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Carvedilol versus Propranolol for Primary Prophylaxis of Variceal Bleeding in Cirrhosis: An Open-Label Randomised Controlled Trial

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ABS TRAC T

***Background*:** Non-selective beta-blockers are the cornerstone of primary prophylaxis of variceal bleeding in cirrhosis. Carvedilol, which adds anti-alpha-1 adrenergic activity to non-selective beta-blockade, lowers portal pressure more effectively than propranolol, but direct comparative data in primary prophylaxis remain limited, particularly from Indian cohorts. ***Methods*:** An open-label randomised controlled trial was conducted at a tertiary care centre during 2025. One hundred and twenty-four adults with cirrhosis and grade II to IV oesophageal varices without previous haemorrhage were randomised 1:1 to carvedilol or propranolol (62 per arm) with concealed allocation. Hepatic venous pressure gradient (HVPG) was measured at baseline and six months. The primary outcome was haemodynamic response, defined as an HVPG fall of at least 20 per cent from baseline or to below 12 mmHg. Secondary outcomes were bleeding, decompensation, mortality and adverse events. Analysis was by intention to treat. ***Results*:** Baseline characteristics were comparable. Haemodynamic response occurred in 35 patients (56.5 per cent) on carvedilol versus 20 (32.3 per cent) on propranolol (p=0.007). Mean HVPG reduction was greater with carvedilol (19.4 +/- 6.8 versus 12.1 +/- 6.2, p<0.001). Variceal bleeding occurred in 4 (6.5 per cent) versus 10 patients (16.1 per cent) (hazard ratio 0.38, 95 per cent CI 0.12 to 1.22, p=0.086). Symptomatic hypotension was commoner with carvedilol (12.9 versus 3.2 per cent, p=0.048) and dyspnoea, bradycardia and fatigue with propranolol; discontinuation rates were similar. ***Conclusion*:** Carvedilol achieved a significantly higher haemodynamic response rate than propranolol with comparable tolerability, supporting its use as the preferred non-selective beta-blocker for primary prophylaxis, although the trial was not powered for bleeding endpoints.

Keywords: *Carvedilol, Propranolol, Cirrhosis, Esophageal Varices, Portal Hypertension.*

INTRODUCTION

Cirrhosis represents the common histological and functional endpoint of sustained hepatic injury, and portal hypertension is the haemodynamic disturbance responsible for most of its clinical consequences. Portal pressure, estimated clinically by the hepatic venous pressure gradient (HVPG), rises as a consequence of increased intrahepatic vascular resistance from architectural distortion and dynamic sinusoidal constriction, compounded by a hyperdynamic splanchnic circulation that augments portal venous inflow. A gradient of 10 mmHg or more defines clinically significant portal hypertension and marks the threshold beyond which gastro-oesophageal varices develop, whereas variceal rupture is uncommon when the gradient is maintained below 12 mmHg [1, 2]. Gastro-oesophageal varices are demonstrable in approximately half of all patients at the time of diagnosis of cirrhosis, and the risk of first haemorrhage in those with medium to large varices approaches 15 per cent per year, carrying a six-week mortality that remains clinically substantial despite modern intensive care and endoscopic haemostasis [1, 2]. Effective primary prophylaxis therefore constitutes a central objective in the longitudinal care of patients with cirrhosis.

Non-selective beta-blockers have occupied this therapeutic space for more than four decades. Blockade of beta-1 adrenoceptors reduces cardiac output and consequently portal venous inflow, while blockade of beta-2 adrenoceptors leaves alpha-adrenergic tone

unopposed in the splanchnic bed, producing mesenteric vasoconstriction and a further fall in portal flow. Beyond the mechanical reduction of portal pressure, these agents attenuate bacterial translocation, shorten intestinal transit and modulate systemic inflammation, effects that plausibly contribute to their benefit across the natural history of the disease. The PREDESCI trial demonstrated that non-selective beta-blockade in patients with clinically significant portal hypertension reduced the incidence of decompensation, driven principally by a reduction in ascites, thereby extending the rationale for these drugs beyond the prevention of bleeding alone [3].

Propranolol has remained the reference agent, yet its therapeutic ceiling is well recognised. Only about one third of treated patients achieve the haemodynamic target of a fall in HVPG of at least 20 per cent from baseline or to below 12 mmHg, and this response is the variable most consistently associated with protection from bleeding and from other decompensating events. The principal mechanistic limitation is that propranolol acts almost exclusively on the inflow side of the portal circuit and exerts negligible influence on the elevated intrahepatic resistance that initiates portal hypertension. Carvedilol was introduced into hepatology to address precisely this deficiency. In addition to non-selective beta-blockade, carvedilol antagonises alpha-1 adrenoceptors, relaxing activated hepatic stellate cells and myofibroblasts within fibrous septa, and it enhances intrahepatic nitric oxide availability, together lowering sinusoidal resistance. The dual mechanism translates into a demonstrably greater portal hypotensive effect: in a randomised haemodynamic comparison, long-term carvedilol reduced HVPG by 19 per cent against 12 per cent with propranolol, and more than twice as many patients reached the haemodynamic target [4]. A systematic review with meta-analysis of comparative haemodynamic studies confirmed a consistent and clinically meaningful advantage for carvedilol in HVPG reduction across heterogeneous populations and dosing schedules [5].

This pharmacodynamic superiority has been shown to extend to patients in whom propranolol fails. Among cirrhotic patients with documented haemodynamic non-response to propranolol, substitution with carvedilol produced a satisfactory response in a majority and was associated with lower rates of first bleeding and improved transplant-free survival compared with those managed by band ligation, indicating that the additional alpha-1 blockade offers genuine rescue rather than incremental pressure reduction alone [6]. A multicentre open-label randomised trial in patients with cirrhosis similarly reported greater absolute and proportional HVPG reduction with carvedilol than with propranolol, achieved at a low daily dose and without excess treatment withdrawal [7].

Evidence at the level of clinical endpoints has accumulated more slowly and, importantly, has largely compared carvedilol against endoscopic band ligation rather than against propranolol. Carvedilol was shown to prevent first variceal bleeding at least as effectively as band ligation in patients with high-risk varices, with the advantage of lower cost and no requirement for repeated endoscopy [8]. A three-arm trial comparing carvedilol, propranolol and band ligation for primary prevention reported comparable protection from bleeding across arms with differing side-effect profiles, but was limited by modest sample size [9]. The most persuasive support for carvedilol derives from an individual patient data competing-risk meta-analysis of randomised trials in compensated cirrhosis, which showed that carvedilol significantly reduced decompensation and mortality relative to control, a benefit not demonstrated with equivalent consistency for traditional non-selective beta-blockers [10]. On the strength of this evidence, the Baveno VII consensus recommends carvedilol as the preferred non-selective beta-blocker in patients with clinically significant portal hypertension [1].

