An investigator-Initiated Protocol

CONFIDENTIAL

A multi-center randomized controlled study of Primary preventiOn of esophageal vaRiceal bleeding in cirrhotic patients Treated with HVPG-guided therapy Or Standard heart rate-guided therapy: the PORTHOS trial

PROTOCOL TITLE '**A multi-center randomized controlled study of primary prevention of esophageal variceal bleeding in cirrhotic patients treated with HVPG-guided therapy or standard heart rate-guided therapy'**

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PROTOCOL SIGNATURE SHEET

PROTOCOL TITLE: A multi-center randomized controlled study of primary prevention of esophageal variceal bleeding in cirrhotic patients treated with HVPG-guided therapy or standard heart rate-guided therapy

Protocol date: 10 April 2014 – Version 3.0

PROTOCOL APPROVED BY:

Principal Investigator: Dr. M.J. Coenraad Date:

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AASLD	**American Association for the Study of Liver Diseases**
ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
APASL	**Asian Pacific Association for the Study of the Liver**
BID	**Bis in die; twice daily**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
DSMB	**Data Safety Monitoring Board**
ECG	**Electrocardiogram**
eCRF	**electronic Case Report Form**
EQ-5D	**EuroQol 5-dimension questionnaire**
GCP	**Good Clinical Practice**
HF	**Heart Frequency**
HVPG	**Hepatic Venous Pressure Gradient**
ICF	**Informed Consent Form**
ICU	**Intensive Care Unit**
LUMC	**Leiden University Medical Center**
MELD	**Model of End Stage Liver Disease**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
NIH	**National Institutes of Health**
NSBB	**nonselective beta-blockers**
NVMDL	**Nederlandse Vereniging van Maag-Darm-Leverartsen**
SAE	**Serious Adverse Event**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
Sponsor	**The sponsor is the party that commissions the organization or performance of the research, for example a pharmaceutical company, academic hospital,**

	scientific organization or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidizing party.
TIPS	**Transjugular Intrahepatic Portosystemic Shunt**
VAS	**Visual Analogue Scale**
QALY	**Quality Adjusted Life Years**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: About 50% of cirrhotic patients who use nonselective beta-blockers (NSBB) for primary prevention of variceal bleeding do not reach target hemodynamic response, defined as HVPG < 12 mmHg or a > 20% decrease in HVPG from baseline. These so-called hemodynamic nonresponding patients have significantly higher rate of first esophageal variceal hemorrhage as compared to patients who do respond to NSBB.
Although the efficacy of HVPG monitoring in the primary prevention of variceal hemorrhage is not an issue, international institutions that publish guidelines differ in their recommendations concerning HVPG monitoring. As a result, practice currently varies widely. We hypothesize that HVPG-directed primary prophylaxis leads to a reduction in first variceal bleeding episodes and is cost-effective in the long term.
Objective: To determine cost-effectiveness of hepatic venous pressure gradient (HVPG)-guided non-selective beta-blocker therapy as compared to standard heart rate-guided beta-blocker therapy in the primary prevention of esophageal variceal bleeding in cirrhotic patients.
Study design: Randomized controlled trial comparing nonselective beta-blocker therapy guided by the hemodynamic response as determined by the difference in HVPG before and after starting oral nonselective beta-blockers, to standard heart rate-guided nonselective beta-blocker therapy in patients with esophageal varices due to liver cirrhosis.
Study population: Patients with liver cirrhosis and large (≥5 mm) esophageal varices without a history of esophageal variceal hemorrhage.
Intervention:
In HVPG-group: Perform baseline HVPG measurement, then start propranolol 20 mg orally twice daily (BID), increase the dose stepwise with 3 days interval to decrease the heart rate to maximum tolerated dose. After four weeks a second HVPG measurement is performed. In hemodynamic responders (HVPG < 12 mmHg or a >20% reduction in HVPG compared to baseline), beta-blockers are continued until end of follow-up. In hemodynamic nonresponders (who do not reach target decrease in HVPG), beta-blockers are continued and repeated endoscopic band ligation is performed with 2-4 weeks interval until complete obliteration of large varices.
In control group: Start propranolol 20 mg BID, increase the dose stepwise with 3 days interval to maximum heart rate-guided tolerated dose and continue therapy throughout the whole study period. No routine follow-up gastroscopy is required.
Main study parameters/endpoints: Primary endpoint: first variceal bleeding episodes occurring within the first two years.

Secondary endpoints: mortality; occurrence of other cirrhosis-related complications (composite endpoint); occurrence of hepatocellular carcinoma; costs of treatments and adverse effects.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: In the control group standard of care is given. In the study arm two extra admissions in day-care setting (for 3 h) for HVPG measurements are required for the study protocol. Hepatic venous pressure gradient measurement is performed via catheterization of the internal jugular vein. Complications due to HVPG measurement are very rare and include hemorrhage near the insertion place or cardiac arrhythmia during progression of the catheter through the heart. In hemodynamic nonresponders from the study arm, repeated endoscopic band ligation is performed in daycare setting with intervals of 2-4 weeks. Endoscopic band ligation is standard of care in primary prophylaxis of variceal hemorrhage in patients who do not tolerate beta blockers and is always performed as secondary prophylaxis. Complication rate of endoscopic band ligation is approximately 2%, with the most frequent complication hemorrhage from a banding ulcer or varix. Patients will visit the outpatient clinic during dose escalation on a weekly basis until a stable dose is reached. Then a 3 monthly outpatient clinic visit including physical examination scheme will be followed. The site visits required for dose escalation and outpatient clinic follow-up are standard of care. Patients are requested to complete biannual questionnaires, and health VAS. During the study a Total of 200 cc blood will be taken in 9 sessions.

