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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 2018 *et al*, [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 2017 *et al*, [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 2009 *et al*, [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 2014 *et al*, [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 2015 *et al*, [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 2012 *et al*, [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 2014 *et al*, [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 2017 *et al*, [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 2017 *et al*, [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

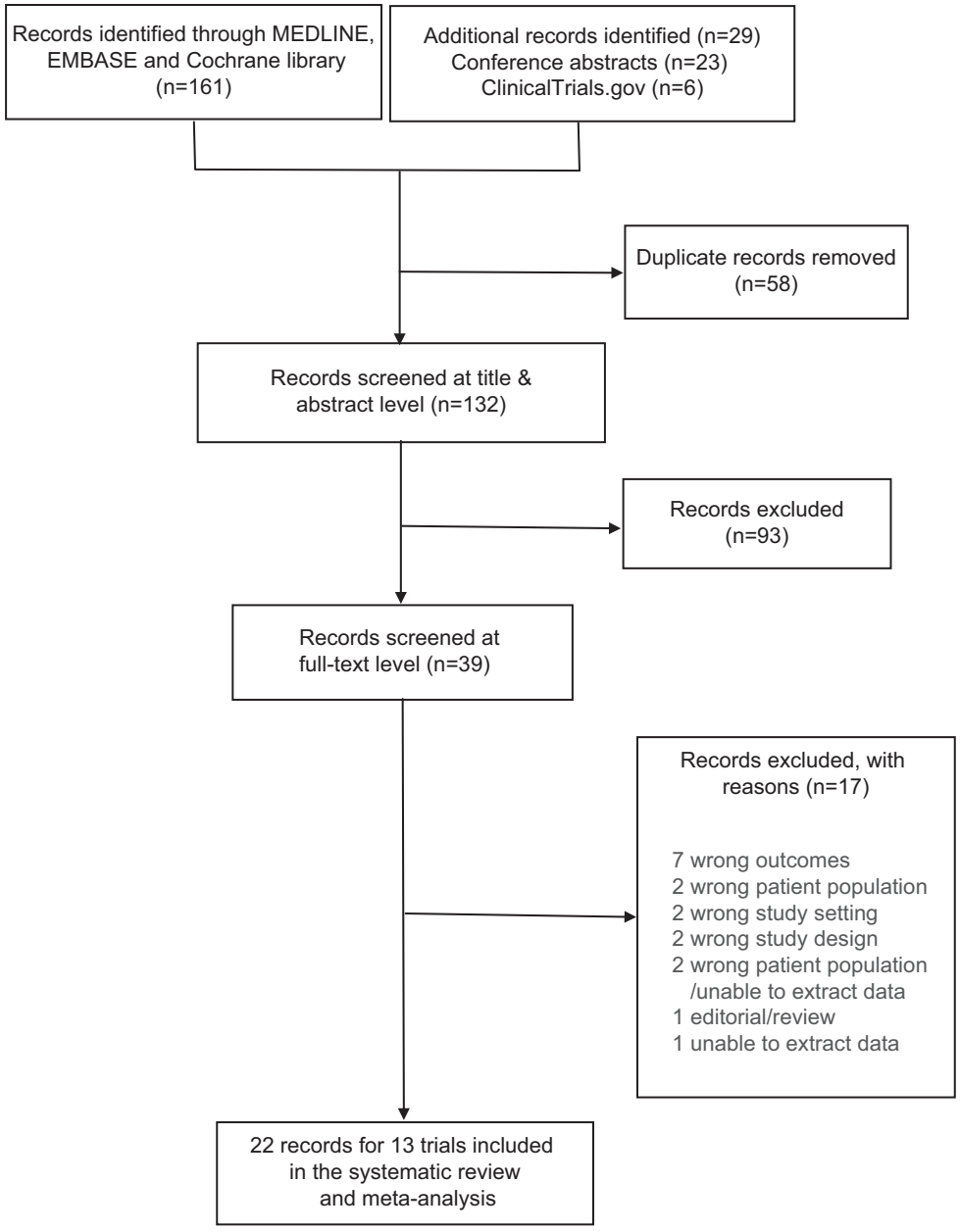

Figure 1 Prisma flow diagram

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

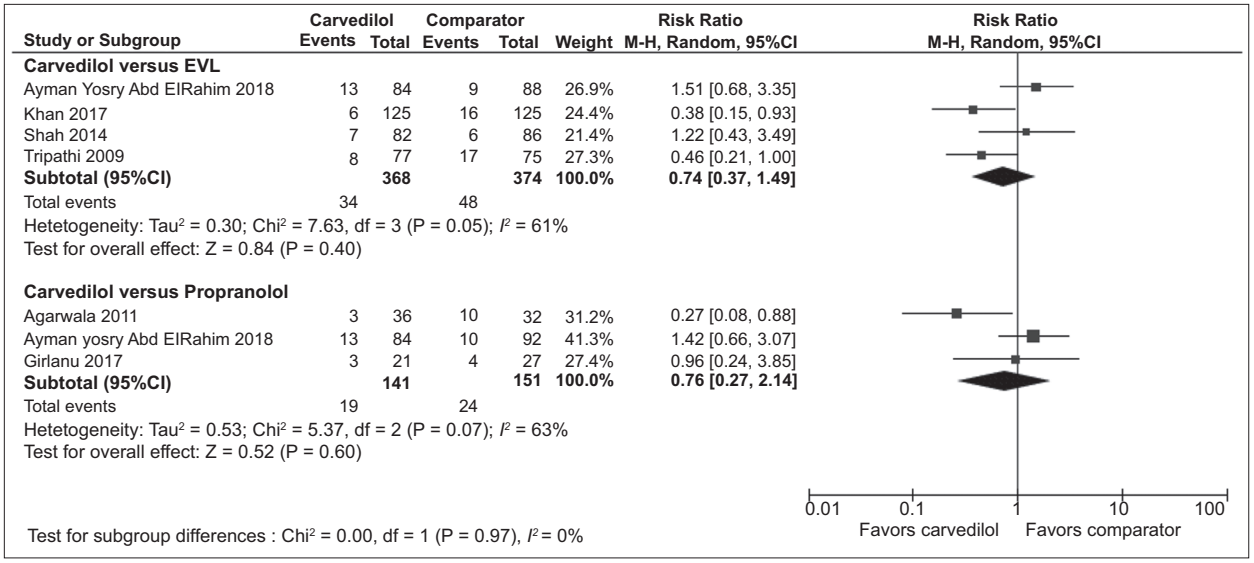

Figure 2 Risk ratio for incidence of variceal bleeding, primary prophylaxis
CI, confidence interval; EVL, endoscopic variceal ligation; M-H, Mantel-Haenszel