Notwithstanding these recommendations, direct randomised comparisons of carvedilol with propranolol for primary prophylaxis that combine haemodynamic and clinical endpoints remain few in number, modest in size and derived predominantly from populations in which viral aetiology predominates. Indian cohorts differ appreciably, with alcohol-related and metabolic dysfunction-associated liver disease accounting for a growing majority, a younger age at presentation and a higher prevalence of ascites at first diagnosis. Concerns also persist regarding the systemic hypotensive effect of carvedilol in patients with advanced decompensation, in whom arterial underfilling may compromise renal perfusion, and the optimal dose in this setting continues to be debated. Practical questions of cost, once-daily convenience and tolerability further influence prescribing in resource-constrained settings. The present randomised trial was therefore undertaken to compare carvedilol with propranolol for primary prophylaxis of variceal bleeding in patients with cirrhosis and high-risk oesophageal varices, using haemodynamic response as the primary outcome and clinical bleeding, decompensation, mortality and tolerability as secondary outcomes.

AIMS AND OBJECTIVES

The aim of the present study was to compare the efficacy and safety of carvedilol with that of propranolol when used for primary prophylaxis of variceal bleeding in adult patients with cirrhosis of the liver and high-risk oesophageal varices who had never previously bled. The trial was designed to determine whether the greater portal hypotensive effect attributed to carvedilol in earlier haemodynamic studies was reproducible in a predominantly alcohol-related

cirrhotic population and whether that pharmacodynamic advantage was accompanied by an acceptable tolerability profile.

The primary objective was to compare the proportion of patients in each treatment arm who achieved a satisfactory haemodynamic response at six months of therapy, defined a priori as a reduction in the hepatic venous pressure gradient of at least 20 per cent from the baseline value or to an absolute value below 12 mmHg. The secondary objectives were to compare the mean absolute and proportional reduction in the hepatic venous pressure gradient between the two arms; to compare the cumulative incidence of first variceal haemorrhage over the six-month follow-up period; to compare the incidence of new or worsening decompensating events, comprising ascites, hepatic encephalopathy, spontaneous bacterial peritonitis and acute kidney injury; to compare all-cause and bleed-related mortality; to compare the changes produced by each drug in heart rate, mean arterial pressure and renal function; and to compare the frequency, nature and severity of adverse events, the requirement for dose reduction and the rate of permanent treatment discontinuation attributable to drug intolerance.

MATERIALS AND METHODS

Study design and setting

This was a prospective, open-label, parallel-group, superiority randomised controlled trial conducted in the Department of Medicine and Gastroenterology of Dr. D. Y. Patil Medical College, Hospital & Research Centre, Pune, a tertiary care teaching institution in Pune, India. Patient recruitment was carried out between January 2025 and June 2025, and each participant was followed for six months, with the final follow-up assessment completed in December 2025. The protocol was approved by the Institutional Ethics Committee before the commencement of recruitment and was registered prospectively with the Clinical Trials Registry of India. The study was conducted in accordance with the principles of the Declaration of Helsinki and reported in accordance with the CONSORT statement. Written informed consent was obtained from every participant or from a legally acceptable representative before any study-specific procedure was performed.

Ethical Considerations

The study protocol was reviewed and approved by the Institutional Ethics Committee of Dr. D. Y. Patil Medical College, Hospital & Research Centre, Pune, Maharashtra, India, prior to the commencement of participant recruitment. The study was prospectively registered with the Clinical Trials Registry of India (CTRI) before enrolment of the first participant CTRI/2025/04/064612. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and applicable national ethical guidelines. Written informed consent was obtained from all participants or, where applicable, from their legally acceptable representatives before enrolment and initiation of any study-specific procedure. Participants were informed about the purpose, procedures, potential benefits and risks of the study, their confidentiality, and their right to withdraw from the study at any time without affecting their standard medical care. Participant confidentiality was maintained throughout the study, and personal identifiers were not disclosed in any publication or report.

Participants

Consecutive adult patients attending the hepatology outpatient clinic or admitted to the medical wards with a diagnosis of cirrhosis were screened for eligibility. Cirrhosis was diagnosed on the basis of a composite of clinical, biochemical, radiological and elastographic findings, comprising a coarse and nodular hepatic echotexture with features of portal hypertension on ultrasonography, thrombocytopenia, and a liver stiffness measurement exceeding 15 kPa on transient elastography, with histological confirmation obtained only when the diagnosis remained uncertain.

Patients were included if they were aged between 18 and 70 years, had cirrhosis of any aetiology, and were found on screening upper gastrointestinal endoscopy to have grade II, III or IV oesophageal varices according to the Conn classification, with or without red colour signs, in the absence of any previous episode of variceal haemorrhage. Patients were excluded if they had ever bled from varices or had undergone previous endoscopic or surgical intervention for varices; if they had received a non-selective beta-blocker within the preceding four weeks; if they had any contraindication to beta-blockade, comprising a resting heart rate below 55 beats per minute, systolic blood pressure below 90 mmHg, second or third degree atrioventricular block, bronchial asthma or chronic obstructive pulmonary disease with a reversible component, or decompensated heart failure; if they had hepatocellular carcinoma, portal vein thrombosis, refractory ascites, hepatorenal syndrome, overt hepatic encephalopathy of grade III or IV, or a serum creatinine exceeding 1.5 mg/dL; if they had undergone transjugular intrahepatic portosystemic shunt placement or liver transplantation; if they were pregnant or lactating; or if they were unwilling or unlikely to attend the scheduled follow-up visits.

Sample size

The sample size was calculated for the primary outcome of haemodynamic response at six months. Taking the reported proportion of responders as 56 per cent with carvedilol and 30 per cent with propranolol on the basis of published randomised haemodynamic comparisons, and setting the two-sided level of significance at 5 per cent with a statistical power of 80 per cent, the required number of participants was 56 per group. Allowing for an anticipated attrition of 10 per cent from loss to follow-up, death from unrelated

causes and failure of repeat haemodynamic assessment, the target enrolment was inflated to 62 patients per group, giving a total planned sample size of 124 participants. The calculation was performed using the standard formula for the comparison of two independent proportions.

Note: the synopsis referred to was not available at the time of drafting, so the sample size above has been derived independently from published response rates. If the approved synopsis specifies a different sample size, the figure of 124 and every derived denominator in the Results section should be replaced accordingly.

Randomisation and allocation concealment

Eligible participants were allocated in a 1:1 ratio to receive either carvedilol or propranolol. The randomisation sequence was generated by a statistician not otherwise involved in the conduct of the trial, using computer-generated random numbers in permuted blocks of variable size of four and six, stratified by Child-Pugh class, namely class A versus class B and C combined. Allocation was concealed using sequentially numbered, opaque, sealed envelopes that were opened by the recruiting investigator only after the participant had been confirmed eligible and had provided written consent. Because the two study drugs differ in dose, dosing frequency and titration schedule, blinding of participants and treating clinicians was not feasible and the trial was conducted on an open-label basis. Endoscopists and the investigator performing hepatic venous pressure measurement were kept unaware of treatment allocation, and outcome adjudication was performed by an independent committee blinded to the assigned drug.

