BMJ Open

Endoscopic variceal ligation combined with carvedilol versus endoscopic variceal ligation combined with propranolol for the treatment of oesophageal variceal bleeding in cirrhosis: study protocol for a multicentre, randomised controlled trial

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To cite: Li Y, Du L, Zhang S, *et al*. Endoscopic variceal ligation combined with carvedilol versus endoscopic variceal ligation combined with propranolol for the treatment of oesophageal variceal bleeding in cirrhosis: study protocol for a multicentre, randomised controlled trial. *BMJ Open* 2025;**15**:e093866. doi:10.1136/bmjopen-2024-093866

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-093866).

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Received 18 September 2024
Accepted 14 March 2025

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ABSTRACT

Introduction Liver cirrhosis and its severe complication, oesophageal variceal bleeding (EVB), pose significant health risks. Standard treatment for EVB combines non-selective beta-blockers (NSBB) with endoscopic variceal ligation (EVL). Carvedilol, an NSBB with additional benefits, is preferred for compensated cirrhosis. However, no randomised controlled trial (RCT) has compared carvedilol with propranolol, a conventional NSBB, in combination with EVL for secondary prophylaxis. This study aims to compare the effectiveness and safety of these treatments in preventing variceal rebleeding or death in patients with cirrhosis and EVB.

Methods and analysis This multicentre, RCT is scheduled to begin in December 2024, with recruitment and follow-up continuing until December 2026. Eligible participants are patients with liver cirrhosis and EVB. Participants are randomly assigned in a 1:1 ratio to receive EVL combined with either carvedilol or propranolol. The primary endpoint is the incidence of variceal rebleeding or all-cause death. Secondary endpoints include all-cause death, liver-related death, each of the complications of portal hypertension (overt ascites, overt hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, portal vein thrombosis), hepatocellular carcinoma, changes in liver function

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Multicentre randomised controlled design across diverse clinical settings enhances the generalisability of findings and minimises selection bias.
⇒ Stratified randomisation based on disease severity and centre ensures balanced distribution of confounding variables between treatment groups.
⇒ Large sample size of 524 patients is adequately powered to detect significant differences in primary and secondary outcomes between carvedilol and propranolol.
⇒ Comprehensive evaluation of endpoints, including Child-Pugh and Model for End-Stage Liver Disease scores, liver and spleen stiffness, and complications of portal hypertension, allows for an in-depth assessment of treatment effects.
⇒ 1-year follow-up period may not capture long-term efficacy and safety outcomes, potentially limiting the understanding of sustained benefits and adverse events.

(assessed by Child-Pugh and Model for End-Stage Liver Disease scores), changes in liver stiffness, changes in spleen stiffness, and adverse events. Subgroup and sensitivity analyses will be conducted to evaluate the consistency and robustness of the treatment effects. A total sample size of 524 patients (262 per group) is required to detect a significant difference between the treatment arms.

Ethics and dissemination The study protocol has been approved by the ethics committee of the First Hospital of China Medical University (No. 2024-656-2). The study will follow the Declaration of Helsinki and Good Clinical Practice guidelines. The findings of this trial will be disseminated through peer-reviewed publications, conference presentations and healthcare professionals to guide future clinical practice.

Trial registration number Chinese Clinical Trial Registry (Registration number: ChiCTR2400089692).

INTRODUCTION

Liver cirrhosis poses a substantial global health challenge due to complications arising from portal hypertension, leading to significant morbidity and mortality.[1–3] Among these complications, oesophageal variceal bleeding (EVB) is one of the most severe, carrying a considerable risk of death.[3–5] For decades, non-selective beta-blockers (NSBB) have been a cornerstone in managing clinically significant portal hypertension because of their efficacy in reducing portal pressure.[6 7] The combination of NSBB with endoscopic variceal ligation (EVL) has proven more effective than other treatments in preventing rebleeding, establishing it as the recommended standard of care for patients with EVB.[8]

Carvedilol, an NSBB with additional alpha-1 adrenergic blockade, has demonstrated superior haemodynamic benefits over other treatments in several randomised controlled trials (RCTs) and meta-analyses.[9–11] These studies have shown that carvedilol, compared with placebo, traditional NSBB, EVL, or no treatment, not only prevents clinical decompensation, ascites and bleeding but also improves survival rates.[9 12] Consequently, the Baveno VII guidelines recommend carvedilol as the preferred NSBB for managing compensated cirrhotic portal hypertension.[13]

However, early studies indicated that carvedilol might exacerbate sodium retention in about one-third of patients with ascites.[14] Thus, preliminary clinical trials recommended limiting carvedilol use to compensated patients and did not advocate its use for secondary prophylaxis of variceal bleeding. Notably, these adverse events were primarily observed in initial ‘dose-exploring’ studies using high doses of carvedilol, where higher doses of carvedilol were tested. Meanwhile, the side effects were generally mild and transient, resolving with dose reduction while still achieving significant reductions in portal pressure.