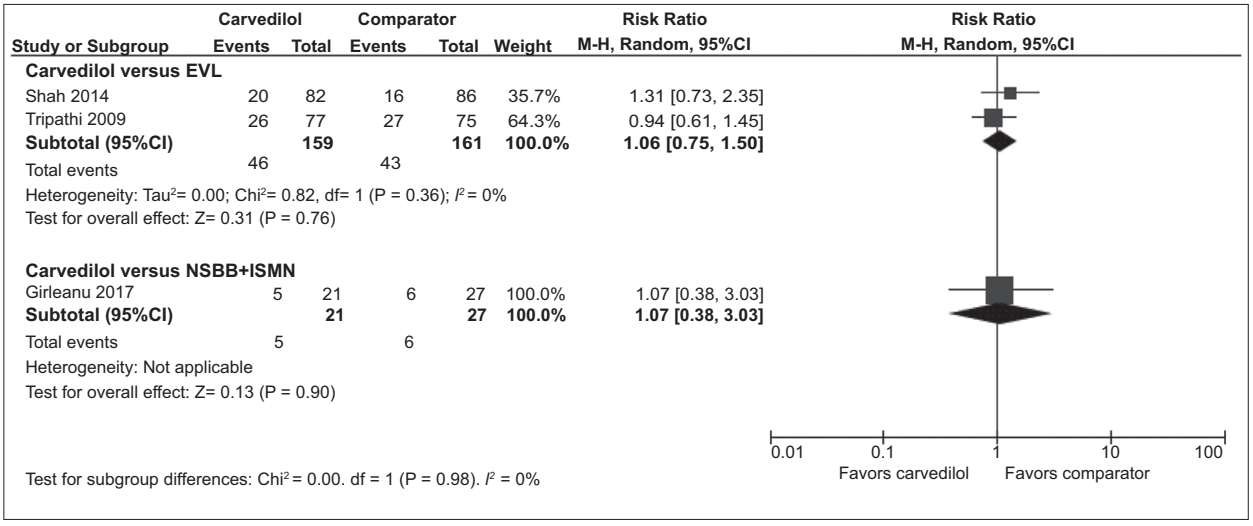

Figure 3 Risk ratio for incidence of all-cause mortality, primary prophylaxis
CI, confidence interval; EVL, endoscopic variceal ligation; M-H, Mantel-Haenszel

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

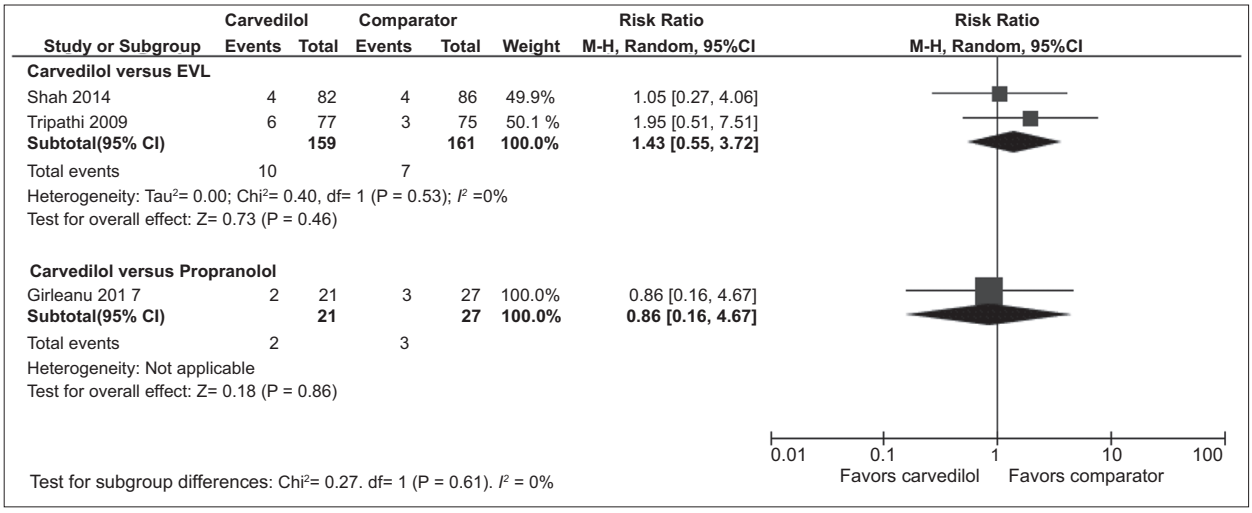

Figure 4 Risk ratio for incidence of bleeding related mortality, primary prophylaxis
CI, confidence interval; EVL, endoscopic variceal ligation; M-H, Mantel-Haenszel

