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Primary prevention of variceal bleeding in people with oesophageal varices due to liver cirrhosis: a network meta-analysis (Review)

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[Intervention Review]

Primary prevention of variceal bleeding in people with oesophageal varices due to liver cirrhosis: a network meta-analysis

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ABSTRACT

Background

Approximately 40% to 95% of people with cirrhosis have oesophageal varices. About 15% to 20% of oesophageal varices bleed in about one to three years. There are several different treatments to prevent bleeding, including: beta-blockers, endoscopic sclerotherapy, and variceal band ligation. However, there is uncertainty surrounding their individual and relative benefits and harms.

Objectives

To compare the benefits and harms of different treatments for prevention of first variceal bleeding from oesophageal varices in adults with liver cirrhosis through a network meta-analysis and to generate rankings of the different treatments for prevention of first variceal bleeding from oesophageal varices according to their safety and efficacy.

Search methods

We searched CENTRAL, MEDLINE, Embase, Science Citation Index Expanded, World Health Organization International Clinical Trials Registry Platform, and trials registers to December 2019 to identify randomised clinical trials in people with cirrhosis and oesophageal varices with no history of bleeding.

Selection criteria

We included only randomised clinical trials (irrespective of language, blinding, or status) in adults with cirrhosis and oesophageal varices with no history of bleeding. We excluded randomised clinical trials in which participants had previous bleeding from oesophageal varices and those who had previously undergone liver transplantation or previously received prophylactic treatment for oesophageal varices.

Data collection and analysis

We performed a network meta-analysis with OpenBUGS using Bayesian methods and calculated the differences in treatments using hazard ratios (HR), odds ratios (OR), and rate ratios with 95% credible intervals (CrI) based on an available-case analysis, according to National

Institute for Health and Care Excellence Decision Support Unit guidance. We performed the direct comparisons from randomised clinical trials using the same codes and the same technical details.

Main results

We included 66 randomised clinical trials (6653 participants) in the review. Sixty trials (6212 participants) provided data for one or more comparisons in the review. The trials that provided the information included people with cirrhosis due to varied aetiologies and those at high risk of bleeding from oesophageal varices. The follow-up in the trials that reported outcomes ranged from 6 months to 60 months. All but one of the trials were at high risk of bias. The interventions compared included beta-blockers, no active intervention, variceal band ligation, sclerotherapy, beta-blockers plus variceal band ligation, beta-blockers plus nitrates, nitrates, beta-blockers plus sclerotherapy, and portocaval shunt.

Overall, 21.2% of participants who received non-selective beta-blockers ('beta-blockers') − the reference treatment (chosen because this was the most common treatment compared in the trials) − died during 8-month to 60-month follow-up.

Based on low-certainty evidence, beta-blockers, variceal band ligation, sclerotherapy, and beta-blockers plus nitrates all had lower mortality versus no active intervention (beta-blockers: HR 0.49, 95% CrI 0.36 to 0.67; direct comparison HR: 0.59, 95% CrI 0.42 to 0.83; 10 trials, 1200 participants; variceal band ligation: HR 0.51, 95% CrI 0.35 to 0.74; direct comparison HR 0.49, 95% CrI 0.12 to 2.14; 3 trials, 355 participants; sclerotherapy: HR 0.66, 95% CrI 0.51 to 0.85; direct comparison HR 0.61, 95% CrI 0.41 to 0.90; 18 trials, 1666 participants; beta-blockers plus nitrates: HR 0.41, 95% CrI 0.20 to 0.85; no direct comparison). No trials reported health-related quality of life. Based on low-certainty evidence, variceal band ligation had a higher number of serious adverse events (number of events) than beta-blockers (rate ratio 10.49, 95% CrI 2.83 to 60.64; 1 trial, 168 participants).