Further RCTs focusing on primary prophylaxis of variceal bleeding in high-risk patients, many of whom had ascites, demonstrated that carvedilol effectively prevented bleeding without adverse effects.[15 16] These studies also showed high efficacy in preventing bleeding and raised no alarms on adverse effects in patients with ascites. Additionally, a recent retrospective study by Jachs *et al* highlighted several advantages of carvedilol in secondary prophylaxis, including a higher proportion of patients achieving a favourable haemodynamic response, which correlated with improved clinical outcomes such as reduced bleeding risk and enhanced survival.[17]

Despite these promising findings, no RCT has directly compared the efficacy of carvedilol with conventional NSBB, such as propranolol, in combination with EVL for secondary prophylaxis.[18] This study aims to address this gap by comparing the effectiveness of carvedilol and propranolol in preventing variceal rebleeding or death, to determine the optimal pharmacological strategy for secondary prophylaxis.

METHODS AND ANALYSIS

Trial design and setting

This is a prospective, multicentre, randomised, open-label, parallel-group study. The study begins with a screening phase, during which informed consent is obtained and baseline assessments are conducted. Participants are then randomly assigned (1:1) to receive EVL combined with either carvedilol or propranolol. Following randomisation, participants enter a 12-month follow-up period with visits scheduled every 3 months. The primary endpoint is the time from randomisation to first variceal rebleeding or death. Secondary endpoints include all-cause death, liver-related death, each of complications of portal hypertension (overt ascites, overt hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, portal vein thrombosis), hepatocellular carcinoma, changes in liver function (assessed by Child-Pugh and Model for End-Stage Liver Disease (MELD) scores), changes in liver stiffness, changes in spleen stiffness and the occurrence of adverse events. Data will be collected during clinic visits and via telemedicine. The study adheres to Good Clinical Practice guidelines, the Declaration of Helsinki, and regulatory requirements, with ethical approval from all participating centres. The study will begin in 2024 and is expected to conclude in 2026. The overall study design is outlined in figure 1.

Participant selection

Inclusion criteria (eligible patients must meet all the following criteria)

- Age: 18–75 years;
- Endoscopically confirmed EVB;
- Time interval between index bleeding and randomisation greater than 5 days;
- Cirrhosis: diagnosed based on clinical presentation, laboratory tests, imaging tests or liver biopsy.

Exclusion criteria (participants will be excluded if they meet any of the following conditions)

- Uncontrolled bleeding before randomisation;
- History of gastric variceal bleeding;
- Non-cirrhotic portal hypertension;
- Hepatocellular carcinoma or other malignancies;

