Assessing the safety of discontinuing non-selective beta-blockers in cirrhotic patients with managed primary aetiological factors according to Baveno VII consensus

(Short title: Stop-NSBB Study)

Clinical study protocol

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1. BACKGROUND

1.1 Significance of cirrhosis and portal hypertension

Liver cirrhosis is the common final pathway of various chronic liver diseases. Globally, mortality due to cirrhosis have risen from 899 000 in 1990 to 1.32 million deaths in 2017. Additionally, as of 2017, 112 million and 10.6 million people were living with compensated and decompensated cirrhosis, respectively (1). Portal hypertension stands out as the primary cause of cirrhotic complications, such as ascites and variceal haemorrhage. Accurate diagnosis of clinically significant portal hypertension is crucial because the administration of non-selective beta-blockers (NSBBs) can reduce the risk of variceal haemorrhage and hepatic decompensation (2, 3).

Chronic liver disease is highly prevalent in Hong Kong. A community screening study in Hong Kong in 2015-2016 indicated that the prevalence of hepatitis B surface antigen was still 7.8% (4). Studies by our group have further highlighted the extent of the problem, revealing that 26% of the local population and a staggering 73% of patients with type 2 diabetes suffer from metabolic dysfunction-associated steatotic liver disease (5, 6). These chronic liver diseases carry a significant risk of progressing to cirrhosis and hepatic decompensation.

1.2 Non-invasive assessment of portal hypertension

Historically, the gold standard for assessing portal hypertension requires the measurement of hepatic venous pressure gradient, an invasive procedure rarely performed outside research settings (7). However, accumulating data support the use of non-invasive tests to assess portal hypertension. Specifically, liver stiffness measurement (LSM) through vibration-controlled transient elastography reflects the degree of liver fibrosis and the severity of cirrhosis. Furthermore, the platelet count reflects whether a patient with cirrhosis has hypersplenism secondary to portal hypertension. Additionally, spleen stiffness measurement (SSM) may be an even more direct evaluation of portal hypertension and has been used to ascertain improvements in portal hypertension following the initiation of NSBB (8, 9). Based on existing data, the latest Baveno VII consensus has endorsed the use of these non-invasive tests to rule out (if LSM <15 kPa and platelet count $>150\times10^9$/L) and to confirm (if LSM ≥25 kPa) the presence of clinically significant portal hypertension (10).

In a randomised controlled trial involving 548 patients with radiological cirrhosis, our group demonstrated that LSM+SSM was non-inferior to routine endoscopy in detecting varices and preventing future variceal haemorrhage (11, 12). Furthermore, we validated the use of LSM-based criteria for excluding the presence of varices requiring treatment across a range of chronic liver diseases, including patients with or without hepatocellular carcinoma (13-15). Additionally, we reported the natural history of patients falling within the grey zone according to the Baveno VII criteria. Importantly, we identified factors associated with hepatic decompensation in this specific patient population (16).

1.3 Emerging concept: hepatic recompensation and reversal of cirrhosis and portal hypertension

As a number of chronic liver diseases can now be well controlled or cured, it is increasingly apparent that cirrhosis can resolve over time when the primary aetiology is controlled (17). Reports have also emerged, suggesting an improvement in portal hypertension and even hepatic recompensation in such circumstances (18). This has led to the practical recommendation on discontinuing NSBB in patients with LSM <25 kPa after removal or suppression of the primary aetiological factor, in the absence of varices (10). Removal or suppression of the primary aetiological factor includes sustained virological response in chronic hepatitis C, complete hepatitis B virus DNA suppression in chronic hepatitis B patients, and long-term abstinence from alcohol in those with alcohol-related liver disease. Nonetheless, it is crucial to note that these recommendations are based on tenuous evidence (C.2 recommendation). While cessation of NSBB in patients no longer requiring it can reduce unnecessary expenses (prescription and monitoring) and side effects, it remains imperative to confirm the safety of this approach through well-designed, prospective studies.