Based on low-certainty evidence, beta-blockers plus nitrates had a higher number of 'any adverse events (number of participants)' than beta-blockers alone (OR 3.41, 95% CrI 1.11 to 11.28; 1 trial, 57 participants). Based on low-certainty evidence, adverse events (number of events) were higher in sclerotherapy than in beta-blockers (rate ratio 2.49, 95% CrI 1.53 to 4.22; direct comparison rate ratio 2.47, 95% CrI 1.27 to 5.06; 2 trials, 90 participants), and in beta-blockers plus variceal band ligation than in beta-blockers (direct comparison rate ratio 1.72, 95% CrI 1.08 to 2.76; 1 trial, 140 participants).

Based on low-certainty evidence, any variceal bleed was lower in beta-blockers plus variceal band ligation than in beta-blockers (direct comparison HR 0.21, 95% CrI 0.04 to 0.71; 1 trial, 173 participants). Based on low-certainty evidence, any variceal bleed was higher in nitrates than beta-blockers (direct comparison HR 6.40, 95% CrI 1.58 to 47.42; 1 trial, 52 participants).

The evidence indicates considerable uncertainty about the effect of the interventions in the remaining comparisons.

Authors' conclusions

Based on low-certainty evidence, beta-blockers, variceal band ligation, sclerotherapy, and beta-blockers plus nitrates may decrease mortality compared to no intervention in people with high-risk oesophageal varices in people with cirrhosis and no previous history of bleeding. Based on low-certainty evidence, variceal band ligation may result in a higher number of serious adverse events than beta-blockers. The evidence indicates considerable uncertainty about the effect of beta-blockers versus variceal band ligation on variceal bleeding. The evidence also indicates considerable uncertainty about the effect of the interventions in most of the remaining comparisons.

PLAIN LANGUAGE SUMMARY

Treatment to prevent first bleeding from dilated veins in the oesophagus resulting from advanced scarring of the liver

What was the aim of this Cochrane Review?

We aimed to find the best available treatment for prevention of first bleeding from oesophageal varices (enlarged veins in the food pipe (oesophagus)) in people with advanced liver scarring (liver cirrhosis, or late stage scarring of the liver with complications). People with cirrhosis and oesophageal varices are at significant risk of bleeding and death. Therefore, treatment is important, but the benefits and harms of different treatments available are currently unclear. The review authors collected and analysed 66 randomised clinical trials (clinical studies where people are randomly put into one of two or more treatment groups) with the aim of finding what the best treatment is. During analysis of data, we used standard Cochrane methods, which allow the comparison of only two treatments at a time. We also used advanced techniques that allow comparison of multiple treatments at the same time (referred to as 'network (or indirect) meta-analysis').

Date of literature search

December 2019

Key messages

We found that only one of the trials was conducted without flaws, and because of this, there is high to very high uncertainty in the findings. Approximately one in five trial participants with cirrhosis and oesophageal varices who never had bleeding previously and received the standard treatment of beta-blockers died within five years of treatment.

The funding source for the research was unclear in 50 trials; commercial organisations funded five trials. There were no concerns regarding the source of funding for the remaining 11 trials.

What was studied in the review?

This review looked at adults of any sex, age, and ethnic origin with advanced liver disease due to various causes and oesophageal varices, but never had bleeding from the oesophageal varices. Participants were given different treatments for prevention of first bleeding from oesophageal varices. The authors excluded studies in people who had previous bleeding from the oesophageal varices and those who had had a liver transplant or already received treatment for oesophageal varices previously. The average age of participants, when reported, ranged from 40 years to 63 years. The treatments included 'non-selective beta-blockers' or simply 'beta-blockers' (drugs that slow the heart and decrease the force of heart pumping resulting in decrease pressure in the blood vessels; they also increase the pressure in the gut blood vessels decreasing the amount of blood reaching the oesophageal veins), endoscopic sclerotherapy (injecting clotting agents into the enlarged veins by looking through a tube inserted through the mouth), variceal band ligation (inserting elastic bands around the widened veins by using a tube inserted through the mouth), and nitrates (medicines that decrease the pressure in the gut blood vessels by widening them). The review authors wanted to gather and analyse data on death (percentage dead at maximal follow-up), quality of life, serious and non-serious side effects, percentage of people who developed bleeding, and development of other complications of advanced liver disease.

