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# Carvedilol for prevention of variceal bleeding: a systematic review and meta-analysis

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## Abstract

**Background** Beta-blockers are used for prophylaxis of variceal bleeding. Our aim was to assess the efficacy and safety of carvedilol for primary or secondary prevention of variceal bleeding in patients with cirrhosis.

**Methods** We searched Medline, Embase, CENTRAL and gray literature sources for randomized controlled trials (RCTs) comparing carvedilol with placebo or any active intervention. We synthesized data using random effects models. We summarized the strength of evidence using GRADE criteria.

**Results** We included 13 trials with 1598 patients. Carvedilol was as efficacious as endoscopic variceal ligation (EVL) (4 RCTs, risk ratio [RR] 0.74, 95% confidence interval [CI] 0.37-1.49) or propranolol (3 RCTs, RR 0.76, 95%CI 0.27-2.14) for primary prevention of variceal bleeding. Likewise, carvedilol was as efficacious as EVL (3 RCTs, RR 1.10, 95%CI 0.75-1.61), non-selective beta-blockers (NSBBs) plus isosorbide-5-mononitrate (2 RCTs, RR 1.02, 95%CI 0.70-1.51) or propranolol (2 RCTs, RR 0.39, 95%CI 0.15-1.03) for secondary prevention of variceal bleeding. Carvedilol was associated with lower all-cause mortality compared to EVL (3 RCTs, RR 0.51, 95%CI 0.33-0.79). There was no difference in any other efficacy outcome. Finally, there were no significant differences in the safety profiles compared with EVL and NSBBs. Our confidence in the effect estimates for all outcomes was very low.

**Conclusion** Carvedilol is as efficacious and safe as standard-of-care interventions for the primary and secondary prevention of variceal bleeding.

**Keywords** Carvedilol, variceal bleeding, meta-analysis

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## Introduction

Esophageal varices (EV) are found in approximately 30% of patients with cirrhosis at the time of first diagnosis [1]. EV bleeding is a life-threatening complication of portal hypertension, responsible for almost 80% of all bleeding episodes in patients with cirrhosis [2]. The annual rate of variceal hemorrhage ranges from 5-15% [3,4], depending on the presence of several risk factors [5]. In addition, variceal rebleeding occurs at a rate of 63% within a time frame of 1-2 years [6]. Despite the improvement in management procedures, EV hemorrhage still accounts for high mortality rates [7].

Guidelines support the use of non-selective beta-blockers (NSBBs) such as propranolol or nadolol for prophylaxis of variceal bleeding. Carvedilol is a potent beta-blocker, with mild anti-alpha 1 adrenergic activity that causes downregulation of

intrahepatic resistance and an additional decrease in hepatic venous pressure gradient (HVPG), that has been used for primary prophylaxis of variceal hemorrhage [8,9]. Evidence suggests that only 40% of patients treated with NSBBs reach appropriate HVPG levels [10,11]. The use of carvedilol has been associated with hemodynamic regulation in 56% of propranolol non-responders [11]. However, the efficacy of carvedilol compared with standard-of-care approaches remains to be demonstrated. To provide a thorough summary of existing evidence, we performed a systematic review and meta-analysis investigating the efficacy and safety of carvedilol for primary or secondary prophylaxis of variceal hemorrhage in patients with cirrhosis.

## Materials and methods

This systematic review and meta-analysis was conducted in compliance with a pre-specified protocol and according to the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) statement (Supplementary material, Table S1) [12].

### Study eligibility criteria

We included all randomized controlled trials (RCTs) with a follow-up duration of at least 6 months, comparing carvedilol with placebo or any active intervention, either alone or in combination, in adults with cirrhosis and EV, irrespective of any previous history of variceal bleeding. We applied no limitations based on language, date or type of publication.

### Identification and selection of the studies

We compiled a search strategy using relevant terms for carvedilol and the condition of interest (EV and variceal bleeding) (Supplementary material, Table S2). We systematically searched Medline, Embase and the Cochrane central register of controlled trials for relevant trials up to May 2018. We also screened conference proceedings from United European Gastroenterology (UEG) Week, American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL), Digestive Disease Week (DDW), and the American College of Gastroenterology annual meetings from 2010-2017. Finally, we scanned clinicaltrials.gov for additional completed trials.

All records retrieved from major electronic databases were imported into reference management software (EndNote X7, Thomson Reuters, New York City, New York). After removal of duplicates, references were screened for eligibility by 2 independent reviewers (KM and AK), firstly at title and abstract level and subsequently at full-text level. Eligible trials identified in gray literature were juxtaposed against records from electronic databases. Screening was performed using online software (Covidence, Veritas Health Innovation Ltd, Melbourne, Australia). Any discrepancies during the screening process were resolved by consensus.

### Data collection process

Two reviewers (KM and AM) independently performed data extraction. We utilized a predesigned extraction form to abstract data from eligible trials relating to trial characteristics, participants' baseline characteristics and outcomes of interest. Any disagreements at this stage were settled by a third reviewer (PP). Multiple reports for the same trial were collated in order to maximize the information yield.

### Risk of bias in individual studies

Risk of bias was assessed in duplicate by 2 independently working reviewers (KM and AP) using the revised Cochrane risk-of-bias tool (ROB) 2.0 [13]. Any disagreements at this stage were resolved by consensus. The trials were graded as low risk, some concerns, or high risk of bias depending on the evaluation of 5 distinct domains within the tool. These were randomization, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of reported results. Regarding the domain of randomization, evaluation was performed at trial level, whereas all other domains were assessed separately for every outcome. The overall risk of bias of a trial was considered low if all domains were at low risk of bias and high if there was at least 1 domain at high risk of bias or at least 3 domains with some concerns. In any other case a trial was deemed to have some concerns for bias.

### Outcome measures

The primary outcome was the incidence of variceal bleeding, as defined by the authors of each individual study. Secondary efficacy outcomes included all-cause bleeding, all-cause mortality, bleeding-related mortality and incidence of variceal progression from small to large varices. Safety outcomes assessed included incidence of adverse events (AE) (as defined by individual study investigators) and discontinuation due to AE. All outcome measures were synthesized separately for trials assessing the use of carvedilol for primary or secondary prophylaxis, except for the incidence of AE and withdrawal due to AE.

