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Original Article

Carvedilol Versus Other Nonselective Beta Blockers for Variceal Bleeding Prophylaxis and Death: A Network Meta-analysis

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Abstract

Background and Aims: We aimed to perform a network meta-analysis (NWM) to examine comparative effectiveness of non-selective beta blockers (NSBBs) on prophylaxis of gastroesophageal variceal bleeding (GVB) and mortality benefit. ***Methods:*** MEDLINE (OVID) and EMBASE databases were searched for eligible randomized clinical trials (RCTs) from inception to July 3, 2021. Outcomes of interest included primary/secondary prophylaxis of GVB, failure to achieve hepatic venous pressure gradient (HVPG) decremental response, liver-related and all-cause mortality. A Bayesian NWM was performed to derive relative risk (RR) with 95% credible intervals (CrIs). The ranking probability of each NSBB was assessed by surface under cumulative ranking curve (SUCRA). ***Results:*** Thirty-three RCTs including 3,188 cirrhosis patients with gastroesophageal varices were included. Compared with placebo, nadolol ranked first for reducing variceal bleeding [RR:0.25, (95% CrI:0.11–0.51); SUCRA:0.898], followed by carvedilol [RR:0.33, (95% CrI: 0.11–0.88); SUCRA:0.692] and propranolol [RR:0.52, (95% CrI:0.37–0.75); SUCRA:0.405]. Carvedilol was more effective than propranolol in achieving HVPG decremental response [RR:0.43, (95% CrI: 0.26–0.69)]. Carvedilol ranked first for reducing all-cause mortality [RR: 0.32, (95% CrI:0.17–0.57); SUCRA:0.963), followed by nadolol [RR:0.48, (95% CI:0.29–0.77); SUCRA:0.688], and propranolol [RR:0.77, (95% CI:0.58–1.02); SUCRA: 0.337]. Similar findings were observed for liver-related mortality. Carvedilol ranked the safest. The RR of adverse events was 4.38, (95% CrI:0.33–161.4); SUCRA:0.530, followed by propranolol [RR: 7.54, (95% CrI:1.90–47.89); SUCRA:0.360], and nadolol [RR: 18.24, (95% CrI:91.51–390.90); SUCRA:0.158]. ***Conclusions:*** Carvedilol is the preferred NSBB with better survival benefit and lower occurrence of adverse events among patients with gastroesophageal varices.

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Introduction

More than 160 million people have cirrhosis worldwide, and approximately 1 million patients with cirrhosis die every year.[1] Cirrhosis can lead to hepatic decompensation, hepatocellular carcinoma and mortality.[2] Recently, cirrhosis has also been shown to affect COVID-19 vaccine immunogenicity.[3] Around 30% of patients with cirrhosis have esophageal varices at diagnosis and progress to 90% after 10 years.[4] After the first episode of variceal bleeding, the chance of rebleeding is up to 70%, with a mortality rate of 20–35%.[5,6] While nonselective beta blockers (NSBBs) and endoscopic variceal band ligation (EVL) are similarly effective for primary prophylaxis of esophageal variceal bleeding, combining EVL with an NSBB is the most effective approach for secondary prophylaxis.[7]

NSBBs decrease portal hypertension by reducing cardiac output and splanchnic vessel vasoconstriction by blocking beta-1 and beta-2 adrenergic receptors. The NSBBs recommended for preventing variceal bleeding include propranolol, nadolol, and carvedilol.[7] NSBBs also prevent liver decompensation and improve survival in patients with clinically significant portal hypertension (CSPH).[8] There are two-arm RCTs comparing two different NSBBs that had conflicting results, likely because they were statistically under powered.[9,10] Currently, there are no three-arm RCTs that directly compared

