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Combination Therapy as Primary Prophylaxis for High-Risk Esophageal Varices

HEPATOLOGY

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This summary reviews Tevethia HV, Pande A, Vijayaraghavan R, et al. 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.' Gut 2024; 73: 1844-53.

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STRUCTURED ABSTRACT

Question: Is combination therapy with non-selective beta blockers plus variceal band ligation (VBL) superior to monotherapy with either treatment for preventing first variceal bleed in patients with decompensated cirrhosis (Child-Turcotte-Pugh B and C cirrhosis) and high-risk esophageal varices?

Design: Single center, unblinded, randomized controlled trial (RCT) with block randomization scheme.

Setting: Institute of Liver and Biliary Sciences, New Delhi, India from January 2017 through December 2018.

Patients: Inclusion criteria included: (a) individuals 18-75 years old; (b) cirrhosis based on liver biopsy or imaging; (c) Child-Turcotte-Pugh (CTP) score of 7-13; (d) endoscopically confirmed large (> 5 mm) esophageal varices or small

(< 5 mm) esophageal varices with red color signs (aka “red wale” signs) of red streaks or patches on top of varices; and, (e) no prior history of variceal bleeding. Exclusion criteria included hepatocellular carcinoma, known contraindication to non-selective beta blockers, portal vein thrombosis, platelet count < 30,000 per ml, concurrent anticoagulant use, and prior history of transhepatic intrajugular porto-systemic shunt (TIPS).

Interventions/Exposure: Patients randomized to non-selective beta blocker monotherapy received carvedilol 3.125 mg twice daily and increased their dose by 3.125mg weekly up to maximum dose of 12.5 mg twice daily. Patients randomized to VBL monotherapy underwent upper endoscopy with Cook’s multiband (6-shooter) ligator every 3 weeks until eradication of varices. Patients randomized to combination therapy received the same protocol for both carvedilol therapy and VBL. Endoscopists were blinded about whether patients were in combination therapy vs VBL monotherapy groups. Clinic visits were conducted within 1 week of study initiation and again at 3, 6, 9, and 12 months with additional visits if adverse events occurred. Hepatic venous pressure gradient (HVPG) was measured at baseline and 12 months.

Outcome: The primary outcome was incidence of first variceal bleed after 12 months of follow-up. Secondary outcomes included, but were not limited to, reduction in hepatic venous pressure gradient, survival at 12 months, incidence of post-VBL ulcer bleeding, and incidence of spontaneous bacterial peritonitis (SBP) and acute kidney injury (AKI). Per investigators, definition of variceal bleeding was consistent with Baveno IV criteria.

Data Analysis: Intention-to-treat (ITT) analysis was performed with censoring of patients who were lost to follow-up if they had not developed any outcome after the last clinic visit. Time-to-event analysis was performed using Cox proportional hazards regression method and Kaplan-Meier method.

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Results: Between January 2017 and December 2018, 463 patients were screened and 330 patients with decompensated cirrhosis were enrolled (n=110 per group) with mean age 51 years old, 85% male, mean CTP score-8.9, and etiology of cirrhosis was primarily non-alcoholic fatty liver disease (47%) or alcoholic liver disease (28%). Mean baseline HVPG was 16.6-17.4 mm HG across treatment groups. Although no statistically significant differences were identified in baseline de-

mographics, non-selective beta blocker monotherapy and VBL monotherapy groups had 54% of patients with Grade 2 varices with red color signs and 46% with Grade 3-4 large varices, while the combination therapy group had the reverse trend with 46% with Grade 2 varices with red color signs and 54% with Grade 3-4 varices. Mean carvedilol dose achieved in monotherapy group was 10.6 mg and was 9.8 mg in the combination therapy group.