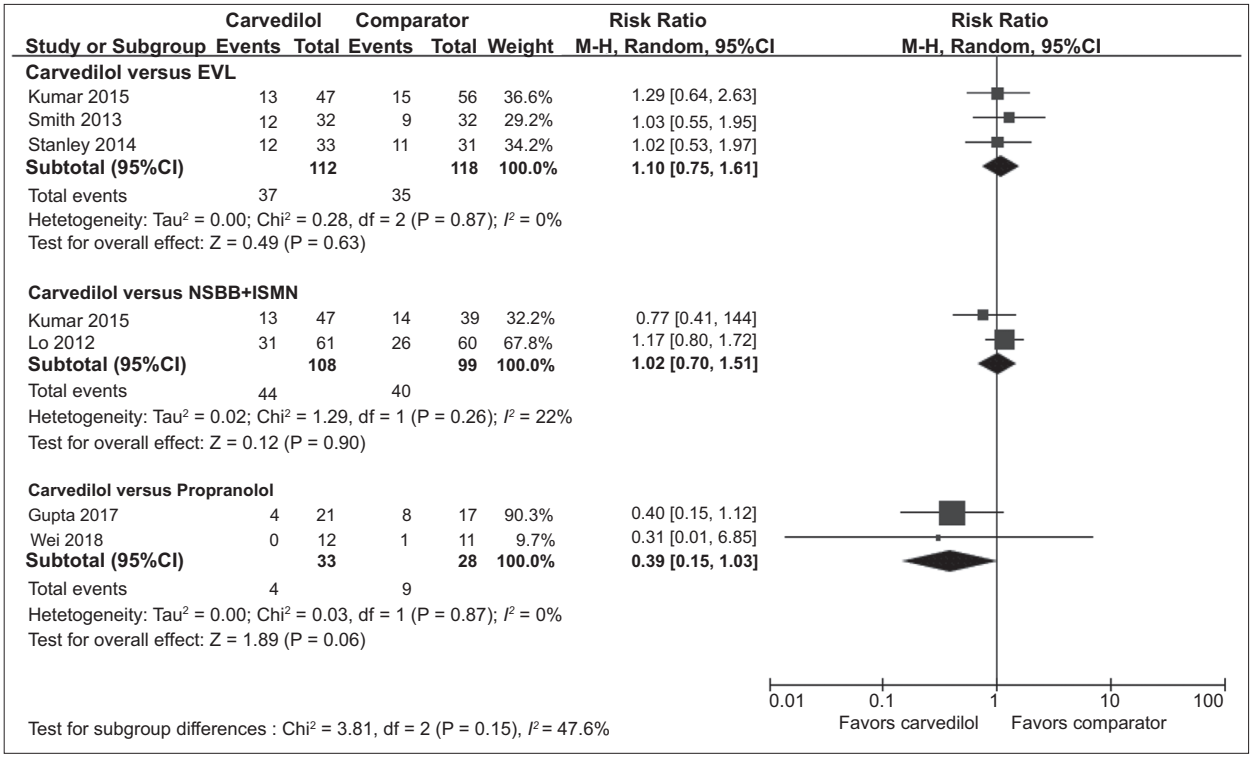

Figure 5 Risk ratio for incidence of variceal bleeding, secondary prophylaxis
CI, confidence interval; EVL, endoscopic variceal ligation; NSBB, non-selective beta-blocker; ISMN, isosorbide-5-mononitrate; M-H, Mantel-Haenszel

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

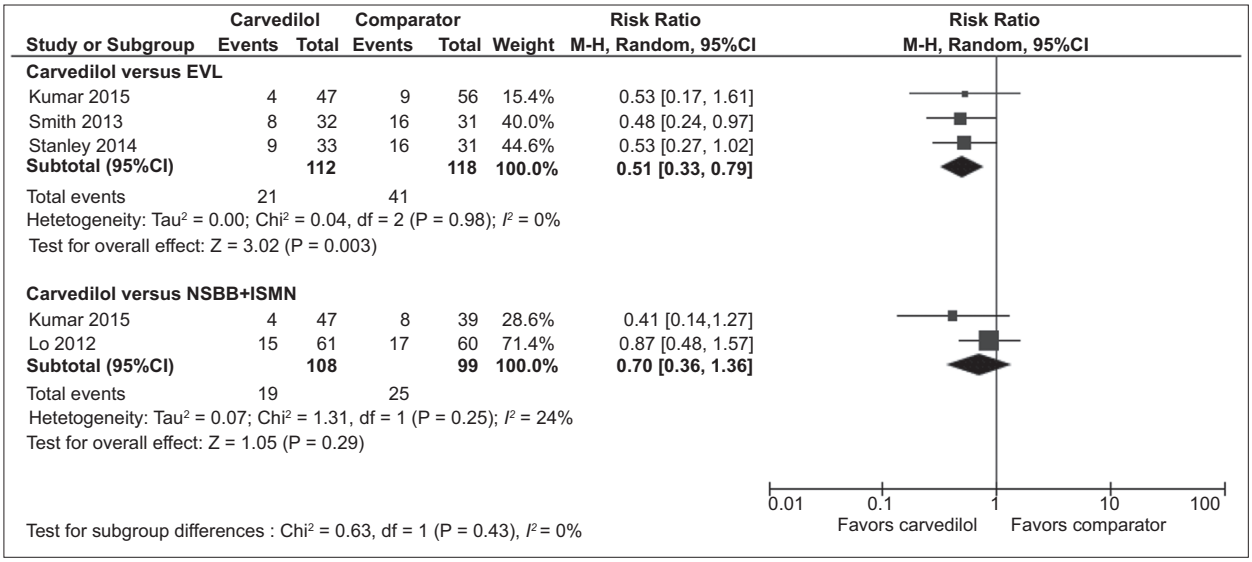

Figure 6 Risk ratio for incidence of all-cause mortality, secondary prophylaxis
CI, confidence interval; EVL, endoscopic variceal ligation; NSBB, non-selective beta-blocker; ISMN, isosorbide-5-mononitrate; M-H, Mantel-Haenszel