Keywords: NSBB; Carvedilol; Nadolol; Propranolol; Varices; Cirrhosis; CPSH.
Abbreviations: CrI, credible interval; CSPH, clinically significant portal hypertension; EVL, endoscopic variceal band ligation; GVB, gastroesophageal variceal bleeding; HVPG, hepatic venous pressure gradient; NSBB, nonselective beta blocker; NWM, network meta-analysis; RCT, randomized clinical trial; RR, relative risk; SUCRA, surface under cumulative ranking curve.
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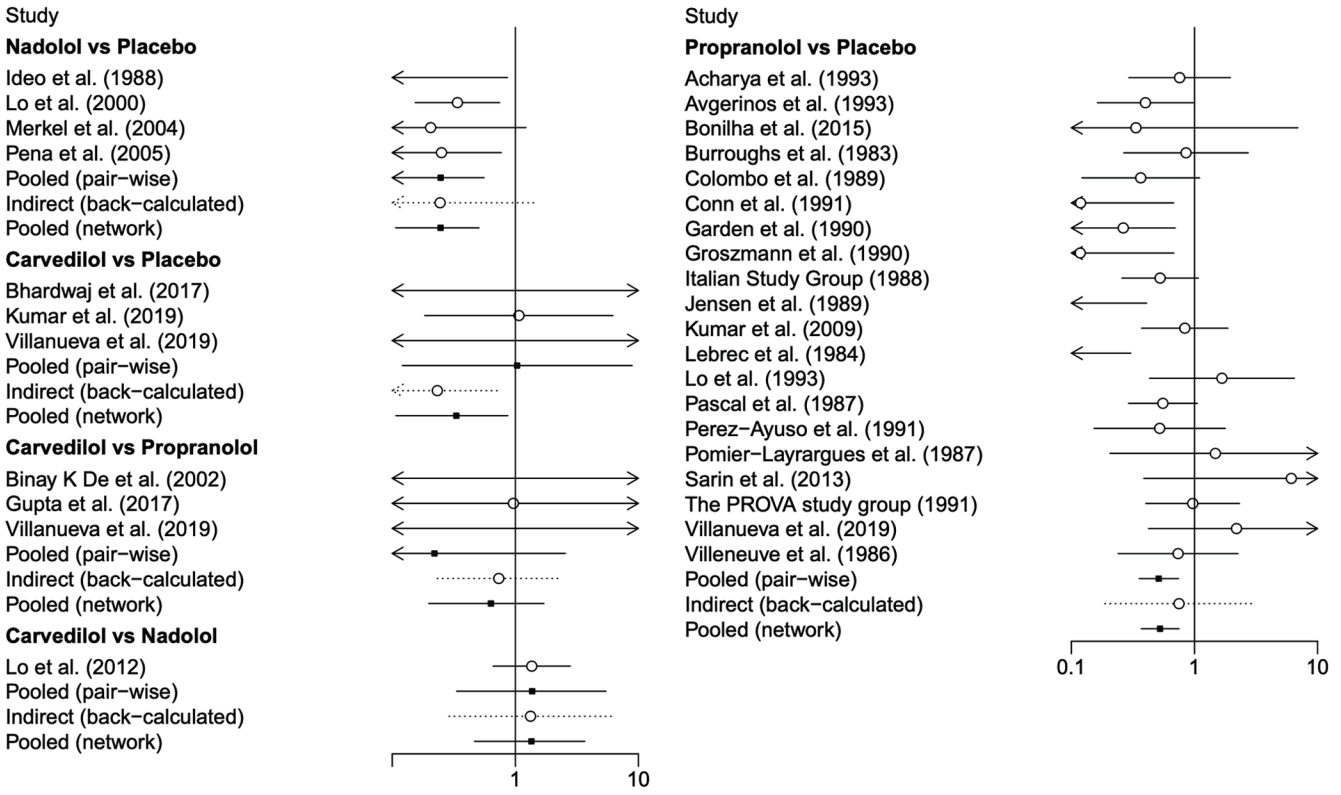

Fig. 1. Network forest plot of primary/secondary prophylaxis of variceal bleeding in 31 individual direct pair comparisons grouped in five regimen pairwise meta-analysis.

the effectiveness of all three NSBBs on the abovementioned beneficial clinical responses, which is not optimal for making clinical decisions on the choice of NSBB.[11]

Network meta-analysis (NWM) analyzes multiple treatment options at the same time across randomized clinical trials (RCTs) and assesses comparative effectiveness of multiple interventions. NWM simultaneously analyzes direct evidence from RCTs by comparing treatments of interest and indirect evidence from RCTs comparing treatments of interest with a common comparator to estimate the mixed effect of direct and indirect evidence. Previous NWMs on different interventional modalities (NSBBs, isosormbide mononitrate, EVL and transjugular intrahepatic portosystemic shunt) showed that NSBBs are preferred for primary prophylaxis of esophageal variceal bleeding, and have survival benefits in patients who already have first episode of variceal bleeding.[12,13] However, no study has been performed to specifically compare the effectiveness of different NSBBs on primary/secondary prophylaxis of variceal bleeding, all-cause mortality, and liver-related mortality. We perform a systematic review and NWM to compare the effectiveness of different NSBBs on primary/secondary prophylaxis of variceal bleeding and survival benefit among cirrhosis patients with gastroesophageal varices.

