Original research

Combination of carvedilol with variceal band ligation in prevention of first variceal bleed in Child-Turcotte-Pugh B and C cirrhosis with high-risk oesophageal varices: the 'CAVARLY TRIAL'

Harsh Vardhan Tevethia,[1] Apurva Pande,[1] Rajan Vijayaraghavan,[1] Guresh Kumar,[2] Shiv Kumar Sarin [1]

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/gutjnl-2023-331181).

[1]Hepatology, Institute of Liver and Biliary Sciences, New Delhi, India
[2]Biostatistics, Institute of Liver and Biliary Sciences, New Delhi, India

Correspondence to
Professor Shiv Kumar Sarin, Hepatology, Institute of Liver and Biliary Sciences, New Delhi, Delhi 110070, India; shivsarin@gmail.com

HVT and AP are joint first authors.

Received 26 September 2023
Accepted 1 July 2024

To cite: Tevethia HV, Pande A, Vijayaraghavan R, *et al*. *Gut* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/gutjnl-2023-331181

ABSTRACT

Objectives Beta-blockers and endoscopic variceal band ligation (VBL) have been preferred therapies for primary prophylaxis of variceal bleeding. However, the choice of therapy in patients with advanced liver disease with high-risk varices is not clear. A comparison of these therapies alone or in combination to prevent the first variceal bleed in advanced cirrhosis patients was carried out.

Design 330 Child-Turcotte-Pugh (CTP) B and C cirrhosis patients, with 'high-risk' varices were prospectively enrolled (n=110 per group) to receive carvedilol (group A), VBL (group B) or combination (group C). Primary endpoint was reduction in the incidence of first variceal bleed at 12 months. The secondary endpoints included overall mortality, bleed-related mortality, new-onset decompensation, change in hepatic vein pressure gradient (HVPG) and treatment-related adverse events.

Results The patients were predominantly males (85.2%), aged 51.4±10.5 years with CTP score of 8.87±1.24, MELD score 15.17±3.35 and HVPG-16.96±3.57 mm Hg. The overall incidence of variceal bleed was 23.8% (n=78) at 1 year. Intention-to-treat analysis showed that the combination arm (group C) significantly reduced the incidence of first variceal bleed by 62.9% as compared with group B (HR 0.37, 95% CI 0.192 to 0.716, p<0.003) and by 69.3% as compared with group A (HR 0.31, 95% CI 0.163 to 0.578, <0.001). The overall mortality was 13.6% (45/330). The 1-year mortality in group C was lowest among the three groups (A, B, C=20%, 14.5%, 6.3%, p=0.012). Reduction in HVPG (20.8% vs 25.1%, p=0.54) and the rate of non-response to carvedilol (53.4% vs 41.25%, p=0.154) were not different between group A and C patients. The incidence of new-onset ascites, spontaneous bacterial peritonitis, shock, and acute kidney injury and postbleed organ failure was also comparable between the groups.

Conclusion In CTP B and C cirrhosis patients with high-risk varices, combination of carvedilol and VBL is more effective than either therapy alone, for primary prevention of variceal bleeding.

Trial registration number NCT03069339.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with Child-Turcotte-Pugh B and C cirrhosis have a higher risk of variceal bleeding and incident mortality.
⇒ Prophylaxis for variceal bleeding includes use of either variceal band ligation (VBL), or non-selective beta-blockers with conflicting data for efficacy for Child-Turcotte-Pugh B and C patients.
⇒ The comparative efficacy of these monotherapies as well as potential benefits of combining the two modalities have not been evaluated in the setting of primary prophylaxis for the prevention of variceal bleeding in advanced cirrhosis.

WHAT THIS STUDY ADDS

⇒ Combination of VBL and carvedilol (group C) significantly reduced the incidence of first variceal bleed as compared with either VBL (group B) by 62.9% (p<0.003) and carvedilol (group A) by 69.3% (p<0.001) in patients with advanced cirrhosis.
⇒ With careful monitoring and dose titration, carvedilol was found to be well tolerated in advanced cirrhosis patients.
⇒ All-cause mortality was lower in the combination arm as compared with the carvedilol and VBL arms (6.3%, 20% and 14.5%, respectively, p=0.012).
⇒ Time to first variceal bleed was also significantly longer in the combination arm as compared with the other groups.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Combination therapy (VBL+carvedilol) should be the treatment of choice for primary prophylaxis in patients with Child-Turcotte-Pugh B and C cirrhosis with high-risk varices since it significantly reduces the incidence of variceal bleed as well as mortality.

INTRODUCTION

Prevention of first variceal bleed is the most appropriate strategy to reduce clinical decompensation

and bleed-related mortality which can range up to 20% at 6 weeks.[1] Non-selective β-blockers and endoscopic variceal band ligation (VBL) are the mainstay for the prevention of variceal bleeding, especially for medium to large oesophageal varices.[2] In patients with compensated cirrhosis and large high-risk varices, various studies have shown the efficacy of non-selective β-blockers(NSBBs) as well as VBL in effectively preventing variceal bleeding as well as reducing bleed-related mortality.[3] Non-selective beta-blockers have been shown to be the key component of the combination therapy and improved survival.[4]

In patients with decompensated cirrhosis, however, there is limited clarity on the choice of NSBB or VBL for primary prophylaxis. Beta-blocker therapy was shown to increase the incidence of spontaneous bacterial peritonitis (SBP) and acute kidney injury (AKI).[5] VBL therapy may be associated with a higher rate of formation of post-VBL ulcers and more rebleeds.[6] Such events are more likely to occur in decompensated cirrhosis patients. It is important to stratify such patients needing primary prophylaxis and investigate the efficacy of these two therapies. Furthermore, it is likely that a combination of these two therapies, with the inherent strength of each, may be more effective than either monotherapy in preventing the first variceal bleed.

Carvedilol, a non-selective β-blocker, in addition to its potent beta-blocking effect has intrinsic anti–α1-adrenergic activity and α-blocking properties and making it more potent than conventional NSBB.[7] In a randomised trial, carvedilol was found to be more effective in decreasing the incidence of first variceal bleeding compared with VBL alone, with no difference in overall mortality or bleed-related mortality.[6] However, in this study, patients with both small and large varices were included.

Hepatic venous pressure gradient (HVPG), an indirect measure of portal pressure, has been shown to be an independent predictor of variceal bleeding and death. Recent meta-analysis has shown reduced risk of bleeding, risk of decompensation or death in patients treated with NSBB who have responded to treatment based on HVPG reduction.[8] In patients with ascites also, carvedilol usage showed survival benefit.[9] It must be emphasised that this study was retrospective in nature.