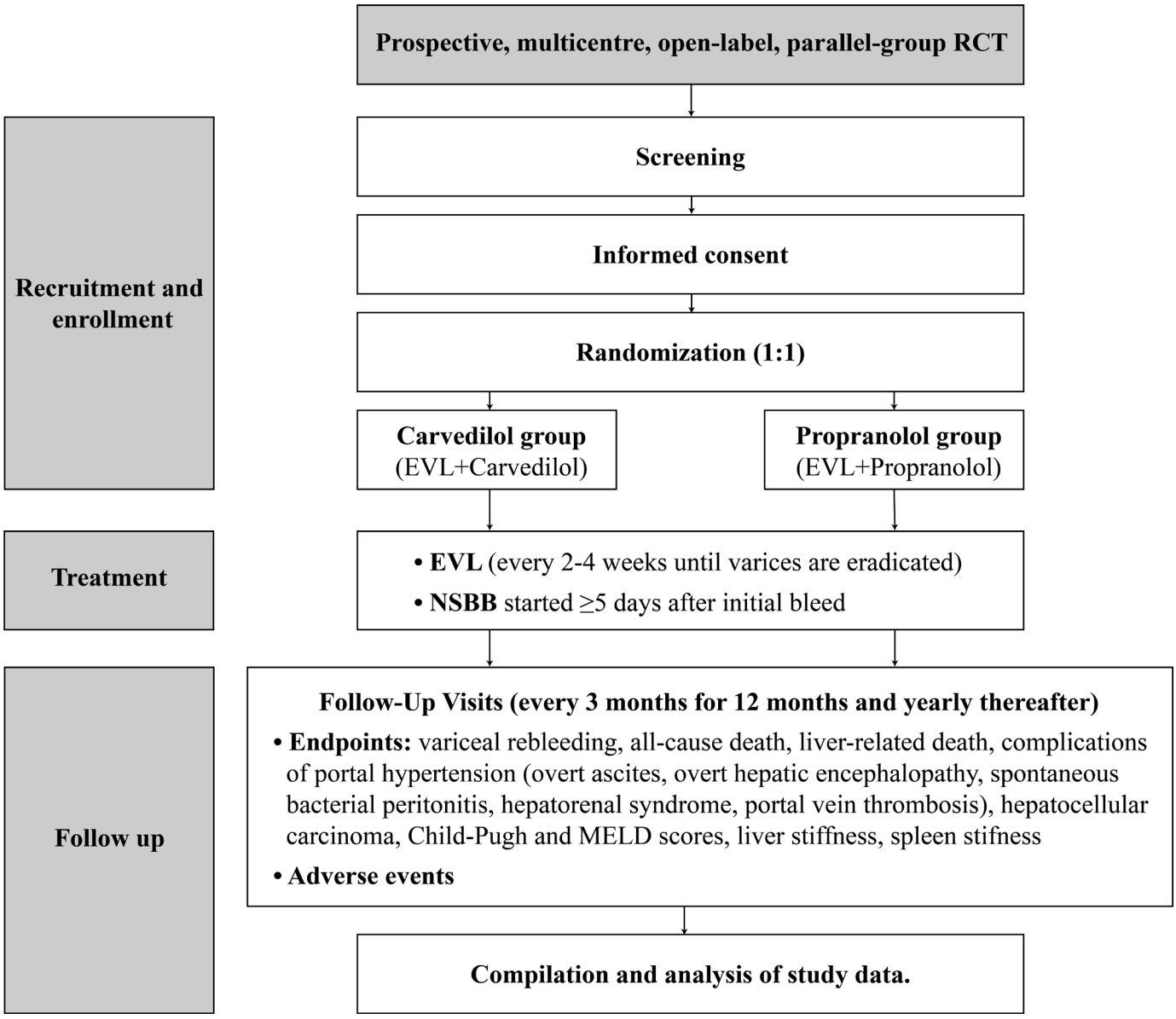

Figure 1 Flowchart of the RCT study plan. RCT, randomised controlled trial.

- Child-Turcotte-Pugh (CTP) score of C;
- Previous treatment with more than one session of endoscopic variceal ligation or other treatments for EVB, including endoscopic injection sclerotherapy (EIS), transjugular intrahepatic portosystemic shunt (TIPS) or surgery;
- Portal vein thrombosis or portal cavernoma;
- Currently receiving anticoagulant therapy;
- Use of NSBB in the past 2 weeks;
- Chronic renal insufficiency with serum creatinine greater than 2 mg/dL;
- Grade III/IV hepatic encephalopathy;
- Refractory ascites;
- Contraindications to NSBB, including heart block, sinus bradycardia, severe hypotension, heart failure, chronic obstructive pulmonary disease, asthma, uncontrolled diabetes or severe peripheral arterial disease;
- Terminal illnesses such as heart failure or renal failure, or other conditions with an expected survival of less than 12 months;
- Pregnancy or lactation;
- Unsuitable for EVL;
- Refusal to participate or inability to provide informed consent.

Recruitment and randomisation

Before enrollment, all eligible participants will undergo an informed consent process. Researchers will provide comprehensive information about the study's purpose, procedures, potential risks and benefits, and the voluntary nature of participation. Participants will have the opportunity to ask questions and discuss their involvement with family or advisors before providing written informed consent (online supplemental appendix 1).