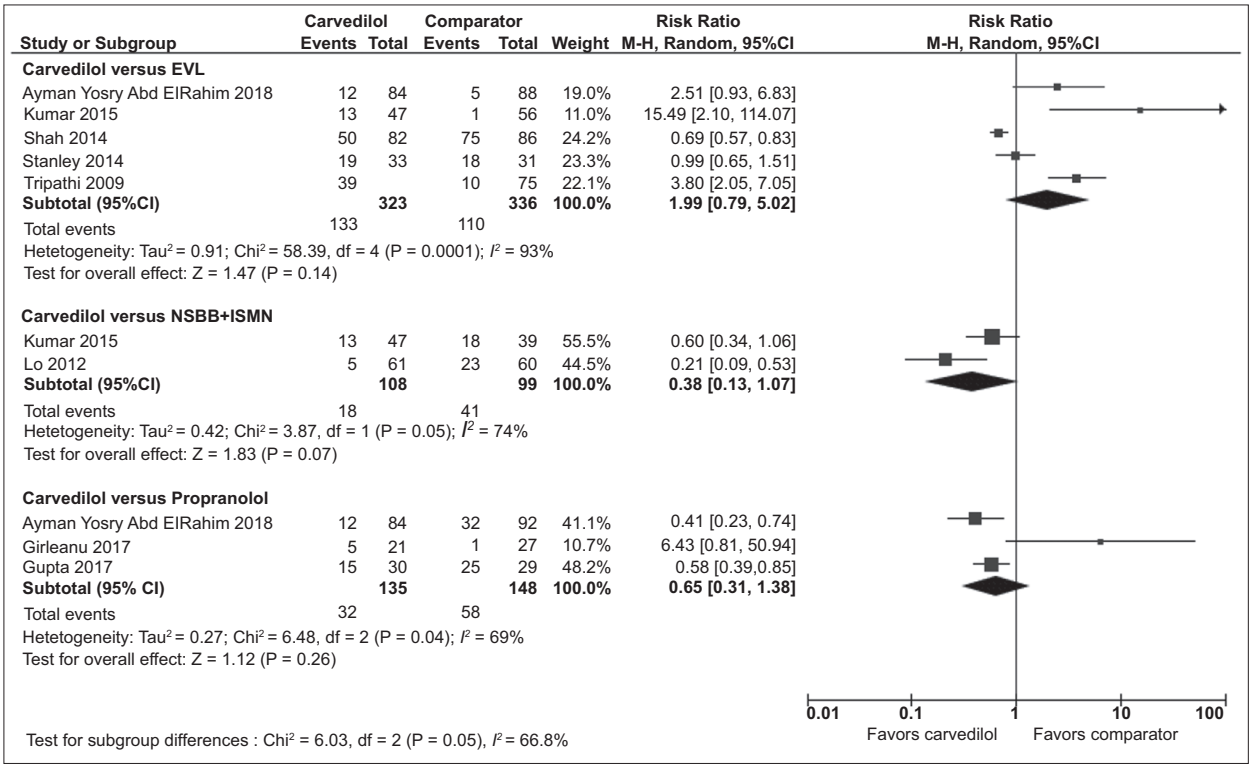

Figure 7 Risk ratio for incidence of any adverse event
CI, confidence interval; EVL, endoscopic variceal ligation; NSBB, non-selective beta-blocker; ISMN, isosorbide-5-mononitrate; M-H, Mantel-Haenszel

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.

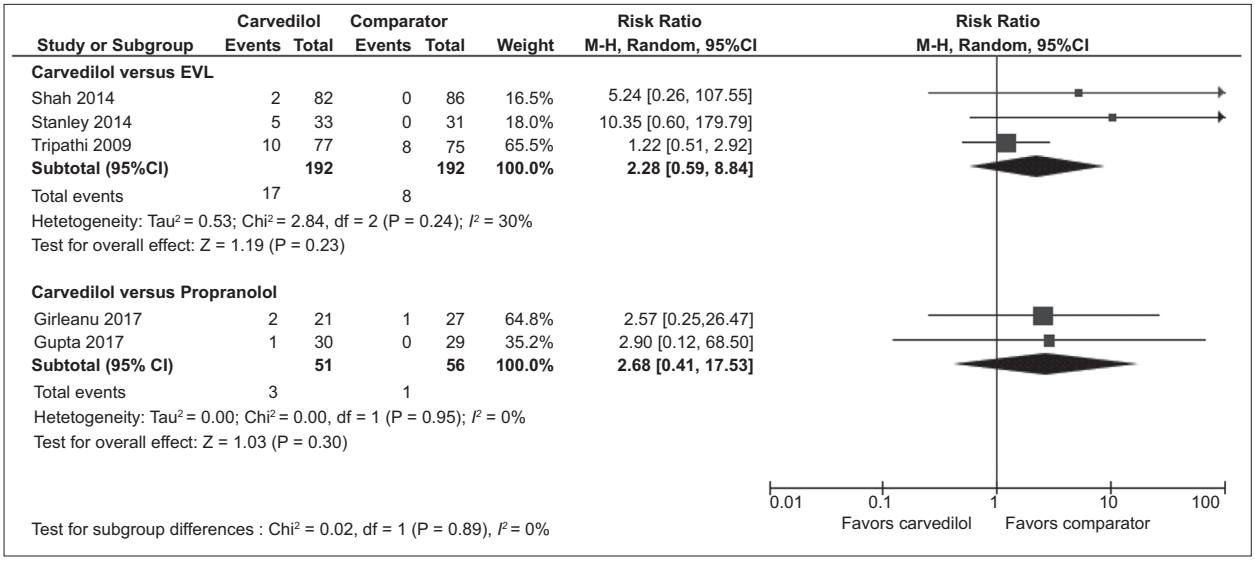

Figure 8 Risk ratio for incidence of withdrawal due to adverse events
CI, confidence interval; EVL, endoscopic variceal ligation; M-H, Mantel-Haenszel

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

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Supplementary Material

Supplementary Table 1 Prisma checklist

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4,5
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table S2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6,7 Table 1
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

(Contd...)