There have been several studies which have compared the role of VBL and beta-blockers as therapies for the primary prophylaxis of variceal bleeding.[10]A few studies have shown superiority of VBL as compared with NSBBs[11 12] while others have suggested superiority or non-inferiority of both the therapies.[13] However, there are no studies which have specifically compared these two therapies in patients with advanced cirrhosis with 'high-risk' varices. In the Baveno VII consensus, the importance of stratification of patients, as per the severity of liver disease, was emphasised and therapies are required to be individualised and tailored for specific groups of patients.[2]

There are also limited data on the combination of both beta-blockers and VBL for primary prophylaxis of variceal bleeding. Conceptually, if VBL is done along with portal pressure reduction by usage of β-blockers, the chances of bleeding from varices should be lower. We hypothesised that a combination of VBL and carvedilol is superior to either VBL monotherapy or carvedilol given alone for prevention of first variceal bleed in Child-Turcotte-Pugh (CTP) B and C cirrhosis with high-risk varices.

The present study primarily aimed to determine the efficacy of combination therapy compared with monotherapies (carvedilol or VBL) in the prevention of first variceal bleed in patients with advanced cirrhosis at 1 year. The secondary objectives of the study included degree of reduction in the HVPG, survival, incidence of post-VBL ulcer bleed, and the incidence of development of new onset complications over 1 year.

PATIENTS AND METHODS

Study design

This was an open-label, randomised controlled trial conducted between January 2017 and December 2019 at the Institute of Liver and Biliary Sciences (ILBS), New Delhi, India. This study followed the CONSORT guidelines for randomised controlled trials. This study was registered at ClinicalTrials.gov with identifier number—NCT03069339. All the authors had contributed and had access to the data.

Eligibility criteria

Patients ranging between 18 and 75 years of age, diagnosed with cirrhosis of the liver based on imaging or liver biopsy, with a CTP score between 7 and 13, having either large oesophageal varices (>5 mm) or small 'high-risk' oesophageal varices (<5 mm in size with the presence of red colour signs) and with no prior history of variceal bleed, were included in the study after a written informed consent. Patients having contraindications to β-blockers, hepatocellular carcinoma, portal vein thrombosis, patients with CTP<7 or ≥13, platelet count <30 × 10^9/L, use of anticoagulant, a history of VBL treatment, pregnancy, lactation, prior transhepatic intrajugular portosystemic shunt (TIPS) procedure, prior shunt surgery, AKI, chronic kidney disease or non-availability of written consent were excluded.

Patients

Prospectively enrolled patients who met the eligibility criteria were enrolled and randomised to receive one of the treatment arms; carvedilol monotherapy (group A), VBL (group B) or a combination (carvedilol plus VBL, group C). The assessment of eligibility and randomisation of the patient was done on the same day. The treatment was also initiated on the same day or the following day. There was no delay in prescribing the therapy and the initiation of the therapy, to avoid any immortal time bias.

Patients who received carvedilol were asked to maintain a diary and were trained to self-record their blood pressure and heart rate with a portable home-based electronic instrument. Carvedilol dose was escalated on weekly basis with the aim to reach up to the maximum tolerable dose, achieve a target heart rate of 55–60 bpm or at least 25% reduction from baseline. Patients who were to receive variceal ligation either as monotherapy or as combination, underwent upper GI endoscopy (UGIE) and VBL based on institution protocol (every 3 weeks till eradication) on the following day after the randomisation. In the combination arm, carvedilol was started on the day the patient was subjected to VBL. A total of 330 patients were included in the trial, with 110 cases randomised to each of the three study groups. Patients were also advised for HVPG monitoring, if they consented for the procedure.

Treatment

The patients who were randomised to receive carvedilol, either as monotherapy on in combination, were instructed to start with 3.125 mg two times per day for a week and then to increase the dose by 3.125 mg weekly up to a maximum dose of 12.5 mg two times per day while maintaining daily pulse rate and blood pressure record.[14–16] The dosage was increased to the level where the pulse rate was between 55 and 60 beats per minute (bpm) and the systolic blood pressure was maintained above 90 mm Hg. Patients were instructed to maintain a diary and to self-report, either in person or telephonically in case of any adverse event.

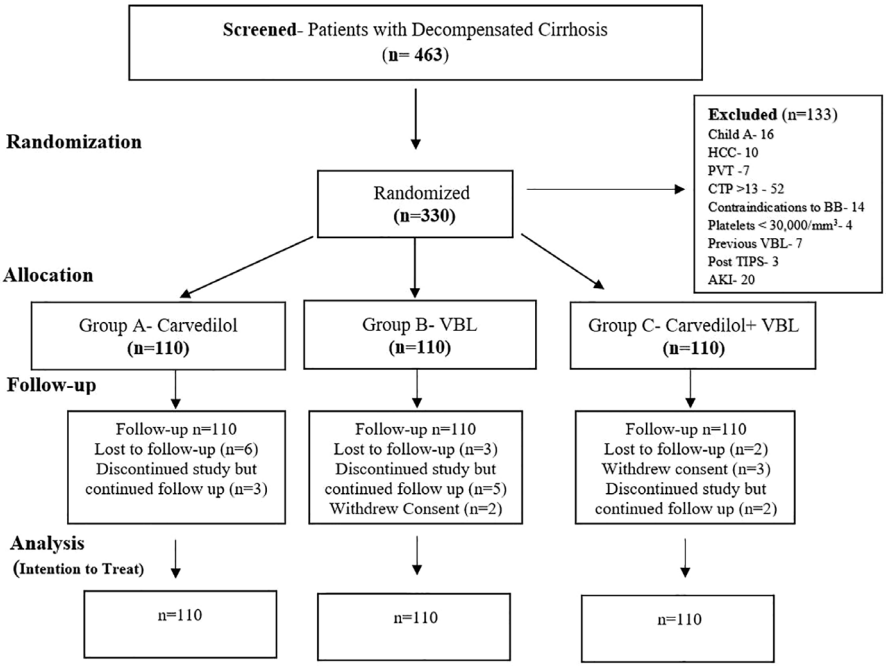


Figure 1 CONSORT chart. AKI, acute kidney injury; CONSORT, Consolidated Standards of Reporting Trials; CTP, Child-Turcotte-Pugh; HCC, hepatocellular carcinoma; PVT, portal vein thrombosis; VBL, variceal band ligation.

The patients who were randomised to undergo VBL, either monotherapy or in combination, underwent UGIE. Patients were asked to come for the procedure after overnight fasting or at least 5 hours of fasting. Initially, screening endoscopy was done with Olympus scope (outer diameter of 9.8 mm), followed by band ligation with Cook's multiband ligator (6-shooter), mounted on the scope. Each endoscopic procedure was done after preanaesthetic check and under continuous anaesthetist monitoring. Postprocedure observation was done in ambulatory facility for at least 4 hours and at the time of discharge, patients were instructed to take semisolid diet for 2 days along with a proton pump inhibitor and sucralfate syrup for 2 weeks. They were advised to undergo VBL every 3 weeks until eradication of the varices. In case of any adverse event, they were asked to immediately seek medical attention in emergency room or at the nearest clinic.

Follow-up

Patients were followed up for 1-year duration and new occurrence of variceal bleed, liver-related decompensation and treatment-related adverse events were recorded.