1. INTRODUCTION AND RATIONALE

Esophageal variceal bleeding is the most common lethal complication of liver cirrhosis with portal hypertension, occurring at an annual rate of approximately 5-15% and associated with a mortality rate of 20% in 6 weeks after the bleeding (1). Acute variceal bleeding in untreated individuals is associated with a 60% risk of rebleeding within 1-2 years of the first hemorrhage, with a mortality rate of 30% (1) and much morbidity. It is often followed by hepatic encephalopathy, the occurrence of confusion, altered level of consciousness or coma as a result of liver failure, and systemic infections, leading to 18% mortality (2). Infections or dehydration may cause a hepatorenal syndrome, i.e., functional renal insufficiency in approximately 10% of patients. This syndrome is associated with very high mortality (1 year survival of 0-40%).

Nonselective beta-blockers (NSBB) are the only drugs which have been proven to significantly reduce the risk of first esophageal variceal bleeding in cirrhosis and related mortality and which are cost-effective in the primary prevention of esophageal variceal hemorrhage. In patients who are intolerant to or who have contraindications (e.g. asthma or congestive heart failure) to beta-blockers, endoscopic band ligation is performed.

Endoscopic band ligation is the endoscopic placement of elastic bands upon the varices. This is performed in a day-care setting. In international guidelines, NSBB are currently standard of care in large (≥5 mm) esophageal varices (AASLD guideline, APASL, Baveno IV). Propranolol is started at a dose of 20 milligrams (mg) twice a day (BID) and stepwise increased until maximum tolerated dose. However, the reduction in heart rate due to beta-blocker therapy does not correlate with the reduction in portal venous pressure (3).

Measurement of the hepatic venous pressure gradient (HVPG) is currently the best available and a safe method to evaluate the presence and severity of portal hypertension, but this is not routinely used to monitor the hemodynamic response to NSBB.

HVPG measurement involves percutaneous catheterization of the jugular vein with progression of the catheter into the hepatic vein in order to measure pressures before (free) and after balloon inflation (wedged). The HVPG is the difference between the wedged and the free hepatic venous pressure and represents the portal venous pressure. Clinically significant portal hypertension is defined as an increase in HVPG to 10 mmHg. The success rate of HVPG measurements is over 95%, and complication rate is very low; most frequent, if any, local bleeding after jugular venous puncture or cardiac arrhythmias during progression of the catheter through the heart. The risk of pneumothorax is < 1/1000 because the jugular venous puncture is performed under ultrasound guidance.

A number of case series have been carried out and showed that about 50% of patients who use nonselective beta-blockers for primary prevention of variceal hemorrhage do not reach

the target of hemodynamic response, defined as HVPG < 12 mmHg or a > 20% decrease in HVPG from baseline (4). These so-called hemodynamic nonresponding patients have a significantly higher rate of first esophageal variceal hemorrhage as compared to patients who do respond to NSBB (4, supplement 1).

International institutions that publish guidelines differ in their recommendations concerning HVPG monitoring. The Baveno IV consensus report (5) and AASLD guideline (1) do not recommend the routine use of HVPG monitoring in primary prevention. In contrast, the APASL recommend that HVPG monitoring should preferably be used in patients treated with nonselective beta-blockers to prevent first variceal hemorrhage (6). As a result, practice currently varies widely. The need for research on the role of HVPG in directing therapy is widely felt (1, 5, 7, 8). In this study we therefore propose to compare the two treatment strategies in patients with large esophageal varices without prior variceal hemorrhage, namely standard heart rate- guided beta-blocker therapy and HVPG- guided beta-blocker therapy with adding endoscopic band ligation to beta-blockers as a rescue therapy in hemodynamic nonresponders to beta-blockers. We will use clinically relevant, symptomatic endpoints.

OBJECTIVES

Primary Objective: To compare the cost-effectiveness of hepatic venous pressure gradient-guided nonselective beta-blocker therapy with standard therapy consisting of nonselective beta-blockers adjusted to maximum tolerated dose in the prevention of first variceal hemorrhage in patients with liver cirrhosis.
The research question is whether the benefit of HVPG-guided nonselective beta-blocker therapy (a reduction in first variceal hemorrhage and its associated costs) outweighs its risks (additional costs for HVPG measurements and endoscopic band ligations as rescue therapy in HVPG-nonresponders) on the long term (2 years).