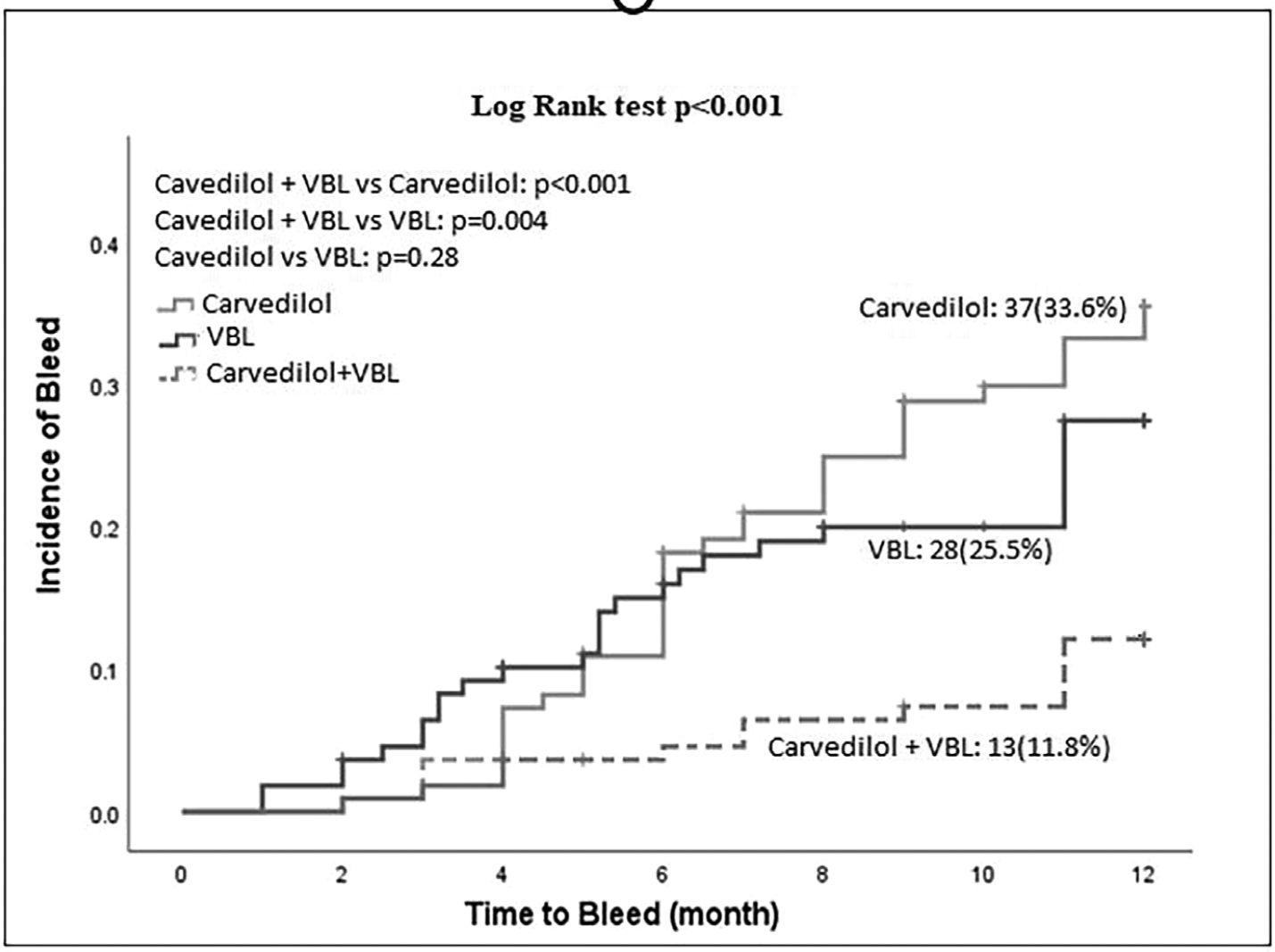
In the ITT analysis, the overall incidence of first variceal bleed was significantly lower in the combination therapy group vs non-selective beta blocker monotherapy or VBL monotherapy: 11.8% vs 33.6% vs 25.5%, respectively, $P < 0.002$ (Figure 1). Per Cox proportional hazard regression, combination therapy reduced the incidence of first variceal bleed by 69% (hazard ratio [HR] = 0.31; 95% confidence intervals [CI]: 0.16-0.58) vs carvedilol and by 63% (HR = 0.37; 95% CI: 0.19-0.72) vs VBL. All-cause mortality at 1 year was also significantly lower in the combination therapy group vs non-selective beta blocker monotherapy or VBL monotherapy: 6.3% vs 20% vs 14.5%, respectively, P=0.012.

Paired hepatic venous pressure gradients at baseline and 12 months were obtained in 223 patients and demonstrated significant reductions in HVPG of 21%-25% in the carvedilol monotherapy and combination therapy groups, but no significant reduction in the VBL monotherapy group. Post-VBL ulcer-related bleeding occurred in 10.9% of patients. Transient dysphagia occurred in 20% of post-VBL patients. Fatigue (19.1%) was the most common adverse event reported in carvedilol-treated patients.