Supplementary Table 1 *(Continued)*

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
Rerults			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9, Tables S3-S9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-11, Figures 2-8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-11, Tables S10-S21
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12-13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Supplementary Table 2 Search strategy

Medline via PubMed (Mai 2018)	
#1	Carvedilol [tw]
#2	«carvedilol»[Supplementary Concept]
#3	Carvedilol
#4	«carvedilol»[All Fields]
#5	KRKA* or hexal* or carvil* or coreg* or dilatrend* or eucardic* or carloc* or actavis* or kredex* or coropres* or querto* or BM14190* or BM-14190*
#6	OR #1-5
#7	Esophageal and gastric varices [mh]
#8	Esophageal varices [mh]

(Contd...)

Supplementary Table 2 *(Continued)*

Medline via PubMed (Mai 2018)	
#9	Esophageal variceal hemorrhage [mh]
#10	Variceal hemorrhage [mh]
#11	Variceal bleeding [mh]
#12	Gastrointestinal bleeding [mh]
#13	Gastrointestinal bleeding [tw]
#14	Oesophageal varices [mh]
#15	(Esophag* OR oesophag*) AND (varic* OR varix)
#16	(Varix or varic*) AND (bleed* OR hemorrhage OR prevent* or prophyla*)
#17	OR #7-16
#18	Randomised controlled trial [mh]
#19	Randomized controlled trial [mh]
#20	Double Blind Method [mh]
#21	Single Blind Method [mh]
#22	Random Allocation [mh]
#23	Clinical trial [mh]
#24	(singl* or doub* or treb* or tripl*) AND (blind or mask) [tw]
#25	Clinical trial phase i [tw]
#26	Clinical trial phase ii [tw]
#27	Clinical trial phase iii [tw]
#28	Clinical trial phase iv [tw]
#29	Controlled clinical trial [tw]
#30	Randomized controlled trial [tw]
#31	Randomised controlled trial [tw]
#32	Multicenter study [tw]
#33	Clinical trial [tw]
#34	Randomly allocated [tw]
#35	(Crossover* or cross over*) [tw]
#36	Cross-over studies [mh]
#37	OR #18-36
#38	#6 and #17 and #37

Embase via Ovid (Mai 2018)	
#1	carvedilol/
#2	carvedilol.mp.
#3	KRKA* or hexal* or carvil* or coreg* or dilatrend* or eucardic* or carloc* or actavis* or kredex* or coropres* or querto* or BM14190* or BM-14190*).mp.
#4	OR# 1-3
#5	Esophagus varices/
#6	exp esophagus varices/
#7	esophageal varices.mp.
#8	esophageal variceal hemorrhage.mp.

(Contd...)

Supplementary Table 2 *(Continued)*

Medline via PubMed (Mai 2018)

#9	variceal hemorrhage.mp.
#10	variceal bleeding.mp.
#11	gastrointestinal bleeding/
#12	gastrointestinal bleeding.mp.
#13	oesophageal varices/
#14	((esophag$ or oesophag$) and (varic$ or varix)).mp.
#15	((varix or varic$) and (bleed$ or hemorrhage or prevent$ or prophyla$)).mp.
#16	Esophagus varices/
#17	OR# 5-17
#18	randomized controlled trial/
#19	controlled clinical study/
#20	randomised controlled trial/
#21	single blind procedure/
#22	Double Blind Procedure/
#23	crossover procedure/
#24	randomi?ed controlled trial$.mp.
#25	Rct.mp.
#26	random allocation.mp.
#27	single blind$.mp
#28	double blind$.mp.
#29	triple blind$.mp.
#30	((singl$ or doub$ or treb$ or tripl$) and (blind or mask)).mp.
#31	(crossover$ or cross over$).mp.
#32	OR#18-31
#33	#4 and #17 and #32

Cochrane Central Register of Controlled Trials (Mai 2018)

#1	Carvedilol
#2	KRKA* or hexal* or carvil* or coreg* or dilatrend* or eucardic* or carloc* or actavis* or kredex* or coropres* or querto* or BM14190* or BM-14190*
#3	#1 OR #2
#4	(Esophageal or oesophageal) and (varices)
#5	(Varix or varices) and (bleeding or hemorrhage or prevention or prophylaxis)
#6	MeSH descriptor: [Esophageal and Gastric Varices] explode all trees
#7	MeSH descriptor: [Gastrointestinal Hemorrhage] explode all trees
#8	#4 or #5 or #6 or #7
#9	#3 and #8

Supplementary Table 3 Risk of bias assessment for variceal bleeding

Study	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of reported results	Overall bias
Primary prophylaxis						
Agarwala *et al* 2011 [20]	Some concerns	Some concerns	Low	Low	Some concerns	High
Girleanu *et al* 2011 [21]	Some concerns	Some concerns	Low	Low	Low	Some concerns
Khan *et al* 2017 [23]	Some concerns	Low	Low	Low	Low	Some concerns
Tripathi *et al* 2009 [24]	Low	Low	Low	Low	Low	Low
Shah *et al* 2014 [25]	Low	Low	Low	Low	Low	Low
Ayman Yosry Abd ElRahim *et al* 2017 [22]	Some concerns	Some concerns	High	Low	Low	High
Secondary prophylaxis						
Kumar *et al* 2015 [27]	Some concerns	Some concerns	Some concerns	Low	Low	High
Smith *et al* 2013 [28]	Some concerns	Some concerns	Some concerns	Low	Low	High
Wei *et al* 2018 [29]	Low	Some concerns	Some concerns	Low	Low	Some concerns
Gupta *et al* 2016 [30]	Low	Some concerns	Some concerns	Low	Low	Some concerns
Lo *et al* 2012 [31]	Low	Low	Low	Low	Low	Low
Stanley *et al* 2014 [32]	Low	Low	High	Low	Low	High