Methods

Data sources and searches

We searched the electronic databases MEDLINE (OVID) and EMBASE from inception to July 3, 2021. Keywords included esophageal and gastric varices, portal hypertension. Detailed search strategy can be found in Supplementary File 1. This review was conducted and reported in following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Study selection

Two reviewers (KSC, CHM) screened the titles and abstracts independently for inclusion. Full texts were retrieved if they met the inclusion criteria and assessed independently by the two reviewers, and dissonance were resolved by WKS and MFY. Inclusion criteria included (1) a study population of cirrhosis patients with gastroesophageal varices; intervention with NSBBs (carvedilol, nadolol, propranolol) and placebo; (3) RCT design, and (4) a primary composite outcome of variceal bleeding (primary and secondary prophylaxis). Secondary outcomes included (1) hepatic venous pressure gradient (HVPG) decremental response of a decrease of ≥10–20%, or a decrease to ≤12 mmHg, (2) all-cause mortality, (3) liver-related mortality (variceal bleeding, hepatic encephalopathy, liver failure, hepatocellular carcinoma, spontaneous bacterial peritonitis, hepatorenal syndrome); and (4) adverse events. Observational studies and those that were not original research, such as systematic reviews, meta-analyses, review articles, conference abstracts, or guidelines were excluded. A summary of studies identified, included, and excluded are shown in the PRISMA flow diagram (Fig. 1).

Data extraction and risk of bias assessment

The risk of bias was assessed following the instructions given in the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0.19. The methodological quality of the trials focused on random sequence generation, allocation

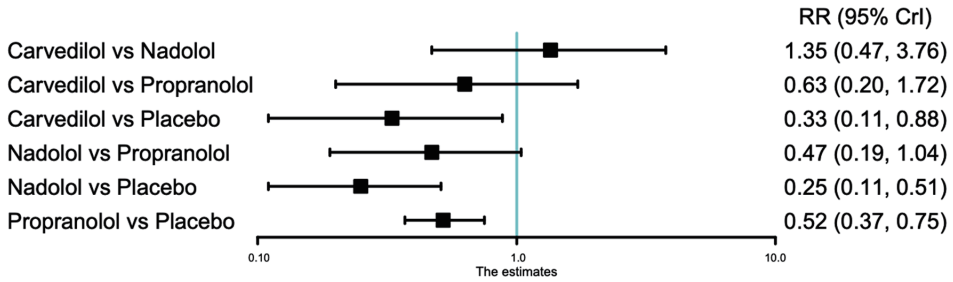

Fig. 2. Network forest plot of primary/secondary prophylaxis of variceal bleeding in six direct and indirect comparisons. CrI, credible interval; RR, relative risk.

concealment, blinding of participants and personnel, incomplete outcome data, and selective reporting.

Data synthesis and analysis

All statistical analyses were conducted in R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) using the "gemtc" and "rjags" packages. To incorporate indirect and direct comparisons, we conducted Bayesian network meta-analyses with random effects model using Markov chain Monte Carlo methods.[14] We assumed consistency in treatment effects from all included studies, where true treatment effects are on average the same from both direct and indirect analyses and heterogeneity was common within networks. Node splitting technique was adopted by comparing the direct and indirect estimates to evaluate network consistency. We used relative risk (RR) and 95% credible intervals (CrIs) to compare different interventions. Network diagrams were used to show direct and indirect comparisons for each primary outcome, with size of nodes and thickness of edges weighted with respect to number of patients included for each intervention and number of direct comparisons among the interventions, respectively. We constructed comparison-adjusted funnel plots with assessment on symmetry for any influence on efficacy results in small-scale trials. To rank hierarchy between interventions for different outcomes, we derived surface under the cumulative ranking curve (SUCRA). It represented the percentage of efficacy or safety achieved by an agent compared with an imaginary agent that is always the best without uncertainty (i.e. SUCRA=1, or 100%).[15] The SUCRA score ranges from 0 to 1 (or 0 to 100%), indicating interventions with a high likelihood of being worst to best. The higher the score, the more likely it was to receive a high ranking. Median ranks would be represented (rank 1–4 on each outcome) with 95% CrI. A p-value of < 0.05 was used to define statistical significance for all measurements except for heterogeneity, for which a p-value of 0.1 was used. We calculated I^2 statistics to assess study heterogeneity (< 25%, 25–75%, and > 75% indicate low, moderate, and high heterogeneity, respectively).