This multicentre study will employ a centralised randomisation method to ensure rigour and fairness. An independent randomisation centre will manage randomisation allocation and drug dispensation for all participating centres. The centre will generate randomisation sequences using a stratified randomisation method, where participants will be stratified based on age, gender, severity of liver disease and presence of ascites. These sequences will be securely distributed via telephone or computer network. When a new participant needs to be randomised, the investigator will input the participant's ID, birth date and gender into the system, which will generate a unique randomisation number. The investigator will use this number to obtain the corresponding trial medication. All randomisation and drug allocation processes will be automatically recorded to ensure data integrity and traceability, with regular audits to ensure compliance with trial design requirements. This centralised method ensures transparency and fairness, avoids human interference and enhances the reliability of the study results.

Treatment

Both groups received EVL therapy, which was repeated every 2–4 weeks until varices were eradicated.

- Carvedilol group: carvedilol was initiated at 6.25 mg/day (6.25 mg once daily) and titrated up to 12.5 mg/day (6.25 mg two times per day) after 3 days, ensuring systolic blood pressure remained above 90 mm Hg.
- Propranolol group: propranolol was initiated at 20 mg two times per day and titrated every 2–3 days until the heart rate decreased to 55–60 beats per minute (maximum dose of 320 mg/day for patients without ascites and 160 mg/day for patients with ascites), ensuring systolic blood pressure remained above 90 mm Hg.

Outcomes and measurements

Outcomes will be measured at baseline and at 3-month intervals during the 12-month follow-up period and yearly afterwards.

Primary endpoint

- Composite of variceal rebleeding or all-cause death: the primary composite endpoint, defined as the time from randomisation to the first occurrence of either variceal rebleeding confirmed by endoscopy or death from any cause within 1 year of randomisation of the last patient.

Secondary endpoints

- All-cause death: defined as death due to any cause during the 12-month follow-up period.
- Liver-related death: defined as death specifically attributable to liver disease complications, such as liver failure, hepatic encephalopathy or variceal bleeding.
- Complications of portal hypertension:
  - Variceal rebleeding: recurrent bleeding from oesophageal varices confirmed by endoscopy.
  - Overt ascites: identified through physical examination signs, validated by ultrasonography or paracentesis, but not by intraperitoneal fluid detectable exclusively by ultrasonography or the presence of ankle oedema alone.[19]
  - Overt hepatic encephalopathy: defined according to West Haven criteria, with symptoms and signs exceeding grade II.[20]
  - Spontaneous bacterial peritonitis: infection of ascitic fluid, confirmed by laboratory analysis.[21]
  - Hepatorenal syndrome: kidney failure associated with severe liver disease, diagnosed clinically and through laboratory tests.[19]
  - Portal vein thrombosis: formation of a clot in the portal vein, confirmed by imaging (ultrasound, CT, MRI).[22]
- Hepatocellular carcinoma: diagnosed through imaging tests (ultrasound, CT, MRI) and alpha-fetoprotein (AFP) levels, or confirmed pathologically.
- Changes in liver function: assessed using changes in Child-Pugh score and MELD score, based on laboratory tests and clinical evaluation.
- Changes in liver stiffness: measured by transient elastography (FibroScan), reflecting fibrosis and cirrhosis progression or regression.
- Changes in spleen stiffness: measured by transient elastography (FibroScan), reflecting cirrhosis and portal hypertension progression or regression.
- Incidence of adverse events: any adverse medical occurrences related to the study medications (carvedilol and propranolol), documented throughout the study duration.

Safety assessments

Safety assessments will be conducted throughout the study to ensure participant well-being. Adverse events (AEs) will be recorded from randomisation until the study's end, categorised by severity, relationship to the study medication, and outcome, with serious adverse events (SAEs) reported immediately to ethics committees and regulatory authorities. Vital signs, including blood pressure, heart rate, respiratory rate and temperature, will be measured at baseline and every 3 months. Regular laboratory tests will monitor liver function (alanine aminotransferase, aspartate aminotransferase, bilirubin, albumin), renal function (serum creatinine, blood urea nitrogen), coagulation parameters (INR) and complete blood count (CBC), with assessments at baseline and every 3 months. Comprehensive physical examinations will be performed at each visit to identify new or worsening conditions. Patient-reported outcomes, via questionnaires at each visit, will capture symptoms and side effects, including impacts on quality of life. Medication adherence will be monitored through pill counts and patient diaries. An independent data monitoring committee (DMC) will regularly review all safety data to identify and address any concerns, ensuring the integrity and safety of the study.