2. STUDY OBJECTIVES

1. We aim to test the hypothesis that recurrent varices will occur in less than 5% of patients with cirrhosis who discontinue non-selective beta-blockers (NSBBs) in accordance with the Baveno VII consensus (i.e., effective management or removal of primary aetiological factor, liver stiffness measurements below 25 kPa, and absence of varices confirmed by endoscopy).
2. We aim to assess the hypothesis that variceal haemorrhage will occur in less than 5% patients with cirrhosis who cease NSBB use, adhering to the Baveno VII guidelines.
3. We aim to identify factors associated with recurrent varices and variceal haemorrhage, with a special focus on serial liver and spleen stiffness measurements obtained by vibration-controlled transient elastography.

3. STUDY DESIGN OVERVIEW

This study is designed as a multicentre, prospective cohort investigation. The study consists of three main parts:

Part 1: We will perform endoscopy on patients with LSM <25 kPa. This part aims to identify both the percentage of patients harbouring varices and the factors associated with their presence.

Part 2: Patients without varices will discontinue NSBB and undergo prospective follow-up. Endoscopy will be repeated at 1 year to determine the rate of recurrent varices and any contributing factors.

Part 3: Patients will continue prospective follow-up to determine the incidence and factors associated with hepatic decompensation, including variceal haemorrhage, with prespecified outcome analysis at 3- and 10-year marks.

Although the study's follow-up extends beyond the financial coverage of the General Research Fund, patients will still continue at least annual follow-up at the participating centres as part of the standard care, with endpoints ascertained at each visit. The General Research Fund will finance Parts 1 and 2 of this project and establish a valuable cohort for the collection of outcome data.

4. PATIENTS

Eligible patients will be identified from the general medical and hepatology clinics in Hong Kong and collaborating countries. At present, investigators from France, Singapore and Malaysia have confirmed their participation.

4.1 Inclusion criteria

To be eligible for enrolment, patients must meet all the following criteria:

- Aged 18 years or above
- Evidence of cirrhosis, based on either radiological and/or clinical features
- History of varices, variceal haemorrhage or portal hypertension warranting NSBB
- Removal or suppression of the primary aetiological factor (i.e., sustained virological response in chronic hepatitis C, complete hepatitis B virus DNA suppression in chronic hepatitis B, and long-term alcohol abstinence in alcohol-related liver disease)
- LSM <25 kPa
- Provision of written informed consent

4.2 Exclusion criteria

Patients with any of the following will be excluded from the study:

- Active aetiological factors not addressed in the inclusion criteria (e.g., autoimmune or hereditary liver diseases). However, hepatic steatosis—commonly coexisting with other liver diseases—is not an exclusion criterion unless accompanied by high plasma alanine aminotransferase >40 U/L or confirmed steatohepatitis.
- Recent hepatic decompensation within the past year (total bilirubin >50 μmol/L, prothrombin time >1.3 times the upper normal limit [unless attributable to use of anti-coagulation], albumin <35 g/L, or presence of ascites, variceal haemorrhage or hepatic encephalopathy). Notably, the Baveno VI criteria used LSM <20-25 kPa and normal platelet count >150×10^9/L to rule out varices requiring

treatment (19). However, in line with the Baveno VII consensus, which sets an LSM <25 kPa as the threshold for considering NSBB discontinuation, thrombocytopenia is not an exclusion criterion to allow the cohort to include a wider spectrum of patients.

- Current or history of hepatocellular carcinoma.
- Radiological evidence of portal vein thrombosis.
- History of other malignancies (unless in complete remission for >5 years).
- History of liver transplantation or liver resection.
- Contraindications to undergoing endoscopy.
- Other clinical indications for NSBB (e.g., cardiovascular disease, arterial hypertension)

5. CLINIC VISITS AND ASSESSMENTS

5.1 Clinical assessments

The following procedures will be performed at baseline, month 3, month 6, and year 1:

- Documentation of medical history and new symptoms
- Documentation of hepatic events and their dates of occurrence (i.e., ascites, spontaneous bacterial peritonitis, variceal haemorrhage, hepatic encephalopathy, hepatorenal syndrome-acute kidney injury, hepatocellular carcinoma, liver transplantation; detailed definitions provided in the full protocol)
- Dates and causes of death for patients who pass away between visits will be recorded
- Standard questionnaires will be used to document smoking and alcohol consumption
- Physical examination
- Anthropometric measurements including body weight, height, waist and hip circumferences, will be collected. Body mass index will be calculated as body weight (kg) divided by height (m) squared
- Blood pressure and pulse rate measured after a 15-minute rest
- Blood tests will include complete blood count, prothrombin time, renal function test, liver blood test (including alanine aminotransferase, aspartate aminotransferase and gamma-glutamyl transpeptidase), and alpha-fetoprotein
- Store 10 mL of clotted blood and 10 mL of EDTA blood for future genetic and biochemical research (with separate consent)

