Clinical Study Protocol

Baveno VII criteria-guided initiation of non-selective beta blocker in patients with compensated advanced chronic liver disease to reduce hepatic decompensation: an open-label randomised controlled trial

Short title: BB_cACLD

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1. BACKGROUND

An estimated 1.5 billion people worldwide had chronic liver diseases in 2020.(1) Progression to cirrhosis leads to potential cirrhotic and portal hypertension-related complications resulting in substantial risk of morbidity and mortality.(2) In the Baveno VI consensus in 2015, the term "compensated advanced chronic liver disease (cACLD)" has been proposed to describe a spectrum of chronic liver diseases ranging from advanced liver fibrosis to compensated cirrhosis.(3) Furthermore in the recently updated Baveno VII consensus, patients with cACLD were subclassified into those with and without clinically significant portal hypertension (CSPH) according to the liver stiffness measurement (LSM) by transient elastography (TE), where LSM ≥25 kPa rules in CSPH with >90% specificity and positive predictive value. On the contrary, LSM <10 kPa rules out cACLD. By combining LSM and platelet count, CSPH can also be ruled out if LSM <15 kPa with platelet count $\geq 150\times10^9$/L with >90% sensitivity and negative predictive value.(4) Identification of cACLD patients with CSPH is crucial in risk stratification and prognostication as it is a risk factor for development of hepatic decompensation and subsequent mortality.

In the Baveno VII criteria, cACLD patients with LSM 15-24.9 kPa and/or platelet count $<150\times10^9$/L cannot be clearly classified into either side and thus are considered in the grey zone.(4) Data from our group, as well as other studies, have suggested an approximation of 40% of patients with cACLD in the grey zone.(5) Despite having a knowledge gap in the natural history and risk of hepatic decompensation in this group of patients worldwide, our preliminary data from a prospective cohort of more than 2700 patients with cACLD showed that the cumulative incidence of decompensation at five years were significantly higher in grey zone (4.2%; 95% confidence interval [CI] 3.1-5.4%) and high risk (of CSPH) groups (11.4%; 95% CI 8.7-14.6%), compared to low risk (of CSPH) group (0.6%; 95% CI 0.2-1.3%).(6) **(Figure 1)** Notably, LSM ≥20 kPa - <25 kPa and platelet count <150 x 10^9/L or LSM ≥15 kPa - <20 kPa and platelet count <110 x 10^9/L are in the grey zone category but have at least 60% risk of CSPH.(4) Thus, those with cACLD in the grey zone, especially at the high-risk grey zone of the Baveno VII criteria remain at a substantial risk of hepatic decompensation.

Meanwhile the Baveno VII criteria endorsed LSM and platelet count cut-offs for chronic hepatitis B (CHB) and C (CHC), alcohol-related liver disease (ARLD) and non-obese (body mass index [BMI] <30kg/m^2) metabolic dysfunction-associated steatotic liver disease (MASLD), those with obese (BMI ≥30kg/m^2) MASLD can be assessed by the ANTICIPATE-

NASH model, by considering BMI as an additional factor on top of LSM and platelet count. A nomogram can be plotted to assess the probability of CSPH based on the ANTICIPATE-NASH model in which the model was supported by the Baveno VII consensus.(5)

Non-selective beta blocker (NSBB) has been well proven to reduce portal pressure and hence portal hypertension-related complications, notably variceal bleeding.(7) As suggested in Baveno VI consensus, patients with LSM <20 kPa and platelet count $\geq 150\times10^9$/L has less than 5% risk of having significant varices and thus can have a screening oesophagogastroduodenoscopy (OGD) exempted.(3) On the contrary, those who fall beyond this criteria should have an OGD done and NSBB initiated if high-risk varices (HRV) (*i.e.* moderate to large oesophageal varices [OV] or OV with red wale sign) are found, to prevent first occurrence of variceal bleeding in patients with cACLD.(6) However in "β blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised, double-blind, placebo-controlled, multicentre trial" by Villanueva *et al.* enrolling patients with compensated cirrhosis and CSPH without HRV, NSBB reduced the risk of developing hepatic decompensation and liver-related mortality in the NSBB group compared to the placebo group (16% *vs.* 27%, hazard ratio 0.51) and the protective effect of NSBB was consistent across subgroups prespecified by the Child's grading, presence of varices or causes of cirrhosis.(8) This landmark trial has shed light on the use of NSBB not just to prevent variceal bleeding, but also hepatic decompensation in cACLD patients with CSPH. Furthermore, carvedilol, owing to its extra alpha-1 adrenergic blocking effect, confers to a greater effect on lowering portal pressure and thus has been the NSBB of choice for treating portal hypertension.(9)

2. HYPOTHESIS

We hypothesize that treating cACLD patients with CSPH and under high-risk grey zone of Baveno VII criteria with carvedilol is superior to not treating them in the absence of HRV, in terms of prevention of first occurrence of hepatic decompensation and mortality.