Results

Supplementary Figure 1 shows the study selection flow diagram. A total of 33 RCTs (3,188 patients) were included in the systematic review and NWM. Background characteristics for each study including patient characteristics and interventions are shown in Supplementary Table 1. The median age was 53.5 [interquartile range (IQR): 49.0–56.0] years and men accounted for 71.0%. Etiologies of cirrhosis, alcoholic cirrhosis, and chronic viral hepatitis accounted for 51.3% and 33.5% respectively. The proportions of Child-Pugh class A, B, C were 47.4%, 38.9%, and 13.4%, respectively. Four different interventions were compared (10 studies included carvedilol, five included nadolol, 26 included propranolol, 27 included placebos/control/no interventions).

Risk of bias assessment and quality assessment

Details on risk of bias assessment in included studies were listed in Supplementary Table 2 and Supplementary Figure 2. In general, the quality of all included studies had low to medium bias risk. Single blinded or nonblinded studies should have a low impact on bias as our study outcome (bleeding, mortality) are objective indicators. Our assessment showed that four studies did not report the method of random sequence generation and 11 did not report the method of allocation concealment.

Publication bias

The comparison-adjusted funnel plot (Supplementary Fig. 3) appeared to be symmetrical, precluding publication bias or small study effects.

Network meta-analysis of primary/secondary prophylaxis of variceal bleeding

The network map of four therapeutic interventions (carvedilol, nadolol, propranolol, placebo) is shown in Supplementary Figure 4, showing five direct and one indirect comparison among the interventions in NWM.

Direct and indirect pair comparisons, league matrix

For the composite outcome of primary and secondary prophylaxis of variceal bleeding, a total of 29 trials with 2,944 participants were included. The network forest plot shows RRs and 95% CrIs of all 31 individual direct pair comparisons grouped in the pairwise meta-analysis of five regimens (Fig. 1). Compared with placebo, the RRs for carvedilol, nadolol, and propranolol were 0.33, 95% CrI: (0.11–0.88), 0.25, 95% CrI: (0.11–0.51), and 0.52, 95% CrI: (0.37–0.75), respectively. Compared with nadolol and propranolol, the RRs for carvedilol were 1.35, 95% CrI: (0.47–3.76) and 0.63, 95% CrI: (0.20–1.72), respectively. There was no significant heterogeneity (I^2=8%). A network forest plot (Fig. 2) shows the RRs and 95% CrIs of all six direct and indirect comparisons in our NWM (five direct and one indirect). A comparative efficacy ranking league matrix comparing the four interventions is shown in Table 1.

Five RCTs evaluated nadolol, four of which compared nadolol with placebo and one compared the combination of nadolol and isosorbide mononitrate (ISMN) with carvedilol alone.[16] Excluding the study using combination of nadolol and ISMN did not change the results except that carvedilol was no longer associated with lower variceal bleeding risk [RR: 0.32, 95% CrI: 0.06–1.20), Supplementary Table 3].

