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Propranolol versus carvedilol for the primary prophylaxis of variceal bleeding: a proposed multicenter, randomized, double-blind trial

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Abstract:

Background: *Bleeding from esophageal varices is one of the most frequent and deadly complications of liver cirrhosis, with six-week mortality rates as high as 30%. The estimation of portal pressure by means of hepatic venous pressure gradient (HVPG) measurement remains the single most accurate predictor of bleeding in individual patients. An increasing number of studies have reported a greater reduction of HVPG using carvedilol compared to the current standard of care, propranolol; however, there are still no clinical trials comparing carvedilol to propranolol head-to-head for the prophylaxis of variceal bleeding.*

Aims: *To compare carvedilol versus propranolol for the prevention of a first variceal bleed (primary prophylaxis) in patients with cirrhosis and esophageal varices.*

Methods: *This is a proposed design and protocol for a multicenter, randomized, active-controlled, double-blind, parallel group, phase III superiority trial, including a total of 452 patients with cirrhosis and esophageal varices that are at high risk of bleeding.*

Potential impact of study: *In view of the encouraging results obtained with carvedilol in prior studies, we believe a trial comparing propranolol to carvedilol in terms of clinical outcomes is necessary to clearly establish whether carvedilol should become the treatment of choice for the primary prohylaxis of variceal bleeding. If this trial is successfully conducted, results can be expected to have a substantial impact on clinical practice and future research directions.*

Keywords: *Cirrhosis, variceal bleeding, variceal hemorrhage, primary prophylaxis, propranolol, carvedilol, non- selective beta blocker*

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INTRODUCTION

Cirrhosis is the final stage of chronic liver disease and has many causes, most notably viral hepatitis, chronic alcohol abuse, and non-alcoholic steatohepatitis (NASH). Patients with cirrhosis almost invariably develop portal hypertension as a result of increased vascular resistance due to widespread fibrosis and altered liver architecture, which in turn give rise to clinical manifestations of hepatic decompensation such as ascites, hepatic encephalopathy, and acute variceal bleeding. Bleeding from esophageal varices is one of the most frequent and deadly complications of liver cirrhosis. The annual risk of developing a first variceal hemorrhage is approximately 12%,1 with six-week mortality rates nearing 30% once a first bleeding episode has occurred.2-6 Several variables have been used to estimate the risk of variceal bleeding, however, the degree of portal pressure as measured by hepatic venous pressure gradient (HVPG) remains the single most accurate predictor of bleeding in individual patients.7,8

Owing to their proven efficacy, safety, and tolerability, non-selective beta-blockers (NSBBs) such as propranolol have been widely used to prevent variceal bleeding in patients with cirrhosis and remain the mainstay of pharmacotherapy to this day.9-12 The effects of NSBBs on portal pressure derive primarily from a

decrease in splanchnic blood flow mediated by beta-2 adrenergic receptor blockade, alongside a reduction in cardiac output which results from their antagonistic action on beta-1 receptors.13 Several studies have shown that patients who achieve a hemodynamic response to NSBBs (defined as a 20% decrease in baseline HVPG or a reduction to values below 12 mmHg) have a markedly decreased risk of bleeding, which results in improved survival.14-16 As a result, medical therapy has been directed towards the attainment of this goal. Recently, considerable effort has been devoted to the search of new drugs with improved potential for the reduction of portal hypertension, of which carvedilol has produced the most promising results. An increasing body of literature has reported a superiority of carvedilol over propranolol for reducing portal hypertension,17 which, interestingly, seems to be linked to an additional effect on intrahepatic vascular tone caused by its intrinsic anti-alpha-1 activity as well as a capacity to enhance the release of nitric oxide (NO).18

Despite these promising data, there are still no clinical trials comparing carvedilol to propranolol head-to-head for the primary or secondary prophylaxis of variceal bleeding; hence, it is still unclear whether the hemodynamic benefits of carvedilol also translate into improved clinical outcomes (i.e., reduced bleeding rates and improved overall survival) while maintaining a favorable side-effect profile. In view of this, we decided to design and develop a research protocol for a randomized, double-blind, multicenter trial comparing carvedilol to propranolol for the primary prophylaxis of variceal bleeding.