3. STUDY DESIGN OVERVIEW

3.1 Study design

The study is a multi-centre, open-label, randomised controlled trial. Eligible patients will be randomised to NSBB arm (*i.e.* receiving carvedilol) or conventional arm (*i.e.* not receiving carvedilol), aiming to test the hypothesis that Baveno VII criteria-guided carvedilol treatment

in cACLD patients in grey zone or with CSPH is superior to not treating them in the absence of HRV, in terms of prevention of first occurrence of hepatic decompensation and mortality.

Consecutive patients in the participating study sites with cACLD fulfilling the high-risk grey zone and CSPH criteria by LSM and platelet count will be invited to this study. These patients are identified from routine clinic visits as well as from retrospective health records. The patients will undergo OGD for screening of OV. Those without HRV will be randomised into NSBB and conventional arms. Patients in the NSBB arm will be started on carvedilol. Those in the conventional arm will not receive NSBB as per current standard of practice.

The expected accrual duration is 24 months with an interim analysis to be performed when all enrolled patients have reached 1 year of follow-up or the primary endpoint. The total follow-up duration is 5 years. The study flowchart is shown in **Figure 2**.

3.2 Study aims

Our primary aim is to assess the effect on the initiation of carvedilol in cACLD patients with CSPH and those under high-risk grey zone by Baveno VII criteria in reducing hepatic decompensation and mortality despite the absence of HRV.

4. SUBJECT SELECTION

Consecutive patients with cACLD fulfilling the high-risk grey zone and CSPH criteria by LSM and platelet count will be screened for the following eligibility criteria:

4.1 Inclusion criteria

- Aged 18 years of above
- Established diagnosis of chronic liver disease(s) of the following etiologies
    - Alcohol-related liver disease (ARLD)
    - Chronic hepatitis B (CHB)
    - Chronic hepatitis C (CHC)
    - Metabolic dysfunction-associated steatotic liver disease (MASLD)
        - Non-obese (BMI <30kg/m^2) and obese (BMI ≥30 kg/m^2)
- In high-risk grey zone or CSPH, by Baveno VII criteria (for ARLD, CHB, CHC and non-obese MASLD) or ANTICIPATE-NASH model (for obese MASLD)(5) within 6 months from screening

- Baveno VII criteria (for ARLD, CHB, CHC and non-obese MASLD)
  - LSM≥25 kPa (CSPH)
  - LSM ≥20 kPa - <25 kPa and platelet count <150 x 10^9/L; or LSM ≥15 kPa - <20 kPa and platelet count <110 x 10^9/L (high-risk grey zone)
- ANTICIPATE-NASH model (for obese MASLD)
  - Predictive probability for CSPH >90% (CSPH)
  - Predictive probability for CSPH ≥60% - <90% (high-risk grey zone)

4.2 Exclusion criteria

- Presence of HRV (*i.e.* moderate to large oesophageal varices [OV] or OV with red wale sign) found in OGD
- Current use of NSBB or any use of NSBB within 6 months before
  - Use of selective beta blocker, such as atenolol or metoprolol, is not excluded
  - Selective beta-blocker will be switched to carvedilol in NSBB arm, and will be kept unchanged in conventional arm if there is clinical need for the selective beta-blocker
- Contraindication to NSBB (*e.g.* Type II/III heart block or baseline bradycardia <60/minute, hypotension with systolic blood pressure (SBP) <100 mmHg, asthma, poorly controlled chronic obstructive pulmonary disease, and peripheral vascular disease)
- Current use of nitrated drugs or any use of nitrated drugs within 6 months before
  - Use of sublingual nitrate, such as glyceryl trinitrate, is not excluded
- Contraindication to OGD (*e.g.* Intestinal perforation or obstruction)
- Current or history of decompensated liver cirrhosis (*i.e.* Child's C cirrhosis, prior decompensating events such as ascites, variceal bleeding, hepatic encephalopathy)
  - Child's B cirrhosis without decompensating events is not excluded
- Current or history of hepatocellular carcinoma (HCC)
- Current or history of portal vein thrombosis
- Transjugular intrahepatic portosystemic shunt (TIPS)
- Liver transplantation
- Serious medical illness with limited life expectancy of less than 6 months
- Pregnancy
- Unable to obtain or refusal of informed consent from patient