Table 1. Network meta-analysis results for various outcomes

Carvedilol			
Bleeding (primary + secondary prophylaxis): 29 studies; 2,944 participants			
1.35 (0.47, 3.76)	Nadolol		
0.63 (0.20, 1.72)	0.47 (0.19, 1.04)	Propranolol	
0.33 (0.11, 0.88)	0.25 (0.11, 0.51)	0.52 (0.37, 0.75)	Placebo
Bleeding (primary prophylaxis): 11 studies; 1,593 participants			
3.02 (0.13, 54.02)	Nadolol		
0.69 (0.05, 5.01)	0.23 (0.02, 1.74)	Propranolol	
0.42 (0.04, 2.89)	0.14 (0.02, 0.92)	0.62 (0.27, 1.61)	Placebo
Bleeding (secondary prophylaxis): 18 studies; 1,351 participants			
1.09 (0.27, 3.56)	Nadolol		
0.60 (0.11, 2.28)	0.55 (0.17, 1.61)	Propranolol	
0.29 (0.06, 1.09)	0.27 (0.09, 0.72)	0.49 (0.30, 0.79)	Placebo
Failure in achieving HVPG decremental response: 10 studies; 692 participants			
0.43 (0.26, 0.69)	Propranolol		
0.23 (0.12, 0.44)	0.54 (0.30, 0.99)	Placebo	
All-cause mortality: 25 studies; 2,710 participants			
0.67 (0.35, 1.28)	Nadolol		
0.42 (0.21, 0.76)	0.62 (0.35, 1.07)	Propranolol	
0.32 (0.17, 0.57)	0.48 (0.29, 0.77)	0.77 (0.58, 1.02)	Placebo
Liver-related mortality: 23 studies; 2,424 participants			
0.58 (0.23, 1.4)	Nadolol		
0.40 (0.15, 0.98)	0.69 (0.36, 1.27)	Propranolol	
0.29 (0.11, 0.70)	0.50 (0.28, 0.85)	0.73 (0.53, 0.99)	Placebo
Adverse events: 22 studies; 2,306 participants			
0.24 (0.01, 9.64)	Nadolol		
0.58 (0.05, 12.93)	2.41 (0.13, 54.26)	Propranolol	
4.38 (0.33, 161.4)	18.24 (1.51, 390.9)	7.54 (1.9, 47.89)	Placebo

Data are presented as pooled relative risk (95% credible intervals).

Rankograms and surfaces under cumulative ranking values

Respective SUCRA values and rankograms are shown in Table 2 and Supplementary Figure 5. Based on ranking league matrix, rankograms, and SUCRA values, nadolol had the best efficacy (SUCRA value 0.898), followed by carvedilol (0.692) and propranolol (0.405).

Primary prophylaxis of bleeding

Eleven trials with a total of 1,593 participants were included (Tables 1 and 2). Compared with placebo, nadolol ranked first for effectiveness in primary prophylaxis of bleeding [RR: 0.14, 95% (CrI: 0.02–0.92); SUCRA: 0.897], followed by carvedilol [RR: 0.42, (95% CrI: 0.04–2.89); SUCRA: 0.558], and propranolol [RR:0.62, (95% CrI: 0.27–1.61); SUCRA: 0.434]. There was no significant heterogeneity (I^2=7%).

Secondary prophylaxis of bleeding

Eighteen trials with 1,351 participants were included (Tables 1 and 2). Compared with placebo, nadolol ranked first for secondary prophylaxis of bleeding [RR: 0.27, (95% CrI: 0.09–0.72), SUCRA: 0.811], followed by carvedilol [RR: 0.29, (95% CrI: 0.06–1.09; SUCRA: 0.728] and propranolol [RR: 0.49, (95% CrI: (0.30–0.79); SUCRA: 0.447]. There was no significant heterogeneity (I^2=8%).

Network meta-analysis of secondary outcomes

Failure to achieve HVPG decremental response: Ten trials with 692 participants were included (Tables 1 and 2). There were no studies investigating the effect of nadolol on HVPG. Compared with placebo, carvedilol ranked first in achieving HVPG decremental response [RR: 0.23, (95% CrI: 0.12–0.44); SUCRA: 0.999], and propranolol ranked second [RR: 0.54, (95% CrI: 0.30–0.99); SUCRA: 0.489]. carvedilol was more effective than propranolol for achieving HVPG decremental response [RR: 0.43, (95% CrI: 0.26–0.69)]. There was no significant heterogeneity (I^2=0%).