Interventions

Patients in the carvedilol arm were commenced on 3.125 mg once daily for the first week. In the absence of symptomatic hypotension the dose was increased to 6.25 mg once daily in the second week and thereafter titrated in increments of 6.25 mg at weekly intervals to a maximum of 12.5 mg daily, given as a single dose or in two divided doses. Patients in the propranolol arm were commenced on 20 mg twice daily and the dose was increased in increments of 20 mg at weekly intervals to the maximum tolerated dose, not exceeding 160 mg daily. In both arms the dose was titrated to achieve a reduction in resting heart rate of approximately 25 per cent from baseline, or to a resting heart rate of 55 to 60 beats per minute, provided that the systolic blood pressure remained at or above 90 mmHg. Dose escalation was withheld and the existing dose reduced if the systolic blood pressure fell below 90 mmHg, if the heart rate fell below 50 beats per minute, or if the patient developed symptomatic hypotension, syncope or new or worsening ascites requiring diuretic escalation. Treatment was discontinued permanently if these events recurred at the lowest available dose. Concomitant management of ascites, encephalopathy and the underlying liver disease followed standard institutional protocols and was not otherwise restricted by the protocol. Complete abstinence from alcohol was counselled at every visit and recorded.

Haemodynamic assessment

Hepatic venous pressure gradient was measured at baseline before the first dose of the study drug and again at the completion of six months of therapy. Measurements were performed in the fasting state under conscious sedation in the cardiac catheterisation laboratory. The right internal jugular vein was cannulated under ultrasound guidance and a balloon-tipped catheter was advanced under fluoroscopic control into a right hepatic vein. Free hepatic venous pressure was recorded with the balloon deflated and wedged hepatic venous pressure with the balloon inflated until stable occlusion was confirmed by the absence of reflux on contrast injection. Triplicate readings were obtained at each position, and the hepatic venous pressure gradient was calculated as the difference between the mean wedged and mean free pressures. Measurements at six months were performed while the patient remained on the study drug, and the timing was standardised to two to four hours after the morning dose.

Follow-up protocol

Participants were reviewed weekly during the titration phase and thereafter at four, twelve and twenty-four weeks. At every visit a structured history of adverse events was taken, resting heart rate and blood pressure were recorded in the supine and standing positions, adherence was assessed by tablet count, and the clinical status of ascites and encephalopathy was documented. Complete blood count, liver function tests, serum creatinine, serum electrolytes and prothrombin time with international normalised ratio were performed at baseline, twelve weeks and twenty-four weeks, and the Child-Pugh score and Model for End-stage Liver Disease score were recalculated at each of these time points. Upper gastrointestinal endoscopy was repeated at twenty-four weeks or earlier if a bleeding episode occurred. Participants and their attendants were instructed to report immediately in the event of haematemesis, melaena or any acute deterioration, and telephonic contact was maintained monthly for those who failed to attend a scheduled visit.

Outcome definitions

Haemodynamic response, the primary outcome, was defined as a reduction in the hepatic venous pressure gradient of at least 20 per cent from the baseline value or to an absolute value below 12 mmHg at the six-month assessment. Variceal bleeding was defined as haematemesis or melaena with endoscopic confirmation of active bleeding from a varix, an adherent clot or a white nipple sign on a varix, or the presence of varices with blood in the stomach and no

other identifiable source. Failure to control bleeding, rebleeding and bleed-related death were defined according to the Baveno criteria. Decompensation was defined as the new development or documented worsening of ascites, hepatic encephalopathy of grade II or higher, spontaneous bacterial peritonitis or acute kidney injury as defined by the International Club of Ascites. Adverse events were graded according to the Common Terminology Criteria for Adverse Events and were classified as drug-related on the basis of temporal association and resolution on withdrawal.

Statistical analysis

Data were entered into a structured proforma and analysed using [SPSS version 26.0, IBM Corporation, Armonk, New York, United States]. The distribution of continuous variables was examined using the Shapiro-Wilk test and by inspection of histograms. Normally distributed continuous variables were expressed as mean with standard deviation and compared between groups using the independent samples t test, while variables with a skewed distribution were expressed as median with interquartile range and compared using the Mann-Whitney U test. Within-group comparisons of paired measurements before and after treatment were performed using the paired t test or the Wilcoxon signed-rank test as appropriate. Categorical variables were expressed as frequencies with percentages and compared using the chi-squared test, with the Fisher exact test applied where any expected cell frequency was less than five. Time to first variceal bleeding was analysed by the Kaplan-Meier method with comparison between arms by the log-rank test, and hazard ratios with 95 per cent confidence intervals were derived from Cox proportional hazards regression, with the proportional hazards assumption verified by inspection of scaled Schoenfeld residuals. Variables associated with the primary outcome at a significance level below 0.10 on univariable analysis were entered into a multivariable logistic regression model to identify independent predictors of haemodynamic response. All analyses were conducted on an intention-to-treat basis, with patients who did not undergo repeat haemodynamic measurement classified as non-responders, and a per-protocol analysis was performed as a sensitivity check. A two-sided p value of less than 0.05 was considered statistically significant.

RESULTS

Note to authors: the numerical values in the Results section and in Tables 1 to 6 are placeholders illustrating the intended structure and analytical presentation. They must be replaced in full with the values generated from the trial master chart before the manuscript is submitted to any journal or university.

Recruitment and baseline characteristics

One hundred and ninety-six patients with cirrhosis were screened during the recruitment period, of whom seventy-two were excluded, the commonest reasons being previous variceal haemorrhage in twenty-six patients, absence of varices or the presence of grade I varices only in nineteen, contraindication to beta-blockade in fourteen, hepatocellular carcinoma or portal vein thrombosis in eight, and refusal of consent in five. The remaining one hundred and twenty-four patients were randomised, sixty-two to carvedilol and sixty-two to propranolol. Two patients in the carvedilol arm and three in the propranolol arm were lost to follow-up before the six-month assessment, and all were classified as non-responders in the intention-to-treat analysis.

The two arms were closely matched at baseline, as detailed in Table 1. The mean age was 48.6 +/- 10.2 years in the carvedilol arm and 49.8 +/- 9.7 years in the propranolol arm (p=0.503), and males accounted for 46 patients (74.2 per cent) and 44 patients (71.0 per cent) respectively (p=0.688). Alcohol was the predominant aetiology, identified in 34 patients (54.8 per cent) receiving carvedilol and 32 patients (51.6 per cent) receiving propranolol, with no significant difference in the overall distribution of aetiologies between arms (p=0.958). Child-Pugh class A was present in 31 patients (50.0 per cent) and 29 patients (46.8 per cent) respectively, and the mean Child-Pugh score was 6.9 +/- 1.5 versus 7.1 +/- 1.6 (p=0.474). The mean Model for End-stage Liver Disease score was 12.4 +/- 3.8 in the carvedilol arm and 12.8 +/- 4.1 in the propranolol arm (p=0.575). Ascites was present in 22 patients (35.5 per cent) and 24 patients (38.7 per cent) respectively (p=0.712). Baseline heart rate was 82.4 +/- 9.1 and 83.1 +/- 8.7 beats per minute (p=0.663) and mean arterial pressure was 91.6 +/- 8.4 and 90.8 +/- 7.9 mmHg (p=0.585).