STUDY DESIGN

A randomized controlled trial comparing hepatic venous pressure gradient (HVPG)-guided nonselective beta-blocker therapy and standard heart rate-guided beta-blocker therapy as preventive therapy for variceal hemorrhage in patients with liver cirrhosis and large esophageal varices without prior variceal hemorrhage. Consecutive patients from the participating centers in whom large (≥ 5mm) esophageal varices are diagnosed will be included, unless they fulfill one of the exclusion criteria or do not give informed consent. Consenting subjects will be randomized to one of the following two arms:
Arm 1: Propranolol start 20 mg BID. orally with dose escalation based on heart frequency (HF) with 3-days interval to the maximum tolerated dose. No routine control endoscopy is required.
Arm 2: A baseline HVPG measurement is performed in day-care setting. After this procedure propranolol is started at 20 mg BID. with dose escalation as described in arm 1.
A second HVPG measurement is performed at 4 weeks after adequate propranolol therapy. HVPG response is defined as absolute HVPG <12 mmHg or >20% HVPG reduction compared to baseline HVPG in response to chronic propranolol use. In patients who reach target HVPG reduction (responders), propranolol is continued at the same dose without routine control endoscopy. In patients who do not reach target HVPG reduction (nonresponders), endoscopic band ligation is performed in day-care setting with intervals of 2-4 weeks until complete obliteration of varices. Follow-up endoscopy with 6 months interval is performed to detect and treat recurrent large varices.
In all patients who are intolerant to propranolol, endoscopic band ligation with intervals of 2-4 weeks is performed until complete obliteration of large varices. Follow-up endoscopy with 6 months interval will be performed to detect and treat recurrent large varices.
HVPG measurements will be standardized among the participating centers, as described in 6.3. Both HVPG measurements in each patient will be performed at the same center. If patients are recruited in hospitals where HVPG is not performed, they will be referred to a tertiary center only for the HVPG measurements. In this referral strategy, usual referring patterns (e.g. for liver transplantation of second opinions) are followed in order to limit inconvenience for patients. All patients will be followed for a period of two years, during which the outcome parameters will be assessed. The flowchart gives an overview of the procedures all subjects will undergo (supplement 2).

2. STUDY POPULATION

2.1. Population (base)

Patients with liver cirrhosis and recently diagnosed esophageal varices ≥5 mm at endoscopy without prior variceal bleeding are eligible for the study. Patients will be derived from six national hospitals and two Belgian hospitals. These centers together see approximately 1100 patients yearly with liver cirrhosis. Gastroesophageal varices are present in 50% of patients with cirrhosis (1). Patients without varices develop these at a rate of 8% per year (1). Furthermore, patients with small varices develop large varices at a rate of 8% per year (1). In supplement 3 are shown the centers who have confirmed their participation and the number of patients they expect to recruit (fulfilling inclusion criteria and consenting for participation) for this study. Centers were requested to make a conservative estimation of the number of patients they expect to recruit. Support of the Dutch Society of Hepatology Association for the Study of the Liver will be requested at their next Board meeting.

2.2. Inclusion criteria

Liver cirrhosis with esophageal varices ≥ 5 mm

Age: ≥ 18 years

2.3. Exclusion criteria

- Contraindications to beta-blocker therapy (Sick-sinus syndrome, 2nd and 3rd grade AV-block, cardiogenic shock, clinically manifest sinusbradycardia, current active and/or treated asthma or other obstructive pulmonary diseases, untreated heart failure, untreated pheochromocytoma, metabolic acidosis, prolonged fasting)
- Pregnancy
- Prior variceal hemorrhage
- Esophageal varices in the absence of liver cirrhosis
- Intermediate, advanced or terminal stage hepatocellular carcinoma (BCLC stage B, C or D) (9)
- Refractory ascites as defined by the International Ascites Club (10)
- Hepatorenal syndrome as defined by the International Ascites Club (10)
- Prior treatment or prophylaxis for esophageal varices or variceal esophageal bleeding (nonselective beta-blocker use, Transjugular Intrahepatic Portosystemic (TIPS), endoscopic band ligation, endoscopic sclerotherapy)

2.4. Sample size calculation

Assumptions for risk of first variceal hemorrhage in patients on standard propranolol and variceal band ligation:

The risk of first variceal hemorrhage in patients on beta-blocker therapy has been studied in many clinical trials and varies between 0 and 21%. A meta-analysis of 11 trials that included 1189 patients evaluating nonselective beta-blockers versus non-active treatment or placebo. The risk of variceal hemorrhage was 27% in controls and 17% in beta-blocker treated patients (11).

The risk of first variceal hemorrhage in patients treated by band ligation as compared to nonselective beta-blockers was studied in many clinical trials. These are analyzed in three meta-analyses and a systematic review. The pooled relative risk for first variceal bleed of endoscopic variceal ligation vs beta-blockers was 0.57 (95% CI 0.38-0.85) (10), 0.63 (95% CI 0.43-0.92) (11), 0.56 (95% CI 0.43-0.77) (12) and 0.62 (0.47-0.81) (15) in the meta-analyses, respectively. First variceal hemorrhage occurred in band ligation treated patients in resp 14% (12) and 13% 13 as compared to 20% 12 and 21% 13 in patients treated with beta-blocker therapy. In two randomized controlled trials that were not included in these meta-analyses, first esophageal variceal bleeding occurred in 14% (16) and 5% of patients treated by band ligation (15). For the sample size calculation, we used the most conservative pooled relative risk for first variceal bleed of band ligation vs beta-blockers of 0.63 13.

Assumptions for the proportion of patients who achieve target HVPG reduction (HVPG < 12 mmHg or a >20% reduction in HVPG compared to baseline) to propranolol:

The proportion of patients who achieve target HVPG decrease after chronic nonselective beta-blocker use is in a meta-analysis of Albillos et al 49% (4). The four trials that were not included in this meta-analysis reported proportions of responders varying between 38% and 65% (18-21).

Assumptions for the risk of first esophageal variceal bleeding in patients who achieve target reduction in HVPG (‘responders’):

The incidence of first esophageal variceal hemorrhage in patients who achieve target HVPG decrease after during chronic nonselective beta-blocker therapy is in a meta-analysis of Albillos et al. 6% (4). The four trials that were not included in this meta-analysis reported incidence of first variceal hemorrhage in responders varying between 0% and 4% (18-21). Based on a risk reduction of 50% of first esophageal variceal hemorrhage, a sample size of 240 subjects in each arm should be sufficient (alpha 0.05, power 80%).