The initial clinic visit was within 1 week of initiation of the protocol and then at 3, 6, 9 and 12 months. Extra visits were allowed in case of adverse events. During each follow-up visit, detailed clinical examination, complete blood counts, kidney and liver function tests were done and assessment for new-onset complications or organ failure was done. UGIE was done at baseline and at three weekly intervals for the patients undergoing VBL until the eradication of varices and at 3-month intervals thereafter. The endoscopists in the study were well trained and experienced in diagnostic and advanced therapeutic endoscopic procedures. Endoscopists were kept unaware of the treatment arm to which the patient was randomised. HVPG was done at baseline and then at 12 months of follow-up. Compliance with the drugs was assessed through periodic telephonic conversations every fortnightly.

Management of treatment failure

Patients who bled while on carvedilol therapy were managed with the standard protocol which included use of vasoactive drugs and emergency VBL to control the bleeding. The patients were managed in the GI bleed ICU. Similarly, if the bleed could not be controlled after VBL or if there was rebleed following the initial control of variceal bleeding, patients were considered for alternative therapies including Ella-Danis stent placement or emergency TIPS insertion depending on their CTP status. A careful note of the postbleed clinical and laboratory parameters was maintained.

Objectives

The primary objective of the study was to assess the reduction in the incidence of first variceal bleed at the end of 1 year in the three study groups. The secondary objectives of the study included HVPG reduction, survival, incidence of post-VBL ulcer bleed, incidence of development of SBP, AKI, episodes of sepsis with or without shock, improvement in CTP and MELD scores and treatment-related adverse events during the 1 year of follow-up. Endpoints were bleed at 12 months and mortality at 12 months in the three groups.

Definitions

Varices grading: Varices were graded as small or large varices; with <5 mm varices as small varices and >5 mm as large varices. The presence of high risk was based on red colour signs, namely, cherry-red spots, red wale marks and haematocystic spots.[17]

Ascites, AKI/HRS, hepatic encephalopathy, SBP were defined as per the standard guidelines.[18]

The worsening of ascites was described as an increase of more than one grade in ascites from baseline.[18]

Variceal bleeding, response to β-blocker therapy, post-VBL ulcer bleed were diagnosed according to the Baveno IV criteria.[19]

Table 1 Baseline demographics of the study population

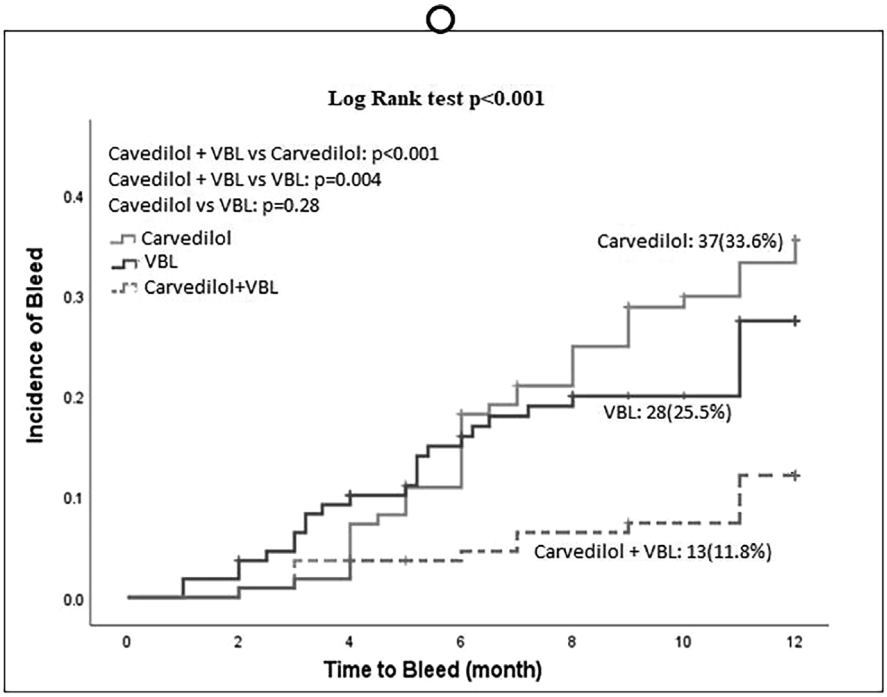
Parameters	Carvedilol (n=110) Group A	VBL (n=110) Group B	Carvedilol+VBL (n=110) Group C	P value
Age (years) (mean±SD)	51.3±11.1	50.6±10.8	52.3±9.6	0.5
Gender (M:F)	90 (81.8%); 20 (18.2%)	95 (86.4%); 15 (13.6%)	96 (87.3); 14 (12.7%)	0.5
Aetiology, n (%)				
NAFLD	56 (50.9)	46 (41.8)	52 (47.3)	0.41
Alcohol	30 (27.3)	35 (31.8)	28 (25.5)	0.64
HBV	2 (1.8)	7 (6.4)	9 (8.2)	0.22
HCV	5 (4.5)	4 (3.6)	8 (7.3)	0.66
AIH	NIL	4 (3.6)	4 (3.6)	–
Cryptogenic	17 (15.5)	14 (12.7)	9 (8.2)	0.19
Varices grade, n (%)				
Grade two with RCS	59 (53.6)	59 (53.6)	50 (45.5)	0.375
Grade three or 4	51 (46.4)	51 (46.6)	60 (54.5)	
Comorbidities, n (%)				0.67
Diabetes mellitus	48 (43.6)	50 (45.5)	54 (49.5)	0.93
Hypertension	22 (20.0)	24 (21.8)	22 (20.2)	0.96
Hypothyroidism	9 (8.2)	9 (8.2)	8 (7.3)	0.35
CAD	4 (3.6)	8 (7.3)	4 (3.6)	
Systolic BP (mm Hg)	120.7±7.2	120±6.9	118.16±7.8	0.09
Pulse rate (beats/min)	85.6±9.42	88.8±12	87.2±10	0.08
Diuretic usage, n (%)	65 (59.1)	76 (69.1)	70 (64.2)	0.3
Haemoglobin (g/L)	85.2 ±12.2	84.3±10.7	86.3±11.6	0.57
Platelet count (×10^9/L)	78±21.7	77.8±9.5	77.4±16.2	0.97
TLC (per cu. mL)	8.6±2.8	8.5±2.7	8.3±2.7	0.59
Blood urea (mg/dL)	60±15.6	61.7±14.8	61.1±16	0.7
Serum creatinine (mg/dL)	0.57±0.16	0.59±18	0.58±0.18	0.78
Serum sodium (mmol/L)	131.4±2.3	131.6±2.2	131.5±2.4	0.82
Total bilirubin (mg/dL)	2.3±0.7	2.3±0.63	2.2±0.75	0.56
AST (IU/L)	39.3±5.2	39.0±5.0	39.1±5.9	0.95
ALT (IU/L)	48.3±15.6	47.5±15.7	47.6±15	0.9
Serum albumin (g/dL)	2.6±0.44	2.5±0.45	2.5±0.42	0.15
PT (seconds)	21.0±2.54	21±2.40	20.8±2.7	0.8
INR	1.9±0.23	1.9±0.22	1.8±0.25	0.47
CTP score	8.80±1.19	8.91±1.35	8.91±1.04	0.77
MELD score	15.13±3.36	15.28±3.44	15.08±3.27	0.9
HVPG (mm Hg)	16.62±3.48	16.85±3.52	17.42±3.70	0.26

Comparison of Baseline demographics,aetiology,laboratory parameters between the 3 groups.
AIH, autoimmune hepatitis; ALT, alanine aminotransaminase; AST, aspartate aminotransaminase; CTP, Child-Turcotte-Pugh; HBV, hepatitis B virus; HCV, hepatitis C virus; HVPG, hepatic vein pressure gradient; INR, international normalised ratio; MELD-Na, model for end stage liver disease sodium; NAFLD, non-alcoholic fatty liver disease; TLC, total leucocyte count; VBL, variceal band ligation.