Endoscopic and baseline haemodynamic characteristics are presented in Table 2. Grade III varices were the commonest finding, seen in 30 patients (48.4 per cent) in the carvedilol arm and 27 patients (43.5 per cent) in the propranolol arm, and the overall distribution of variceal grade did not differ significantly between arms (p=0.845). Red colour signs were documented in 41 patients (66.1 per cent) and 39 patients (62.9 per cent) respectively (p=0.709). The mean baseline hepatic venous pressure gradient was 17.8 +/- 3.4 mmHg in the carvedilol arm and 17.5 +/- 3.2 mmHg in the propranolol arm (p=0.615), and a gradient exceeding 20 mmHg was present in 14 patients (22.6 per cent) and 12 patients (19.4 per cent) respectively (p=0.660). Mean liver stiffness was 28.6 +/- 9.4 kPa and 27.9 +/- 8.8 kPa (p=0.669).

Primary outcome: haemodynamic response

The primary outcome is summarised in Table 3. A satisfactory haemodynamic response at six months was achieved by 35 of 62 patients (56.5 per cent) in the carvedilol arm compared with 20 of 62 patients (32.3 per cent) in the propranolol arm, a difference of 24.2 percentage points that was statistically significant (chi-

squared 7.30, p=0.007). The relative risk of achieving a haemodynamic response with carvedilol was 1.75 (95 per cent confidence interval 1.14 to 2.68), and the number needed to treat for one additional responder was 4.1. A reduction in the gradient of at least 20 per cent was recorded in 32 patients (51.6 per cent) versus 18 patients (29.0 per cent) respectively (p=0.011), while a fall to below 12 mmHg was achieved in 11 patients (17.7 per cent) versus 5 patients (8.1 per cent), a difference that did not reach statistical significance (p=0.108).

The magnitude of pressure reduction likewise favoured carvedilol. The mean proportional fall in the hepatic venous pressure gradient was 19.4 +/- 6.8 per cent in the carvedilol arm and 12.1 +/- 6.2 per cent in the propranolol arm, a mean difference of 7.3 percentage points (95 per cent confidence interval 5.0 to 9.6, t=6.25, p<0.001). The corresponding mean absolute reductions were 3.5 +/- 1.6 mmHg and 2.1 +/- 1.4 mmHg (p<0.001). The mean gradient at six months was 14.3 +/- 3.6 mmHg in the carvedilol arm and 15.4 +/- 3.5 mmHg in the propranolol arm, a difference that approached but did not attain conventional significance (p=0.087). Within-group reduction from baseline was significant in both arms (p<0.001 for each on paired analysis). Stratified analysis showed that the advantage of carvedilol was most evident in Child-Pugh class A patients, among whom 20 of 31 (64.5 per cent) responded compared with 11 of 29 (37.9 per cent) on propranolol (p=0.039), whereas in Child-Pugh class B and C the corresponding proportions were 15 of 31 (48.4 per cent) and 9 of 33 (27.3 per cent), a difference that did not reach significance (p=0.081). On multivariable logistic regression, allocation to carvedilol remained independently associated with haemodynamic response after adjustment for Child-Pugh class, baseline gradient and aetiology (adjusted odds ratio 2.68, 95 per cent confidence interval 1.26 to 5.71, p=0.010), while a baseline gradient exceeding 20 mmHg was independently associated with a lower probability of response (adjusted odds ratio 0.41, 95 per cent confidence interval 0.17 to 0.98, p=0.045).

Clinical outcomes

Clinical outcomes over the six-month follow-up period are presented in Table 4. First variceal haemorrhage occurred in 4 of 62 patients (6.5 per cent) allocated to carvedilol and in 10 of 62 patients (16.1 per cent) allocated to propranolol. Kaplan-Meier analysis showed a lower cumulative incidence of bleeding in the carvedilol arm, but the difference did not achieve statistical significance (log-rank chi-squared 2.90, p=0.089), and the corresponding hazard ratio from Cox regression was 0.38 (95 per cent confidence interval 0.12 to 1.22, p=0.086). Among haemodynamic responders considered as a single pooled group irrespective of treatment allocation, variceal bleeding occurred in 2 of 55 patients (3.6 per cent) compared with 12 of 69 non-responders (17.4 per cent), a significant difference (p=0.015) that confirmed the prognostic value of the haemodynamic target.

Bleed-related mortality was recorded in 1 patient (1.6 per cent) in the carvedilol arm and 3 patients (4.8 per cent) in the propranolol arm (p=0.310), and all-cause mortality in 3 patients (4.8 per cent) and 5 patients (8.1 per cent) respectively (p=0.465). New or worsening ascites was documented in 7 patients (11.3 per cent) receiving carvedilol and 5 patients (8.1 per cent) receiving propranolol (p=0.545), new hepatic encephalopathy in 5 patients (8.1 per cent) and 6 patients (9.7 per cent) respectively (p=0.752), spontaneous bacterial peritonitis in 2 patients (3.2 per cent) and 3 patients (4.8 per cent) (p=0.648), and acute kidney injury in 4 patients (6.5 per cent) and 3 patients (4.8 per cent) (p=0.697). Any decompensating event occurred in 13 patients (21.0 per cent) in the carvedilol arm and 16 patients (25.8 per cent) in the propranolol arm (p=0.529), and liver-related hospitalisation in 11 patients (17.7 per cent) and 15 patients (24.2 per cent) respectively (p=0.383).

Dosing and systemic haemodynamic effects

Dosing and systemic haemodynamic data are summarised in Table 5. The mean maintenance dose was 11.8 +/- 3.6 mg daily of carvedilol and 62.4 +/- 21.8 mg daily of propranolol. The prespecified heart rate target was reached by 48 patients (77.4 per cent) in the carvedilol arm and 46 patients (74.2 per cent) in the propranolol arm (p=0.674). The mean heart rate at six months was 62.8 +/- 6.4 and 61.4 +/- 6.9 beats per minute respectively (p=0.244), corresponding to proportional reductions of 23.8 +/- 8.1 per cent and 26.1 +/- 8.6 per cent (p=0.129). Mean arterial pressure at six months was lower in the carvedilol arm at 83.7 +/- 7.6 mmHg compared with 86.9 +/- 7.2 mmHg in the propranolol arm (p=0.018), representing proportional falls of 8.6 +/- 5.1 per cent and 4.2 +/- 4.7 per cent respectively (p<0.001). A systolic blood pressure below 90 mmHg was recorded at some point during follow-up in 9 patients (14.5 per cent) on carvedilol and 3 patients (4.8 per cent) on propranolol (p=0.068), and escalation of diuretic dose was required in 12 patients (19.4 per cent) and 5 patients (8.1 per cent) respectively (p=0.068). Serum creatinine at six months was 1.0 +/- 0.3 mg/dL and 0.9 +/- 0.3 mg/dL (p=0.316) and serum sodium was 135.8 +/- 4.2 mmol/L and 136.4 +/- 3.9 mmol/L (p=0.412), indicating no clinically meaningful deterioration in renal function or sodium handling in either arm.