Research aim and hypotheses

The aim of this study is to compare carvedilol versus propranolol for the primary prophylaxis of variceal hemorrhage in patients with cirrhosis and esophageal varices.

Our primary hypothesis is that carvedilol is superior to propranolol for preventing a first bleeding episode in patients with cirrhosis. Our secondary hypothesis is that carvedilol does not significantly increase the risk of hepatic or cardiovascular decompensation with respect to propranolol.

METHODS

Trial design and study setting

The trial is designed as a multicenter, randomized, active-controlled, double-blind, parallel group, phase III superiority trial. Patients will be recruited from outpatient clinics located at any of the 10 participating centers. All patients who fulfill eligibility criteria and provide their informed consent for participation will be able to participate in the study.

Study outcomes

The primary endpoint is variceal bleeding, defined by the presence of hematemesis, melena or hematochezia with evidence of active variceal bleeding or signs of recent bleed in upper GI endoscopy, alongside a drop of at least 2 g/dl in circulating hemoglobin concentration (or, in case of blood transfusion, a rise in hemoglobin concentration inferior to 0.5 g/dl per unit of packed red blood cells).

Secondary endpoints include all-cause and bleeding-related mortality, hemodynamic adverse events (systemic hypotension, pre-renal azotemia, or heart failure requiring hospital admission), hepatic decompensation (ascites, hepatic encephalopathy, spontaneous bacterial peritonitis), liver transplantation, and quality of life (QoL).

Eligibility criteria

Inclusion criteria:
- Age between 18 and 75 years;
- Liver cirrhosis of any etiology;
- Esophageal varices at high risk for bleeding (large varices irrespective of Child score OR small varices with red wale marks/Child C score) with or without concomitant gastric varices (GOV-1 or GOV-2).

Exclusion criteria:
- Isolated gastric varices (IGV-1 or IGV-2)
- Previous variceal bleeding episodes;
- Previous endoscopic variceal ligation or sclerotherapy;
- Pregnancy;
- Contraindications for NSBB therapy (baseline pulse rate <50 bpm or systolic blood pressure <90 mmHg; allergy; sick sinus syndrome; second or third degree AV block; severe asthma; severe chronic obstructive pulmonary disease);
- Use of anticoagulant medication;
- Portal vein thrombosis;
- Hepatocellular carcinoma;
- Previous transjugular intrahepatic portosystemic stent shut (TIPS) or portacaval shunt surgery;
- Model for End-stage Liver Disease (MELD) score > 30.

Recruitment

Patients will be recruited using a combination of targeted and broad-based strategies. The targeted strategy will consist of consecutive recruitment from the outpatient clinics located at each of the participating centers. We

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hope to enhance this strategy by providing information about the trial during relevant scientific meetings and via e- mail to physicians included in the mail lists of national and international associations for the study of the liver. The broad-based strategy will entail the creation of a website with information about the trial and broadcasting through social media, newspapers, radio, and television.

Randomization and allocation concealment

All eligible patients will be randomly assigned to each treatment arm using a 1:1 allocation ratio and a computer- generated sequence created by a centralized off-site organization. The sequence will use random block sizes and stratification according to site and will then be provided to an unblinded pharmacist using an interactive voice response system (IVRS). The pharmacist will be responsible for the concealment of the sequence and delivering the drug to each individual patient.

Intervention

Patients will be randomized to either propranolol or carvedilol arms. Dosing of both drugs will be titrated according to heart rate and systolic blood pressure (SBP), with targets of 50-60 bpm and > 90 mmHg, respectively. Patients receiving propranolol will start on a dose of 20 mg BID which will then be escalated weekly in 20 mg steps until the targeted heart rate and/or SBP are reached. Similarly, patients randomized to carvedilol will initially receive 3.125 mg BID and will be escalated in 3.125 mg steps every week to a maximum dose of 25 mg per day.