4.3 Allocation & Randomisation

Patients fulfilling the inclusion and exclusion criteria will be recruited to the study after informed consent is obtained. They will be randomised, at the time of recruitment, in 1:1 ratio to either NSBB arm or conventional arm. Randomisation will be performed by a centralised web-based system and will be stratified by the level of LSM and platelet count (*i.e.* CSPH and grey zone) in variable block sizes of 2 and 4 which will be computer-generated.. Patients in the NSBB arm will receive carvedilol for 60 months whereas those in the conventional arm will not receive carvedilol. An independent staff member will draw and assign the treatment strategies to respective patients that are kept in sealed envelopes.

5. TRIAL TREATMENTS

5.1 Open-label treatment

This is an open-label randomised controlled trial. Patients in the NSBB arm will receive generic carvedilol from the hospital pharmacy, while those in the conventional arm will not receive any specific treatment as per current standard of practice.

The starting dose of oral carvedilol is 6.25mg daily (to be taken once or twice per day) and can be adjusted at each scheduled visit (either by increasing the dosage or frequency of dose administration) according to patients' tolerance, as well as the blood pressure and pulse rate that the SBP should be not lower than 90 mmHg and pulse rate not lower than 55 beats per minute. The dosage of carvedilol can also be titrated or discontinued at unscheduled visit according to patient's condition. In case carvedilol is discontinued, it can be resumed from the starting dose at next scheduled visit if there is no contraindication for carvedilol as mentioned above. The dose of carvedilol will be kept at 6.25-12.5mg per day unless there are additional non-hepatic indications such as arterial hypertension or cardiac disease warranting higher carvedilol dosage.(10) The maximum allowed dose of carvedilol is 50mg daily as per drug instruction.

5.2 Prohibited drugs

Drugs prohibited during the study include non-selective beta-blockers other than carvedilol, such as propranolol, nadolol, labetalol and sotalol. Other selective beta-blockers, such as selective beta-1 blockers namely atenolol, bisoprolol, metoprolol and nebivolol are allowed.

Any systemic nitrated drugs, except sublingual nitrates such as glyceryl trinitrate, are also prohibited during the study.

5.3 Compliance

Drug compliance is assessed with the use of pill counts by our research assistant. We also retrieve over-the-counter drugs and prescriptions from the patients, their families, and their primary care doctors in order to identify any concomitant therapy with prohibited drugs listed above.

6. TRIAL PROCEDURES

6.1 Screening and consent process

1. All patients with cACLD fulfilling the grey zone and CSPH criteria by LSM and platelet count will be invited to this study will be screened for the eligibility criteria.
2. During the consent process, we will explain our current knowledge of preventing hepatic decompensation in patients with cACLD. We will also explain our plan of management, which include regular follow-up by designated investigators, laboratory monitoring, regular transient elastography and HCC surveillance.
3. Patients agreed to participate will give informed written consent.
4. Blood tests including complete blood picture, renal and liver biochemistries, clotting profile, alpha-fetoprotein, and hepatitis serology including hepatitis B surface antigen (HBsAg) and Hepatitis C virus (HCV) antibody will be performed.
    - Hepatitis B e antigen (HBeAg), antibody to hepatitis B e antigen (anti-HBe); Hepatitis B virus DNA (HBV DNA) will be checked if HBsAg is positive
    - Serum HCV RNA will be checked if HCV antibody is positive
5. OGD for screening of OV
    - OGD will be performed in the endoscopy centre of Prince of Wales Hospital or respective endoscopy suites in the participating sites. The examinations will be performed under conscious sedation as day procedures by experienced gastroenterologists and hepatologists who have performed more than 1,000 OGD before. The endoscopic findings will be recorded in a standard format. The presence of varices (OV or gastric varices) and their respective size will be graded according to the modified Paquet classification (grade I, varices extending just above the mucosal level; grade II, varices projecting by one-third of the luminal diameter that cannot be

compressed with air insufflation; grade III, varices projecting up to 50% of the luminal diameter and in contact with each other).(11) The presence of stigmata of high-risk bleeding such as red wale sign will also be recorded. The finding of HRV would be confirmed if the varices are of grade II/III and/or there are stigmata of high risk bleeding on the varices.