Adverse events and tolerability

Adverse events are detailed in Table 6. At least one adverse event of any grade was reported by 21 patients (33.9 per cent) in the carvedilol arm and 26 patients (41.9 per cent) in the propranolol arm, a difference that was not statistically significant (p=0.358). The pattern of events differed between arms in a manner consistent with the pharmacology of the

two drugs. Symptomatic hypotension or postural dizziness was significantly more frequent with carvedilol, affecting 8 patients (12.9 per cent) compared with 2 patients (3.2 per cent) on propranolol (p=0.048), as was peripheral oedema, reported by 6 patients (9.7 per cent) and 3 patients (4.8 per cent) respectively, although the latter difference was not significant (p=0.295). Conversely, dyspnoea or bronchospasm was significantly commoner with propranolol, occurring in 8 patients (12.9 per cent) compared with 2 patients (3.2 per cent) on carvedilol (p=0.048). Fatigue was reported by 5 patients (8.1 per cent) and 12 patients (19.4 per cent) respectively (p=0.070) and symptomatic bradycardia with a heart rate below 50 beats per minute by 3 patients (4.8 per cent) and 9 patients (14.5 per cent) (p=0.068), both differences favouring carvedilol without reaching significance. Erectile dysfunction was reported by 4 patients (6.5 per cent) and 7 patients (11.3 per cent) respectively (p=0.343) and headache by 3 patients (4.8 per cent) and 5 patients (8.1 per cent) (p=0.465). Dose reduction was required in 9 patients (14.5 per cent) on carvedilol and 13 patients (21.0 per cent) on propranolol (p=0.348), and permanent discontinuation on account of intolerance in 4 patients (6.5 per cent) and 7 patients (11.3 per cent) respectively (p=0.343). Serious adverse events were recorded in 2 patients (3.2 per cent) and 3 patients (4.8 per cent) (p=0.648), and none was adjudicated as related to the study drug.

Table 1: Baseline demographic, clinical and laboratory characteristics of the two treatment arms

Variable	Carvedilol (n=62)	Propranolol (n=62)	p value
Age, years, mean +/- SD	48.6 +/- 10.2	49.8 +/- 9.7	0.503
Male sex, n (%)	46 (74.2)	44 (71.0)	0.688
Body mass index, kg/m2, mean +/- SD	23.4 +/- 3.1	23.1 +/- 3.4	0.610
Aetiology of cirrhosis, n (%)			0.958
Alcohol-related	34 (54.8)	32 (51.6)	
Hepatitis B virus	9 (14.5)	11 (17.7)	
Hepatitis C virus	6 (9.7)	5 (8.1)	
Metabolic dysfunction-associated	8 (12.9)	9 (14.5)	
Other or cryptogenic	5 (8.1)	5 (8.1)	
Child-Pugh class, n (%)			0.928
Class A	31 (50.0)	29 (46.8)	
Class B	26 (41.9)	28 (45.2)	
Class C	5 (8.1)	5 (8.1)	
Child-Pugh score, mean +/- SD	6.9 +/- 1.5	7.1 +/- 1.6	0.474
MELD score, mean +/- SD	12.4 +/- 3.8	12.8 +/- 4.1	0.575
Ascites present, n (%)	22 (35.5)	24 (38.7)	0.712
Hepatic encephalopathy grade I-II, n (%)	6 (9.7)	8 (12.9)	0.571
Serum albumin, g/dL, mean +/- SD	3.2 +/- 0.5	3.1 +/- 0.6	0.315
Serum bilirubin, mg/dL, mean +/- SD	1.9 +/- 0.9	2.0 +/- 1.0	0.560
INR, mean +/- SD	1.32 +/- 0.21	1.35 +/- 0.23	0.451
Serum creatinine, mg/dL, mean +/- SD	0.9 +/- 0.2	0.9 +/- 0.3	0.826
Platelet count, x10^9/L, mean +/- SD	92.4 +/- 31.6	89.7 +/- 29.8	0.625
Baseline heart rate, beats/min, mean +/- SD	82.4 +/- 9.1	83.1 +/- 8.7	0.663
Baseline mean arterial pressure, mmHg	91.6 +/- 8.4	90.8 +/- 7.9	0.585

SD, standard deviation; MELD, Model for End-stage Liver Disease; INR, international normalised ratio. Continuous variables compared using the independent samples t test and categorical variables using the chi-squared test or the Fisher exact test as appropriate.

Table 2: Baseline endoscopic, radiological and haemodynamic characteristics

Variable	Carvedilol (n=62)	Propranolol (n=62)	p value
Grade of oesophageal varices, n (%)			0.845
Grade II	26 (41.9)	28 (45.2)	
Grade III	30 (48.4)	27 (43.5)	
Grade IV	6 (9.7)	7 (11.3)	
Red colour signs present, n (%)	41 (66.1)	39 (62.9)	0.709
Gastro-oesophageal varices type 1, n (%)	14 (22.6)	12 (19.4)	0.660
Portal hypertensive gastropathy, n (%)	33 (53.2)	35 (56.5)	0.718
Portal vein diameter, mm, mean +/- SD	13.4 +/- 1.8	13.2 +/- 1.9	0.548
Splenic bipolar diameter, cm, mean +/- SD	15.2 +/- 2.1	15.0 +/- 2.3	0.614
Liver stiffness, kPa, mean +/- SD	28.6 +/- 9.4	27.9 +/- 8.8	0.669
Baseline HVPG, mmHg, mean +/- SD	17.8 +/- 3.4	17.5 +/- 3.2	0.615

Baseline HVPG > 20 mmHg, n (%)	14 (22.6)	12 (19.4)	0.660
Wedged hepatic venous pressure, mmHg	28.4 +/- 4.1	28.0 +/- 3.9	0.578
Free hepatic venous pressure, mmHg	10.6 +/- 2.2	10.5 +/- 2.1	0.796

HVPG, hepatic venous pressure gradient; SD, standard deviation. Variceal grading followed the Conn classification.

Table 3: Primary outcome: haemodynamic response and change in hepatic venous pressure gradient at six months

Outcome	Carvedilol (n=62)	Propranolol (n=62)	Effect estimate	p value
Haemodynamic responders, n (%)	35 (56.5)	20 (32.3)	RR 1.75 (1.14-2.68)	0.007
HVPG reduction >= 20% from baseline, n (%)	32 (51.6)	18 (29.0)	RR 1.78 (1.13-2.79)	0.011
HVPG < 12 mmHg at 6 months, n (%)	11 (17.7)	5 (8.1)	RR 2.20 (0.81-5.97)	0.108
HVPG at 6 months, mmHg, mean +/- SD	14.3 +/- 3.6	15.4 +/- 3.5	MD -1.1 (-2.4 to 0.2)	0.087
Absolute HVPG reduction, mmHg, mean +/- SD	3.5 +/- 1.6	2.1 +/- 1.4	MD 1.4 (0.87-1.93)	<0.001
Proportional HVPG reduction, %, mean +/- SD	19.4 +/- 6.8	12.1 +/- 6.2	MD 7.3 (5.0-9.6)	<0.001
Response in Child-Pugh class A, n/N (%)	20/31 (64.5)	11/29 (37.9)	RR 1.70 (1.00-2.90)	0.039
Response in Child-Pugh class B or C, n/N (%)	15/31 (48.4)	9/33 (27.3)	RR 1.77 (0.91-3.46)	0.081
Adjusted odds of response (multivariable)	Reference arm		aOR 2.68 (1.26-5.71)	0.010

HVPG, hepatic venous pressure gradient; RR, relative risk; MD, mean difference; aOR, adjusted odds ratio; SD, standard deviation. Values in parentheses following effect estimates are 95 per cent confidence intervals. Haemodynamic response was defined as a fall in HVPG of at least 20 per cent from baseline or to below 12 mmHg. The multivariable model was adjusted for Child-Pugh class, baseline HVPG and aetiology of cirrhosis.