What were the main results of the review?

The 66 studies included a relatively small number of participants (6653 people). Sixty studies with 6212 participants provided data for analyses. The follow-up of the trial ranged from six months to five years in studies that reported the outcomes that we were interested in. The review found the following:
– Approximately one in five people with cirrhosis and oesophageal varices (without previous bleeding) who receive the beta-blockers died within five years.
– Beta-blockers, variceal band ligation, sclerotherapy, and beta-blockers plus nitrates all may result in fewer deaths than no treatment.
– Variceal band ligation may result in a higher number of serious side effects than beta-blockers.
– Sclerotherapy, beta-blockers plus nitrates, and beta-blockers plus variceal band ligation may result in more side effects (when serious and non-serious adverse events were put together) than beta-blockers.
– Beta-blockers plus variceal band ligation may result in fewer people who develop bleeding than beta-blockers alone based on a single small trial.
– Nitrates alone may result in more people who develop bleeding than beta-blockers alone.
– The evidence indicates considerable uncertainty about the effect of the interventions in the remaining comparisons.
– None of the trials reported health-related quality of life.

What are our conclusions?

Beta-blockers, variceal band ligation, sclerotherapy, and beta-blockers plus nitrates may decrease the death rate compared to no treatment in people with high-risk oesophageal varices in people with cirrhosis and no history of bleeding. Variceal band ligation may result in a higher number of serious side effects than beta-blockers. The evidence indicates considerable uncertainty about the effect of beta-blockers versus variceal band ligation on variceal bleeding. The evidence also indicates considerable uncertainty about the effect of the interventions in most of the remaining comparisons. Future well designed trials are needed to find out the best treatment to prevent first bleeding from people with cirrhosis and oesophageal varices.

Summary of findings 1. Primary prevention of bleeding in people with oesophageal varices due to liver cirrhosis (common interventions)

Primary prevention of bleeding in people with oesophageal varices due to liver cirrhosis (common interventions)

Patient or population: people with liver cirrhosis and oesophageal varices with no history of bleeding
Settings: secondary or tertiary care
Intervention: various interventions
Comparison: beta-blockers
Follow-up: 6 months to 60 months

Outcomes/interventions	No active intervention		Variceal band ligation		Sclerotherapy		Beta-blockers + variceal band ligation	
Mortality (follow-up: 8–60 months)								
Beta-blockers 212 per 1000 (21.2%)	**HR 2.04** (1.50 to 2.78) **Network estimate**	**221 more per 1000** (107 more to 377 more)	**HR 1.05** (0.80 to 1.38) **Network estimate**	**11 more per 1000** (43 fewer to 81 more)	**HR 1.35** (0.95 to 1.92) **Network estimate**	**75 more per 1000** (10 fewer to 195 more)	**HR 1.11** (0.56 to 2.19) **Network estimate**	**23 more per 1000** (93 fewer to 252 more)
	⊕⊕⊖⊖ **Low certainty** [a],[b]		⊕⊖⊖⊖ **Very low certainty** [a],[b],[c]		⊕⊖⊖⊖ **Very low certainty** [a],[b],[c]		⊕⊖⊖⊖ **Very low certainty** [a],[b],[c]	
	Based on 1200 participants (10 RCTs)		Based on 1640 participants (17 RCTs)		Based on 320 participants (5 RCTs)		Based on 313 participants (2 RCTs)	
Health-related quality of life								
No trials reported health-related quality of life.								
Serious adverse events (number of participants) (follow-up: 11–55 months)								
Beta-blockers 56 per 1000 (5.6%)	—		**OR 0.75** (0.02 to 23.24) **Network estimate**	**13 fewer per 1000** (54 fewer to 522 more)	**OR 0.55** (0.00 to 272.05) **Network estimate**	**24 fewer per 1000** (55 fewer to 886 more)	—	
			⊕⊖⊖⊖		⊕⊖⊖⊖			