- OGD can be exempted if the patient has an OGD performed within three months before recruitment with clear documentation and endoscopic images to allow grading of OV.

6.2 Baseline randomisation visit

Randomisation is carried out with the use of a computer-generated list of random numbers. An independent staff member assigns the treatments according to consecutive numbers that are kept in sealed envelopes. Consented patients are randomly assigned to receive carvedilol or no treatment. Carvedilol will be prescribed in patients randomised to NSBB arm. Blood tests for complete blood picture, renal and liver function tests, and clotting profile will be taken for all patients.

For patients who required OGD for screening of OV, they will be randomized on the same day of the OGD examination if HRV is excluded, and with all other inclusion and exclusion criteria met.

6.3 Assessment during trial period

After randomisation visit, all patients will be followed at respective clinics in the participating sites, with regular monitoring of clinical parameters at the first month, the third month, then every three months for the first year, and then every six months up to five years. The followings will be performed during clinic visit **(Figure 2)**:

- Every scheduled visit
    - Blood pressure and pulse rate measurement
    - History taking and physical examination (in particular the clinical symptoms or signs of hepatic decompensation, such as ascites, hepatic encephalopathy or variceal bleeding)
    - Drug compliance assessment to carvedilol in NSBB arm by a research assistant to count the number of remaining pills; and checking for prohibited drugs
    - Objective assessment of control of the underlying chronic liver disease (for

example asking for drinking habit in those with alcoholic liver disease)

- Blood tests including complete blood picture, renal and liver function tests, and clotting profile, as well as HBV DNA and HCV RNA if relevant
  - Blood tests will be performed at least every 6 months, and additionally at month 1 and month 3 at the discretion of investigators if required.

- Every 6 months
  - Blood test for alpha fetoprotein
  - Ultrasound of the liver
- Every 12 months
  - Transient elastography for LSM and spleen stiffness measurement (SSM), using the machine according to the instructions and training provided by the manufacturer (Echosens, Paris, France)

All the blood tests will be processed by the respective laboratories of the participating sites. Patients will receive ultrasound and TE by research personnel at respective local facilities. All patients will undergo another OGD in 3 years to reassess whether there is occurrence of HRV. Those with HRV will be treated either by NSBB or endoscopic variceal ligation, in line with current international guidelines, during the same OGD examination.(12) Those who develop HRV will be considered meeting the primary endpoint of the study as illustrated below.

Assessment of safety is performed on every clinic visit by medical history taking, physical examination, laboratory parameters, and reports of adverse events and/or serious adverse events. A direct telephone hotline to our research staff will be offered to patients so that they can contact and report to us any adverse events between scheduled visits. Patients who prematurely withdraw from the study will be followed up until the last study visit (i.e. 60 months after the randomisation visit) to detect any delayed clinical events. Unscheduled visits will be arranged if patients develop any clinical evidence of liver complications.

During the unscheduled visits, patients will be assessed by the investigators. Appropriate medical history taking, physical examination, and blood tests including complete blood picture, renal and liver biochemistries, clotting profile, alpha-fetoprotein, as well as other appropriate investigations will be performed. Any adverse events will be recorded and serious adverse events will be reported accordingly.

6.4 Patient safety

Common side effects of carvedilol include dizziness and postural dizziness, headache, hypotension and bradycardia.

The assessment of safety will be based on physical examination, laboratory tests, and observed or reported adverse events. A direct telephone line will be provided for patients and physicians to use to report adverse events that occur between the scheduled visits with the study physicians. Patients who discontinued the study drugs prematurely will be followed until the end of the study, to determine whether adverse events have occurred.

Unscheduled visit will be arranged when patients recognized symptoms of hepatic decompensation such as hematemesis or tarry stool signifying variceal haemorrhage, abdominal distension signifying ascites, and so on, that happened between scheduled visits. This unscheduled visit enables to protect patient safety associated with hepatic decompensation.