### Data synthesis

Outcomes are presented as risk ratios (RR) with 95% confidence intervals (CI). We synthesized data using random effects models. Data from intention-to-treat (ITT) analyses were preferred when available. The threshold of 0.05 was set

as the cutoff significance value (a) for all analyses. We assessed statistical heterogeneity using the $I^2$ statistic, with values lower than 60% indicating low heterogeneity [14]. We aimed to assess the small-study effect by checking the asymmetry of funnel plots and by performing Egger's test [15]. We performed predefined sensitivity analyses, excluding trials at high risk of bias. We also conducted *post-hoc* subgroup analysis based on the mean duration of follow up (≤ or >12 months) to verify the robustness of our conclusions. In studies where the duration of follow up was provided as median (range or interquartile range) rather than mean and standard deviation the latter was calculated as described previously [16,17]. Statistical analyses were implemented using Review Manager 5.3 [18].

### Grading of evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [19] to assess the credibility of our summary estimates. One reviewer (MS) evaluated impression, indirectness, publication bias and risk of bias for all outcomes separately. We used GRADEpro (GRADE Working Group) to generate a summary-of-findings Table.

## Results

### Results of search and trial characteristics

A detailed presentation of the study selection process is depicted in Fig. 1. Our search retrieved 190 records from electronic databases and literature sources. After removal of duplicates, 132 records were screened at title and abstract level and 93 records were excluded. Subsequently, the remaining 39 records were assessed at full text level. Twenty-two records describing 13 [20-32] trials (1598 patients) were finally included in the meta-analysis.

A summary of the main characteristics of the included trials is presented in Table 1. Eight trials were published as full-text manuscripts, whereas the remaining 5 trials were available only in abstract form. Six trials assessed carvedilol for primary prophylaxis of variceal bleeding compared with endoscopic variceal ligation (EVL) [22-25] or propranolol [20-22]. Secondary prophylaxis was evaluated in 6 trials comparing carvedilol with EVL [27,28,32], propranolol [29] or NSBBs plus isosorbide-5-mononitrate (ISMN) [27,31]. One trial compared carvedilol with propranolol for secondary prophylaxis on top of EVL therapy [30]. Only 1 placebo-controlled trial assessed the efficacy of carvedilol for prevention of variceal progression [26]. Mean duration of follow up ranged from 6-26.2 months, while sample size ranged from 25-264 patients. In most trials the mean dose of carvedilol was 12.5 mg/day. Patients' mean age and percentage of men included ranged from 41.7-54.5 years and from 11.4-96.7%, respectively. Baseline information regarding Child-Pugh class, etiology of cirrhosis, size of varices and presence of gastric varices were poorly reported. Most patients had F2 EV with viral related cirrhosis, and had Class B disease according to the Child-Pugh classification. Concomitant gastric varices were present in 98 patients in total (5 trials [22,24-26,31]).

### Risk-of-bias assessment

The risk-of-bias assessment for the primary outcome is summarized in supplemental digital content (Supplementary material, Table S3). Among trials assessing the use of carvedilol for primary prophylaxis, 2 trials were at low risk of bias [24,25], 2 trials were at high risk [20,22], due to a suboptimal description of the randomization process, inadequate blinding, missing outcome data and selection of reported results, while there were some concerns about the remaining 2 trials [21,23], mainly due to poor reporting of the trial's procedures. Among secondary prevention trials, 1 was at low risk of bias [31], whereas 3 trials were at high risk of bias [27,28,32] because of an inadequate description of the randomization process, poor blinding and missing outcome data. Finally, there were some concerns about the overall risk of bias for the remaining 2 trials [29,30], due to missing outcome data and the type of analysis used (per protocol). The risk-of-bias assessment for the secondary outcomes is presented in the supplemental digital content (Supplementary material, Tables S4-S9).

### Analysis of primary and secondary outcomes

#### *Efficacy outcomes*

Carvedilol was as efficacious as EVL (4 RCTs, RR 0.74, 95%CI 0.37-1.49, $I^2$: 61%) or propranolol (3 RCTs, RR 0.76, 95%CI 0.27-2.14, $I^2$ 63%) for the prevention of first variceal bleeding (Fig. 2). There were no differences in the incidence of all-cause and bleeding-related mortality between carvedilol and EVL (2 RCTs, RR 1.06, 95%CI 0.75-1.50, $I^2$: 0% and RR 1.43, 95%CI 0.55-3.72, $I^2$: 0%, respectively) or propranolol (1 RCT, RR 1.07, 95%CI 0.38-3.03, $I^2$: not estimable and RR 0.86, 95%CI 0.16-4.67, $I^2$: not estimable, respectively) (Fig. 3,4). The risk for the incidence of all-cause bleeding could not be assessed because of a lack of relevant data.

One trial [26] reported a lower incidence of progression from small to large varices in patients treated with carvedilol compared to placebo (RR 0.56, 95%CI 0.32-0.98). However, there was no difference in the risk for all-cause mortality (RR 0.25 95%CI 0.06-1.14) and no bleeding episodes were reported in either treatment arm.

For secondary prevention of variceal bleeding, carvedilol was as efficacious as EVL (3 RCTs, RR 1.10, 95%CI 0.75-1.61, $I^2$: 0%), propranolol (2 RCTs, RR 0.39, 95%CI 0.15-1.03, $I^2$: 0%) and NSBBs plus ISMN (2 RCTs, RR 1.02, 95%CI 0.70-1.51, $I^2$: 22%) (Fig. 5). Likewise, carvedilol was as efficacious as EVL (1 RCT, RR 0.87, 95%CI 0.49-1.55, $I^2$: not estimable and RR 4.70, 95%CI 0.58-37.99, $I^2$: not estimable, respectively) or