			Very low certainty [a],c,d		**Very low certainty** [a],c,d			
			Based on 372 participants (5 RCTs)		Based on 85 participants (1 RCT)			
Serious adverse events (number of events) (follow-up: 13 months)								
Beta-blockers 24 per 1000 (2.4 per 100 participants)	—		**RaR 10.49** (2.83 to 60.64) **Network estimate**		—		—	
			⊕⊕⊖⊖ **Low certainty** [a],d					
			Based on 168 participants (1 RCT)					
Any adverse events (number of participants) (follow-up: 11–55 months)								
Beta-blockers 190 per 1000 (19%)	**OR 0.28** (0.02 to 2.91) **Network estimate**	**128 fewer per 1000** (185 fewer to 216 more)	**OR 1.60** (0.54 to 5.15) **Network estimate**	**83 more per 1000** (78 fewer to 357 more)	**OR 1.19** (0.02 to 80.24) **Network estimate**	**28 more per 1000** (186 fewer to 759 more)	—	
	⊕⊖⊖⊖ **Very low certainty** [a],c,e		⊕⊖⊖⊖ **Very low certainty** [a],c,e		⊕⊖⊖⊖ **Very low certainty** [a],c,e			
	Based on 256 participants (2 RCTs)		Based on 728 participants (7 RCTs)		No direct RCT			
Any adverse events (number of events) (follow-up: 12–52 months)								
Beta-blockers 610 per 1000 (61 per 100 participants)	**RaR 0.97** (0.59 to 1.68) **Network estimate**	**16 fewer per 1000** (253 fewer to 415 more)	**RaR 0.77** (0.63 to 0.94) **Network estimate**	**141 fewer per 1000** (226 fewer to 38 fewer)	**RaR 2.49** (1.53 to 4.22) **Network estimate**	**909 more per 1000** (325 more to 1966 more)	**RaR 1.33** (0.93 to 1.92) **Network estimate**	**202 more per 1000** (43 fewer to 563 more)
	⊕⊖⊖⊖ **Very low certainty** [a],c,e		⊕⊕⊖⊖ **Low certainty** [a],e		⊕⊕⊖⊖ **Low certainty** [a],e		⊕⊖⊖⊖ **Very low certainty** [a],c,e	
	No direct RCT		Based on 480 participants (4 RCTs)		Based on 90 participants (2 RCTs)		Based on 140 participants (1 RCT)	

