Study protocol for a randomised controlled trial of carvedilol versus variceal band ligation in primary prevention of variceal bleeding in liver cirrhosis (CALIBRE trial)

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ABSTRACT

Introduction Liver cirrhosis is the fifth largest cause of adult deaths, and a major complication, variceal bleeding is associated with a 1-year mortality of 40%. There is uncertainty on the first-line therapy for prevention of variceal bleeding owing to a lack of adequately powered trials comparing non-selective beta blockers, in particular carvedilol, with variceal band ligation.

Methods and analysis CALIBRE is a multicentre, pragmatic, randomised controlled, open-label trial with an internal pilot. The two interventions are carvedilol 12.5 mg od or variceal band ligation (VBL). Patients with liver cirrhosis and medium to large oesophageal varices that have never bled are eligible for inclusion. The primary outcome is any variceal bleeding within 1 year of randomisation. Secondary endpoints include time to variceal bleed, mortality, transplant-free survival, adverse events, complications of cirrhosis, health-related quality of life, use of healthcare resources, patient preference and use of alternative or crossover therapies. The sample size is 2630 patients over a 4-year recruitment period, across 66 hospitals in the UK.

Ethics and dissemination The study has been approved by a National Health Service (NHS) Research Ethics Committee (REC) (reference number 18/NE/0296). The results of this trial will be submitted for publication in a peer reviewed journal. Participants will be informed via a link to a preview of the publication. A lay summary will also be provided via email or posted to participants prior to publication (ISRCTN reference number: 73887615).

INTRODUCTION

Existing research and current practice Liver disease is the fifth largest cause of adult deaths,1,2 with mortality predicted to double in 20 years.3 Patients with liver disease die younger with the average age of death of 59 years, compared with 82–84 years for heart and lung disease and stroke.1 One of the major complications of cirrhosis is portal hypertension and variceal bleeding. In patients with cirrhosis, varices develop at a rate of 5% per year with 10 year cumulative incidence of 44%.3 At least 3000 patients are admitted to hospital in England per year with variceal bleeding, with inpatient mortality of 15% and 1-year mortality of up to 40%. Increased hospitalisation results in increased use of secondary care and substantial healthcare costs. Since many patients are of working age there are also significant societal implications. Therefore, reducing the risk of the first variceal bleed (primary prevention) is an important clinical and economic goal.

At present, there are two options for primary prevention of variceal bleeding, namely non-selective beta-blockers and variceal band ligation. Beta-blockers used for portal hypertension in the UK are propranolol and carvedilol. A Cochrane review and meta-analysis of 19 trials (with a total of 1504 patients) comparing variceal band ligation versus beta-blockers showed a reduced risk of variceal bleeding with variceal band ligation (risk ratio, 0.67; 95% CI 0.46 to 0.98) with no effect on survival.4 However, the overall quality of evidence was low to moderate. When only high quality trials (seven trials, 713 patients) with minimal bias and sufficient follow-up were studied, the difference in bleeding rates was no longer evident. In another meta-analysis, although adverse events were more frequent with beta-blockers (OR 2.61, 95% CI 1.60 to 4.40, p<0.0001), fatal adverse effects were significantly lower with non-selective beta-blockers (NSBB; OR...
guidelines. Therefore, there is at present disparity in the BSG guidelines are similar to those of international
treatment, whereas the BSG suggests banding if the patient
is intolerant of beta-blockers. The recommendations of
the current guidelines with regard to first-line therapy for
primary prevention.
Many specialists have significant concerns about the
adverse effects of variceal band ligation, in particular
the risk of banding induced bleeding. There are also
concerns about the use of beta-blockers in patients with
advanced cirrhosis with some studies showing higher
mortality, while others report improved survival. In
particular with carvedilol, improved survival has been
suggested. None of these studies are randomised trials
and are therefore limited by their designs and the poten-
tial for confounding and other biases.