Data management

All raw data will be accurately recorded on case report forms (CRFs) and signed by the respective investigators. Completed CRFs will be forwarded to the lead investigator. All raw data will be accurately recorded directly into an Electronic Data Capture (EDC) system by the respective investigators. The EDC system will ensure real-time data entry, validation and secure storage. Completed entries will be reviewed and approved by the lead investigator. Data management experts will oversee the organisation and quality of the data within the EDC system. The ethics committees at all study sites will monitor the processes related to data access and analysis, ensuring compliance with ethical standards and maintaining data integrity.

Sample size calculation

The study hypothesis posits that carvedilol combined with EVL is superior to propranolol with EVL in reducing the composite endpoint of variceal rebleeding or death within 1 year in patients with cirrhosis and EVB. Assuming a 14.5% of annual incidence of the primary endpoint in the propranolol group and 7.1% in the carvedilol group,[17] an anticipated enrollment period of 1 year, follow-up of 1 year after the enrollment of the last patient, with a significance level (α) of 0.05, a power of 90%, and a 10% loss to follow-up, a total of 524 patients (262 per group) are required to detect a significant difference between the treatment arms.

Data analysis plan

All randomised patients will be included in an intention-to-treat (ITT) analysis according to their assigned treatment group. The primary endpoint (the time from randomisation to the first occurrence of either variceal rebleeding confirmed by endoscopy or death) will be summarised using Kaplan-Meier curves and compared using a log-rank test. Cox model will be used to calculate the crude and adjusted HR between two arms and its 95% CI. Covariates in the covariate adjusted analysis will include age, gender, severity of liver disease and presence of ascites. The win-ratio method for the hierarchical composite outcome will be used as a supplementary analysis.

Secondary endpoints will be analysed as follows. Time to event outcomes such as all-cause and liver-related death will be analysed in a similar way as for the analysis of the primary outcome. Binary outcomes will be analysed using generalised linear mixed models and crude and adjusted risk ratios together with their 95% CI will be derived to measure the treatment effects. Continuous outcomes such as changes in liver function (Child-Pugh and MELD scores), liver stiffness and spleen stiffness will be analysed using linear mixed-effects models, from which crude and adjusted mean differences with 95% CI will be calculated. Covariates in the adjusted analyses will be the same ones as for the primary outcome analysis.

Subgroup analyses will assess treatment effects across age categories, gender, severity of liver disease and presence of ascites. Sensitivity analyses will include per-protocol analysis and exclusion of patients lost to follow-up. Missing data will be handled using multiple imputation techniques, with sensitivity analyses to assess their impact.

Adverse events will be compared using χ^2 or Fisher's exact tests.

All statistical analyses will be described in detail in the statistical analysis plan and performed using R version 4.0.2, with a p value <0.05 considered statistically significant.

Ethics and dissemination

The study protocol has been reviewed and approved by the ethics committees of the First Hospital of China Medical University (No. 2024-656-2). Written informed consent will be obtained from all participants prior to enrollment. The study will be conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines.

The results of the study will be disseminated through peer-reviewed journal publications and presentations at national and international conferences. Summary results will also be shared with study participants and relevant stakeholders. The findings are expected to contribute significantly to the optimisation of treatment strategies for patients with cirrhosis and EVB.

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Contributors All authors meet the ICMJE criteria for authorship. YLi, LD, ShuZ and CL revised the protocol and drafted the manuscript. DW supervised the statistical analysis. AC, ZJ and XQ provided overall protocol supervision. The remaining authors, representing the participating institutions, contributed to the discussion and refinement of the study protocol. XQ is the guarantor of the study, ensuring the integrity of the study design, data collection and analysis. All authors have reviewed and approved the final manuscript.

Funding Noncommunicable Chronic Diseases-National Science and Technology Major Project (2023ZD0508700); Artificial Intelligence Field Technology Innovation Project (Applied Basic Research): 2023-JH26/ 10300009; Scientific Research Fund of Liaoning Provincial Education Department (LJKMZ20221167); The Key Research and Development Program of Jiangsu Province (BE2023767a); the Fundamental Research Fund of Southeast University (3290002303A2); Changjiang Scholars Talent Cultivation Project of Zhongda Hospital of Southeast University (2023YJXYYRCPY03); Research Personnel Cultivation Programme of Zhongda Hospital Southeast University (CZXM-GSP-RC125, CZXM-GSP-RC119); China Postdoctoral Science Foundation (2024M750461); National Natural Science Foundation of China (82402413); Natural Science Foundation of Jiangsu Province (BK20241681).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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