**Table 1** Baseline characteristics of included trials

| Author, Year [Ref.] | Treatment arms | Sample size, n | Drug therapy mean dose, mg/day | Mean follow up, months | Mean age, years | Sex, male, n (%) | Child-Pugh score, mean | Child-Pugh class A/B/ C, n | Etiology Viral/ Alcohol/ Other, n | Esophageal Varices size F2/F3, n | Concomitant gastric varices, n |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Primary prophylaxis | | | | | | | | | | | |
| Agarwala *et al* 2011 [20] | Carvedilol | 54 | NR | 6† | NR | NR | NR | NR | NR | NR | NR |
| | Propranolol | 48 | NR | 6† | NR | NR | NR | NR | NR | NR | NR |
| Girleanu *et al* 2017 [21] | Carvedilol | 21‡ | 6.125 | 12.3 | 49 | 33 (68.7) | 7.2 | NR | NR | NR | NR |
| | Propranolol | 27‡ | 40 | | | | | NR | NR | NR | NR |
| ElRahim *et al* 2018 [22] | Carvedilol | 84 | 12.51 | 12† | 51.2 | 29 (34.5) | NR | 25/24/35 | 72/0/12 | 57/27 | 0 |
| | EVL | 88 | NA | 12† | 50.6 | 33 (37.5) | NR | 18/21/49 | 83/0/5 | 51/37 | 0 |
| | Propranolol | 92 | 43.0 | 12† | 51.8 | 40 (43.4) | NR | 17/28/47 | 83/0/9 | 59/33 | 0 |
| Khan *et al* 2017 [23] | Carvedilol | 125 | 12.5 | 6† | 52.0 | 77 (61.6) | NR | NR | NR | NR§ | NR |
| | EVL | 125 | NA | 6† | 54.0 | 70 (56) | NR | NR | NR | NR§ | NR |
| Tripathi *et al* 2009 [24] | Carvedilol | 77 | 12.5‡‡ | 26.2 | 54.2 | 54 (70.1) | 8 | 29/19/29 | NR/57/NR | 71/6 | 10 |
| | EVL | 75 | NA | 25.5 | 54.5 | 55 (73.3) | 8 | 26/19/30 | NR/54/NR | 68/7 | 8 |
| Shah *et al* 2014 [25] | Carvedilol | 82 | 12.5‡‡ | 13.2 | 48.3 | 59 (72) | 7.4 | 37/35/10 | 74/0/8 | 49/33 | 16 |
| | EVL | 86 | NA | 13.4 | 47.2 | 63 (73.3) | 7.2 | 37/37/12 | 77/3/6 | 42/44 | 21 |
| Secondary prophylaxis | | | | | | | | | | | |
| Kumar *et al* 2015 [27] | EVL | 56 | NA | 16.4 | 44.1 | NR | 8.6 | NR | NR/84/NR | NR | NR |
| | NSBBs + ISMN | 39 | NR | | | NR | | NR | | NR | NR |
| | Carvedilol | 47 | NR | | | NR | | NR | | NR | NR |
| Smith 2013 *et al* [28] | EVL | 31 | NA | 23 | 50 | NR | 9¶ | NR | NR/56/NR | NR | NR |
| | Carvedilol | 32 | 12.5‡‡ | | 51 | NR | 9¶ | NR | | NR | NR |
| Wei 2018 [29] | Carvedilol | 13¶ | 10 | 6 | NR | NR | NR | NR | NR | NR | NR |
| | Propranolol | 12¶ | 17.7 | | NR | NR | NR | NR | NR | NR | NR |
| Lo *et al* 2012 [31] | Carvedilol | 61 | 10.4 | 30 | 53 | 7 (11.4) | 7.3 | 24/29/8 | 37/22/2 | 48/9 | 21 |
| | NSBBs + ISMN | 60 | Nadolol:45, ISMN:16 | 29 | 49.8 | 12 (20) | 7.5 | 22/23/15 | 29/26/5 | 41/12 | 16 |
| Stanley *et al* 2014 [32] | Carvedilol | 33 | 12.5‡‡ | 30.7 | 51.4 | 22 (66.6) | 9¶ | 11/28/25 | 0/58/6 | NR | NR |
| | EVL | 31 | NA | 23.5 | 49.6 | 21 (67.7) | 9¶ | | | NR | NR |
| Gupta *et al* 2017 [30]†† | Carvedilol + EVL | 30 | 6.25¶ | 12† | 41.7 | 29 (96.7) | NR | 10/18/2 | 10/14/6 | 15/15* | NR |
| | Propranolol +EVL | 29 | 40¶ | | 45 | 26 (89.7) | NR | 4/21/4 | 7/14/8 | 14/14* | NR |

*(Contd....)*

**Table 1** *(Continued)*

| Author, Year [Ref.] | Treatment arms | Sample size, n | Drug therapy mean dose, mg/day | Mean follow up, months | Mean age, years | Sex, male, n (%) | Child-Pugh score, mean | Child-Pugh class A/B/ C, n | Etiology Viral/ Alcohol/ Other, n | Esophageal Varices size F2/F3, n | Concomitant gastric varices, n |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Variceal progression | | | | | | | | | | | |
| Bhardwaj *et al* 2017 [26] | Carvedilol | 70 | 12 | 21.6 | 48.8 | 60 (85.7) | 6.58 | NR | 12/15/43 | 0/0[§§] | 2 |
| | Placebo | 70 | NR | 21.0 | 48.8 | 59 (84.2) | 6.96 | NR | 23/18/29 | 0/0[§§] | 4 |

† Follow-up period, months. ‡ Cirrhotic patients with occlusive non-malignant related portal vein thrombosis and grade 2 or 3 esophageal varices. § Cirrhotic patients with grade I & II esophageal varices on endoscopy. ¶ Data are median. ‡‡ 6.25 mg daily for 1 week, then the dose increased to 12.5 mg daily. §§ Cirrhotic patients with small esophageal varices (≤5 mm in diameter). ¶¶ Patients achieved variceal eradication after endoscopic treatment. * Grade III / IV esophageal varices. †† Data for 12 months of follow up were obtained from an abstract by Rawat R, *et al*

*NA, not applicable; NR, not reported, NSBBs; non-selective beta-blockers; ISMN, isosorbide-5-mononitrate; EVL, endoscopic variceal ligation*

NSBBs plus ISMN (1 RCT, RR 0.98, 95%CI 0.74-1.31, $I^2$: not estimable and RR 0.66, 95%CI 0.11-3.79, $I^2$: not estimable, respectively) for prevention of all-cause bleeding and bleeding-related mortality. Finally, carvedilol reduced the all-cause mortality compared with EVL (3 RCTs, RR 0.51, 95%CI 0.33-0.79, $I^2$: 0%). However, there was no difference when compared to NSBBs plus ISMN (2 RCTs, RR 0.70, 95%CI 0.36-1.36, $I^2$: 24%) (Fig. 6).

Results from sensitivity analyses for all efficacy outcomes are presented in the supplemental digital content (Supplementary material, Tables S10-S13). Overall, the results remained unchanged in sensitivity analyses excluding studies at high risk of bias.