Data on cost effectiveness in the context of primary
prevention are available from just one publication. This
suggested beta-blockers have reduced overall costs
compared with varicose band ligation. However, in the
2016 National Institute for Health and Care Excellence
(NICE) cirrhosis guidelines, after extrapolation of the
meta-analysis showing less bleeding with varicose band
ligation, varicose band ligation was found to be more cost
effective. There are no cost effectiveness studies along-
side a randomised controlled trial (RCT) comparing

carvedilol with varicose band ligation.

A large RCT at this time would help clinicians decide
on the best treatment in terms of clinical and cost-effec-
tiveness, as the current evidence is based on underpow-
ered and low-quality trials as detailed above.

Carvedilol has been selected as the beta-blocker for
this trial. Carvedilol is a well-tolerated non-selective beta-
blocker which reduces portal blood flow, and in addition
has vasodilating actions due to alpha-1 receptor blockade.
The latter helps to reduce portal pressure further, mainly
through the effects on intrahepatic resistance. Haemo-
dynamic studies demonstrate a greater reduction in
portal pressure than propranolol, and carvedilol can be
effective even in patients not responding to proprano-
olol. Carvedilol also has pleiotropic anti-inflammatory,
antioxidant and antifibrotic properties along with other
roles in enhancing insulin sensitivity and improving mito-
chondrial function that may provide additional bene-
fits in patients with cirrhosis. Propranolol is not always
well tolerated, and a third of patients fail to achieve a
satisfactory reduction in portal pressure. Nadolol is not
commonly used in the UK and has similar haemodynamic
efficacy as propranolol. Therefore, there is considerable
interest in alternatives to propranolol/nadolol, such as
carvedilol.

There are only two RCTs of carvedilol versus varicose
band ligation in primary prevention. The first trial from the UK of 152 patients showed significantly reduced
bleeding in the carvedilol arm (10% vs 23%, relative
hazard 0.41; 95% CI 0.19 to 0.96), with no apparent
effect on survival (35% vs 37%, relative hazard 0.91; 95%
CI 0.53 to 1.55). The second trial from Pakistan of 168
did not show any differences in bleeding (8.5% vs 6.9%,
relative hazard 1.61; 95% CI 0.27 to 9.69) or
mortality (12.8% vs 19.5%, relative hazard 1.53; 95% CI
0.71 to 3.30). In the first trial, patients were randomised
after endoscopy with delays in the first banding session,
leading to a lead time bias against band ligation as a second
endoscopy session was required. CALIBRE endeavours to
minimise this bias by randomisation mainly at the time of
endoscopy. Compliance with varicose band ligation was
better in the second trial, but significantly more patients
had viral hepatitis than alcohol-related cirrhosis which
does not reflect the disease burden of the UK. A recent
randomised placebo controlled trial of 140 patients
showed that carvedilol reduced progression of varices
over a minimum of 24 months follow-up in patients with
small varices, with no difference in bleeding or survival.
Furthermore, the Mayo group recently performed a
network meta-analysis which recommends further larger
prospective trials of carvedilol in cirrhosis to investigate
its potential benefits.

The results of this trial will provide high-quality data
with adequate power and follow-up. If carvedilol is found
to be superior to varicose band ligation, then it will
become first-line therapy in primary prevention. The trial
will also provide a unique cohort for extended follow-up,
since consent will be sought to use routine long-term
data. This will help us understand the long-term impact
of beta-blockers. It is plausible that survival may be better
with carvedilol than varicose band ligation as suggested
in a study of beta-blockers in secondary prevention. If
this is true, it will lead to a paradigm shift in primary
prevention of varicose bleeding. Such a finding will also
encourage further translational research into the under-
lying mechanisms, which could help stratify patients most
likely to benefit from beta-blockers and offer alternative
therapies to non-responders.