COMMENTARY

Why Is This Important?

The 2024 guidelines[1] from the American Association for the Study of Liver Diseases (AASLD) recommend "if high-risk varices are detected, non-selective beta blockers or endoscopic band ligation are recommended; preference is given to non-selective beta blockers (including carvedilol) because of benefits beyond prevention of variceal hemorrhage." The guidelines emphasize that VBL should be performed as primary prophylaxis if the patient has a contraindication to non-selective beta blockers or cannot tolerate non-selective beta blockers. Per the guidelines, this recommendation for primary prophylaxis applies whether the patient has compensated cirrhosis with clinically significant portal hypertension or decompensated cirrhosis. Comparative RCTs of non-selective beta blockers and VBL for primary prophylaxis have produced mixed results, with some studies demonstrating non-inferiority



	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 1. Kaplan-Meier curves of overall incidence of first variceal bleed over 12 months. Reproduced with permission from Tevethia et al. Gut 2024;73:1844–1853.

and others suggesting superiority for VBL, although there is an increased risk of major adverse events with VBL. However, there do not appear to be RCTs that compare combination therapy with non-selective beta blocker monotherapy or VBL monotherapy, especially in patients with decompensated cirrhosis and high-risk esophageal varices. Therefore, the study by Tevethia et al is a welcome addition.

Key Study Findings

The overall incidence of first variceal bleed was significantly lower in the combination therapy group vs non-selective beta blocker monotherapy or VBL monotherapy: 11.8% vs 33.6% vs 25.5%, respectively, $P < 0.002$ (Figure 1). Also, all-cause mortality at 1 year was significantly lower in the combination therapy group vs non-selective beta -blocker monotherapy or VBL monotherapy: 6.3% vs 20% vs 14.5%, respectively, $P = 0.012$.

Caution

The lack of blinding may have biased results toward combination therapy in unknown ways. Future studies would benefit from using placebo tablets along with carvedilol and using blinded adjudicators to review endoscopy reports and hospitalization records to determine if incident variceal bleeding occurred. Since this study was conducted at a single institution in New Delhi, India, similar studies in more diverse settings would be helpful before generalizing these results.

My Practice

In my VA practice, I'll frequently initiate carvedilol therapy in patients with compensated cirrhosis and clinically significant hepatic venous pressure gradient (i.e., HVPG > 10mm Hg) based on non-invasive testing. If the patient doesn't have hypertension, then I'll start at 3.125 mg twice daily with a goal of increasing to 6.25 mg twice daily. This is because carvedilol demonstrates a trend for better tolerance than other non-selective beta blockers along with a possibility of decreasing incidence of ascites and providing a survival advantage.[1] The 2024 AASLD guidelines also now recommend this approach. Therefore, many of my patients with cirrhosis have already been started on carvedilol before decompensation occurs.

Consistent with AASLD guidelines,[1] I focus on using non-selective beta blockers in patients with compensated and decompensated cirrhosis as primary prophylaxis against variceal bleeding since VBL is associated with more severe adverse events. However, I do rely on VBL if the patient cannot tolerate non-selective beta blockers due to fatigue or hypotension (i.e., systolic blood pressure < 90 mm Hg). In the past, I occasionally individualized care and provided combination therapy if patients had particularly large esophageal varices or smaller varices with red wale signs during endoscopic screening/surveillance, but did not utilize a systematic approach to combination therapy. Given the results of the current

study, I expect to change my practice and routinely provide combination therapy for patients with decompensated cirrhosis and high-risk esophageal varices.

For Future Research

While the authors are to be commended for performing the first RCT to compare monotherapy with a non-selective beta blocker or VBL vs combination therapy in patients with decompensated cirrhosis, additional RCTs with blinding and in more diverse settings would be helpful to facilitate broadly generalizing these practices and to further quantify the benefits of combination therapy.

Conflict of Interest

Dr. Schoenfeld reports no potential conflicts of interest for this summary.

REFERENCES

1. Kaplan DE, Ripoli C, Thiele M, et al. AASLD practice guideline on risk stratification and management of portal hypertension and varices in cirrhosis. Hepatology. 2024; 79: 1180-1211.