Blinding

Though we acknowledge that both the assessment and the occurrence of the primary outcome (variceal bleeding) are unlikely to be influenced by treatment disclosure, other outcomes such as QoL are more subjective and therefore more prone to bias due to unblinding. Because of this, we decided to design the study as a double-blind study (i.e., outcome assessors and trial participants will be blinded). To ensure blinding we will provide identical looking 20 mg propranolol and 3.125 mg carvedilol tablets which will be coded and dispensed by the unblinded pharmacist in each site. Dose modifications will be made using single tablet adjustments following a standardized protocol based on target heart rate, SBP, and presence of side effects. Because both treatments belong to a same drug class with similar side effect profiles and have already been extensively used in patients with cirrhosis, emergency unblinding will only be performed if disclosure of the treatment is considered essential for the management of the individual patient. In such cases, the treating physician will contact the Medical Advisor who, if necessary, will instruct the local pharmacist to disclose the information only to the treating physician. The treatment allocation will not be disclosed to the patient or any other study personnel. The patient will then receive treatment outside of the study protocol with whichever therapy is considered appropriate, but will be asked to complete the follow-up as initially planned and will be analyzed according to original randomization.

Study timeline

All potential candidates will attend a baseline visit to assess fulfillment of eligibility criteria and obtain their written informed consent. If criteria are met and the patient provides his/her consent the treating physician will run a series of initial tests, namely: a full lab panel, a liver ultrasound, and an upper GI endoscopy (the latter only if the patient has had none performed during the 6 months prior to the baseline visit). Once these results have been obtained and the patient is confirmed to be eligible he/she will enter randomization and will be followed weekly during 1 month for drug titration and assessment of side effects, and every 3 months thereafter for a total of 2 years. Drug titration will be performed during visits as mentioned above (see interventions). The following information will be recorded during each study visit (in addition to any other data which is considered relevant by the treating physician): laboratory parameters, MELD score, vital signs, physical exam, presence of signs or symptoms suggestive of unnoticed bleeding (e.g., bloody or tarry stools), an adverse events questionnaire, and a World Health Organization Quality of Life (WHOQOL) questionnaire. Study treatment will only be discontinued if the patient presents hemodynamic-related adverse effects (e.g., dizziness, fatigue, dyspnea, deterioration of renal function) that do not subside with dose-reduction, or at patient's own request. A simplified study timeline is provided in Figure 1.

Adherence

Adherence to the trial medication will be encouraged by:
- Providing periodical information to patient, family, and friends regarding disease severity and the importance of receiving prophylactic treatment for variceal bleeding, as well as potential benefits of medication.
- Providing a 24h telephone contact number and e- mail address to answer patient's and families' doubts regarding study treatment.