All-cause mortality: Twenty-five trials with 2,710 participants were included (Tables 1 and 2). Compared with placebo, carvedilol ranked first for reducing all-cause mortality [RR: 0.32, 95% CrI: (0.17–0.57); SUCRA: 0.963], followed by nadolol [RR: 0.48, 95% CrI: (0.29–0.77); SUCRA: 0.688] and propranolol [RR: 0.77, 95% CrI: (0.58–1.02); SUCRA:

Table 2. Surface under the cumulative ranking curve (SUCRA) score and ranking with 95% credible interval

Rank	Carvedilol	Nadolol	Propranolol	Placebo
Efficacy				
Bleeding (primary + secondary prophylaxis)	0.692; 2 (1 to 3)	0.898; 1 (1 to 2)	0.405; 3 (2 to 3)	0.005; 4 (4 to 4)
Bleeding (primary prophylaxis)	0.558; 2 (1 to 4)	0.897; 1 (1 to 3)	0.434; 3 (1 to 4)	0.112; 4 (2 to 4)
Bleeding (secondary prophylaxis)	0.728; 2 (1 to 4)	0.811; 1 (1 to 3)	0.447; 3 (1 to 3)	0.014; 4 (3 to 4)
Failure in achieving HVPG decremental response	0.999; 1 (1 to 1)	n.a.	0.489; 2 (2 to 2)	0.012; 3 (3 to 3)
All-cause mortality	0.963; 1 (1 to 2)	0.688; 2 (1 to 3)	0.337; 3 (2 to 4)	0.012; 4 (3 to 4)
Liver-related mortality	0.953; 1 (1 to 2)	0.664; 2 (1 to 3)	0.370; 3 (2 to 4)	0.012; 4 (3 to 4)
Safety				
Adverse events	0.530; 2 (1 to 4)	0.158; 4 (2 to 4)	0.360; 3 (2 to 4)	0.952; 1 (1 to 2)

HVPG, hepatic venous pressure gradient; n.a., not available.

0.337]. There was no significant heterogeneity (I^2=0%).

Liver-related mortality: Twenty-three trials with 2,424 participants were included (Tables 1 and 2). All three NSBBs showed statistically significant results compared with placebo. Carvedilol ranked first for reducing liver-related mortality [RR: 0.29, (95% CrI: 0.11–0.70; SUCRA: 0.953], followed by nadolol [RR: 0.50, 95% CrI: (0.28–0.85); SUCRA: 0.664] and propranolol [RR: 0.73, 95% CrI: (0.53–0.99); SUCRA: 0.370]. There was no significant heterogeneity (I^2=0%).

Safety outcomes: Twenty-two trials with 2,306 participants were included (Tables 1 and 2). Adverse events included light-headedness, hypotension, bradycardia, cardiac dysrhythmia, congestive heart failure, chest discomfort, cold extremities, breathlessness, asthma, worsening of chronic obstructive lung disease, pulmonary infarction, worsening of ascites, diarrhea, constipation, abdominal discomfort, dysphagia, lethargy, flapping tremor, encephalopathy, stroke, fever, impotence, hypoglycemia, generalized erythema, and dermatitis. Carvedilol ranked the safest among the NSBBs. The RR of adverse events was 4.38, (95% CrI: 0.33–161.40); SUCRA: 0.530], followed by propranolol [RR: 7.54, (95% CrI: 1.90–47.89); SUCRA: 0.360], and nadolol [RR: 18.24, (95% CrI: 1.51–390.90); SUCRA: 0.158. There was no significant heterogeneity (I^2=0%). Specifically for orthostatic hypotension or hypotension, there were no significant differences among the three NSBBs in the NWM (all p > 0.05, data not shown).

Subgroup analysis

Geographic region: Eleven studies were from Asia, 10 reported variceal bleeding and nine reported all-cause mortality; and 22 studies from Western countries, 19 reported variceal bleeding and 16 reported all-cause mortality. For bleeding, non-Asian studies showed nadolol [RR: 0.20; 95% CrI: (0.06–0.57)] and propranolol [RR: 0.42; (95% CrI: 0.27–0.64)] were more effective than placebo (Supplementary Table 4). However, Asian studies did not find statistically significant differences between any NSBB and placebo. There was no significant heterogeneity in Asian (I^2=0%) and non-Asian regions (I^2=6%).

For all-cause mortality, Asian studies showed carvedilol [RR: 0.28; (95% CrI: 0.11–0.65) and nadolol (RR: 0.38; (95% CrI: 0.13–0.98)] were more effective than placebo (Supplementary Table 4). Carvedilol was also more effective than propranolol [RR: 0.32; (95% CrI: 0.09–0.94)]. In non-Asian studies, only carvedilol was more effective than placebo [RR:0.29; (95% CrI: 0.08–0.94)]. There was no significant heterogeneity in either Asian or non-Asian regions (both I^2=0%).