Supplementary Table 4 Risk of bias assessment for all-cause mortality

Study	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of reported results	Overall bias
Primary prophylaxis						
Girleanu *et al* 2017 [21]	Some concerns	Some concerns	Low	Low	Low	Some concerns
Shah *et al* 2014 [25]	Low	Low	Low	Low	Low	Low
Tripathi *et al* 2009 [24]	Low	Low	Low	Low	Low	Low
Bhardwaj *et al* 2017 [26]	Low	Low	Low	Low	Low	Low
Secondary prophylaxis						
Stanely *et al* 2014 [32]	Low	Low	High	Low	Low	High
Lo *et al* 2012 [31]	Low	Low	Low	Low	Low	Low
Kumar *et al* 2015 [27]	Some concerns	Some concerns	Some concerns	Low	Low	High
Smith *et al* 2013 [28]	Some concerns	Some concerns	Some concerns	Low	Low	High

Supplementary Table 5 Risk of bias assessment for bleeding related mortality

Study	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of reported results	Overall bias
Primary prophylaxis						
Girleanu *et al* 2017 [21]	Some concerns	Some concerns	Low	Low	Low	Some concerns
Tripathi *et al* 2009 [24]	Low	Low	Low	Low	Low	Low
Shah *et al* 2014 [25]	Low	Low	Low	Low	Low	Low
Bhardwaj *et al* 2017 [26]	Low	Low	Low	Low	Low	Low
Secondary prophylaxis						
Stanley *et al* 2014 [32]	Low	Low	High	Low	Low	High
Lo *et al* 2012 [31]	Low	Low	Low	Low	Low	Low

Supplementary Table 6 Risk of bias assessment for all-cause bleeding

Study	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of reported results	Overall bias
Stanley *et al* 2014 [32]	Low	Low	High	Low	Low	High
Lo *et al* 2012 [31]	Low	Low	Low	Low	Low	Low

Supplementary Table 7 Risk of bias assessment for variceal progression

Study	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of reported results	Overall bias
Bhardwaj *et al* 2017 [26]	Low	Low	Low	Low	Low	Low

Supplementary Table 8 Risk of bias assessment for any adverse event

Study	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of reported results	Overall bias
Ayman Yosry Abd ElRahim *et al* 2017 [22]	Some concerns	Some concerns	High	Low	Low	High
Girleanu *et al* 2017 [21]	Some concerns	Some concerns	Low	Low	Low	Some concerns
Tripathi *et al* 2009 [24]	Low	Low	Low	Low	Low	Low
Shah *et al* 2014 [25]	Low	Low	Low	Low	Low	Low
Stanley *et al* 2014 [32]	Low	Low	Low	Low	Low	Low
Lo *et al* 2012 [31]	Low	Low	Low	Low	Low	Low
Gupta *et al* 2017 [30]	Low	Some concerns	Low	Low	Low	Some concerns
Kumar *et al* 2015 [27]	Some concerns	Some concerns	Some concerns	Low	Low	High
Bhardwaj *et al* 2017 [26]	Low	Low	Low	Low	Low	Low

Supplementary Table 9 Risk of bias assessment for withdrawal due to adverse events

Study	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of reported results	Overall bias
Girleanu *et al* 2017 [21]	Some concerns	Some concerns	Low	Low	Low	Some concerns
Tripathi *et al* 2009 [24]	Low	Low	high	Low	Low	High
Shah *et al* 2014 [25]	Low	Low	Low	Low	Low	Low
Stanley *et al* 2014 [32]	Low	Low	high	Low	Low	High
Lo *et al* 2012 [31]	Low	Low	Low	Low	Low	Low
Gupta *et al* 2017 [30]	Low	Some concerns	Some concerns	Low	Low	Some concerns
Bhardwaj *et al* 2017 [26]	Low	Low	Low	Low	Low	Low

Supplementary Table 10 Sensitivity analyses based on risk of bias assessment for variceal bleeding

Sensitivity analysis	Comparison	Trials included	Effect estimate, RR	95 % CI	I^2, %
Primary prophylaxis					
Excluding trials at high risk of bias	Carvedilol vs EVL	3	0.56	0.29 to 1.07	36
	Carvedilol vs PPL	1	0.96	0.24 to 3.85	NE
Secondary prophylaxis					
Excluding trials at high risk of bias	Carvedilol vs EVL	All trials were at high risk of bias			
	Carvedilol vs NSBB+ISMN	1	1.17	0.80 to 1.72	NE
	Carvedilol vs PPL	2	0.39	0.15 to 1.03	0

RR, risk ratio; CI, confidence interval; EVL, esophageal variceal ligation; PPL, propranolol; NSBB, non-selective beta blocker; ISMN, isosorbide-5-mononitrate; NE, not estimable

Supplementary Table 11 Sensitivity analyses based on risk of bias assessment for all-cause mortality

Sensitivity analysis	Comparison	Trials included	Effect estimate, RR	95 % CI	I^2, %
Primary prophylaxis					
Excluding trials at high risk of bias	Carvedilol vs EVL	2	1.06	0.75 to 1.50	0
	Carvedilol vs PPL	1	1.07	0.38 to 3.03	NE
Secondary prophylaxis					
Excluding trials at high risk of bias	Carvedilol vs EVL	All trials were at high risk of bias			
	Carvedilol vs NSBB+ISMN	1	0.87	0.48 to 1.57	NE

RR, risk ratio; CI, confidence interval; EVL, esophageal variceal ligation; PPL, propranolol; NSBB, non-selective beta blocker; ISMN, isosorbide-5-mononitrate; NE, not estimable

Supplementary Table 12 Sensitivity analyses based on risk of bias assessment for bleeding-related mortality