Finally, the results for primary prophylaxis were consistent in a subgroup analysis based on duration of follow up (≤12 or >12 months), both against NSBBs (2 RCTs, RR 0.66, 95%CI 0.13-3.40, $I^2$: 81% and 1 RCT, RR 0.96, 95%CI 0.24-3.85, $I^2$: not estimable, respectively) and against EVL (2 RCTs, RR 0.77, 95%CI 0.19-3.02, $I^2$: 81% and 2 RCTs, RR 0.70, 95%CI 0.27-1.82, $I^2$: 54%, respectively). We could not perform subgroup analyses for secondary prophylaxis because of a lack of relevant data (all trials comparing carvedilol with EVL or NSBBs plus ISMN had a mean follow-up duration >12 months, while all trials assessing carvedilol against NSBBs had a mean follow-up duration ≤12 months) (Supplementary material, Table S14).

## Safety outcomes

In terms of the incidence of any AE, carvedilol showed no clear difference compared with EVL (5 RCTs, RR 1.99, 95%CI 0.79-5.02, $I^2$: 93%), NSBB plus ISMN (2 RCTs, RR 0.38, 95%CI 0.13-1.07, $I^2$: 74%) or propranolol (3 RCTs, RR 0.65, 95%CI 0.31-1.38, $I^2$: 69%) (Fig. 7).

Regarding withdrawal due to AE, carvedilol showed a similar risk as both EVL (3 RCTs, RR 2.28, 95%CI 0.59-8.84, $I^2$: 30%) and propranolol (2 RCTs, RR 2.68, 95%CI 0.41-17.53, $I^2$: 0%) (Fig. 8). In 1 trial [31], NSBB plus ISMN had a higher risk of withdrawal due to AE compared to carvedilol (RR 0.03, 95%CI: 0.00-0.43).

In terms of incidence of any AE, carvedilol was associated with a lower risk compared to NSBBs plus ISMN in sensitivity analyses that excluded trials at high risk of bias (Supplementary material, Table S15). For the incidence of withdrawal due to AE, sensitivity analyses excluding studies at high risk of bias generated the same results (Supplementary material, Table S16).

## Grade

Overall, our confidence in the effect estimates for all efficacy and safety outcomes was very low. Substantial heterogeneity, which could not be explained by sensitivity or subgroup analyses, was detected in most of our analyses. Moreover, the number of included studies and the number of events were small. Furthermore, our confidence in the effect estimates was

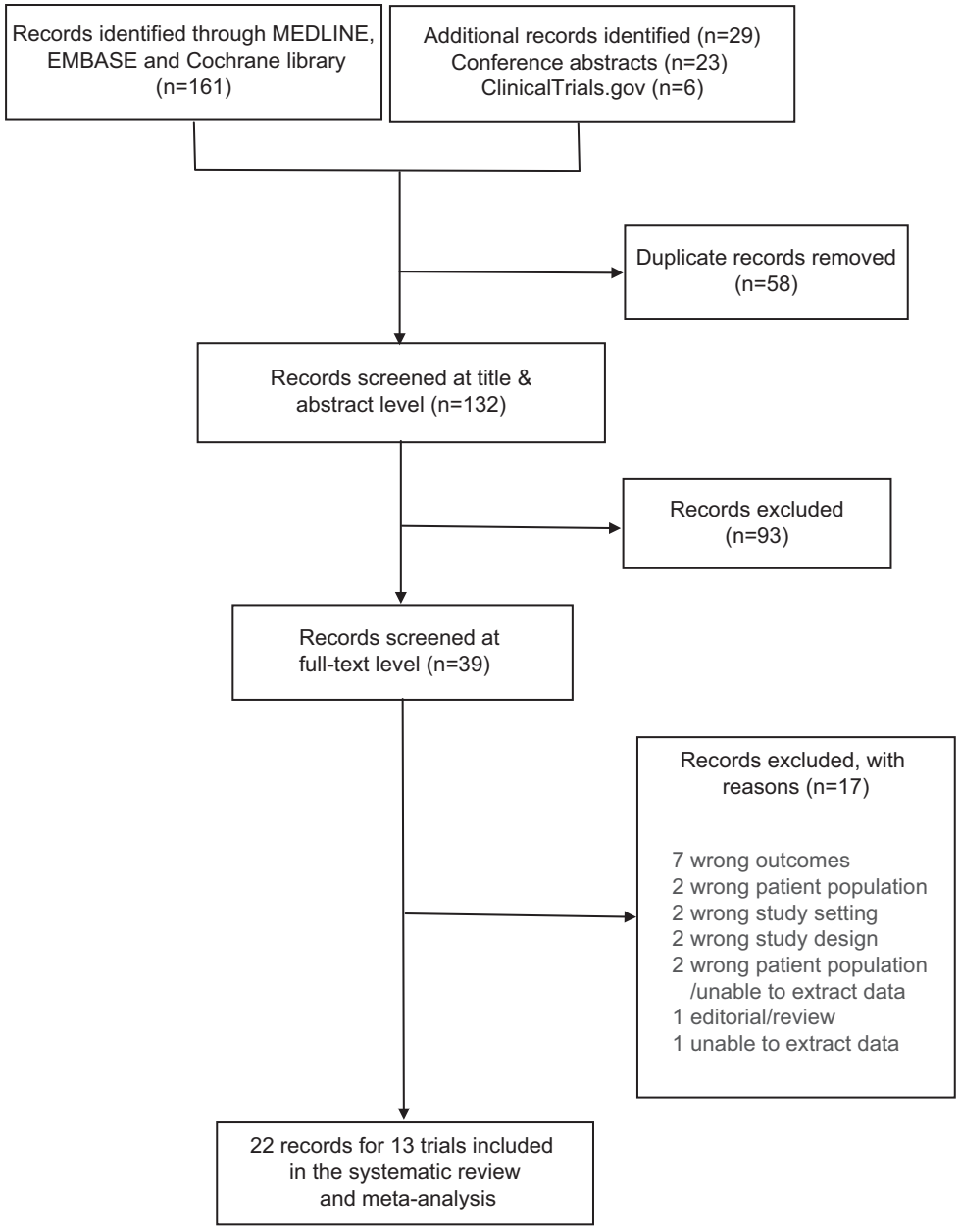


**Figure 1** Prisma flow diagram

downgraded because of the large number of trials with some concerns or at high risk of bias, the small sample size, and the inability to assess publication bias due to the limited number of trials (Supplementary material, Table S17-S21).