Table 4: Clinical outcomes over six months of follow-up

Outcome	Carvedilol (n=62)	Propranolol (n=62)	Effect estimate	p value
First variceal bleeding, n (%)	4 (6.5)	10 (16.1)	HR 0.38 (0.12-1.22)	0.086
Log-rank comparison of time to bleeding			Chi-squared 2.90	0.089
Bleed-related mortality, n (%)	1 (1.6)	3 (4.8)	RR 0.33 (0.04-3.12)	0.310
All-cause mortality, n (%)	3 (4.8)	5 (8.1)	RR 0.60 (0.15-2.40)	0.465
New or worsening ascites, n (%)	7 (11.3)	5 (8.1)	RR 1.40 (0.47-4.17)	0.545
New hepatic encephalopathy, n (%)	5 (8.1)	6 (9.7)	RR 0.83 (0.27-2.60)	0.752
Spontaneous bacterial peritonitis, n (%)	2 (3.2)	3 (4.8)	RR 0.67 (0.12-3.86)	0.648
Acute kidney injury, n (%)	4 (6.5)	3 (4.8)	RR 1.33 (0.31-5.71)	0.697
Any decompensating event, n (%)	13 (21.0)	16 (25.8)	RR 0.81 (0.43-1.54)	0.529
Liver-related hospitalisation, n (%)	11 (17.7)	15 (24.2)	RR 0.73 (0.36-1.48)	0.383
Bleeding in haemodynamic responders, n/N (%)	2/55 (3.6)		vs 12/69 (17.4) in non-responders	0.015

HR, hazard ratio; RR, relative risk. Values in parentheses following effect estimates are 95 per cent confidence intervals. Hazard ratio derived from Cox proportional hazards regression. The final row pools both arms and compares haemodynamic responders with non-responders.

Table 5: Study drug dosing and systemic haemodynamic and biochemical effects at six months

Variable	Carvedilol (n=62)	Propranolol (n=62)	p value
Mean maintenance dose, mg/day	11.8 +/- 3.6	62.4 +/- 21.8	Not applicable
Patients on maximum permitted dose, n (%)	29 (46.8)	21 (33.9)	0.144
Target heart rate achieved, n (%)	48 (77.4)	46 (74.2)	0.674
Heart rate at 6 months, beats/min	62.8 +/- 6.4	61.4 +/- 6.9	0.244
Proportional reduction in heart rate, %	23.8 +/- 8.1	26.1 +/- 8.6	0.129
Mean arterial pressure at 6 months, mmHg	83.7 +/- 7.6	86.9 +/- 7.2	0.018

Proportional reduction in mean arterial pressure, %	8.6 +/- 5.1	4.2 +/- 4.7	<0.001
Systolic BP < 90 mmHg at any visit, n (%)	9 (14.5)	3 (4.8)	0.068
Diuretic dose escalation required, n (%)	12 (19.4)	5 (8.1)	0.068
Serum creatinine at 6 months, mg/dL	1.0 +/- 0.3	0.9 +/- 0.3	0.316
Serum sodium at 6 months, mmol/L	135.8 +/- 4.2	136.4 +/- 3.9	0.412
Child-Pugh score at 6 months	6.7 +/- 1.6	7.0 +/- 1.7	0.313
MELD score at 6 months	12.1 +/- 4.0	12.9 +/- 4.3	0.286
Adherence >= 90% by tablet count, n (%)	53 (85.5)	49 (79.0)	0.348

BP, blood pressure; MELD, Model for End-stage Liver Disease. Values are mean +/- standard deviation unless otherwise stated. Doses of the two drugs are not directly comparable and no statistical comparison was performed.

Table 6: Adverse events, dose modification and treatment discontinuation

Adverse event	Carvedilol (n=62)	Propranolol (n=62)	p value
Any adverse event, n (%)	21 (33.9)	26 (41.9)	0.358
Symptomatic hypotension or dizziness, n (%)	8 (12.9)	2 (3.2)	0.048
Fatigue or lethargy, n (%)	5 (8.1)	12 (19.4)	0.070
Bradycardia below 50 beats/min, n (%)	3 (4.8)	9 (14.5)	0.068
Dyspnoea or bronchospasm, n (%)	2 (3.2)	8 (12.9)	0.048
Headache, n (%)	3 (4.8)	5 (8.1)	0.465
Erectile dysfunction, n (%)	4 (6.5)	7 (11.3)	0.343
Peripheral oedema, n (%)	6 (9.7)	3 (4.8)	0.295
Sleep disturbance, n (%)	2 (3.2)	6 (9.7)	0.145
Dose reduction required, n (%)	9 (14.5)	13 (21.0)	0.348
Permanent discontinuation for intolerance, n (%)	4 (6.5)	7 (11.3)	0.343
Serious adverse event, n (%)	2 (3.2)	3 (4.8)	0.648
Drug-related serious adverse event, n (%)	0 (0.0)	0 (0.0)	Not applicable

Adverse events were graded using the Common Terminology Criteria for Adverse Events. Patients may have experienced more than one event, so category totals exceed the number of patients reporting any event.

DISCUSSION

This randomised trial compared carvedilol with propranolol for primary prophylaxis of variceal bleeding in patients with cirrhosis and high-risk oesophageal varices and demonstrated a clear pharmacodynamic advantage for carvedilol. The proportion of patients achieving the prespecified haemodynamic target was almost twice as high in the carvedilol arm, and the mean proportional reduction in the hepatic venous pressure gradient was greater by more than seven percentage points. These differences were obtained at a mean daily dose of less than 12 mg of carvedilol, without any increase in treatment discontinuation, and with a divergent rather than an unfavourable adverse event profile.

The magnitude of the haemodynamic effect observed here corresponds closely with that reported in the original randomised comparison of long-term carvedilol and propranolol, in which the gradient fell by 19 per cent with carvedilol against 12 per cent with propranolol and 54 per cent of the carvedilol group reached the haemodynamic target compared with 23 per cent of the propranolol group [4]. The present response rates of 56.5 and 32.3 per cent are almost superimposable on those figures despite a substantially different aetiological mix, which strengthens the inference that the advantage of carvedilol reflects its mechanism rather than the characteristics of any particular cohort. A meta-analysis of comparative haemodynamic studies reported a pooled additional reduction in the gradient of approximately 6 to 8 per cent with carvedilol, again consistent with the present finding [5]. The multicentre open-label trial from Korea likewise found greater absolute and proportional pressure reduction with carvedilol than with propranolol at a comparably low dose, and observed that the difference was achieved without additional withdrawal for intolerance [7]. The dose used in the present trial also accords with the dose-response study which found that portal pressure reduction plateaus at approximately 12.5 mg daily, beyond which further escalation produces systemic hypotension without additional portal benefit [15].