5.2 Vibration-controlled transient elastography

LSM and SSM assessments will be carried out using vibration-controlled transient elastography (FibroScan 630 Expert, Echosens, Paris, France). Operators with a minimum of 500 examinations completed and trained according to the manufacturer's guidelines will conduct the tests (20). Examinations will be performed at baseline, month 3, month 6, and year 1. Ten measurements will be

recorded each for the liver and spleen, and their median value will be used to derive the corresponding stiffness. The machine's automated probe selection tool will determine the use of M and XL probes for LSM, while the dedicated 100Hz probe will be required for SSM.

LSM is considered reliable if there are ten or more valid measurements, and the interquartile range-to-median ratio of the measurements is ≤0.3. While no standardised reliability criteria exist for SSM, variability of SSM will be tracked in this study.

5.3 Upper gastrointestinal endoscopy

Upper gastrointestinal endoscopy will be performed by experienced endoscopists with a minimum of 100 prior examinations, at baseline and year 1. The scope of the examination will include the oesophagus, stomach, and the first and second parts of the duodenum. The size of varices will be graded using the modified Paquet classification (grade I for varices extending just above the mucosal level; grade II for varices projecting by one-third of the luminal diameter and non-compressible upon air insufflation; and grade III for varices projecting up to 50% of the luminal diameter and in contact with each other) (21). Additionally, the location and presence of red wale markings and cherry red spots will be documented.

5.4 Follow-up

Other follow-up procedures will be considered part of the standard of care and will be covered by local resources. These include but are not limited to the treatment of chronic liver disease and co-morbid conditions as well as surveillance for hepatocellular carcinoma through periodic abdominal ultrasonography and/or alpha-fetoprotein testing. Patients will be scheduled for at least one annual visit or more frequently, as clinically indicated. At each visit, incident hepatic events will be documented.

6. DATA PROCESSING AND ANALYSIS

6.1 Analysis datasets

Part 1: This analysis will include all eligible patients who meet the inclusion and exclusion criteria and undergo endoscopy at baseline.

Part 2: The intention-to-treat analysis will include all patients with no varices at baseline and have discontinued at least one dose of NSBB. Those who resume NSBB or are lost to follow-up will be classified as treatment failures (i.e., assumed to have recurrent varices). The per- protocol analysis will focus on all patients who undergo follow-up endoscopy at 1 year or resume NSBB, with the resumption of NSBB being classified as treatment failure, as previously noted.

Part 3: This part will include all patients with no varices at baseline who have also discontinued at least one dose of NSBB. Data will be censored at the point of patient death or liver transplantation. Patients who experience relapses of the primary aetiological factor (e.g., recurrent hepatitis C virus infection, virological breakthrough in chronic hepatitis B, and relapse of alcohol consumption) will be given the options to either resume NSBB or continue regular surveillance by transient elastography according to the Baveno VI criteria.

6.2 Primary endpoint

The primary endpoint of this study is recurrent varices at the one-year mark among patients who have discontinued NSBB. Due to substantial intra- and inter-observer variability in the diagnosis of grade I varices, this study will define recurrent varices as the detection of grade II or III varices according to the modified Paquet classification (21).

The proportion of patients with recurrent varices and the corresponding 95% confidence interval (CI) will be calculated. Factors associated with recurrent varices will be compared between patients with and without recurrent varices. Continuous variables will be compared using the unpaired *t* test or Mann-Whitney *U* test as appropriate. For categorical variables, either the chi-square or Fisher exact test will be used. In the unlikely scenario where over 30 patients develop recurrent varices, a multivariable binary logistic regression model will be performed to identify independent factors associated with recurrent varices.