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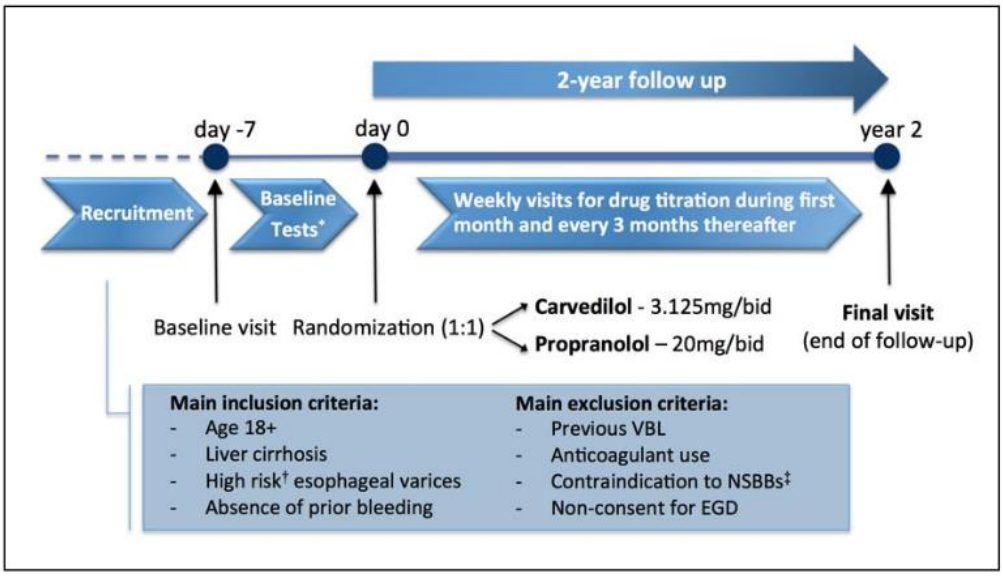

Figure 1. Study Timeline.

*Full lab panel, liver ultrasound, and upper GI endoscopy (only if no reliable exam performed during previous year).

†High risk: Large varices irrespective of Child score OR small varices with red wale marks/Child C score.

‡Baseline pulse rate <50 bpm or systolic blood pressure <90 mmHg allergy, sick sinus syndrome, second or third degree AV block, severe asthma, or severe chronic obstructive pulmonary disease.

- Providing counseling to patients with suspected poor adherence.

Adherence to the trial medication will be assessed by:

- Monitoring heart rate and blood pressure during clinical visits.
- Routine pill counts.

Sample size calculation

In order to prove superiority of carvedilol with a power of 80% at the 5% significance level, 271 subjects will be required in each treatment arm. This calculation was performed using a log-rank test based on the following assumptions: a) bleeding rates in the carvedilol and propranolol groups will be 7 and 15% at a median 2 years follow-up, respectively; and b) losses to follow up will not exceed 10%. These values have been derived from separate trials reporting bleeding rates of carvedilol and propranolol, most of which are included in the aforementioned meta-analysis. We believe these figures represent a more realistic estimate of the effect size difference between both drugs than those used in prior trials.

Statistical analysis plan

Numerical data will be reported as means with accompanying standard deviations or as medians with interquartile ranges; categorical data will be presented as counts and percentages. Assessment of normality will be performed using the Kolmogorov –Smirnov test. Bleeding and mortality rates will be expressed using the Kaplan-Meier method and differences analyzed using a log-rank test. Independent predictors of bleeding will be estimated using a Cox proportional hazards model, adjusting for patient's age, recruitment site, size of varices, Child-Pugh class, and any other variables which are considered to influence outcome and are unevenly distributed after randomization. Differences in continuous secondary outcomes will be computed using the unpaired Student's t- test or the Wilcoxon rank sum test as appropriate. Categorical outcomes will be analyzed using the $\chi 2$ test or Fisher's exact test.

All calculations and statistical analyses will be computed using an intention-to-treat analysis with Stata 14.1 (StataCorp, College Station, Texas, USA). P-values below .05 will be considered to indicate statistical significance. Missing data will be handled with a multiple imputation method.

Data monitoring

A Data Monitoring Committee (DMC) composed by independent individuals with the relevant expertise will monitor trial conduct and safety. Given potential concerns about meeting sample size requirements, DMC will also be responsible for reviewing patient accrual rate every 3 months and informing individual site coordinators in case of suspected deviation from the original objectives.

Bearing in mind that the experience with carvedilol in patients with cirrhosis is already fairly broad and that the DMC will perform a continuous assessment of trial

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data, we do not believe that an interim analysis for safety is warranted.