Beta-blockers as first-line therapy in primary preven-
tion will lead to a large change in practice as NICE
guidance presently recommends varicose band ligation.
Beta-blockers require much less National Health Service
(NHS) resources than varicose band ligation for primary
prevention, which usually requires at least 3–5 treatments
to eradicate varices followed by indefinite endoscopic
surveillance. There is no requirement for patients on
carvedilol for primary prevention to undergo endoscopic

Trial rationale

The main focus of the research is the comparison of
beta-blockers and varicose band ligation in the preven-
tion of the first varicose bleed. There have been two
important guidelines published in the UK in 2015–2016
from NICE and the British Society of Gastroenterology
(BSG). NICE favours banding for primary preven-
tion, whereas the BSG suggests banding if the patient
is intolerant of beta-blockers. The recommendations of
the BSG guidelines are similar to those of international
guidelines. Therefore, there is at present disparity in
the current guidelines with regard to first-line therapy for
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to eradicate varices followed by indefinite endoscopic
surveillance. There is no requirement for patients on
carvedilol for primary prevention to undergo endoscopic
surveillance. Bed pressures for other elective procedures could be eased and waiting times improved.

**Internal pilot trial**
The first 12 months of the CALIBRE trial will constitute an internal pilot, to assess and confirm logistics, and to determine if it is both feasible and practical for the trial to continue. Integrated qualitative research with patients and staff will contribute to assessments of feasibility and acceptability as detailed later. The qualitative research could lead to changes in the trial protocol as necessary to minimise potential barriers to recruitment and facilitate recruitment in the main trial. The results of the internal pilot will be assessed by the Data Monitoring Committee (DMC), Trial Steering Committee (TSC) and the funder.

**Primary objective**
The primary aim of this study is 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.

**Secondary objectives**
These include the effect of carvedilol and variceal band ligation on survival, development of other complications of cirrhosis and adverse events. The study will also investigate cost-effectiveness, patient preference and use of alternative or cross over therapies.

**METHODS AND ANALYSIS**

**CALIBRE trial design**
CALIBRE is a multicentre, pragmatic, randomised controlled, open-label trial with an internal pilot. Approximately 66 Acute NHS Trusts/Health Boards in the UK will be involved in trial recruitment. The detailed trial design is described below.

**Eligibility criteria**
To be eligible for CALIBRE, a patient must have cirrhosis, and medium varices (Grade II varices that do not flatten on air insufflation and do not occlude the lumen) or large varices (Grade III varices which are larger than the largest varix (Grade II or Grade III), age of patient decompensation (ascites or encephalopathy), size of the largest varix (Grade II or Grade III), 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.

**Trial treatment/intervention**

**Carvedilol**
Participants will be prescribed 12.5 mg od. They will be seen in a follow-up clinic at 4 weeks to assess for any short-term adverse events such as symptomatic hypotension, gastrointestinal side effects like nausea, swelling of hands and feet, blurred vision, lethargy, headache, sexual dysfunction and shortness of breath. These patients will not be offered routine endoscopic surveillance, as per standard of care. Participants will be asked about adherence with their trial medication at each follow-up visit and their response documented in the medical notes and subsequently transcribed onto the Follow-Up Case Report Forms (CRFs).
Tripathi D, et al. BMJ Open Gastro 2019;6:e000290. doi:10.1136/bmjgast-2019-000290

Figure 1  Trial schema.

Variceal band ligation
The procedure will be performed as per the BSG guidelines. Adherence to variceal band ligation will be documented on the Follow-Up CRFs using information available in the participant’s medical notes.

Treatment modification
Figure 5 outlines the process for treatment modifications in the event of intolerance. At clinician’s discretion, participants that are intolerant of carvedilol or variceal band ligation can be crossed over to the other arm at any point.

Outcome measures and study procedures
Primary outcome
Any variceal bleeding within 1 year of randomisation. The first variceal bleed is defined as hematemesis and/or melena with either: (1) endoscopic evidence of variceal bleeding or stigmata of recent haemorrhage and at least a 2 g/L reduction in haemoglobin within 24 hours of admission or (2) massive upper gastrointestinal bleeding leading to death. The definition includes bleeding from banding ulceration.