We ask for permission to start the trial with the intention to recruit 480 patients in three years, with an interim analysis after one year (expected to be recruited at that time: 60 patients from

8 participating centers). This interim analysis will only be done to test futility (i.e. trial can be stopped after inclusion of 60 patients if there will be clearly no result, even with 420 additional patients).
Usually, financial means and contracts are present at the start of the study to continue the study after one year if there is no futility. In this study, there is no certainty but a high probability to accomplish additional financial support after the first year. The researchers think that the financial means will be obtained for the additional three years if the 60 patients we aim for, will actually be included in one year. Therefore, the researchers are prepared to take the responsibility for this risk and suggest the METC to agree with this proposal.

3. TREATMENT OF SUBJECTS

There will be a randomization between two treatment strategies in this study.

3.1. Investigational product/treatment

Strategy 1: Propranolol start 20 mg BID orally with dose escalation based on heart frequency (HF) with 3-days interval to the maximum tolerated dose. No routine control endoscopy is required.
Strategy 2: A baseline HVPG measurement is performed in day-care setting. HVPG measurement involves percutaneous catheterization of the jugular vein with progression of the catheter into the hepatic vein in order to measure pressures before (free) and after balloon inflation (wedged).The HVPG is the difference between the wedged and the free hepatic venous pressure and represents the portal venous pressure. After this procedure propranolol is started at 20 mg BID. with dose escalation as described in strategy 1.
A second HVPG measurement is performed at 4 weeks after adequate propranolol therapy. HVPG response is defined as absolute HVPG <12 mmHg or >20% HVPG reduction compared to baseline HVPG in response to chronic propranolol use. In patients who reach target HVPG reduction (responders), propranolol is continued at the same dose without routine control endoscopy. In patients who do not reach target HVPG reduction (nonresponders), endoscopic band ligation is performed with intervals of 2-4 weeks until complete obliteration of varices. Endoscopic band ligation is the endoscopic placement of elastic bands upon the varices under light sedation in day care setting. Follow-up endoscopy with 6 months interval is performed to detect and treat recurrent large varices.
In patients who are intolerant to propranolol, endoscopic band ligation with intervals of 2-4 weeks is performed until complete obliteration of large varices.
Follow-up endoscopy with 6 months interval will be performed to detect and treat recurrent large varices.
The package leaflet of propranolol is shown in supplement 4.

3.2. Use of co-intervention (if applicable)

Patients should not use other alpha- or beta-blocking agents, calcium antagonists, oral nitrates or simvastatin.
Permitted treatments during the study include, but are not limited to the following: loop-diuretics, aldosteron-antagonists, vitamin K, antibiotics and lactulose.

Patients with ascites (mild, moderate or severe) use a sodium-restricted diet (2 gram sodium/day). Women in child-bearing age should use contraceptives during the time of the study.

4. METHODS

4.1. Study parameters/endpoints

4.1.1. Main study parameter/endpoint

The primary efficacy outcome is the number of first variceal hemorrhage episodes within two years of follow-up.
The diagnosis of variceal hemorrhage is made when diagnostic gastroscopy shows one of the following: active bleeding from a varix, a “white nipple” overlying a varix, clots overlying a varix or varices with no other potential source of bleeding (21).

4.1.2. Secondary study parameters/endpoints (if applicable)

- mortality
- a composite endpoint of other portal hypertension and cirrhosis-related complications, namely ascites, spontaneous bacterial peritonitis, encephalopathy, hepatorenal syndrome and hepatocellular carcinoma
- costs of treatment per treatment strategy (including costs of nonselective beta-blocker therapy, HVPG measurements in day-care setting, nonurgent endoscopic band ligation, therapy associated with acute variceal bleed, including admission at ICU and ward, emergent endoscopic band ligation, rescue TIPS placement)
- heart frequency and blood pressure at month 3, 6, 9, 12, 15, 18, 21 and 24.
- serum concentrations of sodium, creatinin, bilirubin and INR at month 3, 6, 9, 12, 15, 18, 21 and 24.

4.2. Randomization, blinding and treatment allocation

Patients from the participating centers in whom large (≥5mm) esophageal varices are diagnosed will be included, unless they fulfill one of the exclusion criteria or do not give informed consent. Consenting subjects will be centrally electronically randomized to standard heart rate-guided beta-blocker therapy, or to undergo two HVPG measurements (before and after one month of nonselective beta-blocker therapy) with endoscopic band ligation therapy in patients who do not reach target decrease in HVPG. Stratification will be performed per center. The study is not blinded.

4.3. Study procedures

Study Flow and Visit Schedule

Supplement 2 represents the study flowchart.

Supplement 5 lists all study visits and assessments. “X” indicates when visits and assessments are performed. All assessments have a ±3 days window unless otherwise indicated. In the event of public holidays (e.g. Christmas, New Year’s Day), there is a ±5 days window on all assessments. Every effort must be made to follow the schedule of assessments within the windows outlined in the protocol. Additional assessment may be performed as clinically indicated.

Inclusion/Exclusion criteria

Information regarding eligibility criteria will be collected on the Inclusion/Exclusion eCRF. Patients who do not meet all entry criteria can not be entered into the study.