## Discussion

In this systematic review and meta-analysis, very low-quality evidence suggests that carvedilol has a beneficial effect on the prevention of variceal bleeding in patients with cirrhosis. Limited data from 1 trial indicate that carvedilol may delay the progression from small to large varices. Carvedilol is as efficacious as EVL or NSBBs for primary prevention of variceal bleeding. In addition, very low-quality evidence indicates that carvedilol is as efficacious as propranolol in the prevention of rebleeding after successful variceal eradication with EVL. Finally, carvedilol is well tolerated and has safety profiles comparable with those of other interventions.

The efficacy of carvedilol has been explored in a previous systematic review [33], but this incorporated a limited number of trials and focused mainly on surrogate outcomes related to variceal bleeding. Compared to this meta-analysis, we identified a beneficial effect of carvedilol against EVL on mortality. This could be attributed to the inclusion of 2

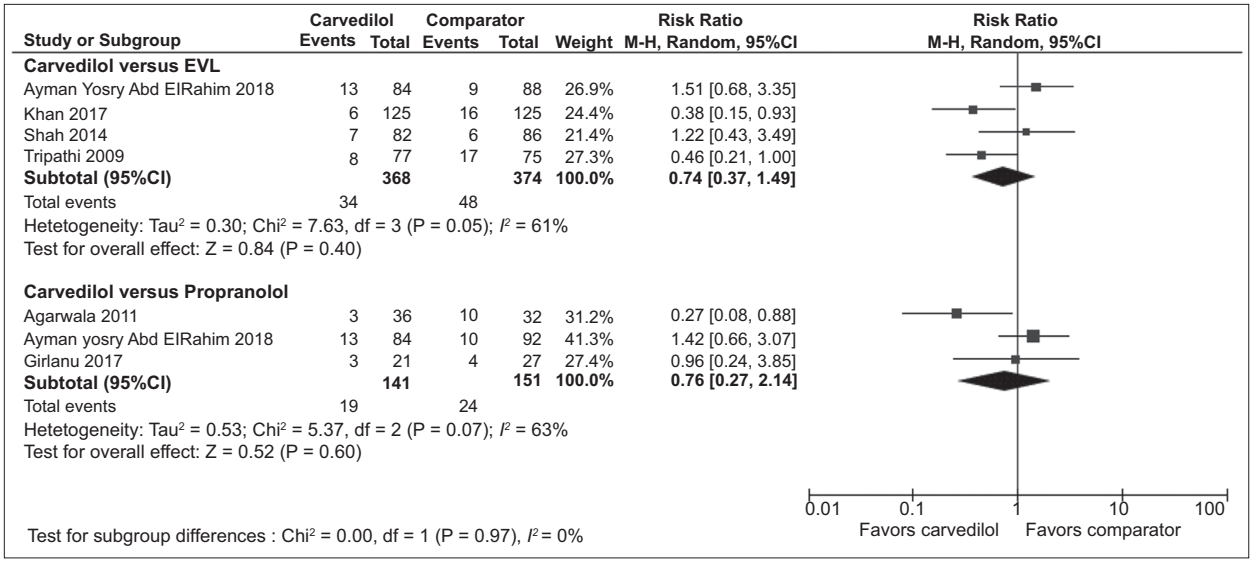


**Figure 2** Risk ratio for incidence of variceal bleeding, primary prophylaxis
*CI, confidence interval; EVL, endoscopic variceal ligation; M-H, Mantel-Haenszel*

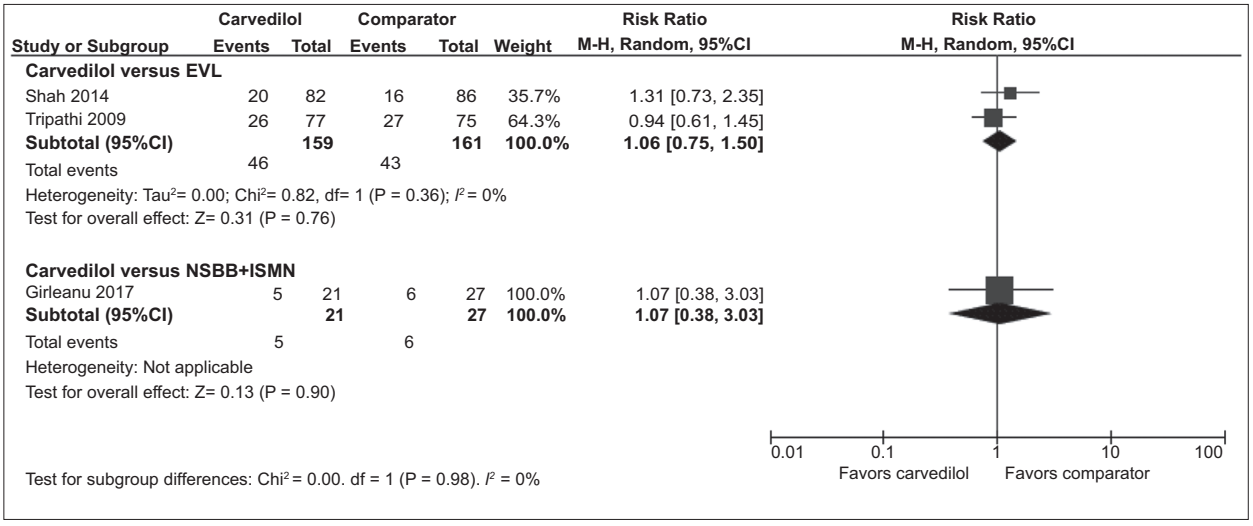


**Figure 3** Risk ratio for incidence of all-cause mortality, primary prophylaxis
*CI, confidence interval; EVL, endoscopic variceal ligation; M-H, Mantel-Haenszel*

additional trials assessing secondary prophylaxis [27,28] that had better precision. In addition, a recently published Cochrane meta-analysis evaluated the effects of carvedilol compared with the conventionally used NSBBs in patients with cirrhosis [34]. Our findings were in line with the results of the aforementioned meta-analysis in terms of both efficacy and safety-related outcomes. Notably, the Cochrane meta-analysis included RCTs with a duration of at least 1 week and further provided evidence for the ability of carvedilol to decrease HVPG. Under this scope, carvedilol proved more efficacious than traditionally used NSBBs; however, this finding was not accompanied by a difference in the incidence of upper gastrointestinal bleeding. Zacharias *et al* performed a subgroup analysis based on trial duration by setting the cutoff value at 3 months. This analysis was similar to ours (cutoff value 6 months) and yielded the same conclusion. A major difference between the 2 meta-analyses is that we further evaluated the beneficial and harmful effects of carvedilol compared with EVL. Although EVL is an invasive procedure, it represents the cornerstone in the prophylaxis of variceal bleeding, for either primary or secondary prevention. Consequently, we consider our meta-analysis to be the most comprehensive in terms of existing comparisons.