Statistical analysis

According to previous literature, the incidence of bleeding with carvedilol was 10.4% and with VBL, 22.5% at 1 year of follow-up.[6] In this study, however, nearly half of the patients had compensated cirrhosis. We, therefore, made sample size calculations assuming that the incidence of bleeding would be 15%, 30%, 10% in the carvedilol, VBL and the combination arm (carvedilol+VBL), respectively. The size was calculated on the basis of taking two different incidences and adjusting for alpha error. With alpha taken as 5%, power 80%, we needed to enrol 276 case in three arms. Further with 10% drop-out rate, it was decided to enrol 330 cases, that is, 110 cases in each arm. The STATA V.17 software was used for sample size calculation (online supplemental figure 4). The allocation of patients to different arms was done randomly by block randomisation method, taking the block with size as 10 in each arm. Randomisation was done by a dedicated trial co-ordinator.

The data were entered in Microsoft Excel format and were analysed by using SPSS V.28 (IBM) and Stata V.17. Baseline categorical patient data were expressed as a proportion and continuous data were represented as mean±SD or median (IQR). To compare among the groups, either one-way analysis of variance followed by post hoc comparison by Bonferroni method or Kruskal-Wallis test was used. To compare between bleeder or non-bleeder, either Student's t-test or Mann-Whitney U test was applied, depending on the normality of the data. The categorical data were analysed using χ^2 test or Fisher's exact test. The change between prevalues and postvalues was analysed using paired t-test or McNemar test depending on whether the variable is continuous or categorical. Survival analysis was carried out using Cox proportion hazard regression analysis. Besides this, survival plots were compared using Kaplan-Meier method and significance was assessed using log-rank test. The assumption for equality of proportionality was also checked. The time-to-event



	Time	0	2	4	6	8	10	12
Carvedilol	At Risk	110	109	104	96	84	75	69
	Events	0	1	6	14	24	32	37
VBL	At Risk	110	101	89	81	76	75	64
	Events	0	5	11	16	20	21	28
Carvedilol+ VBL	At Risk	110	109	107	103	102	101	96
	Events	0	1	3	7	8	9	13

Figure 2 Kaplan-Meier curves representing overall incidence of first variceal bleed (ITT) in study population over 12 months in carvedilol arm (group A, blue line), VBL arm (group B, red line) and carvedilol+VBL arm (group C, green line). ITT, intention-to-treat; VBL, variceal band ligation.

analysis was performed using survival analysis by Cox proportional hazard regression method (HR with 95% CI) and Kaplan-Meier method followed by log rank test. Statistical analysis was done according to general regulatory recommendations and according to an intention-to-treat (ITT) strategy. Patients who were lost to follow-up or those who withdrew consent were censored if they had not developed any outcome after the last documented visit. Besides this, competing risk analysis was also done considering liver transplant and TIPS as competing events. We also compared the incidence of organ failures in the different arms in patients following a bleed. Furthermore, we undertook survival analysis between bleeders and non-bleeders by using bleed as a time dependent covariate and also by using the Landmark analysis.[20 21] To see the changeover period of time, we applied repeated measure analysis followed by post hoc comparison by least square deviation method. Significance was defined as two-tailed $p<0.05$.

RESULTS

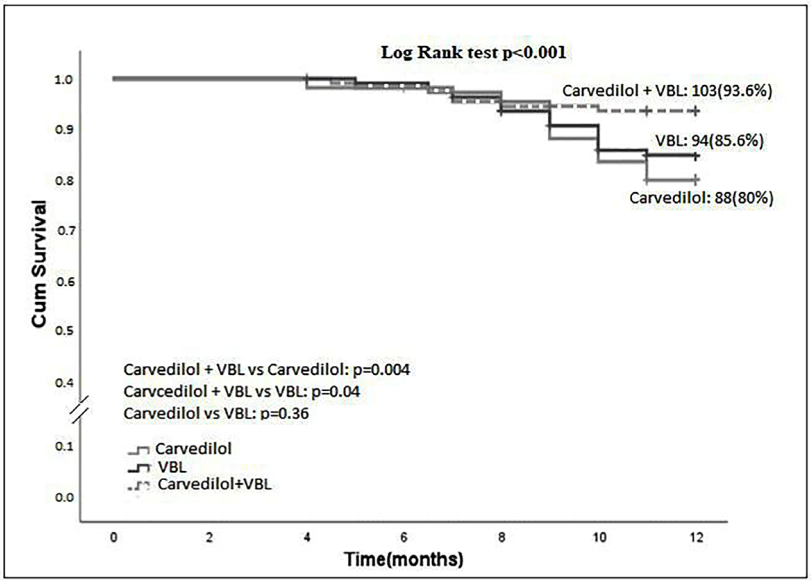
Baseline characteristics

A total of 463 patients with advanced liver cirrhosis were screened during the study period, out of which 133 patients were excluded (figure 1). The trial was conducted between January 2017 and December 2018. 330 patients were randomised into three groups, either to carvedilol monotherapy group (group A, n=110), VBL group (group B, n=110) or carvedilol plus VBL group (group C, n=110). Baseline parameters were comparable in each group. The proportion of males was more (85.2%) with mean age of 51.4±10.5 years. The common aetiology of cirrhosis was non-alcoholic fatty liver disease (NAFLD)-related cirrhosis with 154 (46.6%) patients followed by alcohol-related cirrhosis seen in 93 (28.2%) patients. Common comorbid conditions included diabetes mellitus (n=152, 46.2%), hypertension (n=68, 20.7%) and hypothyroidism (n=26, 7.9%). The detailed baseline demographic characteristics are depicted in table 1 whereas the overall data and comparisons are given at online supplemental table 2. The change in parameters is given in online supplemental table 1.