Sensitivity analysis	Comparison	Trials included	Effect estimate, RR	95%CI	I^2, %
Primary prophylaxis					
Excluding trials at high risk of bias	Carvedilol vs EVL	No trial was at high risk of bias for this outcome			
	Carvedilol vs PPL	No trial was at high risk of bias for this outcome			
Secondary prophylaxis					
Excluding trials at high risk of bias	Carvedilol vs EVL	Data were available from one trial at high risk of bias for this outcome			
	Carvedilol vs NSBB+ISMN	No trial was at high risk of bias for this outcome			

RR, risk ratio; CI, confidence interval; EVL, esophageal variceal ligation; PPL, propranolol; NSBB, non-selective beta blocker; ISMN, isosorbide-5-mononitrate

Supplementary Table 13 Sensitivity analyses based on risk of bias assessment for all-cause bleeding

Sensitivity analysis	Comparison	Trials included	Effect estimate, RR	95%CI	I^2, %
Secondary prophylaxis					
Excluding trials at high risk of bias	Carvedilol vs EVL	Data were available from one trial at high risk of bias for this outcome			
	Carvedilol vs NSBB+ISMN	No trial was at high risk of bias for this outcome			

RR, risk ratio; CI, confidence interval; EVL, esophageal variceal ligation, NSBB, non-selective beta blocker, ISMN, isosorbide-5-mononitrate

Supplementary Table 14 Subgroup analysis for variceal bleeding based on the duration of follow up

Subgroup	Comparison	Trials included	Effect estimate, RR	95%CI	I^2, %
Primary prophylaxis					
Trials with ≤12 months of follow up	Carvedilol vs NSBBs	2	0.66	0.13 to 3.40	81
	Carvedilol vs EVL	2	0.77	0.19 to 3.02	81
Trials with >12 months of follow up	Carvedilol vs NSBBs	1	0.96	0.24 to 3.85	NE
	Carvedilol vs EVL	2	0.70	0.27 to 1.82	54
Secondary prophylaxis	Unable to perform subgroup analysis				

RR, risk ratio; CI, confidence interval; EVL, esophageal variceal ligation; NSBBs, non-selective beta clockers; NE, not estimable

Supplementary Table 15 Sensitivity analyses based on risk of bias assessment for any adverse event

Sensitivity analysis	Comparison	Trials included	Effect estimate, RR	95%CI	I^2, %
Excluding trials at high risk of bias	Carvedilol vs EVL	2	0.79	0.56 to 1.11	59
	Carvedilol vs NSBB+ISMN	1	0.21	0.09 to 0.53	NE
	Carvedilol vs PPL	2	1.61	0.12 to 21.35	84

RR, risk ratio; CI, confidence interval; EVL, esophageal variceal ligation; PPL, propranolol; NSBB, non-selective beta blocker; ISMN, isosorbide-5-mononitrate; NE, not estimable

Supplementary Table 16 Sensitivity analyses based on risk of bias assessment for withdrawal due to adverse events

Sensitivity analysis	Comparison	Trials included	Effect estimate, RR	95%CI	I^2, %
Excluding trials at high risk of bias	Carvedilol vs EVL	1	5.24	0.26 to 107.55	NE
	Carvedilol vs PPL	2	2.68	0.41 to 17.53	0

RR, risk ratio; CI, confidence interval; EVL, esophageal variceal ligation; PPL, propranolol; NE, not estimable

Supplementary Table 17 Certainty of evidence for efficacy outcomes (carvedilol vs EVL)

Carvedilol compared to EVL										
Certainty assessment							Summary of findings			
№ of patients (trials)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty	Study event rates (%)		Relative effect (95%CI)	Absolute effect (95% CI)
							With carvedilol	With EVL		
Primary prophylaxis of variceal bleeding										
742 (4 RCTs)	Not serious	Serious[a]	Not serious	Derious[b]	Dtrongly suspected[c]	⊕○○○ VERY LOW	34/368 (9.2%)	48/374 (12.8%)	RR 0.74 (0.37 to 1.49)	33 fewer per 1.000 (from 63 more to 81 fewer)
Secondary prophylaxis of variceal bleeding										
230 (3 RCTs)	Dserious[d]	Not serious	Not serious	Serious[b]	Dtrongly suspected[c]	⊕○○○ VERY LOW	37/112 (33.0%)	35/118 (29.7%)	RR 1.10 (0.75 to 1.61)	30 more per 1.000 (from 74 fewer to 181 more)
All-cause mortality when used for primary prophylaxis										
320 (2 RCTs)	Not serious	Derious[e]	Not serious	Derious[e]	Dtrongly suspected[c]	⊕○○○ VERY LOW	46/159 (28.9%)	43/161 (26.7%)	RR 1.06 (0.75 to 1.50)	16 more per 1.000 (from 67 fewer to 134 more)
All-cause mortality when used for secondary prophylaxis										
230 (3 RCTs)	Derious[d]	Not serious	Not serious	Derious[b]	Dtrongly suspected[c]	⊕○○○ VERY LOW	21/112 (18.8%)	41/118 (34.7%)	RR 0.51 (0.33 to 0.79)	170 fewer per 1.000 (from 73 fewer to 233 fewer)
Bleeding-related mortality when used for primary prophylaxis										
320 (2 RCTs)	Not serious	Derious[e]	Nnot serious	Derious[b]	Dtrongly suspected[c]	⊕○○○ VERY LOW	10/159 (6.3%)	7/161 (4.3%)	RR 1.43 (0.55 to 3.72)	19 more per 1.000 (from 20 fewer to 118 more)

a. Substantial heterogeneity (I^2 >50%) was detected which could not be explained with a subgroup analysis

b. The optimal information size criterion was not met, and the sample size was small

c. Publication bias is suspected due to rigorous search strategy and few included studies

d. The proportion of information from studies with serious concerns about risk of bias is sufficient to affect the interpretation of results

e. There was no substantial heterogeneity detected but only 2 studies with few events were included

CI, confidence interval; RR, risk ratio; EVL, esophageal variceal band ligation; RCT, randomized controlled trial