Child-Pugh class: Only three studies reported variceal bleeding outcome with stratification by Child-Pugh status A and B/C, all of which compared propranolol with placebo. We performed a meta-analysis with subgroup analysis to evaluate effectiveness of propranolol in different Child-Pugh classes (Supplementary Fig. 6). Propranolol was significantly more effective in Child-Pugh A patients [RR: 0.47; (95% CI: 0.23–0.97)] but not Child-Pugh B/C patients [(RR: 0.67; (95% CI: 0.42–1.07))]. There was low and moderate heterogeneity in Child-Pugh class A (I^2=16%) and Child-Pugh class B/C (I^2=28%).

Discussion

In this NWM of 33 RCTs including 3,188 cirrhosis patients with gastroesophageal varices, nadolol ranked best and carvedilol second among NSBBs for both primary and secondary prophylaxis against variceal bleeding. On the other hand, carvedilol ranked best in reducing all-cause mortality and liver-related mortality. NSBBs reduce portal blood flow via both beta-1 adrenergic blockade (decrease in cardiac output) and beta-2 adrenergic blockade (splanchnic vasoconstriction).[17] NSBBs are recommended for primary and secondary prophylaxis of variceal bleeding. They also reduce portal hypertension, prevent hepatic decompensation,[8] and improve survival in patients with CSPH.[7] Therefore, NSBBs are the cornerstone of the management of CSPH, as highlighted in the recent Baveno VII consensus.

However, thus far no three-armed RCTs comparing the effects of NSBBs, namely propranolol, nadolol, and carvedilol used individually, have been performed. NWM thus provides insight into the best NSBB to prescribe when considering the benefit-risk profile. Our study is the first NWM to address this clinical question, and we showed that the most effective NSBB for primary and secondary prophylaxis of variceal bleeding was nadolol, followed by carvedilol and propranolol. Compared with placebo, nadolol, carvedilol, and propranolol reduced the first and/or subsequent variceal bleeding risk by 75%, 67% and 48%, respectively. Nadolol was the only NSBB shown to reduce first variceal bleeding by 86% with statistical significance, while only nadolol and propranolol reduced subsequent variceal bleeding. Carvedilol reduced variceal bleeding only when both primary and secondary prophylaxis

were treated as a composite outcome but not as individual outcomes, which was likely observed because of lack of statistical power. Nevertheless, differences between carvedilol and nadolol were not significant. A previous NWM showed that NSBBs reduced first bleeding of esophageal varices by 36%, and that carvedilol was superior to other NSBBs (nadolol and propranolol grouped together) for primary prophylaxis of esophageal variceal bleeding.[13] The discrepancy might be explained by the fact that the nadolol and propranolol results were pooled together in the previous NWM.

Compared with nadolol and propranolol, carvedilol influences anti-alpha 1 adrenergic activity that reduces porto-collateral resistance by its vasodilatory effect on the intrahepatic circulation.[18] That partly explains why carvedilol leads to a greater degree HVPG reduction compared with propranolol. A meta-analysis of five studies showed that the overall mean weighted difference in the percentage reduction in HVPG was –7.24 mmHg when comparing carvedilol with propranolol.[19] However, in that meta-analysis, the RR for failure in achieving a hemodynamic response with carvedilol [pooled RR: 0.67, 95% CI: (0.44–1.01)] did not reach statistical significance, and was likely caused by a type II error.[19] That meta-analysis included five trials with 175 subjects, whereas our study included 10 trials with 692 subjects. Although NSBBs and EVL have similarly effectiveness for primary prophylaxis of esophageal variceal bleeding, an RCT found that carvedilol was superior to EVL.[20] Our NWM found that carvedilol had a 57% lower risk of failure in achieving a hemodynamic response than propranolol. However, studies comparing nadolol with carvedilol or propranolol for HVPG reduction are currently lacking.