Hence, our systematic review is the most updated summary of evidence on the efficacy and safety of carvedilol compared to the current standard of care in patients with EV. In addition, we collected and appraised evidence focused on clinically important outcomes, supporting the use of carvedilol in the prophylaxis of variceal bleeding. Further strengths of our work include a thorough literature search

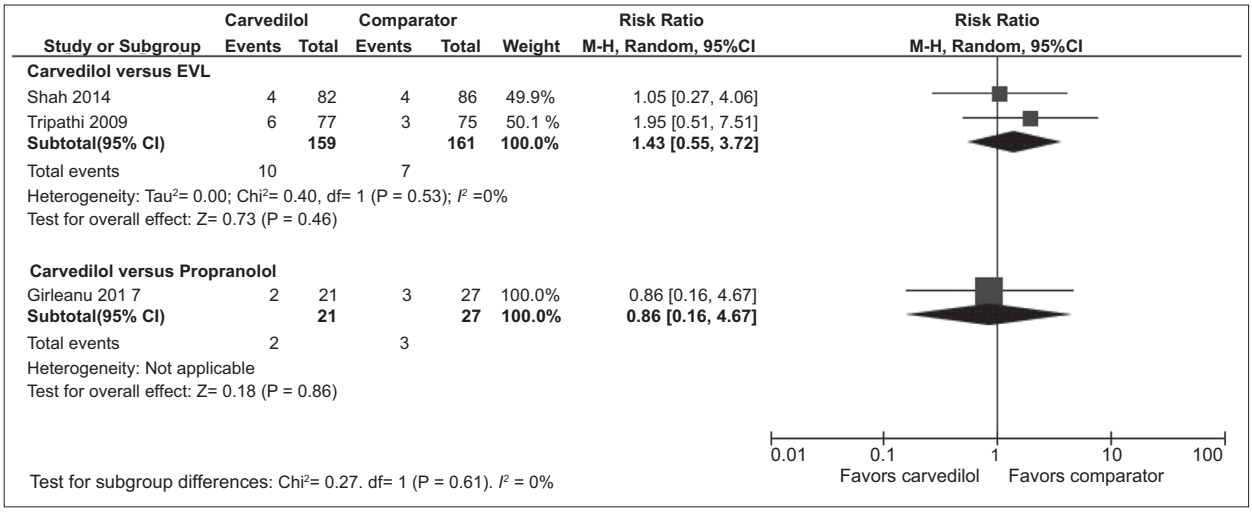


**Figure 4** Risk ratio for incidence of bleeding related mortality, primary prophylaxis
*CI, confidence interval; EVL, endoscopic variceal ligation; M-H, Mantel-Haenszel*

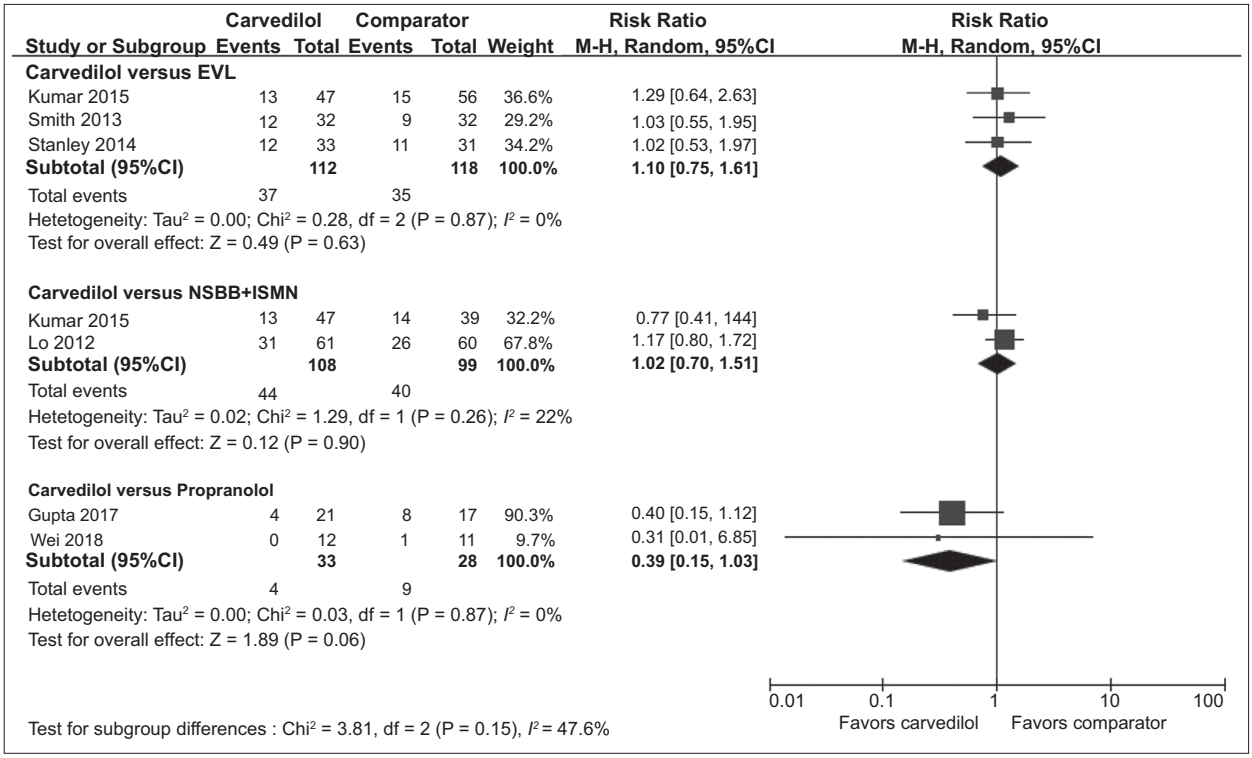


**Figure 5** Risk ratio for incidence of variceal bleeding, secondary prophylaxis
*CI, confidence interval; EVL, endoscopic variceal ligation; NSBB, non-selective beta-blocker; ISMN, isosorbide-5-mononitrate; M-H, Mantel-Haenszel*

both of major electronic databases and of grey literature, without imposing any limitations, from which we extracted data for a variety of clinically important outcomes related to safety and efficacy. We explored the robustness of conclusions by assessing the methodological integrity of included studies, using the most updated methodological tool [13], and we performed multiple sensitivity analyses. Finally, we evaluated the confidence in our estimates using the GRADE approach.