Supplementary Table 18 Certainty of evidence for efficacy outcomes (carvedilol vs NSBB+ISMN)

Carvedilol compared to NSBB+ISMN										
Certainty assessment							Summary of findings			
№ of patients (trials)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty	Study event rates (%)		Relative effect (95%CI)	Absolute effect (95%CI)
							With carvedilol	With NSBB+ISMN		
Secondary prophylaxis of variceal bleeding										
207 (2 RCTs)	Not serious	Serious[a]	Not serious	Serious[b]	Strongly suspected[c]	⨁◯◯◯ VERY LOW	44/108 (40.7%)	40/99 (40.4%)	RR 1.02 (0.70 to 1.51)	8 more per 1.000 (from 121 fewer to 206 more)
All-cause mortality when used for secondary prophylaxis										
207 (2 RCTs)	Not serious	Serious[a]	Not serious	Serious[b]	Strongly suspected[c]	⨁◯◯◯ VERY LOW	19/108 (17.6%)	25/99 (25.3%)	RR 0.70 (0.36 to 1.36)	76 fewer per 1.000 (from 91 more to 162 fewer)

a. There was no substantial heterogeneity detected but only 2 studies with few events were included

b. The optimal information size criterion was not met, and the sample size was small

c. Publication bias is suspected due to rigorous search strategy and few included studies

CI, confidence interval; RR, risk ratio; NSBB, non-selective beta blockers; ISMN, isosorbide-5-mononitrate

Supplementary Table 19 Certainty of evidence for efficacy outcomes (carvedilol vs propranolol)

Carvedilol compared to propranolol										
Certainty assessment							Summary of findings			
№ of patients (trials)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty	Study event rates (%)		Relative effect (95%CI)	Absolute effect (95%CI)
							With carvedilol	With propranolol		
Primary prophylaxis of variceal bleeding										
292 (3 RCTs)	Not serious	Serious[a]	Not serious	Serious[b]	Strongly suspected[c]	⨁◯◯◯ VERY LOW	19/141 (13.5%)	24/151 (15.9%)	RR 0.76 (0.27 to 2.14)	38 fewer per 1.000 (from 116 fewer to 181 more)
Secondary prophylaxis of variceal bleeding										
61 (2 RCTs)	Not serious	Serious[d]	Not serious	Very serious[b]	Strongly suspected[c]	⨁◯◯◯ VERY LOW	4/33 (12.1%)	9/28 (32.1%)	RR 0.39 (0.15 to 1.03)	196 fewer per 1.000 (from 10 more to 273 fewer)

a. Substantial heterogeneity (I^2 >50%) was detected which could not be explained with a subgroup analysis

b. The optimal information size criterion was not met, and the sample size was small

c. Publication bias is suspected due to rigorous search strategy and few included studies

d. There was no substantial heterogeneity detected but only 2 studies with very few events were included

CI, confidence interval; RR, risk ratio;

Supplementary Table 20 Certainty of evidence for any adverse event

Certainty assessment							Summary of findings			
№ of patients (trials)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty	Study event rates (%)		Relative effect (95%CI)	Absolute effect (95%CI)
							With carvedilol	With comparator		
Carvedilol vs EVL										
659 (5 RCTs)	Not serious	Serious[a]	Not serious	Serious[b]	Strongly suspected[c]	⨁◯◯◯ VERY LOW	133/323 (41.2%)	109/336 (32.4%)	RR 1.99 (0.79 to 5.02)	341 more per 1.000 (from 75 fewer to 1.000 more)
Carvedilol vs propranolol										
283 (2 RCTs)	Not serious	Sserious[d]	Not serious	Serious[b]	Strongly suspected[c]	⨁◯◯◯ VERY LOW	32/135 (23.7%)	58/148 (39.2%)	RR 0.65 (0.31 to 1.38)	137 fewer per 1.000 (from 149 more to 270 fewer)
Carvedilol vs NSBB+ISMN										
207 (2 RCTs)	Not serious	Serious[d]	Not serious	Serious[b]	Strongly suspected[c]	⨁◯◯◯ VERY LOW	18/108 (16.7%)	41/99 (41.4%)	RR 0.38 (0.13 to 1.07)	257 fewer per 1.000 (from 29 more to 360 fewer)

a. Substantial heterogeneity (I^2>75%) was detected which could not be explained with sensitivity analyses

b. The optimal information size criterion was not met, and the sample size was small

c. Publication bias is suspected due to rigorous search strategy and few included studies

d. Substantial heterogeneity (I^2 >50%) was detected which could not be explained with sensitivity analyses

RR, risk ratio; CI, confidence interval; EVL, esophageal variceal ligation; NSBB, non-selective beta blocker; ISMN, isosorbide-5-mononitrate

Supplementary Table 21 Certainty of evidence for withdrawal due to adverse events

Certainty assessment							Summary of findings			
№ of patients (trials)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty	Study event rates (%)		Relative effect (95%CI)	Absolute effect (95%CI)
							With carvedilol	With comparator		
Carvedilol vs EVL										
384 (3 RCTs)	Not serious	Sserious	Not serious	serious	Strongly suspected[c]	⨁◯◯◯ VERY LOW	17/192 (8.8%)	8/192 (4.1%)	RR 2.28 (0.59 to 8.84)	
Carvedilol vs propranolol										
107 (2 RCTs)	Not serious	Serious[a]	Not serious	Serious[b]	Strongly suspected[c]	⨁◯◯◯ VERY LOW	3/51 (5.9%)	1/56 (1.8%)	RR 2.68 (0.41 to 17.53)	30 more per 1.000 (from 11 fewer to 295 more)

a. There was no substantial heterogeneity detected but only 2 studies with very few events were included

b. The optimal information size criterion was not met, and the sample size was small

c. Publication bias is suspected due to rigorous search strategy and few included studies

CI, confidence interval; RR, risk ratio; RCT, randomized controlled trial; EVL, endoscopic variceal ligation