6.5 Subject withdrawal

A patient must be withdrawn from the study if he/she withdraws consent. Subjects who (1) experience adverse events, or (2) have pre-existing violation of entry criteria may remain in the study unless the investigator determines that it is not in the subject's best interest to continue. The specific reason for withdrawal should be indicated.

Subjects who withdraw from the study are invited to attend the clinic visit until month 60 visit to determine the endpoints. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, the best effort should be made to document any subject outcomes, if possible.

7. ENDPOINT ASSESSMENT

7.1 Primary endpoint

The primary endpoint is a composite of incident HRV, hepatic decompensation or death. HRV is defined, as aforementioned, by moderate to large OV or OV with red wale sign. Hepatic decompensation is defined by the presence of ascites, variceal bleeding or overt hepatic encephalopathy. Ascites is defined by compatible clinical signs and confirmed with ultrasound or paracentesis. Intraperitoneal fluid detected only by ultrasound is not considered an endpoint.

Variceal bleeding will be suspected if patients are presented with haematemesis or melaena or a decrease in the haemoglobin level of at least 2 g/dL. The diagnosis is made when OGD shows one of the following features: active bleeding from a varix, a “white nipple” overlying a varix, clots overlying a varix, or varices with no other potential source of bleeding.(12) Overt hepatic encephalopathy is evidenced if there is symptom or sign compatible with West Haven criteria grade II or above.(13) Hepatorenal syndrome is diagnosed with the presence of ascites if there is an increase in serum creatinine ≥0.3 mg/dL within 48 hours or ≥50% increase in serum creatinine that is known or presumed to have occurred within the preceding seven days, after excluding hypovolemia, shock, nephrotoxic agents and structural kidney damage.(14)

7.2 Secondary endpoints

Secondary endpoints include (1) the development of each hepatic decompensation event, (2) development of HCC, (3) change in hepatic function in terms of Child-Pugh and model for end-stage liver disease (MELD) scores, (4) change in LSM and SSM, (5) adverse events and (6) survival until the last clinic visit.

8. POSSIBLE RISKS AND ADVERSE EVENT REPORTING

8.1 Possible risks and discomfort

There is minimal discomfort in blood taking, undergoing transient elastography and ultrasonography. Major complications of OGD include bleeding and perforation but the major complication rate is overall less than 0.1%. Carvedilol may cause dizziness and postural dizziness, headache, hypotension and bradycardia in some patients, and these will be assessed at every follow-up visit.

The adverse event reporting period for this study Is from signing the informed consent through 30 days after the last follow-up visit.

8.2 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

Two telephone enquiry hotlines for reporting subject's adverse events are available during office hours. Two gastroenterologists are available after office hours including public holidays to handle adverse events. 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 final 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). An unscheduled visit will be performed if subjects have to withdraw early from the study.

8.3 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 Chinese University of Hong Kong – New Territories East Cluster Combined Research Ethics Committee [Joint CUHK-NTEC 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.

9. DATA ANALYSIS AND STATISTICAL METHODS

9.1 Sample size determination

According to the landmark PREDESCI trial, hepatic decompensation or death occurred in 16% of cACLD patients with CSPH taking NSBB compared to 27% of those without NSBB, with a hazard ratio of 0.5. Our study is designed as a superiority trial with a composite endpoint of incident HRV, hepatic decompensation and death. As patients in grey zone are also recruited in our study, and also from our previous study that 45% of patients were in grey zone compared to 19% in CSPH group suggesting that we will expectedly recruit more patients in the grey zone than CSPH group, it is reasonably believed that the rates of hepatic decompensation and death for both NSBB and conventional arm will be less than what was observed in PREDESCI trial. Including incident HRV in the composite endpoint, we expect an approximately 14% and 28% cumulative incidences of the composite endpoints at 60 months, respectively, taken into consideration from our preliminary data. **(Figure 1)** Together with consideration of a planned interim analysis at 1 year of follow-up after patient enrollment, as well as the implementation of stratified randomisation, a sample size of 402 evaluable subjects randomised into a 1:1 ratio (201 patients in each arm) would provide 90% power to demonstrate superiority of the NSBB

arm (to start carvedilol in cACLD patients in high-risk grey zone or with CSPH by Baveno VII criteria) compared to the conventional approach, using a 2-sided 95% confidence interval (CI). To allow for a 15% dropout rate, the target enrolment would be **474 subjects (237 subjects in each arm)**.