Two NWMs showed that NSBBs (grouped as whole) reduced mortality by 30–51% in cirrhosis patients with esophageal varices.[13,21] In our NWM, both carvedilol and nadolol reduced all-cause and liver-related mortality compared with placebo, while propranolol reduced only liver-related mortality. Importantly, carvedilol ranked the best in reducing all-cause mortality (68% lower risk) and liver-related mortality (71% lower risk) in this NWM. It is not surprising that carvedilol confers better survival given its greater effectiveness in achieving a hemodynamic response. Portal hypertension leads to fatal cirrhotic complications like variceal bleeding, ascites with ensuing spontaneous bacterial peritonitis (SBP), and hepatorenal syndrome. Additionally, independent of the effect on portal pressure, NSBBs reduce intestinal permeability, bacterial translocation, systemic inflammation, and hence SBP.[22,23] Carvedilol reduces oxidative stress and suppresses release of inflammatory cytokines and mitochondrial dysfunction, which are common events in decompensated cirrhosis.[24] That may partly explain why carvedilol ranked the best in reducing mortality despite the fact that nadolol ranked the best for primary and secondary prophylaxis of variceal bleeding in our NWM. In addition, there are currently no head-to-head comparisons of nadolol and carvedilol in the outcome of bleeding. There are also no studies evaluating the decremental HVPG response to nadolol.

Owing to its vasodilatory activity caused by alpha-1 adrenergic blockade, carvedilol is postulated to lead to a greater decrease in mean arterial pressure (MAP) compared with other NSBBs, and hence have more side effects. However, a meta-analysis of six studies did not reveal a statistically significant difference in either the weighted mean difference of MAP in carvedilol versus propranolol users or in the frequency of adverse events.[19] Nevertheless, Sinagra *et al*.[19] raised the concern of clinical significance despite statistical nonsignificance based on a study reporting higher incidence of orthostatic hypotension (14/65 carvedilol- and 9/60 propranolol-treated patients).[25] However, our NWM found that carvedilol was safer than the other NSBBs. Specifically differences in the occurrence of orthostatic hypotension or hypotension among the three NSBBs in our NWM were not significant (all $p > 0.05$; data not shown). Subgroup analysis showed that the beneficial effects for primary and secondary prophylaxis of variceal bleeding were limited to nadolol and propranolol in non-Asian subjects. The mortality benefit of carvedilol was observed in both Asian and non-Asian subjects. Caution should be exercised in interpreting these results because the subgroup analysis was underpowered.

Several limitations of this NWM must be acknowledged. First, the follow-up time of studies varied, and death events may have taken longer to occur. Second, the majority of patients (84.8%) had alcoholic cirrhosis or chronic viral hepatitis, and none had isolated gastric varices. The results may not be generalizable to other etiologies of cirrhosis and those with isolated gastric varices. Gastric varies bleed less frequently than esophageal varices, and cyanoacrylate injection is more effective than NSBBs for both primary and secondary prophylaxis of gastric variceal bleeding, although only propranolol was studied.[26–28] Third, as individual patient data were not available, subgroup analysis by age, sex, and race could not be performed because they were not reported in the included studies. In particular, the heterogenicity of drug doses affected the internal validity of the comparison, and thus will be accounted for in future studies. Fourth, with regard to HVPG determination, potential parameters such as portal vein flow velocity, portal vein flow volume, portal vein pulsatility index, damping index, portal vein caliber variation, etc, which are helpful in determining the influence of portal circulation hemodynamics, were not investigated in the included studies.[29,30] For instance, a high portal pulsatility index seems to be associated with risk of venous congestion,[31] while the damping index might serve as a supplementary tool in evaluating the severity of portal hypertension.[32] Fifth, although an RCT showed that NSBBs reduced the risk of hepatic decompensation in patients with CSPH by 49% compared with placebo,[8] RCTs comparing different NSBBs on preventing hepatic decompensation are lacking. Finally, despite the overall risk of bias being low to medium, it still existed. It should be noted that six of the 33 studies do not include a placebo for comparison, which increased performance bias. There is need of more and larger studies and better study design to minimize bias.

Conclusions

Of the available NSBBs, carvedilol may be preferable for cirrhosis patients with gastroesophageal varices in view of better mortality benefit and lower occurrence of adverse events. Further studies are required to study whether carvedilol has benefit over other NSBBs in preventing hepatic decompensation.

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Conflict of interest

MFY has been an editorial board member of *Journal of Clinical and Translational Hepatology* since 2022. The other authors have no conflict of interests related to this publication.

Author contributions

Study conceptualization, formal analysis and drafting of the

manuscript (KSC, CHM), data interpretation and editing of the manuscript (LKL), support in statistical analysis (XHM), and review and editing of the manuscript (LYM, WKS, MFY).

Data sharing statement

Data are available upon reasonable request to the corresponding author.

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