Primary objective

Reduction in the incidence of first variceal bleed at the end of 1 year

The overall incidence of variceal bleed at the end of 1 year was 23.8% (N=78). As per ITT analysis, the overall incidence of first variceal bleed in the carvedilol monotherapy (group A) was 33.6% (n=37), VBL group (group B) was 25.5% (n=28) and in carvedilol plus VBL group (group C) was 11.8% (n=13). On comparison between the groups, a significant difference was seen in the combination arm as compared with either carvedilol ($p<0.001$) or VBL group ($p<0.002$) (figure 2). Mean dose in carvedilol group was 10.59±2.81 mg and in combination arm (VBL+carvedilol) was 9.77±2.8 mg ($p<0.03$). The combination arm (group C) significantly reduced the incidence of the first bleed by 62.9% (HR 0.37, 95% CI 0.192 to 0.716, $p<0.003$) as



	Time	0	2	4	6	8	10	12
Carvedilol	At Risk	110	110	110	107	103	78	87
	Events	0	0	0	2	6	14	22
VBL	At Risk	110	110	110	107	97	93	86
	Events	0	0	0	2	7	10	16
Carvedilol+VBL	At Risk	110	110	109	109	106	101	101
	Events	0	0	1	1	4	7	7

Figure 3 Kaplan-Meier curves representing cumulative survival in study population over 12 months in carvedilol arm (group A, blue line), VBL arm (group B, red line) and carvedilol+VBL arm (group C, green line). VBL, variceal band ligation.

compared with VBL group (group B) and 69.3% as compared with the carvedilol group (group A) (HR 0.31, 95% CI 0.163 to 0.578, p<0.001).

Secondary objectives

Overall and bleed-related mortality between three groups

The overall mortality in the three groups was 13.6% (45/330). The mortality in the combination group (group C) was significantly reduced as compared with both the groups (p<0.005) (figure 3). A total of 45 (13.6%, 95% CI 10.1% to 17.8%) patients died during the study period; mortality in carvedilol monotherapy group was 20% (95% CI 12.9% to 28.7%), in VBL group was 14.5% (95% CI 8.5% to 22.5%) and in carvedilol plus VBL group was 6.3% (95% CI 2.6% to 12.6%) (p=0.012). Of 330 cases, 13 (3.94%) patients underwent TIPS while 7 (2.12%) patients underwent liver transplant (table 2). There was no difference in the proportion of patients undergoing TIPS or liver transplantation between the groups.

On subgroup analysis, the overall survival was significantly higher in patients who did not have variceal haemorrhage as a decompensating event as compared with the bleeders (p=0.001) (figure 4). Bleed-related overall mortality was seen in 25/330 (7.58%, 95% CI 4.96% to 10.98%) patients; with 13/110 (11.82%, 95% CI 6.45% to 19.36%) in the carvedilol arm, 9/110 (8.18%, 95% CI 3.81% to 14.96%) in the VBL arm and 3/110 (2.73%, 95% CI 0.57% to 7.76%) patients in the combination arm. 'Time to first variceal bleed' was significantly longer in the combination arm as compared with the carvedilol and VBL arm (p<0.001) (table 2).

Since the comparison of bleeders and non-bleeders was not randomised, we undertook to analyse the data, keeping bleed as a time-dependent variate and determined the outcomes in

Table 2 Outcomes in the three study groups at 12 months

Variable	Carvedilol Group A	VBL Group B	Carvedilol plus VBL Group C	P value
Death (12 months)*	22 (20%)	16 (14.5%)	7 (6.4%)	0.01
Time to bleed (in months)*	9.70±2.95	9.63±3.58	11.22±2.20	0.00
Time to death (in months)	11.29±1.58	11.11±1.69	11.58±1.38	0.08
Liver transplant	3 (2.7%)	2 (1.8%)	2 (1.8%)	0.86
TIPS	4 (3.6%)	6 (5.5%)	3 (2.7%)	0.57

*This table depicts lower mortality as well as time to bleed in combination arm as compared to other study groups Group C versus group A (p<0.001), group C versus group B (p<0.001).
TIPS, transhepatic intrajugular portosystemic shunt; VBL, variceal band ligation.

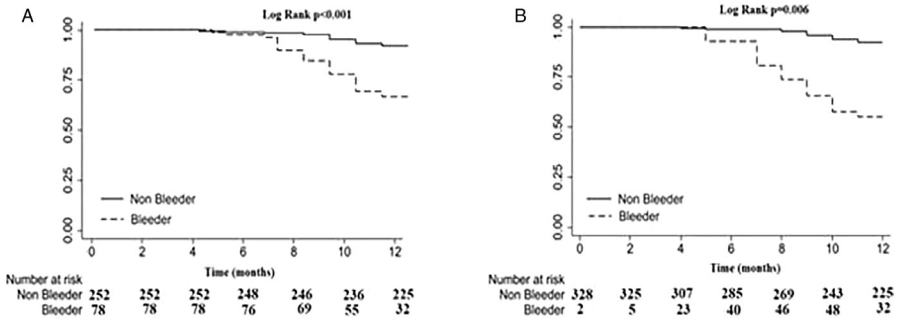


Figure 4 A Kaplan-Meier curves representing overall survival in the study population without considering bleed as time dependent covariate and B, is Kaplan-Meier curve after considering bleed as time dependent covariate in study population over 12-months duration, among bleeders (solid line) compared to non-bleeders (dotted line).

the three study groups. We compared the mortality without or with the immortal time bias (figure 4A,B). The HR for overall bleed-related mortality increased from 4.79 (2.66–8.64) to 7.37 (4.08–13.31) using bleed as a time dependent covariate.

We also compared the mortality between the individual treatment arms with or without the immortal time bias using time variate–covariate analysis and landmark time analysis. Using the former method, the analysis showed that there was a slight increase in the absolute death rate in the carvedilol arm by 2.2% and in the VBL arm by 0.4%. The mortality rate was reduced by 2.5% in the combination arm (online supplemental table 3). The landmark time analysis method showed that that there was no change in mortality in each of the study arms for different landmark time points; baseline, 1 month 3 months (online supplemental table 4). Furthermore, we analysed the outcomes between bleeders and non-bleeders using the Forest plot method up to 7 months. The HR in different treatment arms was comparable, whether we included immortal time bias or not (online supplemental figure 5).

All these analyses affirm that our study is not impacted by immortal time bias. There is no heterogeneity among the different estimates obtained from different landmark time points.

Competing risk analysis for all the three groups was performed with liver transplant, TIPS as competing events (table 3). Platelet count, CTP score, diuretic usage were significant predictors for overall mortality and platelet count and VBL sessions were significant in competing risk analysis (table 4).

HVPG reduction

We were able to perform paired HVPG measurements in 223 (67.6%) patients. Among them 169 (73.5%) patients had HVPG reduction. Clinically significant reduction in HVPG of >20% was seen in 26.7%, whereas >10% reduction was seen in 57.3% of the patients. The reduction in HVPG in carvedilol group was from 16.6±3.58 to 13.14±3.33 mm Hg (ΔHVPG=−3.46 mm Hg, 20.8% reduction), in the combination arm from 17.9±3.59 to 13.4±2.55 mm Hg (ΔHVPG=−4.50 mm Hg, 25.1% reduction) and in VBL arm from 17.5±3.65 to 17.0±3.65 mm Hg (ΔHVPG=−0.5 mm Hg, 2.85% reduction). On comparison between the groups, no significant reduction in HVPG was seen between the carvedilol and the combination arm (p=0.54) (online supplemental figure 1). The rate of non-response to beta-blockers in group A (carvedilol) was 53.4% whereas in the combination arm, it was 41.25%, the difference was not significant (p=0.154).