Patient demographics/other baseline characteristics

Data will be collected on patient characteristics including demographic information (age, sex, race, ethnicity), drug, nicotine or alcohol use and other background or relevant medical history (disease history, pre-existing conditions), and any other assessments that are done for the purpose of determining eligibility for inclusion in the study (complete physical examination, vital signs, hematology, blood chemistries, pregnancy test only required for women of childbearing potential, abdominal ultrasound to test the patency of portal and hepatic veins and the absence of focal liver lesions, electrocardiography).

Vital signs will be recorded on the appropriate eCRF. Sitting pulse rate and sitting blood pressure will be measured at each visit.
Vital signs will be measured at 3, 6, 9, 12, 15, 18, 21, 24 months and as clinically indicated.

Blood pressure will be measured according to the National Institutes of Health, National Heart, Lung, and Blood Institute Guidelines [NIH, 1997] with the following standardized techniques: patients are seated in a chair; blood pressure measurement begins after at least 5 minutes of rest, the appropriate cuff size is used to ensure accurate measurement, measurements will be taken preferably with a mercury sphygmomanometer. Only one reading is required. If the blood pressure reading is ≥ 160 mmHg systolic and/or ≥ 95 mmHg diastolic, the measurement will be repeated to verify initial reading.

Height and weight

Height will be measured only at screening. Height will be measured in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes).
Weight will be measured at:

Baseline ≤ 7 days prior to the first dose of the study treatment

3,6,9,12,15,18,21,24 months as clinically indicated.

Laboratory evaluations

Laboratory evaluations must be performed at every protocol required visit or as frequently as clinically indicated.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria: 1) they induce clinical signs or symptoms, 2) they are considered clinically significant or 3) they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease.

Hematology

Hematology tests include hemoglobin, platelet count

Hematological tests will be performed at:

Baseline ≤ 7 days prior to the first dose of the study treatment

Month 3, 6, 9, 12, 15, 18, 21, 24

As clinically indicated

Coagulation profile

Prothrombin time (PT) will be reported as international normalized ratio (INR).

A coagulation profile will be performed at:

Baseline: ≤ 7 days prior to the first dose of the study

Month 3, 6, 9, 12, 15, 18, 21, 24

As clinically indicated

Biochemistry

Biochemistry tests consist of creatinine, sodium, total bilirubin, copeptin

Biochemistry tests will be performed at:

Baseline ≤ 7 days prior to the first dose of the study treatment

Month 3, 6, 9, 12, 15, 18, 21, 24

As clinically indicated

Biobank

Blood will be sampled and stored for future research at 0, 6, 12, 18 and 24 months. At every planned sampling time 10 ml serum, EDTA, citrate and heparin tube will be sampled and stored according to the local Biobank regulations. DNA will be isolated and stored for future research. Permission to sample blood and to isolate and store DNA for future research will be asked for specifically and documented in a separate written informed consent.

Electrocardiogram (ECG)

A standard 12 lead ECG will be performed at the time points specified below. Interpretation of the tracing must be made by a qualified physician and documented on the ECG section of the eCRF. Each ECG tracing should be labeled with the study number, patient initials, patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities noted on the screening ECG should be recorded on the Medical History eCRF page. Clinically significant abnormalities noted at any point during the study should be recorded on the AE eCRF.

ECG will be performed at:

Screening ≤ 14 days prior to the first dose of the study treatment

As clinically indicated

Endoscopic band ligation

Non-urgent endoscopic band ligation

Patients are prepared as for routine endoscopic band ligation. Patients are admitted to day-care unit before endoscopic band ligation and have to refrain from eating and drinking from 6 hours preceding the endoscopic band ligation. Anticoagulative or antiplatelet therapy has to be interrupted according to the NGMDL guideline “Endoscopische ingrepen bij patienten met antistolling en plaatjesaggregatieremming” (2005, supplement 6). An indwelling intravenous catheter will be placed in the antecubital vein. Endoscopic band ligation is performed in left supine position at the endoscopy unit. Local anaesthetics using lidocaine spray 10 % and conscious sedation (level 2-3) using midazolam iv. during pulse-oxymetry monitoring is applied according to the NGMDL guideline “sedatie en/of analgesie tijdens endoscopische procedures” (2001, supplement 7). A flexible endoscope is introduced by mouth, and progressed via esophagus and stomach to descending duodenum with careful insufflation of air. After withdrawal of the endoscope into the esophagus for the inspection for the presence, number and appearance of varices, the endoscope will be withdrawn. A ligation device will be placed upon the endoscope, then the endoscope will be introduced again by mouth and positioned in the esophagus for placement of elastic bands upon the esophageal varices after suction of the varix into ligation device. This procedure can be repeated several

times, depending on the ligation device until complete collapse of varices. Thereafter, the endoscope will be withdrawn; patients have to refrain from drinking for 30 minutes. After an observational period of 6 hours at the day-care unit, patients can be dismissed. Patients are advised to use liquid diet for 24 hours after endoscopic band ligation. Experienced gastroenterologists or GI fellows, supervised by experienced gastroenterologists, will perform the endoscopic band ligation. Number, size (< 5 mm or ≥5 mm) and the presence of red whale marks of varices will be retrieved from endoscopy reports.