We hypothesise that non-invasive tests could detect recurrence of portal hypertension at earlier timepoints. Therefore, we will examine baseline and follow-up LSM, SSM, platelet count, and their combinations as potential predictors of recurrent varices.

6.3 Secondary endpoints

<u>Prevalence of varices in screening cohort</u>

In the initial screening cohort of all patients who undergo endoscopy, we will calculate the proportion and 95% CI of patients with LSM <25 kPa who still harbour varices at baseline despite NSBB treatment and removal or suppression of the primary aetiological factor.

We will compare variables associated with varices between patients with and without varices at baseline. Continuous variables will be compared using unpaired *t* test or Mann-Whitney *U* test as appropriate, while categorical variables will be compared using the chi-square test or Fisher exact test. If over 30 patients exhibit varices at baseline, a multivariable binary logistic regression model will be performed to identify independent factors associated with varices.

<u>Resumption of NSBB and variceal haemorrhage</u>

For patients discontinuing NSBB, the secondary endpoint is resumption of NSBB or variceal haemorrhage during follow-up. The latter is defined as clinical symptoms of upper gastrointestinal bleeding (i.e., haematemesis, coffee ground vomiting, and/or tarry stool) and endoscopic evidence of variceal haemorrhage (active spurting or oozing from varices, or presence of stigmata of recent haemorrhage [e.g., red wale sign, cherry red spot, fibrin clot] with no alternative source of bleeding). The incidence rate of variceal haemorrhage, along with the 95% CI will be calculated. Factors associated with recurrent haemorrhage will be compared using the same statistical methods mentioned above. In the unlikely scenario where over 30 patients develop variceal haemorrhage, a multivariable Cox proportional hazard model will be applied to identify independent variables associated this event. Additionally, death and liver transplantation will be competing events precluding at-risk patients from developing variceal haemorrhage. Thus, should over 10% of the cohort either die or undergo liver transplantation during follow-up, a competing risk analysis will be conducted using the Fine-Gray model.

Other decompensating events

Other decompensating events include ascites and hepatic encephalopathy post-NSBB cessation, and the statistical methods used will be similar to those for variceal haemorrhage.

6.4 Sample size calculation

In our previous study involving 818 patients with chronic hepatitis B and compensated advanced chronic liver disease well managed by oral antiviral drugs, only three (0.4%) developed variceal haemorrhage at a mean follow-up of 58 months (22). With a sample size of 300 patients, the study will have a two-sided 95% CI with a width of 0.037 (0.0125-0.0496) when up to 2.5% of patients develop the primary endpoint (23, 24). As per clinical practice standards, a miss rate of varices requiring treatment of up to 5% is generally considered acceptable for implementing non-invasive tests (10). Accordingly, this threshold (upper bound of the 95% CI <5%) will be taken as criteria of success (i.e., safe to discontinue NSBB according to the Baveno VII criteria). To mitigate the impact of potential patient dropout, we will allow for a dropout rate of up to 20%. Therefore, a total sample size of 375 patients is required.

6.5 Anticipated challenges and contingency plans

Our team possesses the expertise and track records required to execute this study successfully. Our preliminary data support the feasibility of our sample size and event rate estimates. The study's multicentre design further bolsters the likelihood of its successful completion. In case of challenges in recruitment, we have plans to include additional collaborating sites. Currently, our university is leading a multicentre Asian study on the natural history of metabolic dysfunction-associated steatotic liver

disease with participating sites in China, Japan, South Korea, Taiwan, Malaysia and Singapore. There is potential to expand the proposed project and accelerate enrolment.

Given that this is the first prospective study examining the safety of NSBB discontinuation in this patient group, we will establish an independent Data and Safety Monitoring Board with planned interim analyses when the first 100 patients and all enrolled patients have reached 1 year of follow-up. If the rate of recurrent varices at 1 year exceeds 5% or if other safety concerns arise, the Board will recommend the study's early termination. In that case, Part 3 (NSBB-free follow-up for 10 years) would be discontinued. Patients with recurrent varices would resume NSBB, while those without recurrent varices or still within the first year of follow-up will be offered the options of resuming NSBB or regular endoscopic surveillance.