Secondary outcomes
1. Time to first variceal bleed in days (from randomisation).
2. Mortality at 1 year (from randomisation):
   1. All-cause mortality.
   2. Liver related mortality.
   3. Cardiovascular mortality.
3. Transplant free survival at 1 year (from randomisation).
4. Adverse events related to treatment (up to 12 months after randomisation):
Figure 2  Consent process (planned endoscopy where no diagnosis of varices has yet been made).

1. Dysphagia requiring discontinuation of treatment.
2. Symptomatic hypotension requiring change in treatment.
3. Dyspnoea.
4. Gastrointestinal upset.
5. Other complications of cirrhosis:
   1. New onset ascites confirmed clinically or on imaging and graded as per International Club of Ascites recommendations.  
2. New onset encephalopathy defined using West Haven Criteria.  
3. Spontaneous bacterial peritonitis.
4. Hepatocellular carcinoma.
5. Any renal dysfunction as per International Club of Ascites—Acute Kidney Injury (ICA-AKI) definitions.
6. Health-related quality of life (EQ-5D-5L) from randomisation to 6 and 12 months.
7. Use of healthcare resources, costs and cost-effectiveness based on the outcomes of cost per variceal bleeding avoided within 1 year of randomisation, cost per Quality-adjusted Life-year (QALY) estimated using the EQ-5D-5L and cost per death avoided at 1 year.

8. Patient preference. We will conduct qualitative interviews with patients and staff during the pilot phase. These interviews will explore patients’ experience of and preferences related to treatment (Carvedilol or VBL). This will provide the basis to describe qualitatively patients’ experience of the trial interventions. These qualitative data will complement quantitative outcome assessment.

9. Use of alternative therapies.

10. Crossover therapies.

Schedule of assessments
This is detailed in table 1.

Statistical considerations
Sample size
The sample size calculation has been based on published data from both a Cochrane review and meta-analysis of...
Figure 4  Consent process following an inpatient referral.

Analysis of outcome measures

A separate Statistical Analysis Plan (SAP) will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of these analyses is given below.

The primary comparison groups will be composed of those randomised to carvedilol versus those randomised to variceal band ligation. All analyses will be based on the intention-to-treat principle, that is, all participants will be analysed in the group to which they were allocated irrespective of compliance with the randomised allocated treatment or other protocol violations. For all major outcomes, summary statistics and differences between groups (eg, mean differences, relative risks) will be presented, with 95% CIs and p values from 2-sided tests also given. Treatment effects will be adjusted for the minimisation variables. P<0.05 will be considered statistically
Figure 5  Process for treatment modifications in the event of intolerance.
significant and there will be no adjustment for multiple testing.

**Primary outcome measures**

The primary outcome measure of the study is variceal bleeding within the first year after randomisation. This outcome is a binary outcome (i.e., yes/no). The number and percentage of participants experiencing variceal bleeding within 1 year of randomisation will be reported by treatment group. An adjusted relative risk and 95% CI will be estimated from a log-binomial model to take into account the minimisation variables.

The p value from the associated $\chi^2$ test will be produced and used to determine statistical significance.

**Secondary outcome measures**

The secondary outcomes for the trial include continuous, categorical and time-to-event data items.

**Time-to-event outcomes (eg, time to first variceal bleed)**

Time to event outcomes will be compared between treatment groups using standard survival analysis methods. Kaplan-Meier survival curves will be constructed for visual presentation of time-to-event comparisons. Cox proportional hazard models will be fitted to obtain adjusted treatment effects which will be expressed as HRs with 95% CIs.

**Categorical outcomes (eg, dysphagia requiring discontinuation of treatment)**

For binary secondary outcomes, the number and percentage of participants reporting each outcome will be reported by treatment group. An adjusted relative risk and 95% CI will be estimated from a log-binomial regression model. The p value from the associated $\chi^2$ test will be produced and used to determine statistical significance.