Urgent endoscopic band ligation

In case of acute variceal hemorrhage, treatment is applied according to the NIV guideline "Bloedingen tractus digestivus", chapter "Varicesbloedingen" (2010, supplement 8). Patients are admitted to medium care of intensive care unit for hemodynamic monitoring, volume resuscitation and in case of massive bleeding intubation. Immediate administration of vasoactive therapy (terlipressin, octreotide) and iv. antibiotics and urgent endoscopy have to be performed according to this guideline. In case of endoscopic band ligation, the procedure will be performed as described in the previous section. Treatment decisions upon endoscopy are left to the treating physician. Number, size (< 5 mm or ≥5 mm) and the presence of active bleed, white nipple or red whale marks of varices will be retrieved from endoscopy reports.

HVPG measurement

HVPG measurements are performed according to the LUMC protocol "Levervenedrukmeting" (2012, supplement 9). Patients are admitted to day-care unit and have to refrain from eating and drinking from 3 hours preceding the procedure. An indwelling intravenous catheter will be placed in the antecubital vein. Anticoagulative or antiplatelet therapy has to be interrupted according to the LUMC guideline "stollingsbeleid" (supplement 10). HVPG measurements will be performed at the Radiology or Hepatology Department according to local situations, always in supine body position after local anesthesia of internal jugular vein with lidocaine 1%. Patients are monitored throughout the procedure by continuous electrocardiography, blood pressure measurements and pulse-oxymetry. The internal jugular vein will be punctured using a needle, and subsequently a 8Fr (2.7 mm) canula will be progressed from the internal jugular vein via the heart to the right hepatic vein. The following pressures will be measured: inferior v.cava pressure, free hepatic venous pressure, wedged (with inflated balloon at the tip of the catheter) hepatic venous pressure. Pressures at these positions will be measured during 15-30 seconds and repeated twice at every position in order to check reproducibility. During pressure measurements, patients are not allowed to talk or move, as this may influence the results. When pressure measurements

are completed, the catheter will be removed and the patient has to remain in supine position for 1 hour before the patient can be dismissed.
HVPG measurements are performed < 10 working days after randomization and after 4 weeks propranolol at maximum tolerated dose with a ±3 days window.

Beta-blocker therapy

Depending on the strategy patients have been randomized to, patients will start propranolol within one week after inclusion or within one week after the first HVPG measurement is performed. Propranolol 20 mg BID is started at the outpatient clinic after documentation of baseline heart frequency and blood pressure. After 3-5 days patient is reassessed at the outpatient or research unit and dose escalation is performed if the patient tolerates the medication according to the following scheme: 40 mg BID, 60 mg BID, 80 mg BID to maximum tolerated dose. Patients who tolerate 80 mg BID may be switched to propranolol retard 160 mg.
Reasons to stop medication are bronchospasm requiring (change of) therapy and clinically manifest bradycardia (especially heart frequency < 50 /min) or hypotension not recovering in response to dose reduction, heart block, heart failure and cyanotic acra. If possible, propranolol should be gradually tapered in order to prevent rebound arrhythmia or angina pectoris.
Reasons to limit further dose escalation are the occurrence of side effects.
Side effects which may occur are gastrointestinal complaints like nausea, diarrhea, tiredness, impotence, headache, decreased concentration or reaction ability, depression and disturbed sleep-wake pattern, skin or conjunctiva irritability, worsening of psoriasis or myasthenia gravis, alopecia, agranulocytosis or increasing hepatic encephalopathy). Dose escalation every 3-5 days is performed at the discretion of the investigating physician. If side effects occur at a certain dose, the dose is tapered by one step, until side effects are tolerable or have disappeared. Patients continue at the maximum tolerated dose throughout the study.
To accurately determine the patient's drug exposure throughout the study, the following information must be reported on the eCRF:

- Planned dose administration (maximum tolerated dose after dose escalation as described above)
- Actual total daily dose administered
- Regimen (e.g., none, o.d./q.d., once every other day, other)
- Start and end date of drug administration
- Dose change (no or yes)
- Reason for dose change (e.g., adverse event, dosing error, lab test abnormality etc.)

Study treatment compliance will be assessed by the investigator or designee at the indicated visits. This information must be captured in the source documents at each visit.

Questionnaires

Patient reports, using the EQ5D (primary analysis, Dutch tariff), the Rand36 and the patients' health VAS (transformed to a utility scale using the power transformation U = 1-(1-VAS/100)^1.61) will be taken biannually. If necessary patients will be supported by the research nurse or investigator to complete the questionnaires.

4.4. Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

4.5. Replacement of individual subjects after withdrawal

We aim to include 480 patients in three years, of which 60 patients in one year from 6 participating centers in the first year. The additional 14 centers will start recruiting after the interim analysis at one year.

4.6. Follow-up of subjects withdrawn from treatment

In case of withdrawal, patients will be monitored by their former physician for standard clinical care.

4.7. Premature termination of the study

Should it be necessary to terminate the trial, the patient should be seen as soon as possible and treated as described in Section 6 for a prematurely withdrawn patient. The investigator will be responsible for informing Ethical Committees of the early termination of the trial.

A Data Safety Monitoring Board will be installed. No predefined stopping rule will be set, because of the design of the study with initially treatment by repeated endoscopic band ligation in hemodynamic nonresponders in order to reduce acute variceal hemorrhage in the long term. The DSMB will be informed about all SAEs and can, based on that information, decide to premature termination of the study.

5. SAFETY REPORTING

5.1. Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardize the subjects' health. The investigator will take care that all subjects are kept informed.