However, certain limitations have to be acknowledged. Despite an exhaustive literature search we identified only 13 eligible studies, almost half of which (38%) were available only in abstract form. The overall sample size was limited, leading to wide CIs in our summary estimates. The majority of studies were of poor quality, mainly due to suboptimal reporting of the randomization procedures, inadequate blinding (especially when carvedilol was compared with EVL) and missing outcome data. Apart from that, there was a high degree of

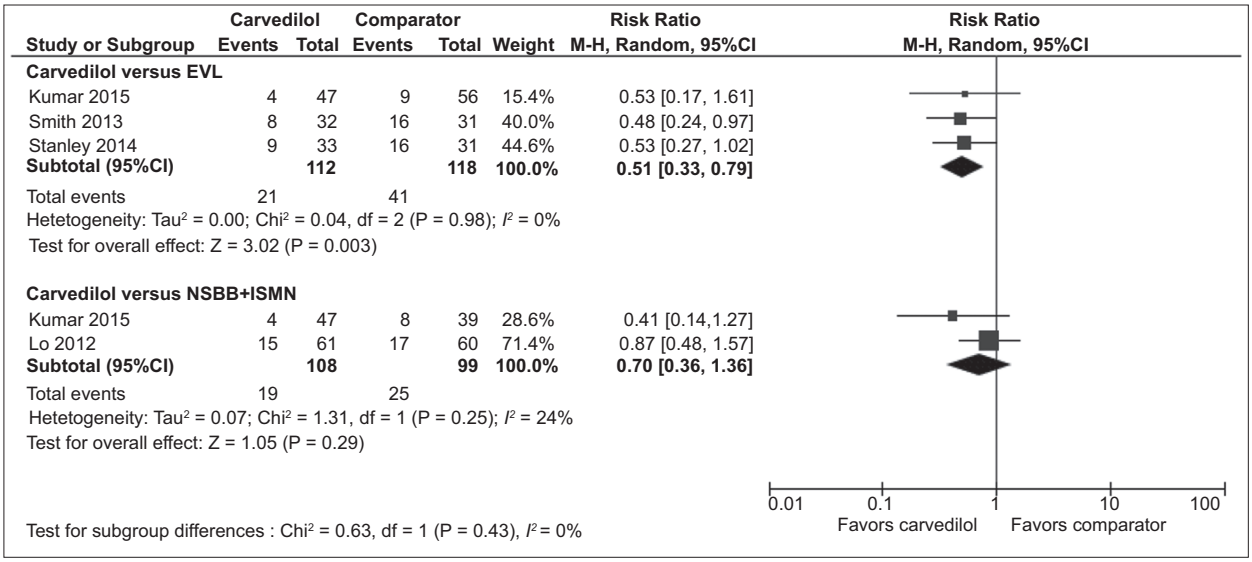


**Figure 6** Risk ratio for incidence of all-cause mortality, secondary prophylaxis
*CI, confidence interval; EVL, endoscopic variceal ligation; NSBB, non-selective beta-blocker; ISMN, isosorbide-5-mononitrate; M-H, Mantel-Haenszel*

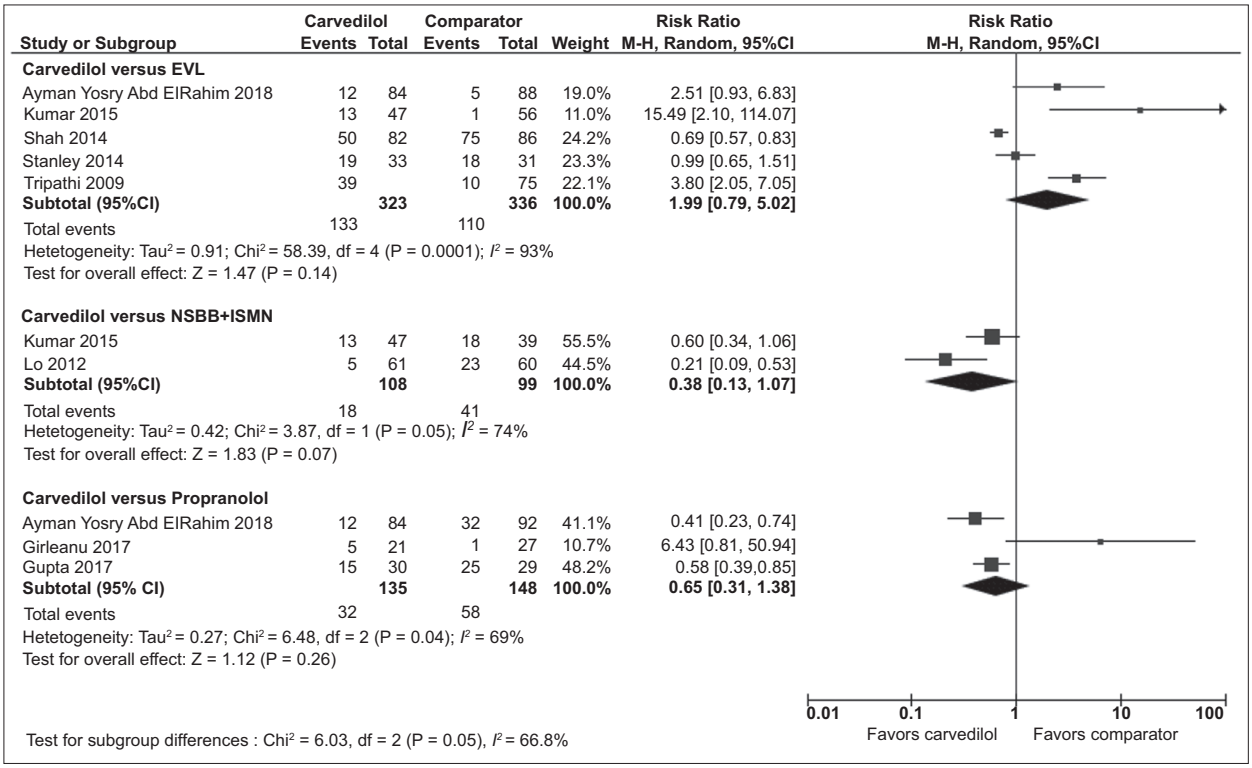


**Figure 7** Risk ratio for incidence of any adverse event
*CI, confidence interval; EVL, endoscopic variceal ligation; NSBB, non-selective beta-blocker; ISMN, isosorbide-5-mononitrate; M-H, Mantel-Haenszel*