9.2 Data analysis

Data will be analysed by both intention-to-treat (ITT) and per-protocol approaches. The ITT population consists of all randomised subjects who have received at least one dose of the treatment according to the randomised treatment strategy.

Patients who withdraw from the study or refuse to have the follow-up will be censored at the last clinic visit. Failure to take at least 70% of the study drugs or the use of prohibited drugs is regarded as non-compliance with the protocol.

Data will be analysed using Statistical Product and Service Solutions (SPSS) version 25.0 (SPSS, Inc., Chicago, Illinois). Continuous variables will be expressed in mean ± standard deviation or median (interquartile range [IQR]), as appropriate, while categorical variables will be presented as number (percentage). Qualitative and quantitative differences between subgroups will be analysed by chi-square or Fisher's exact tests for categorical parameters and Student's *t* test or Mann-Whitney test for continuous parameters, as appropriate. Qualitative and quantitative differences between ordinal subgroups will be analysed by chi-squared test for linear trend or Fisher's exact tests for categorical parameters and one-way ANOVA or Kruskal-Wallis test for continuous parameters, as appropriate. Patients will be followed until the occurrence of the endpoint, and censored upon the time of liver transplantation or at the end of follow-up period, whichever occurs earlier. Patients who withdraw consent will be censored assuming no endpoints developed after the last documented clinic visit. The primary and secondary endpoints will be analysed as time-to-event variables with hazard ratio and 95% CI calculated. Event rates of endpoints will be compared with stratified log-rank test based on the stratifying factor for the time to the first event after randomization. Survival will be estimated by Kaplan-Meier method. Cox proportional hazard models will be employed to compare the two study arms with respect to the primary endpoint, adjusting for baseline risk factors such as cause of cACLD and baseline LSM. Primary analysis will be performed with adjustment of the stratifying factor. A prespecified subgroup analysis will be performed in CSPH and high-risk grey zone groups. All statistical tests were two-sided. Using the Lan and

DeMets analogue of the O'Brien-Fleming sequential boundary, the *p*-values for statistical significance for the primary analysis are 0.00366 and 0.04875, respectively, for the interim analysis and for the final analysis. If statistical significance is achieved in the primary endpoint at the interim analysis, superiority will be declared and the study will be terminated.

10. QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Data management

Only the research executive and the Principal Investigators have access right to the database using their login user names and passwords. Subjects' information is kept anonymous. They are identified by their study numbers and initials to maintain subjects' confidentiality. All the data in the CRF will be entered to the electronic database by the research nurses within 48 hours of the subject's visit. Amendment to the electronic database can only be made by the study coordinator.

The research executive is responsible for cross checking the data. After completion of the study, the database will be locked. Only the Principal Investigator has the access right to the locked data. All databases will be back up once per two weeks by the server system of our centre.

10.2. Study Management

10.2.1. Monitoring

The research executive will perform source data verification (a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study). This will require direct access to all original records for each subject (e.g., clinic charts). A Data and Safety Monitoring Board, consisting of two physicians and one bio-statistician not involved in this study, will be formed for reviewing data of the study on an ongoing basis to ensure safety of the study subjects as well as validity and integrity of the data, and make periodic recommendations to the study team on whether to continue, modify, or prematurely terminate the study.

10.2.2. Auditing and Inspection

The Clinical Research Management Office and Joint CUHK-NTEC CREC at the Chinese University of Hong Kong will perform auditing and inspection, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities are

conducted, and data are recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements.

10.2.3 Changes to the protocol

If a protocol amendment is deemed necessary, we will notify our Joint CUHK-NTEC CREC about the amendment or a new version of the study protocol (Amended Protocol) to seek their approval. Approval of the revised Informed Consent Form by the Joint CUHK-NTEC CREC is required before the revised form is used.

11. ETHICS

11.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favourable opinion in writing by our Joint CUHK-NTEC CREC. The protocol must be re-approved by our Joint CUHK-NTEC CREC annually. Progress reports and notifications of serious and unexpected adverse drug reactions will be provided to our Joint CUHK-NTEC CREC.

11.2. 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 our Joint CUHK-NTEC CREC. This study is designed based on a thorough knowledge of the scientific background, a careful assessment of risks and benefits, have a reasonable likelihood of benefit to the population studied and will be conducted by suitably trained investigators using approved protocol.