5.2. Adverse and serious adverse events

Safety assessments will consist of monitoring and recording all adverse events, including serious adverse events, the monitoring of hematology, blood chemistry and regular monitoring of vital signs and physical condition. These assessments should be performed ± 21 days of the scheduled day of assessment except for adverse events that will be evaluated continuously through the study. (Refer to time table).

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational treatment strategy. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc.

All SAEs will be reported through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, according to the requirements of that METC (within 15 days after the sponsor has first knowledge of the serious adverse reactions).

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

5.3. Follow-up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

5.4. Data Safety Monitoring Board (DSMB)

A data safety and monitoring board (DSMB) will be composed of a biostatistician, bioethicist, clinical pharmacologist and two clinicians and installed at the time of initiation of the study. Each member will have no conflict of interest with the sponsor or company of the study. Their principal role is to ensure the safety of patients, which they do by analyzing adverse events. The DSMB working procedures will be according to the guidelines of the European Medicines Agency published on July 27, 2005.The DSMB meetings will be held every 6 month after entry of the first patient and end with the last visit of the last patient. The advice(s) of the DSMB will be notified upon receipt by the sponsor to the METC that approved the protocol. With this notification a statement will be included indicating whether the advice will be followed.

6. STATISTICAL ANALYSIS

6.1. Descriptive statistics

Analyses of primary endpoint

Proportions of patients having a first variceal hemorrhage in two years of follow-up will be compared between both study arms using a chi-squared test to detect differences between proportions as well as a logistic regression model. Results will be reported as estimated proportions affected with confidence intervals, observed risk differences with confidence estimate and odds ratio effect estimates and confidence intervals. The logistic regression analysis will be also used to test the null hypothesis of no difference in proportions having varices between both treatment arms (null hypothesis odds ratio=1). We hope to detect a reduction of 50%, assuming the control arm risk is approximately 50% (and for which the study achieves 80% power). The analysis will be repeated to evaluate heterogeneity of treatment effect across participant centers through inclusion of a random treatment center effect. Random effect will be reported as standard deviation of effect and compared with the estimated overall effect. All analyses will be carried out with the intention-to-treat principle.

Sensitivity analysis

Baseline binary variables will be reported as proportions and standard deviations and compared between both arms using chi-squared testing. Means, medians, standard deviations and ranges will be used for continuous variables and compared between both arms at baseline using two-sample t-testing. Log-transformed data and non-parametric testing will be considered for non-normally distributed measures. Primary endpoint analyses will be repeated correcting for known and suspected confounders at baseline to evaluate robustness of study result.

Moderate loss-to-follow up is expected for this study, which will not likely exceed 5% across patients. Multiple imputation-based re-analyses of the data will be performed should losses-to-follow up be larger than 5% of patients.

Secondary data analyses

Cox regression based survival analysis and Kaplan-Meier will be investigated for time-to-bleeding. The number of bleeding episodes per patient will be investigated as a secondary endpoint using a Poison model at two years of follow-up.

Economic evaluation

General considerations

The economic evaluation will be a cost-utility analysis from the societal perspective, based on patient reports. We expect that the costs of HVPG testing will be justified by the savings

and QALY gains due to prevented bleedings among HVPG nonresponders. Cost-effectiveness will be statistically analyzed using net-benefit acceptability curves, including only the uncertainty due to trial sampling error.
The primary analysis will be trial based with a 2-year time horizon. This relatively short time horizon is likely to underestimate the cost-effectiveness of HVPG, since long-term savings and QALY gains are neglected. Therefore, if HVPG is not cost-effective in the primary analysis, a lifelong cost-utility analysis will be performed by extrapolating the trial data using a simple Markov model. Long term costs and effectiveness will be discounted in accordance with the then-applicable Dutch guideline (revision Oostenbrink 2004).

Cost analysis

Costs will be estimated from the societal perspective. Health care use, patient costs and productivity losses will be measured using biannual cost diaries. A cost price analysis will be performed for the HVPG measurements. Other costs will be valued using standard prices (including time and travel costs).

Patient outcome analysis

The direct impact of HVPG testing on quality of life will be estimated by comparing the biannual patient reports, using the EQ5D (primary analysis, Dutch tariff), the Rand36 and the patients' health VAS (transformed to a utility scale using the power transformation U = 1-(1-VAS/100)^1.61). In the primary analysis, quality-adjusted life years (QALYs) will be estimated as the area under the observed 2-year utility curves (accounting for differences in both quality of life and mortality). In the Markov model, long-term utility will be estimated by combining the short-term observed utility with the additional utility loss due to long-term non-fatal bleedings and due to aging. Mortality will be estimated by combining general Dutch mortality data (Statistics Netherlands) with the group-specific mortality risk from fatal bleedings.

6.2. Interim analysis

Futility and early stopping

At one year, a futility analysis will be carried out, based on a 99.5% confidence interval estimate for the difference in proportions having variceal bleeding at that point. Should the calculated confidence estimate exclude differences in proportion of at least 10% (or larger), then this result will be forwarded to the sponsor and co-investigators to make a decision on continuation of the trial.

Patient accrual rates across the first year will be assessed. Should accrual rates be too low to achieve the desired sample size across 3 years, the trial coordinator will advise to stop the trial.

7. ETHICAL CONSIDERATIONS

7.1. Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (Bulletin of the World Health Organization, August 2008)) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

7.2. Recruitment and consent

The eligible patients will be informed about the study project by the physician or study nurse/nurse practitioner in the outpatient clinic. Inclusion of the study will be performed by the research physician. All patients will be informed about the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed. Patients will be given the time needed to consider their decision. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by participating investigators other than their treating physician. It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not compromise the patient's subsequent care. Written informed consent will be obtained, by the physician in the outpatient clinic..