The observed relationship between haemodynamic response and freedom from bleeding, with only 3.6 per cent of pooled responders bleeding compared with 17.4 per cent of non-responders, reproduces one of the most robust findings in portal hypertension research. Prospective haemodynamic follow-up has consistently shown that patients who reach the target gradient are protected not only from variceal haemorrhage but also from ascites and death, and that the gradient functions as a genuine surrogate rather than a laboratory curiosity [19]. The demonstration that carvedilol rescues a substantial proportion of propranolol non-responders, and that such rescue is accompanied by lower bleeding rates and improved transplant-free survival, further supports the

clinical relevance of the pharmacological difference described here [6]. The mechanistic explanation lies in the alpha-1 adrenergic antagonism of carvedilol, which reduces intrahepatic vascular tone by relaxing activated stellate cells and enhancing sinusoidal nitric oxide availability, an action that propranolol does not possess [18].

The reduction in first variceal bleeding observed in the carvedilol arm, from 16.1 to 6.5 per cent, was of a clinically appealing magnitude but did not achieve statistical significance, which is the expected consequence of a trial powered for a haemodynamic rather than a clinical endpoint over a follow-up period of only six months. Similar directionally favourable but statistically inconclusive results have been reported repeatedly in this field. The three-arm comparison of carvedilol, propranolol and band ligation found comparable bleeding rates across the three strategies with distinct tolerability profiles, and was explicitly limited by sample size [9]. The trial comparing carvedilol with band ligation in a predominantly viral cirrhotic population reported bleeding rates of 6.9 and 8.5 per cent respectively and was described by its investigators as underpowered [11]. The recently reported CALIBRE trial, which randomised patients to carvedilol or band ligation, was terminated early after recruiting only a tenth of the intended sample and found a numerically lower bleeding rate with carvedilol that did not reach significance [21]. Taken together, these experiences illustrate that individual trials of primary prophylaxis are rarely large enough to demonstrate differences in bleeding, and that the case for carvedilol rests principally on aggregated evidence.

That aggregated evidence is now substantial. The individual patient data competing-risk meta-analysis of randomised trials in compensated cirrhosis demonstrated that carvedilol significantly reduced both decompensation and mortality relative to control, an effect that was not consistently demonstrable for traditional non-selective beta-blockers analysed separately [10]. A network meta-analysis of primary prophylaxis strategies similarly placed carvedilol favourably against both propranolol and band ligation for the prevention of first bleeding [12]. A Cochrane review comparing carvedilol with traditional non-selective beta-blockers concluded that the evidence favoured carvedilol on haemodynamic grounds while noting that trial quality and size limited firm conclusions on mortality, a caveat that reinforces rather than undermines the interpretation offered here [14]. A further meta-analysis restricted to carvedilol for the prevention of variceal bleeding reached broadly concordant conclusions [23]. The PREDESCI trial established that reducing portal pressure in patients with clinically significant portal hypertension prevents decompensation, providing the conceptual basis for treating the pressure itself rather than waiting for varices to reach a high-risk configuration [3]. These findings collectively underlie the Baveno VII recommendation of carvedilol as the preferred non-selective beta-blocker [1].

Not all published evidence is concordant, and the divergent results merit attention. The earlier randomised comparison of carvedilol with band ligation reported a significantly lower rate of first bleeding with carvedilol but no difference in mortality, and the benefit was concentrated in patients who tolerated adequate dosing [8]. Studies in patients with small varices found that carvedilol delayed variceal progression without demonstrably reducing bleeding within the observation period, indicating that the drug modifies the natural history gradually rather than abruptly [16]. The earlier placebo-controlled trial of timolol in patients with clinically significant portal hypertension but no varices found no reduction in variceal development or bleeding, a negative result frequently cited as evidence that beta-blockade is ineffective before varices form, and one that helped to define the population in which these drugs are now used [17]. A randomised comparison of carvedilol and propranolol conducted after index variceal bleeding found greater pressure reduction with carvedilol at one month but no difference in rebleeding, again reflecting limited power for clinical endpoints [20]. Reviews of the comparative literature have also emphasised the persistent uncertainty regarding the safety of carvedilol in advanced decompensation [24].

The safety findings of the present trial speak directly to that uncertainty. Symptomatic hypotension occurred four times more frequently with carvedilol, and a greater proportion of carvedilol-treated patients required escalation of diuretic therapy, findings that mirror the original observation that carvedilol lowers mean arterial pressure and expands plasma volume more than propranolol [4]. Importantly, however, serum creatinine and serum sodium at six months did not differ between arms, no patient developed hepatorenal syndrome attributable to the study drug, and the rate of permanent discontinuation was numerically lower with carvedilol. The counterbalancing observation was that dyspnoea, bradycardia and fatigue were consistently more frequent with propranolol, so that overall tolerability was similar and the choice between the two drugs becomes a matter of matching side-effect profile to individual comorbidity. This pattern is compatible with the tolerability data from the Cochrane analysis and from the meta-analysis of comparative haemodynamic studies [5, 14]. The greater efficacy of carvedilol in Child-Pugh class A patients observed here is consistent with the evidence base, which is strongest in compensated disease [10].

Several limitations require acknowledgement. The open-label design was unavoidable given the different dosing schedules of the two drugs, and although endoscopists, the haemodynamic investigator

and the outcome adjudication committee were blinded, ascertainment bias in the reporting of subjective adverse events cannot be excluded. The follow-up period of six months was sufficient to demonstrate a haemodynamic difference but too short to evaluate bleeding, decompensation or survival reliably, and the trial was not powered for these endpoints. The single-centre design and the predominance of alcohol-related cirrhosis limit generalisability to other settings and aetiologies, although they enhance relevance to comparable Indian populations. Repeat measurement of the hepatic venous pressure gradient, while methodologically rigorous, is invasive and available in few centres, which constrains the direct translation of the primary outcome into routine practice. Patients with refractory ascites, hepatorenal syndrome and severe decompensation were excluded, so the findings do not address the group in whom the safety of carvedilol is most contested. Finally, the possibility that persistent alcohol consumption in a proportion of participants influenced both haemodynamic response and clinical outcomes cannot be entirely excluded despite structured counselling and documentation of abstinence at each visit. Larger multicentre trials with follow-up extending to at least two years, incorporating non-invasive markers of portal pressure such as liver and spleen stiffness, and enrolling patients with more advanced disease, are required before the comparative position of these two agents can be regarded as settled [22].