Changes in CTP and MELD scores

During follow-up, patients had serial increase in CTP score, which was non-significant between the groups, at baseline as well as at different time points (online supplemental figure 2). Similarly, changes in MELD score over time were non-significant between groups (online supplemental figure 3). We also studied development of organ failures and ACLF during the follow-up period (table 5). There was no significant difference in the development of organ failures and ACLF between the three treatment arms.

Adverse events and safety profile

Worsening ascites was seen in 29 (8.79%) patients; 12 (11.1%) in carvedilol, 7 (6.6%) in VBL and 10 (8.8%) in combination group. Change in diuretic dose requirements was reported in 110 (33.6%) patients. SBP was reported during the study duration in 23 (6.96%) patients and AKI occurred in 6 (1.82%) patients (tables 6 and 7).

Common side effects related to carvedilol treatment were fatigue (19.1%) with five patients developing bradycardia (4.5%) of which one patient developed hypotensive episode (table 7). Four (22.2%) patients in the carvedilol group and three patients in the combination arm (2.7%) required dose reduction. None of the adverse events were fatal. The number of adverse events in all three groups was not significant (p=0.64).

Table 3 Overall and competing risk analysis between the study groups

	Overall comparison			Competing risk analysis		
Group	HR	95% CI	P value	HR	95% CI	P value
Carvedilol	1	–	–	1	–	–
VBL	0.74	0.39 to 1.42	0.34	0.69	0.30 to 1.61	0.39
Combination arm	0.30	0.13 to 0.71	0.07	0.22	0.06 to 0.77	0.01

VBL, Variceal Band Ligation.

Table 4 Overall and competing risk analysis of predictors of mortality

	Overall comparison			Competing risk analysis		
Groups	HR	95% CI	P value	HR	95% CI	P value
Age	1.00	0.97 to 1.03	0.20	1.01	0.97 to 1.04	0.49
Gender	0.84	0.35 to 2.00	0.70	1.06	0.36 to 3.05	0.90
Platelet count	1.01	1.00 to 1.02	0.03	1.01	1.00 to 1.02	0.03
CTP Score	1.74	1.35 to 2.23	0.01	1.30	0.95 to 1.79	0.09
MELD Score	1.06	0.83 to 1.08	0.21	1.05	0.94 to 1.18	0.34
Diuretic usage	0.36	0.17 to 0.79	0.01	0.69	0.29 to 1.64	0.40
VBL sessions	0.87	0.92 to 1.09	0.89	0.72	0.52 to 0.98	0.03

CTP, Child-Turcott-PughTurcot Pugh Score; MELD, Model for End-Stage Liver Disease; VBL, variceal band ligation.

Management of treatment failure

14 (12.7%) patients in the carvedilol group bled and were subjected to emergency VBL along with terlipressin infusion for 5 days and were managed in the GI-bleed ICU. These patients were subsequently managed as patients with acute variceal bleed. 10 (71.4%) of these patients required blood transfusion.

In the VBL group, post-VBL ulcer-related bleeding was reported in 12 (10.9%) patients. These patients required hospitalisation and admission in local hospital or at our GI-bleed ICU for treatment and monitoring. They were managed with splanchnic vasoconstrictors. Active bleeding was not reported at the time of relook endoscopy and none of the patients with post-VBL ulcer-related bleed required rescue intervention like ELLA-Danis stent placement or emergency TIPS for failure to control bleed.

The most common reported adverse event in the VBL group was dysphagia after the band ligation seen in 45 (20.4%) patients. The episodes were transient and improved after 24–48 hours.

DISCUSSION

This study is the first randomised trial comparing monotherapy with carvedilol, VBL or a combination of the two therapies for the prevention of first variceal bleeding in patients with CTP B and C cirrhosis having high-risk varices. We found that a combination of carvedilol and VBL reduced significantly more the incidence of first variceal bleed at 1 year compared with the monotherapies. The combination therapy also conferred survival benefits in this group of patients. This finding represents an important milestone for proposing combination of both the modalities in patients with advanced cirrhosis and high-risk varices.

It is known that variceal bleeding as a decompensating event leads to increased risk of mortality.[10] Our study demonstrates that addition of VBL to beta-blocker therapy effectively reduces the portal pressure leading to reduced risk of bleeding. The concept is unique as none of the previous studies have combined carvedilol with VBL for primary prophylaxis. Traditionally, a comparison between VBL and beta blockers has shown mixed results with majority not showing any significant benefit while some reporting benefit in favour of VBL.[10 22 23] The present study reports that a combination of VBL with carvedilol significantly reduced the incidence of first bleed by 62.9% as compared with VBL monotherapy group ($p<0.003$) and 69.3% as compared with the carvedilol monotherapy group ($p<0.001$). The overall mortality (6.4% vs 20%) as well as the bleed-related mortality (2.73% vs 11.8%) was also significantly lower in the combination arm compared with the carvedilol arm ($p<0.01$).

Our study also incorporated repeat measurement of HVPG after 12 months. This could be accomplished in more than two-thirds of the patients. HVPG is indeed the most reliable assessment of portal pressure. There was no difference in the reduction in HVPG in the combination arm as compared with carvedilol monotherapy arm (25.1% vs 20.8% $p=0.54$).

Our findings are at variance to a previously published trial by Tripathi *et al*,[6] where carvedilol was found to be superior to VBL in the prevention of variceal bleed. However, it needs to be clarified that in the study by Tripathi *et al*, the majority of the patients had small varices with or without red-coloured signs and the interval between the VBL sessions was shorter which could possibly had led to increased post-VBL bleeding rates. The smaller sample size as well as the lack of haemodynamic monitoring by HVPG in their study are major limitations in the applicability of their study. Furthermore, they gave a fixed dose of 12.5 mg/day of carvedilol, with which the heart rate could be reduced only to a mean of 70 beats per minute. This may not be considered adequate beta-blockade. Shah *et al*[13] also compared both the modalities and found non-superiority of either therapy. Their study was, however, underpowered and lacked HVPG assessment.

The results of our study have a special implication as it relates to specific group of advanced cirrhosis patients belonging to CTP 7–13 category. In this group of patients, the combination therapy demonstrated survival benefit as compared with monotherapy with either VBL or carvedilol.

The specific advantage of combining carvedilol with VBL cannot be overemphasised. It is well established that early reduction in portal pressure as well as its long-term sustained reduction is associated with reduced incidence of variceal bleeding. The development of post-VBL ulcers and bleed generally takes a week or more.[24] During this period, the beta-blocker therapy can provide its beneficial effects. The reduced portal pressure by NSBB is likely to be of help in preventing rebleeds from the post-VBL ulcer. These beneficial effects persist throughout the

Table 5 Development of organ failures in the three treatment arms following a bleed

Variable	Carvedilol (Grade A, n=110)	VBL (Grade B, n=110)	Combination (Grade C, n=110)	P value
Respiratory failure	6 (5.5)	7 (6.4)	5 (4.5)	0.840
Circulatory failure	9 (8.2)	5 (4.5)	7 (6.4)	0.543
Hepatic failure	1 (0.9)	0	0	1.000
Coagulation failure	10 (9.1)	11 (10)	8 (7.3)	0.767
Kidney failure	6 (5.5)	6 (5.5)	2 (1.8)	0.303
Brain failure	7 (6.4%)	8 (7.3)	5 (4.5)	0.689

VBL, variceal band ligation.