11.3. Written 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 both English and 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 Form.

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 our Joint CUHK-NTEC CREC.

11.4 Emergency contact persons

Dr. Jimmy Che-To Lai (Principal investigator)

Tel: 3505-4205

11.5 Procedures in case of medical emergency

Dr. Jimmy Che-To Lai is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. A medical emergency usually constitutes a serious adverse event and should be reported to our CREC.

12. REFERENCES

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13. FIGURES

Figure 1. Incidence of hepatic decompensation in different Baveno VII categories from a prospective cohort of 2,763 patients with compensated advanced chronic liver disease (cACLD)

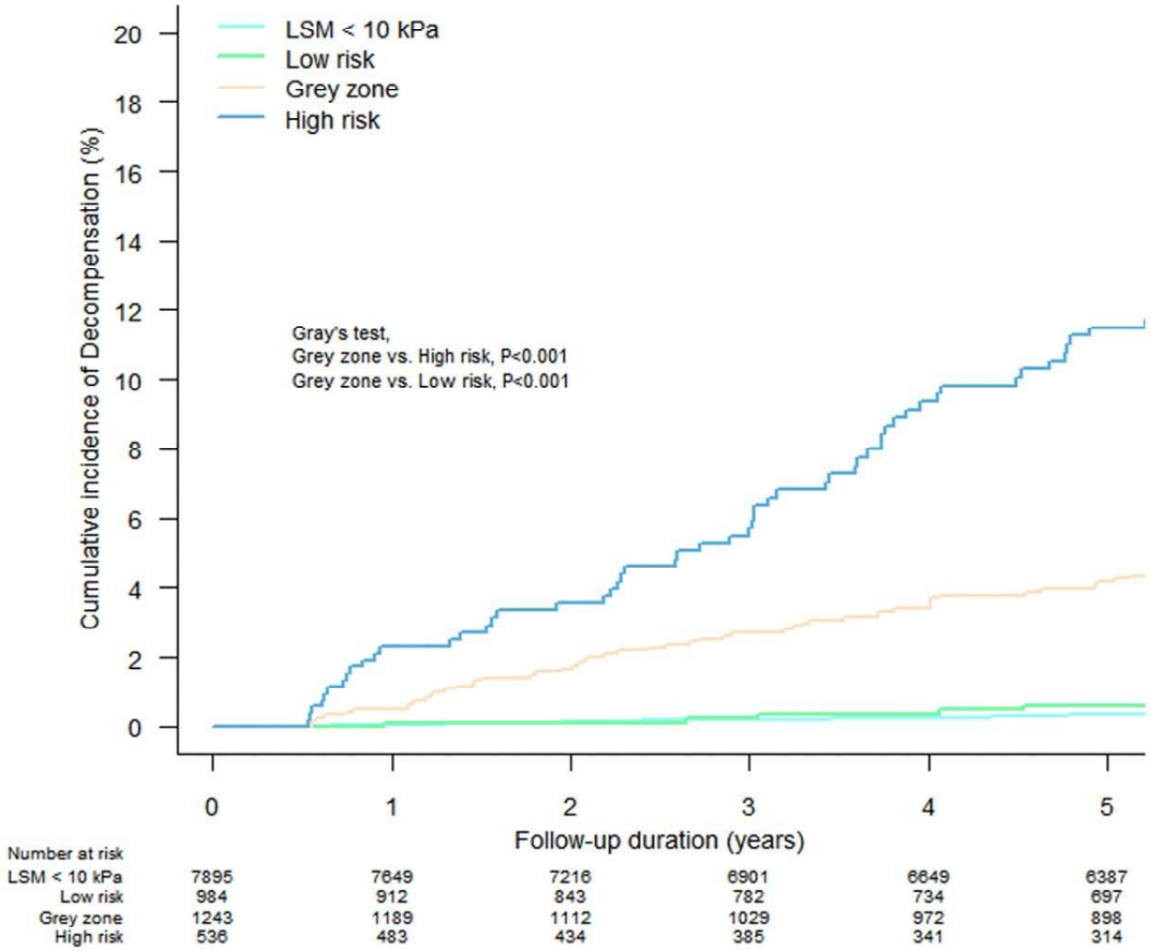


Figure 2. Study flowchart