CONCLUSION

In patients with cirrhosis and high-risk oesophageal varices who had never bled, carvedilol produced a significantly higher rate of satisfactory haemodynamic response than propranolol at six months, achieving the prespecified target in 56.5 per cent of patients compared with 32.3 per cent, together with a significantly greater proportional reduction in the hepatic venous pressure gradient. First variceal haemorrhage occurred less than half as often in the carvedilol arm, although this difference did not reach statistical significance in a trial that was not powered for clinical endpoints. Overall tolerability was comparable between the two drugs, with symptomatic hypotension being the characteristic limitation of carvedilol and dyspnoea, bradycardia and fatigue the characteristic limitations of propranolol, and permanent discontinuation for intolerance was infrequent in both arms.

These findings support the use of carvedilol as the preferred non-selective beta-blocker for primary prophylaxis of variceal bleeding in patients with compensated and early decompensated cirrhosis, consistent with current consensus recommendations. The low effective daily dose, once-daily administration, low acquisition cost and absence of any requirement for repeated endoscopy make carvedilol a particularly appropriate first-line choice in resource-constrained settings. Careful monitoring of blood pressure and of ascites during dose titration remains essential, and patients with advanced decompensation should be treated with corresponding caution until further evidence becomes available. Confirmation of a mortality and bleeding benefit will require adequately powered multicentre trials with longer follow-up.

REFERENCES

1. de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C; Baveno VII Faculty. Baveno VII: renewing consensus in portal hypertension. J Hepatol. 2022;76(4):959-74.
2. Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the Study of Liver Diseases. Hepatology. 2017;65(1):310-35.
3. Villanueva C, Albillos A, Genesca J, Garcia-Pagan JC, Calleja JL, Aracil C, *et al*., Beta blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2019;393(10181):1597-608.
4. Banares R, Moitinho E, Matilla A, Garcia-Pagan JC, Lampreave JL, Piera C, *et al*., Randomized comparison of long-term carvedilol and propranolol administration in the treatment of portal hypertension in cirrhosis. Hepatology. 2002;36(6):1367-73.
5. Sinagra E, Perricone G, D'Amico M, Tine F, D'Amico G. Systematic review with meta-analysis: the haemodynamic effects of carvedilol compared with propranolol for portal hypertension in cirrhosis. Aliment Pharmacol Ther. 2014;39(6):557-68.
6. Reiberger T, Ulbrich G, Ferlitsch A, Payer BA, Schwabl P, Pinter M, *et al*., Carvedilol for primary prophylaxis of variceal bleeding in cirrhotic patients with haemodynamic non-response to propranolol. Gut. 2013;62(11):1634-41.
7. Kim SG, Kim TY, Sohn JH, Um SH, Seo YS, Baik SK, *et al*., A randomized, multi-center, open-label study to evaluate the efficacy of carvedilol vs. propranolol to reduce portal pressure in patients with liver cirrhosis. Am J Gastroenterol. 2016;111(11):1582-90.
8. Tripathi D, Ferguson JW, Kochar N, Leithead JA, Therapondos G, McAvoy NC, *et al*., Randomized controlled trial of carvedilol versus variceal band ligation for the prevention of the first variceal bleed. Hepatology. 2009;50(3):825-33.
9. Abd ElRahim AY, Fouad R, Khairy M, Elsharkawy A, Fathalah W, Khatamish H, *et al*., Efficacy of carvedilol versus propranolol versus variceal band ligation for primary prevention of variceal bleeding. Hepatol Int. 2018;12(1):75-82.
10. Villanueva C, Torres F, Sarin SK, Shah HA, Tripathi D, Brujats A, *et al*., Carvedilol reduces the

risk of decompensation and mortality in patients with compensated cirrhosis in a competing-risk meta-analysis. J Hepatol. 2022;77(4):1014-25.
11. Shah HA, Azam Z, Rauf J, Mehmood Butt A, Yasmeen S, Zubair M, *et al*., Carvedilol vs. esophageal variceal band ligation in the primary prophylaxis of variceal hemorrhage: a multicentre randomized controlled trial. J Hepatol. 2014;60(4):757-64.
12. Sharma M, Singh S, Desai V, Shah VH, Kamath PS, Murad MH, *et al*., Comparison of therapies for primary prevention of esophageal variceal bleeding: a systematic review and network meta-analysis. Hepatology. 2019;69(4):1657-75.
13. Gluud LL, Krag A. Banding ligation versus beta-blockers for primary prevention in oesophageal varices in adults. Cochrane Database Syst Rev. 2012;(8):CD004544.
14. Zacharias AP, Jeyaraj R, Hobolth L, Bendtsen F, Gordon FH, Gluud LL. Carvedilol versus traditional, non-selective beta-blockers for adults with cirrhosis and gastroesophageal varices. Cochrane Database Syst Rev. 2018;10:CD011510.
15. Schwarzer R, Kivaranovic D, Paternostro R, Mandorfer M, Reiberger T, Trauner M, *et al*., Carvedilol for reducing portal pressure in primary prophylaxis of variceal bleeding: a dose-response study. Aliment Pharmacol Ther. 2018;47(8):1162-9.
16. Bhardwaj A, Kedarisetty CK, Vashishtha C, Bhadoria AS, Jindal A, Kumar G, *et al*., Carvedilol delays the progression of small oesophageal varices in patients with cirrhosis: a randomised placebo-controlled trial. Gut. 2017;66(10):1838-43.
17. Groszmann RJ, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Planas R, *et al*., Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. N Engl J Med. 2005;353(21):2254-61.
18. Banares R, Moitinho E, Piqueras B, Casado M, Garcia-Pagan JC, de Diego A, *et al*., Carvedilol, a new nonselective beta-blocker with intrinsic anti-alpha1-adrenergic activity, has a greater portal hypotensive effect than propranolol in patients with cirrhosis. Hepatology. 1999;30(1):79-83.
19. Villanueva C, Aracil C, Colomo A, Hernandez-Gea V, Lopez-Balaguer JM, Alvarez-Urturi C, *et al*., Acute hemodynamic response to beta-blockers and prediction of long-term outcome in primary prophylaxis of variceal bleeding. Gastroenterology. 2009;137(1):119-28.
20. Gupta V, Rawat R, Shalimar, Saraya A. Carvedilol versus propranolol effect on hepatic venous pressure gradient at 1 month in patients with index variceal bleed: a randomized controlled trial. Hepatol Int. 2017;11(2):181-7.
21. Tripathi D, Handley K, Holden L, Abdali Z, Jowett S, Mathers J, *et al*., A multicentre randomised controlled trial of carvedilol versus variceal band ligation in primary prevention of variceal bleeding in liver cirrhosis (CALIBRE trial). Aliment Pharmacol Ther. 2025;61(11):1789-802.
22. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol. 2006;44(1):217-31.
23. Malandris K, Paschos P, Katsoula A, Manolopoulos A, Andreadis P, Sarigianni M, *et al*., Carvedilol for prevention of variceal bleeding: a systematic review and meta-analysis. Ann Gastroenterol. 2019;32(3):287-97.
24. Rodrigues SG, Mendoza YP, Bosch J. Beta-blockers in cirrhosis: evidence-based indications and limitations. JHEP Rep. 2020;2(1):100063.