foreseen. All tests, apart from a quality of life questionnaire, are standard of care procedures so the usual precautions and standard clinical protocols will be followed. Endoscopies/gastroscopies will be performed by experienced clinicians as standard of care practice following established guidelines. The participants will not know which treatment they are receiving but procedures are in place to reveal this if there are concerning side effects. The researchers do not foresee any reason for the study procedures to cause harm or distress. Should there be any concern or sign of distress being caused due to study involvement, reasons for this will be explored, and referrals to appropriate services made. The study is being carried out in experienced specialist clinical departments with teams that are experienced in research.

Where is the study run from?
King's College Hospital (UK)

When is the study starting and how long is it expected to run for?
September 2018 to December 2026

Who is funding the study?
NIHR Health Technology Assessment Programme (UK)

Who is the main contact?
Dr Vishal Patel / Dr Mark McPhail (Chief Investigators)
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Contact information

Type(s)
Public, Scientific, Principal investigator

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Type(s)
Public, Scientific, Principal investigator

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kch-tr.boppptrial@nhs.net

Additional identifiers

ClinicalTrials.gov (NCT)
NCT03776955

Clinical Trials Information System (CTIS)
2018-002509-78

Protocol serial number
HTA 17/32/04; 1.0

Study information

Scientific Title
Beta-blockers Or Placebo for Primary Prophylaxis of oesophageal varices (BOPPP): a blinded, multi-centre, clinical effectiveness and cost-effectiveness randomised controlled trial

Acronym
BOPPP

Study objectives
Treating patients with small varices with NSBB for primary prophylaxis of variceal bleeding is clinically and cost-effective.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 20/03/2019, NHS HRA Yorkshire and the Humber – Leeds West (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ; 0207 104 8018; nrescommittee.yorkandhumber-leedswest@nhs.net), ref: 19/YH/0015.

Primary study design
Interventional

Study design
Multicentre blinded (participant, clinician and analyst) randomized controlled trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Participants with cirrhosis and small varices without evidence of previous bleeding

Interventions
Current interventions as of 24/04/2026:

Oral carvedilol 6.25 mg to 12.5 mg once daily vs oral placebo 1 to 2 tablets once daily

Patients who are recruited to the study with small varices will be randomised to either beta-blockers (carvedilol) or a placebo. The randomisation sequence will be generated in an ongoing manner using varying permuted blocks of size 4 to 12, within each site in a 1:1 ratio (Carvedilol: Placebo).

Participants will be observed closely for up to 3 years for bleeding from their varices or other complications of cirrhosis or side effects of taking medication. This is the amount of time needed to observe for bleeding when the varices are small. The trialists will review the patients every 6 months including assessing the varices by a camera test called an endoscopy at the beginning and of each year until the study is finished.

During the study patients will be involved with the conduct and management of the research, and the trialists will feedback to recruited patients the results at the end. They will assess the barriers and facilitators of doctors in primary care - such as General Practitioners - in adjusting the dose of the tablets to optimise treatment effects, and assess patients' views on taking part in the trial, and whether the side effects justify the potential benefits of reducing the risk of bleeding. It is estimated that this risk could be reduced from 20% of patients having significant bleeding to 10% over 3 years.

The trialists will measure the impact of beta-blockers on the overall costs to the NHS of caring for people with cirrhosis during the trial. They will then assess the impact of treatment on both mortality and quality of life using a combined measure, the Quality Adjusted Life-Year (QALY). They will use a mathematical prediction model to estimate the impact of treatment on costs, mortality and quality of life over a patient's lifetime. They will assess whether any increased costs are justified by better outcomes for patients and represent good value for money for the NHS budget.

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Intervention Type
Drug

Phase
Phase IV

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

Primary outcome(s)
Current primary outcome measure as of 29/08/2024:
All-cause decompensation will be assessed through follow-up visits at 6, 12, 18, 24, 30, and 36 months post-randomisation, and also ongoing forms, adverse event forms and patient medical records. Each component (variceal haemorrhage, new or worsening ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, increases in Child-Pugh or MELD scores, and liver-related death) will be evaluated at these time points as well as continuously. The event time is defined as the period from randomisation to the first occurrence of any of the all-cause decompensation components listed. For those without events, data will be censored at the last follow-up or medical record review. This approach aligns with the methods used for other primary and secondary outcomes in the current study record, ensuring consistency and comprehensive data collection.

Previous primary outcome measure:
Time to first variceal haemorrhage, as defined by Baveno IV criteria. Variceal bleed assessed by endoscopy at 6, 12, 18, 24, 30 and 36 months with additional measurement at any ad hoc bleed event (i.e. SAE) and at study completion.