Table 6 Liver-related events related to interventions in the study groups

Adverse event	Carvedilol (n=110)	VBL (n=110)	Carvedilol+VBL (n=110)	P value
Worsening ascites, n (%)	12 (11.1)	7 (6.6)	10 (8.8)	0.33
Change in diuretics dosage, n (%)	38 (34.5)	35 (31.8)	37 (33.6)	0.23
New onset AKI, n (%)	5 (4.5)	0	1 (0.3)	0.26
SBP, n (%)	13 (12)	3 (2.7)	7 (6.3)	0.16

AKI, acute kidney Injury; SBP, spontaneous bacterial peritonitis; VBL, variceal band ligation.

treatment period as was observed by reduction in the HVPG levels at 12 months compared with the bassline values. Reduction in portal pressure by portosystemic shunts (either surgical or transcutaneous intrahepatic portosystemic shunt) is known to reduce incidence of variceal bleeding.[25]

NAFLD-related cirrhosis was the predominant aetiology, followed by alcohol and viral aetiologies in our study. This is slightly at variance from the previous studies in which the majority of the study population had virus and alcohol as the major aetiologies for cirrhosis.[26 27] This has clinical implications as a recently published trial has shown that patients with NAFLD have relatively lower HVPG.[28] Despite this, another recent study showed a higher prevalence of portal hypertension-related decompensation at any value of HVPG as compared with patients with hepatitis C-related cirrhosis.[29] Even a recently concluded trial by Jachs *et al* had shown that response to the NSBBs is lower in cirrhosis patients with diabetes.[30] These findings suggest that in NASH cirrhosis, greater reduction of HVPG would be required for preventing decompensation including variceal bleed, ascites, etc. This further affirms the point that for the primary prevention of variceal bleeding especially in patients with NASH, combination therapy would lead to greater reduction of portal hypertension and help improve survival.

Table 7 Direct treatment-related events in individual groups

Carvedilol arm (group A)		
Total number of events-31	**Carvedilol (n=110)**	**CTCAE**
Weakness/dizziness, n (%)	21 (19.1)	1,2
Bradycardia episodes, n (%)	5 (4.5)	2
Hypotension episodes, n (%)	1 (1)	2
Dysphagia, n (%)	0	–
Dose reduction of carvedilol, n (%)	4 (3.6)	–
Intolerant to carvedilol, n (%)	0	–
Variceal band ligation (VBL) (group B)		
Total number of events-36	**VBL (n=110)**	**CTCAE**
Weakness/dizziness, n (%)	0	–
Bradycardia episodes, n (%)	0	–
Hypotension episodes, n (%)	0	–
Post-VBL ulcer bleed, n (%)	8 (7.3)	2, 3, 4
Post-VBL dysphagia, n (%)	28 (25.4)	2
Carvedilol+VBL (group C)		
Total number of events-30	**Carvedilol+VBL (n=110)**	**CTCAE**
Weakness/dzziness, n (%)	5 (4.5)	1,2
Bradycardia episodes, n (%)	0	–
Hypotension episodes, n (%)	1 (1)	2
Post-VBLulcer bleed, n (%)	4 (3.7)	2, 3, 4
Post-VBL dysphagia, n (%)	17 (15.4)	2
Dose reduction of carvedilol, n (%)	3 (2.7)	–
Intolerant to carvedilol, n (%)	0	–

CTCAE, Common Terminology Criteria for Adverse Events; VBL, Variceal Band Ligation.

The adverse event profile of carvedilol appeared favourable with none of the patients requiring total withdrawal of the drug. Even rates of hypotension which are believed to be frequent with carvedilol as compared with other NSBBs, especially in patients with CTP B and C patients with ascites were also seen in a minority of patients, possibly due to careful titration and monitoring of the dose. Written instructions for the patient and primary care physician were provided to each patient. A close follow-up was maintained for all the patients during the clinical visits followed by periodic telephonic conversations every fortnightly. New-onset ascites and other decompensating events were also comparable in both the arms. There was also no difference in the incidence of development of organ failures following a bleed in the three treatment arms. None of the drug-related events was fatal. We, therefore, propose that the dose of carvedilol should be titrated and monitored in CTP B and C patients requiring primary prophylaxis. The results of benefits with beta-blockers as observed in our study seem to be consistent with the earlier published studies.[31] Other studies have shown the benefits of carvedilol in the prevention of hepatic decompensation, especially development of ascites.[5] New-onset AKI was reported in six patients (five in group 1 (carvedilol) and 1 in group 3 (combination arm). This was managed with dose reduction and albumin infusions. In fact, all patients were managed with regular albumin infusion and maintaining the serum albumin levels above 3 g/dL. Data are limited on the use of carvedilol in decompensated cirrhosis. Previous work from Bañares *et al* showed no incidence of AKI with long-term usage of carvedilol though the sample size was comparatively smaller to this study.[14] In our study, even the rates of new-onset ascites appear to be consistent with the previously published data with slightly better rates in patients receiving combination therapy, though the difference was not significant. In the VBL arm, post-VBL dysphagia was common while post-VBL ulcer bleed was seen in 5% of the patients, none were fatal and bleeding was controlled.

Our trial has a few limitations, some of which were related to the nature of the disease and the therapies offered. The trial could not be made double blind, as blinding was not easy and safe. With two groups of patients, receiving carvedilol, which requires proper monitoring of heart rate and blood pressure, blinding was difficult. The mean dose of carvedilol in our study was slightly lower in carvedilol group (10.59±2.81 mg/day) and in combination group (9.77±2.8 mg/day) as compared with proposed 12.5 mg/day in previous studies. However, these studies were based on small sample sizes. In our experience, 12.5 mg/day is a rather high dose for patients with decompensated cirrhosis and can cause more adverse events. We need further randomised studies to determine the effective and safe dosage in this group of cirrhosis patients. Another limitation was that non-invasive tests including transient elastography as

well as CT imaging could not be performed in all the patients. However, these were not the primary or secondary objectives of the study. In studies related to prophylaxis of variceal bleeding it is important to ensure that there is minimum time lapse between the randomisation and the initiation of the therapy. In our study, the randomisation and initiation of the treatment in the three arms were undertaken on the same day or the following day and there was no immortal time bias.

In conclusion, our results clearly demonstrate that a combination of carvedilol and VBL is more effective than either therapy given alone in the primary prophylaxis of first variceal bleed in patients with advanced cirrhosis and high-risk varices. We suggest that for this category of patients, a combination therapy of portal pressure reduction by carvedilol combined with VBL should be recommended.