**Continuous outcomes (EQ-5D-5L)**

Continuous outcomes will be reported using means and SD. The EQ-5D-5L will be compared between treatment groups with adjusted mean differences and 95% CIs estimated using linear regression models. Change in EQ-5D-5L score from baseline will also be modelled.
Economic evaluation
A separate Health Economics Analysis Plan will be produced, providing a comprehensive description of the planned economic evaluation. Briefly, a within-trial analysis will be conducted from a National Health Service and Personal Social Services (NHS/PSS) perspective to calculate cost per variceal bleed avoided, cost per QALY gained and cost per death avoided. If evidence from the trial shows differences in terms of important outcomes (eg, rebleeding or mortality) that have significant cost or outcome implications beyond the trial period, a model-based economic evaluation will additionally be conducted.

Analysis of qualitative data
During the internal pilot, interviews will be recorded with the consent of participants and transcribed clean verbatim for analysis. Analysis will be conducted with reference to recordings, transcripts and field notes taken at the time of data collection. A thematic analysis of content will be informed by the Framework analytical approach.24 Following initial familiarisation with the interview data, development of thematic frameworks and data coding will proceed in an iterative manner. Data collection and analysis will run concurrently so that emergent analytical themes can inform further data collection, and particularly comparative analytical questioning between patients allocated to carvedilol and variceal band ligation.

Planned subgroup analyses
Subgroup analyses will be limited to the same variables used in the minimisation algorithm. Subgroup analyses will be limited to the primary outcome. Tests for statistical heterogeneity will be performed prior to any examination of effect estimates within subgroups. The results of subgroup analyses will be treated with caution and will be used for the purposes of hypothesis generation only.

Missing data and sensitivity analyses
Every attempt will be made to collect full follow-up data on all study participants, and it is thus anticipated that missing data will be minimal. Participants with missing primary outcome data will not be included in the primary analysis in the first instance. This presents a risk of bias, and sensitivity analyses will be undertaken to assess the possible impact of the risk. In brief, this will include worst-case assumptions and/or multiple imputation methods. Further sensitivity analyses will include an analysis on the per-protocol population and an unadjusted analysis. Any sensitivity analyses will not, irrespective of their differences, supplant the planned primary analyses. Full details will be included in the SAP.

Planned interim analyses
Interim analyses of major outcome measures and safety data will be conducted and provided in strict confidence to the independent DMC. Details of the agreed plan will be written in the SAP.

Planned final analyses
The final analysis for the study will occur once all participants have completed the 1-year assessment, and the corresponding outcome data have been validated as ready for analysis.

ETHICS AND DISSEMINATION
Ethical considerations
CALIBRE was granted ethical approval by the North East—York Research Ethics Committee (REC), reference number: 18/NE/0296. The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research 2017, the applicable UK Statutory Instruments (which include the Medicines for Human Use Clinical Trials 2004 and subsequent amendments and current UK Data Protection Regulations). This trial will be carried out under a Clinical Trial Authorisation (CTA) in accordance with the Medicines for Human Use Clinical Trials regulations.

Dissemination
Results of this trial will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the CI or delegate and authorship will be determined by the trial publication policy. Participants will be informed of the outcome of the trial via a link to a preview of the publication. A lay summary will also be provided via email or posted to participants prior to publication.

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Contributors
DT is Chief Investigator and involved in all aspects of protocol design and lead author of the manuscript. PH, PR, IR and JF assisted in design of the protocol in particular clinical aspects. PD is lead for patient involvement in protocol design, with particular contributions to clinical aspects and consent pathways. In this role, he was assisted by JWF. JM is lead for the qualitative aspects of the protocol. In this role, he was assisted by CP. SJ is lead for health economic aspects of the protocol. PB is involved in all aspects of protocol design, with particular attention to methodology. KH is lead for the statistical aspects of the protocol. MG, GS and KA reviewed the protocol with particular attention to management and operations. All authors reviewed and approved the final manuscript.

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Competing interests
None declared.
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