Key secondary outcome(s)
1. Mortality at 6 weeks, 6, 12, 18, 24, 30 and 36 months with additional measurement at any ad hoc bleed event (i.e. SAE) and at study completion
2. Number of hospitalisations at 6 weeks, 6, 12, 24, and 36 months
3. Oesophageal varices grade, based on UK guidelines of 1 (varices that collapse to inflation of

the oesophagus with air), 2 (between grade 1 and 3) and 3 (varices which are large enough to occlude the lumen), at 12, 24, and 36 months
4. Cirrhosis severity, assessed using the Child-Pugh Score for Cirrhosis Mortality at 6, 12, 18, 24, 30 and 36 months with additional measurement at any ad hoc bleed event (i.e. SAE)
5. Severity of end-stage liver disease, assessed using the Model for End-Stage Liver Disease (MELD) score at 6, 12, 18, 24, 30 and 36 months with additional measurement at any ad hoc bleed event (i.e. SAE)
6. Development of hepatic decompensation at 6, 12, 18, 24, 30 and 36 months with additional measurement at any ad hoc bleed event (i.e. SAE), measured using the following:
6.1. Presence of spontaneous bacterial peritonitis (ascitic fluid cell PMN cell count >250/mm3)
6.2. New hepatic encephalopathy (defined by West-Haven Grade >1 [overt HE])
6.3. New or worsening ascites defined by clinical examination or ultrasound
7. Healthcare usage at 1 week, 6, 12, 18, 24, 30 and 36 months with additional measurement at any ad hoc bleed event (i.e. SAE) and at study completion; cost of treatment and quality adjusted life expectancy (QALE) across trial arms with adjustment for pre-specified baseline characteristics
8. Quality of life assessed using EQ-5D-5L score at randomisation, 6, 12, 18, 24, 30 and 36 months with additional measurement at any ad hoc bleed event (i.e. SAE)

Completion date
31/12/2026

Eligibility

Key inclusion criteria
Current key inclusion criteria as of 24/04/2026:

1. Age >18 years
2. Cirrhosis and portal hypertension, defined by any two of the following:
2.1. Characteristic clinical examination findings; one or more of:
2.1.1. Jaundice, ascites, caput medusae, spider naevi, palmar erythema, asterixis
2.2. Characteristic liver function tests, haematological panel and coagulation profile abnormalities
2.2.1. hyperbilirubinaemia (serum total bilirubin > 30 umol/l)
2.2.2. thrombocytopenia (platelet count <120 x109 / L)
2.2.3.international normalised raio (INR) > 1.5
NB These blood tests may be normal in well compensated cirrhosis – if cirrhosis is confirmed on other investigations, normal blood tests suggest well compensated disease.
2.3. Characteristic radiological findings; one or more of:
2.3.1. Heterogeneous, small liver with irregular contour
2.3.2. Splenomegaly
2.3.3. Ascites
2.3.4. Varices
2.3.5. Recanalized umbilical vein
2.4. Fibrosis score > stage 4 on liver biopsy
2.5. FibroScan liver stiffness measurement >15 kPa without other explanation
3. Small oesophageal varices – defined as <5mm in diameter or completely disappear on moderate insufflation at gastroscopy within the last 3 months
4. Not received a beta-blocker in the last week
5. Capacity to provide informed consent

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5. Capacity to provide informed consent
6. Fluent in the English Language

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
120 Years

Sex
All

Total final enrolment
763

Key exclusion criteria

Current key exclusion criteria as of 24/04/2026:

1. Non-cirrhotic portal hypertension
2. Medium/large oesophageal varices (current or history of)
3. Isolated gastric, duodenal, rectal varices with or without evidence of recent bleeding
4. Previous variceal haemorrhage
5. Known intolerance to beta blockers
6. Contraindication to beta blocker use:
6.1. Heart rate <50 bpm
6.2. Known 2nd degree or higher heart block
6.3. Sick sinus syndrome
6.4. Systolic blood pressure <85mm Hg
6.5. Chronic airways obstruction (asthma/COPD)
6.6. Floppy Iris Syndrome
6.7. CYP2D6 Poor Metaboliser
6.8. Cardiogenic shock
6.9. History of severe hypersensitivity reaction to beta blockers
6.10. Untreated phaeochromocytoma
6.11. Severe peripheral vascular disease
6.12. Prinzmetal angina
6.13. NYHA IV heart failure
7. Unable to provide informed consent
8. Child Pugh C cirrhosis
9. Already receiving a beta-blocker for another reason that cannot be discontinued
10. Pregnant or lactating women
11. Graft cirrhosis post liver transplantation
12. Evidence of active malignancy without curative therapy planned
13. Women of childbearing potential not willing to use adequate contraception during the period of IMP dosing, if relevant
14. Patients who have been on a CTIMP within the previous 3 months
15. Clinical symptoms consistent with COVID-19 (a high temperature, a new continuous cough or a loss or change to sense of smell or taste) at the time of randomisation

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Date of first enrolment
01/04/2019

Date of final enrolment
19/07/2024

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
King's College Hospital
King’s Health Partners Clinical Trials Office
Denmark Hill
London
England
SE5 9RS

Sponsor information

Organisation
King’s College Hospital NHS Foundation Trust

ROR
https://ror.org/01n0k5m85

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

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		16/04/2024	17/04/2024	Yes	No
HRA research summary			28/06/2023	No	No
Other publications	results of the embedded qualitative study	03/02/2022	04/02/2022	Yes	No
Other publications	results of the embedded qualitative study	17/10/2022	18/10/2022	Yes	No
Plain English results	version 3.0	31/05/2023	29/08/2024	No	Yes
Protocol file	version 4.0	31/05/2023	29/08/2024	No	No