Contributors All authors contributed to conceptualisation (AP and SKS), data curation (AP, HVT and RV), formal analysis and visualisation (AP, HVT, RV, GK and SKS), writing of the original draft (AP and HVT), reviewing and editing (all authors) or supervision (HVT and SKS). Guarantor of the article: Shiv Kumar Sarin.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This single-centre study adhered to the Declaration of Helsinki and was approved by the institutional ethics committee-F.25/5/107/ILBS/AC/2016/11252/295.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

ORCID iD

Shiv Kumar Sarin http://orcid.org/0000-0002-0544-5610

REFERENCES

1 Sarin SK, Kumar A, Angus PW, *et al*. Diagnosis and management of acute variceal bleeding: Asian Pacific Association for Study of the Liver recommendations. *Hepatol Int* 2011;5:607–24.
2 de Franchis R, Bosch J, Garcia-Tsao G, *et al*. Baveno VII - renewing consensus in portal hypertension. *J Hepatol* 2022;76:959–74.
3 Garcia-Tsao G, Abraldes JG, Berzigotti A, *et al*. 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;65:310–35.
4 Garcia-Tsao G, Bosch J. Management of varices and Variceal hemorrhage in cirrhosis. *N Engl J Med* 2010;362:823–32.
5 Mandorfer M, Bota S, Schwabl P, *et al*. Nonselective B blockers increase risk for hepatorenal syndrome and death in patients with cirrhosis and spontaneous bacterial peritonitis. *Gastroenterology* 2014;146:1680–90.
6 Tripathi D, Ferguson JW, Kochar N, *et al*. Randomized controlled trial of carvedilol versus variceal band ligation for the prevention of the first variceal bleed. *Hepatology* 2009;50:825–33.
7 Bañares R, Moitinho E, Piqueras B, *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;30:79–83.
8 Turco L, Villanueva C, La Mura V, *et al*. Lowering portal pressure improves outcomes of patients with cirrhosis, with or without ascites: a meta-analysis. *Clin Gastroenterol Hepatol* 2020;18:313–27.
9 Sinha R, Lockman KA, Mallawaarachchi N, *et al*. Carvedilol use is associated with improved survival in patients with liver cirrhosis and ascites. *J Hepatol* 2017;67:40–6.
10 Sarin SK, Wadhawan M, Agarwal SR, *et al*. Endoscopic variceal ligation plus propranolol versus endoscopic Variceal ligation alone in primary prophylaxis of variceal bleeding. *Am J Gastroenterology* 2005;100:797–804.
11 Sarin SK, Lamba GS, Kumar M, *et al*. Comparison of endoscopic ligation and propranolol for the primary prevention of variceal bleeding. *N Engl J Med* 1999;340:988–93.
12 Gluud LL, Krag A. Banding ligation versus beta-blockers for primary prevention in oesophageal varices in adults. *Cochrane Database Syst Rev* 2012;15:CD004544.
13 Shah HA, Azam Z, Rauf J, *et al*. Carvedilol vs. esophageal variceal band ligation in the primary prophylaxis of variceal hemorrhage: a multicentre randomized controlled trial. *J Hepatol* 2014;60:757–64.
14 Bañares R, Moitinho E, Matilla A, *et al*. Randomized comparison of long-term carvedilol and propranolol administration in the treatment of portal hypertension in cirrhosis. *Hepatology* 2002;36:1367–73.
15 Bhardwaj A, Kedarisetty CK, Vashishtha C, *et al*. Carvedilol delays the progression of small oesophageal varices in patients with cirrhosis: a randomised placebo-controlled trial. *Gut* 2017;66:1838–43.
16 Vijayaraghavan R, Jindal A, Arora V, *et al*. Hemodynamic effects of adding simvastatin to carvedilol for primary prophylaxis of variceal bleeding: a randomized controlled trial. *Am J Gastroenterol* 2020;115:729–37.
17 Sarin SK, Kumar A, Angus PW, *et al*. Primary prophylaxis of gastroesophageal variceal bleeding: consensus recommendations of the Asian Pacific Association for the Study of the Liver. *Hepatol Int* 2008;2:429–39.
18 European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, European Association for the Study of the Liver. EASL clinical practice guidelines for the management of patients with decompensated cirrhosis. *J Hepatol* 2018;69:406–60.
19 de Franchis R. Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol* 2005;43:167–76.
20 Hernán MA, Sauer BC, Hernández-Díaz S, *et al*. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. *J Clin Epidemiol* 2016;79:70–5.
21 Gleiss A, Oberbauer R, Heinze G. An unjustified benefit: immortal time bias in the analysis of time-dependent events. *Transpl Int* 2018;31:125–30.
22 Jutabha R, Jensen DM, Martin P, *et al*. Ran-domized study comparing banding and propranolol to prevent initial variceal hemorrhage in cirrhotics with high-risk esophageal Varices. *Gastroenterology* 2005;128:870–81.
23 Psilopoulos D, Galanis P, Goulas S, *et al*. Endoscopic variceal ligation vs. propranolol for prevention of first variceal bleeding: a randomized controlled trial. *Eur J Gastroenterol Hepatol* 2005;17:1111–7.
24 Sarin SK, Govil A, Jain AK, *et al*. Prospective randomized trial of endoscopic sclerotherapy versus variceal band ligation for esophageal varices: influence on gastropathy, gastric varices and variceal recurrence. *J Hepatol* 1997;26:826–32.
25 García-Pagán JC, Caca K, Bureau C, *et al*. Early use of TIPS in patients with cirrhosis and variceal bleeding. *N Engl J Med* 2010;362:2370–9.
26 Abd ElRahim AY, Fouad R, Khairy M, *et al*. Efficacy of carvedilol versus propranolol versus variceal band ligation for primary prevention of variceal bleeding. *Hepatol Int* 2018;12:75–82.
27 Lo GH, Chen WC, Wang HM, *et al*. Controlled trial of ligation plus nadolol versus nadolol alone for the prevention of first variceal bleeding. *Hepatology* 2010;52:230–7.
28 Sourianarayanane A, Talluri J, Humar A, *et al*. Stage of fibrosis and portal pressure correlation in nonalcoholic steatohepatitis. *Eur J Gastroenterol Hepatol* 2017;29:516–23.
29 Bassegoda O, Olivas P, Turco L, *et al*. Decompensation in advanced nonalcoholic fatty liver disease may occur at lower hepatic venous pressure gradient levels than in patients with viral disease. *Clin Gastroenterol Hepatol* 2022;20:2276–86.
30 Jachs M, Hartl L, Simbrunner B, *et al*. Carvedilol achieves higher hemodynamic response and lower rebleeding rates than propranolol in secondary prophylaxis. *Clin Gastroenterol Hepatol* 2023;21:2318–26.
31 D'Amico G, Garcia-Pagan JC, Luca A, *et al*. Hepatic vein pressure gradient reduction and prevention of variceal bleeding in cirrhosis: a systematic review. *Gastroenterology* 2006;131:1611–24.