Likewise, we do not plan to perform interim analyses for efficacy or futility. The rationale for avoiding an early efficacy analysis is based on our power calculations, which revealed an exceedingly low probability of proving superiority before at least 80% of the total number of predicted events had been reached, at which point the risk of a false positive result outweighs the potential benefits of terminating the trial early. With respect to futility, we believe stopping the trial early for this reason may leave us unable to determine whether carvedilol is merely ineffective or actually harmful. This is an important distinction to make since carvedilol would likely remain as a second line treatment in non-responders to propranolol.

DISCUSSION

With over 38,000 deaths per year in the US and over a million worldwide, liver cirrhosis constitutes a huge public health concern that affects the rich and the poor alike[15]. In countries where it is available, liver transplantation has become the treatment of choice for patients with end-stage liver disease, with 5-year survival rates reaching 70% in most developed countries. In spite of this, most patients do not have access to liver transplantation and those who do will often die before they reach the operating room, usually due to infections or complications related to variceal bleeding.

According to current guidelines, patients at high risk for variceal hemorrhage require prophylactic treatment with either NSBBs, endoscopic variceal ligation, or both, depending on whether or not they have a prior history of bleeding. [15,21,22] The effectiveness of NSBBs rests largely on their ability to decrease portal hypertension, however, recent studies have demonstrated that over 60% of patients do not present a hemodynamic response to propranolol and therefore remain at increased risk for hemorrhage. This has led to the search for more effective treatments, of which carvedilol appears to be the forerunner due to its improved potential for the reduction of portal pressure.[23]

Six studies have been published to date comparing the short and long-term effects of carvedilol and propranolol on HVPG, all of which report a clear superiority of carvedilol in this arena. A recent meta-analysis of these trials showed that the mean reduction in HVPG caused by carvedilol was 8.49% (95% CI, 12.36% - 4.63%) greater than that of propranolol[17]. Considering these favorable results, it seems somewhat surprising that only 1 trial has compared both drugs in terms of clinical endpoints, albeit only as secondary outcomes and with a follow-up of only 90 days[24]. The reason for this lack of studies appears to be two fold. First, the sample size required to yield adequate statistical power for a study comparing bleeding rates is considerably large, which makes it all the more challenging if we take into account that patients with cirrhosis often have poor adherence to medication and a substantial rate of loss to follow-up. In fact, this problem has been acknowledged by authors of previous trials comparing carvedilol to endoscopic variceal ligation for the primary prohylaxis of variceal bleeding. [26,27] In order to tackle this problem our main strategy is to include a large number of recruiting centers and concentrate our efforts on optimizing follow-up and adherence, instead of focusing solely on recruitment. Additionally, because statistical power depends on total number of events (i.e., bleeding episodes) rather than the actual number recruited of subjects, we plan to improve study efficiency by selecting patients with high bleeding risk and expanding follow-up to a median of 2 years.

The second reason for the lack of studies examining clinical outcomes of carvedilol is likely to be a problem with funding. Pharmaceutical companies have traditionally been unwilling to sponsor studies using NSBBs in patients with cirrhosis, which continue to be used off-label for this indication[25]. Our main approach to this issue will be to reduce costs by avoiding unnecessary expenses, primarily those derived from HVPG measurements. The utility of HVPG in assessing efficacy and identifying non- responders to propranolol has already been established by several high-quality studies;[7,8,23] therefore, we believe its use would only contribute to increase costs while adding little relevant information to the study.

CONCLUSION

In view of the encouraging results obtained with carvedilol in prior studies, we believe a trial comparing propranolol to carvedilol in terms of clinical outcomes is necessary to clearly establish whether carvedilol should become the treatment of choice for the primary prohylaxis of variceal bleeding. If this trial is successfully conducted, results can be expected to have a substantial impact on clinical practice and future research directions.

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Conflict of interest and financial disclosure

The authors followed the International Committee or Journal of Medical Journals Editors (ICMJE) form for disclosure of potential conflicts of interest. All listed authors concur with the submission of the manuscript, the final version has been approved by all authors. The authors have no financial or personal conflicts of interest. No funding was received for this work.

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