heterogeneity, especially in the analysis of any AE, probably due to the inconsistent and poor reporting of AEs. It is worth mentioning that only 1 trial [31] provided a definition for both serious and any AE, while an additional trial [32] provided a definition for serious AE only. The dose of carvedilol was not reported in several trials and, when provided, it differed among trials. Carvedilol-related adverse events, such as systemic hypotension, appear to be dose-dependent. This adds an extra dimension to the increased heterogeneity in the analysis of AEs. Finally, the small-study effect could not be evaluated because of the limited number of trials, while publication bias cannot be excluded.

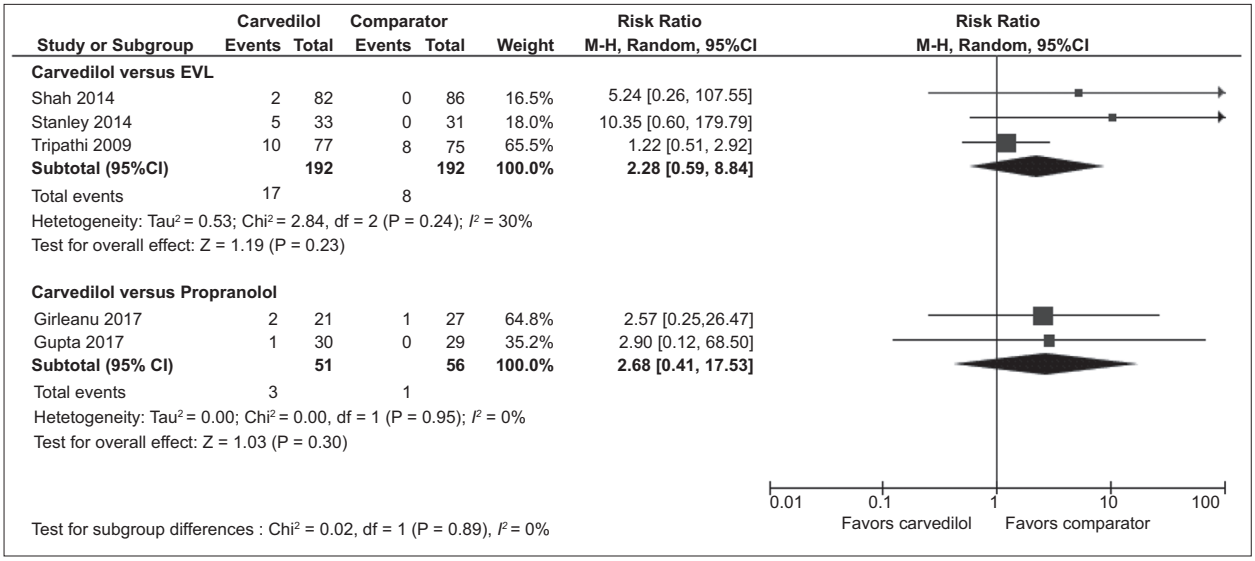


**Figure 8** Risk ratio for incidence of withdrawal due to adverse events
*CI, confidence interval; EVL, endoscopic variceal ligation; M-H, Mantel-Haenszel*

Our analyses support the Baveno VI consensus guidelines for portal hypertension, in which carvedilol is considered to be a valid first-line treatment in patients with medium or large size varices and no previous history of variceal bleeding. On the other hand, existing guidelines do not support the use of carvedilol for secondary prophylaxis, given the lack of evidence comparing carvedilol to standard of care. However, we identified 2 small trials in which carvedilol was found to be as efficacious as propranolol in preventing rebleeding after variceal eradication with EVL [29,30]. In addition, our review showed that carvedilol improves survival compared with EVL, even though they have a similar effect on the risk of rebleeding. This indicates that carvedilol might have a beneficial impact, not only via a reduction in portal hypertension, but also through other protective properties of NSBBs, such as reduction in bacterial translocation and bacterial infections [35,36]. Although our findings indicate that carvedilol is equally efficacious to EVL or propranolol for the prevention of variceal rebleeding, the small number of participants included in these analyses undermines the certainty of our results. Overall, our evidence supports the use of carvedilol in combination with EVL for secondary prevention. However, the limitations of the available trials (small sample size, short duration of follow up, and unclear risk-of-bias estimation) underline the need for high-quality trials to confirm these initial findings. In the absence of adequate direct evidence, a network meta-analysis evaluating the different therapeutic options of patients on prophylaxis for variceal bleeding could provide a better and more precise insight into this area.

In conclusion, carvedilol is a safe and efficacious treatment option for the primary and secondary prophylaxis of variceal bleeding. In addition, it may also delay variceal progression. However, our confidence in these conclusions is very low, given the imprecision, heterogeneity and potential risk of bias of the available evidence. This underlines the need for adequately powered, high-quality clinical trials.

## Summary Box

**What is already known:**

- Carvedilol is a guideline-recommended treatment option for the primary prophylaxis of variceal bleeding
- Carvedilol's efficacy in the context of secondary prevention of variceal bleeding is under consideration
- Randomized controlled trials present data regarding its efficacy and safety

**What the new findings are:**

- Carvedilol is equally efficacious to endoscopic variceal ligation (EVL), for both primary and secondary prophylaxis of variceal bleeding
- Very low-quality evidence indicates that carvedilol reduces all-cause mortality compared to EVL in patients with a previous history of variceal bleeding
- Very low-quality evidence suggests that carvedilol is as efficacious as propranolol for the prevention of variceal rebleeding after variceal eradication

See Supplementary Tables at www.annalsgastro.gr

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