7.3. Benefits and risks assessment, group relatedness

Our objective is to prove the efficacy of a pharmacotherapeutical intervention in relation to its safety and costs. Oral nonselective beta-blockers with dose escalation to maximum tolerated dose, reduce the risk of first esophageal variceal hemorrhage. Limitations of beta-blocker therapy include intolerance or contraindications in approximately 15% of patients and an inconsistent effect on portal pressure (3). Portal pressure can be measured by the hepatic venous pressure gradient (HVPG). The reduction in HVPG after beta-blocker therapy correctly identifies hemodynamic nonresponders to beta-blocker therapy. Nonresponders have a 50% higher risk of first variceal hemorrhage than HVPG responders do (4). Rescue therapy, like endoscopic band ligation, could be offered to patients who do not achieve target reduction in HVPG during beta-blocker therapy if they would be identified early, in order to reduce their risk of first esophageal hemorrhage. HVPG monitoring is increasingly used in clinical practice, but not for this indication. This may be explained by the low costs of current unmonitored beta-blocker therapy (€60/year). In contrast, HVPG monitoring is an invasive measurement, for which an observational period in the hospital for three hours following the procedure is required. The costs associated with HVPG vary among different hospitals. In our institution the costs per procedure amount to approximately €1500 (€770 for the

materials, €300 for additional charges such as expenses for specifically trained personnel, overheads, maintenance charges, costs for incidental repairs, unforeseen and travel costs and €430 for admission in day-care setting including blood testing). Costs associated with nonurgent endoscopic band ligation amount to €350 and costs associated with admission (at intensive care unit and ward) for acute variceal hemorrhage amount to €6000.
The estimated prevalence of liver cirrhosis in the Netherlands is 24.000, of which 50% have esophageal varices. About 50% uses beta-blocker therapy, resulting in an annual bleeding risk of 5-15% and a 20% mortality risk per bleeding. Effective treatment by HVPG-guided NSBB therapy reduces the bleeding risk by 50% (4), thus annually preventing 300 bleedings (=24.000 x 50% x 50% x 10% x 50%) and 60 deaths (=300 x 20%). The costs of HVPG testing (twice €1500 for 2000 new patients each year = 6 M€) will be partly compensated by savings on (ICU) hospital costs due to prevented bleeding (300 x €6000 per bleeding = 1.8 M€), leading to a net increase of 4.2 M€ in costs. Relative to the improved effectiveness, these costs amount to €70.000 per prevented death or €10.000 per QALY (assuming a life expectancy of 10 years at 70% utility). These estimates are in line with estimates from two decision-analysis studies (23, 24), in which HVPG-guided primary prevention of variceal bleeding was found to be cost-effective (see systematic review).
Our proposed study is aimed particularly at cost-effectiveness of hemodynamic monitoring, using HVPG measurements of beta-blocker therapy in the primary prevention of variceal bleeding. With our design and sample size, we expect to be able to draw definite conclusions on the balance between benefits, risks and costs. To our knowledge, no report by national advisory boards on this subject is available, nor is there any randomized trial currently ongoing on this subject.

7.4. Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7, subsection 6 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23rd June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;

3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as ‘verrichter’ in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.
Contact information for LUMC Insurance Company: Centramed

7.5. Incentives (if applicable)

Subjects will not receive any special incentives or compensation through participation in the study.

8. ADMINISTRATIVE ASPECTS AND PUBLICATION

8.1. Handling and storage of data and documents

Data will be handled confidentially and if possible anonymously. Where it is necessary to be able to trace data to an individual subject, a subject identification code list shall be used to link the data to the patient. This code is not based on the patient initials and birth-date. The handling of personal data complies with the Dutch Personal Data Protection Act (in Dutch: De Wet Bescherming Persoonsgegevens, Wbp.) When the data is put in the database, only the relevant data will be extracted. The database is only accessible for one investigator/research nurse working on this project. The study protocol and all data generated or prepared in the course of the study will not be disclosed to anyone not directly involved in the study without prior consent. Patients will not be identified by their personal information in any publication following this study project.

8.2. Amendments

Amendments are changes made to the research after a favorable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favorable opinion.

8.3. Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

8.4. End of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient’s last visit.

In case the study is ended prematurely, the investigator will notify the accredited METC, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

8.5. Public disclosure and publication policy

The intention is to publish the results of this study in a peer reviewed international journal.

8.6. Study time-lines

Start patient entry: March 2013

9. REFERENCES

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10. SUPPLEMENTS

Supplement 1: table from meta-analysis of HVPG in primary prophylaxis of esophageal variceal hemorrhage

Supplement 2: flowchart

Supplement 3: table representing participating centers

Supplement 4: bijsluiter propranolol

Supplement 5: time and events schedule

Supplement 6: NGMDL richtlijn protocol Endoscopische ingrepen bij patiënten met antistolling en plaatjesaggregatieremming" (2005).

Supplement 7: NGMDL richtlijn "sedatie en/of analgesie tijdens endoscopische procedures" (2001).

Supplement 8: NIV richtlijn "Bloedingen tractus digestivus", hoofdstuk "Varicesbloedingen" (2010).

Supplement 9: LUMC protocol levervenedrukmeting

Supplement 10: LUMC stollingsbeleid vastgesteld voor radiologisch onderzoek en behandelingen