Endoscopy is an invasive procedure. Based on our previous clinical trials (25), a small percentage (typically <5%) of patients may decline the follow-up endoscopy at 1 year. These patients will still be included in the intention-to-treat and per protocol analyses as described above, ensuring that their data continues to contribute to the study's findings.

If a patient exhibits LSM <25 kPa at 1 year and refuses follow-up endoscopy, he/she will continue NSBB-free follow-up in Part 3 of this project, aligning with the Baveno VII recommendations. Conversely, if a patient exhibits LSM ≥25 kPa at 1 year and declines the follow-up endoscopy, we will recommend resumption of NSBB.

7. ETHICS

7.1 Ethics review

The final study protocol, including the final version of the Informed Consent Form, must be approved in writing by the Joint The Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (CUHK-NTEC CREC). The protocol must be re-approved by the CREC annually. All subsequent protocol amendments must be approved by the CREC.

7.2 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements and the CREC.

7.3 Informed consent

The investigator(s) will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. The informed consent forms are

available in traditional Chinese. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allow time to consider the information provided. The subject's signed and dated informed consent must be obtained before conducting any procedure specific for the study. The Principal Investigator must store the original, signed Informed Consent Forms. One copy of the signed Informed Consent Form must be given to the subject. If modifications are made according to local requirements, the new version has to be approved by the CREC.

7.4 Data sharing

In line with current international standard of accountability and transparent reporting, data from this study may be shared with outside parties upon reasonable request. Care will be taken to remove sensitive data (name, identity numbers and dates of birth) before data sharing.

8. ADVERSE EVENT REPORTING

The adverse event reporting period for this study is from signing the informed consent through 6 months of follow-up. Because the study will not involve study drugs or invasive procedures, there will not be any per protocol post-treatment follow-up or adverse event reporting after the study period. Rather, an appropriate clinic appointment will be arranged at the end of the study according to the clinical situation.

8.1 Adverse events

An adverse event is any undesirable medical event occurring in the subject within the trial period, whether or not it is related to the study intervention.

The severity of an adverse event is defined as:
Mild: Transient symptoms, no interference with the subject's daily activities
Moderate: Marked symptoms, moderate interference with the subject's daily activities
Severe: Severe interference with the subject's daily activities.

The relationship of an adverse event to the study intervention is defined as:
Probable: Good reasons and sufficient documentation to assume a causal relationship
Possible: A causal relationship is conceivable and cannot be dismissed
Unlikely: The event is unlikely related to the study intervention

A telephone enquiry hotline for reporting subject's adverse events is available. The investigator will record all relevant information including signs and symptoms of the event, the onset time, the date of the event, the laboratory findings, concomitant drugs, and the outcome. All adverse events will be followed up until we have reached a defined outcome of the event, which can be one of the followings: (1) recovered with sequelae (for chronic conditions), (2) recovered, or (3) the management of the adverse event is taken over by another physician when the study ends.

A clinical laboratory adverse event is any clinical laboratory abnormality that suggests a disease and/or organ toxicity is of sufficient severity that requires active intervention (i.e. change of dose, discontinuation of drug, more frequent follow-up or further investigation).

8.2 Serious adverse events

A serious adverse event is an adverse event that results in one of the following outcomes:

- Death
- Life-threatening
- In-patient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect

The definitions of causal relationship to study intervention are the same as those for adverse events. We have a 24-hour on-call system to handle serious adverse events. The investigator will assess and treat the subjects as soon as possible. A standard serious adverse event form will be used (provided by the CREC at http://intranet.ccter.cuhk.edu.hk/sae/) to report the events within 24 hours after acknowledgement. We will arrange unscheduled follow-up visits immediately or within 24 hours on receiving the subject's self-report of serious adverse events after the subjects have been discharged or if the subject has already been admitted to the hospital. Our investigators will assess the subject within 24 hours. The study team will record all relevant information including signs and symptoms of the event, the onset time, the date of the event, the laboratory findings, concomitant drugs, and the final outcome. A follow-up serious adverse event form will be sent within 14 days after submitting the initial serious adverse event form. Serious adverse events related to the study drug will be followed up until the subject has "recovered", "recovered with sequelae" or "died". SAE reports will be sent to our ethics committee. An unscheduled visit will be performed if subjects have to withdraw early from the study.

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