Liver transplantation (follow-up: 11–52 months)								
Beta-blockers 48 per 1000 (4.8%)	**HR 1.36** (0.35 to 5.80) **Network estimate**	**18 more per 1000** (31 fewer to 231 more)	**HR 1.41** (0.83 to 2.43) **Network estimate**	**20 more per 1000** (8 fewer to 69 more)	—		**HR 2.40** (0.19 to 77.48) **Network estimate**	**67 more per 1000** (39 fewer to 952 more)
	⊕⊖⊖⊖ **Very low certainty** [a],c,d		⊕⊖⊖⊖ **Very low certainty** [a],c,d				⊕⊖⊖⊖ **Very low certainty** [a],c,d	
	Based on 161 participants (1 RCT)		Based on 380 participants (5 RCTs)				Based on 140 participants (1 RCT)	
Symptomatic variceal bleeding (follow-up: 15–44 months)								
Beta-blockers 180 per 1000 (18%)	**HR 1.14** (0.56 to 2.40) **Network estimate**	**24 more per 1000** (79 fewer to 251 more)	**HR 0.80** (0.47 to 1.36) **Network estimate**	**36 fewer per 1000** (96 fewer to 64 more)	**HR 0.91** (0.44 to 1.95) **Network estimate**	**16 fewer per 1000** (100 fewer to 171 more)	**HR 1.13** (0.45 to 2.87) **Network estimate**	**23 more per 1000** (99 fewer to 337 more)
	⊕⊖⊖⊖ **Very low certainty** [a],c,d		⊕⊖⊖⊖ **Very low certainty** [a],c,d		⊕⊖⊖⊖ **Very low certainty** [a],c,d		⊕⊖⊖⊖ **Very low certainty** [a],c,d	
	Based on 140 participants (1 RCT)		Based on 330 participants (3 RCTs)		Based on 141 participants (1 RCT)		Based on 140 participants (1 RCT)	
Any variceal bleeding (follow-up: 6–55 months)								
Beta-blockers 97 per 1000 (9.7%)	**HR 2.71** (0.97 to 7.68) **Network estimate**	**165 more per 1000** (3 fewer to 647 more)	**HR 0.72** (0.33 to 1.51) **Network estimate**	**27 fewer per 1000** (65 fewer to 49 more)	**HR 1.02** (0.33 to 3.27) **Network estimate**	**1 more per 1000** (65 fewer to 219 more)	**HR 0.21** (0.04 to 0.71) **Direct estimate**	**76 fewer per 1000** (93 fewer to 28 fewer)
	⊕⊖⊖⊖ **Very low certainty** [a],b,c		⊕⊖⊖⊖ **Very low certainty** [a],b,c		⊕⊖⊖⊖ **Very low certainty** [a],b,c		⊕⊕⊖⊖ **Low certainty** [a],d	
	Based on 208 participants (2 RCTs)		Based on 879 participants (9 RCTs)		Based on 175 participants (3 RCTs)		Based on 173 participants (1 RCT)	

Other features of decompensation (follow-up: 18–55 months)					
Beta-blockers 162 per 1000 (16.2 per 100 participants)	—	**RaR 1.11** (0.44 to 2.86) **Network estimate**	**18 more per 1000** (90 fewer to 302 more)	—	—
		⊕⊖⊖⊖ **Very low certainty** [a,c,d]			
		Based on 130 participants (2 RCTs)			

*Ranking was not provided because of the considerable uncertainty in the ranking.

CrI: credible interval; **HR:** hazard ratio; **OR:** odds ratio; **RaR:** rate ratio; **RCT:** randomised clinical trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

General comment: The GRADE classification was based on the main results.
[a]Downgraded one level for risk of bias because the trial(s) included in the analysis was/were at high risk of bias.
[b]Downgraded one level for inconsistency because there was evidence of statistical heterogeneity.
[c]Downgraded one level for imprecision because the credible intervals were wide (included clinical benefit and harms).
[d]Downgraded one level for imprecision because the sample size was small.
[e]Downgraded one level for indirectness because there was evidence of statistical inconsistency.

Summary of findings 2. Primary prevention of bleeding in people with oesophageal varices due to liver cirrhosis (all interventions)

Patient or population: people with liver cirrhosis and oesophageal varices with no history of bleeding
Settings: secondary or tertiary care
Intervention: various interventions
Comparison: beta-blockers
Follow-up: 6–60 months

Interventions	Relative effect (95% CrI)	Anticipated absolute effect* (95% CrI)			Certainty of evidence
		Beta-blockers	Various interventions	Difference	

Mortality **Total studies: 58** **Total participants: 5936** Follow-up: 8–60 months					
Beta-blockers	**Reference**				—
No active intervention (10 RCTs, 1200 participants)	**HR 2.04** (1.50 to 2.78) **Network estimate**	**212 per 1000**	**433 per 1000** (319 to 589)	**221 more per 1000** (107 more to 377 more)	⊕⊕⊖⊖ **Low certainty** a,b
Variceal band ligation (17 RCTs, 1640 participants)	**HR 1.05** (0.80 to 1.38) **Network estimate**	**212 per 1000**	**222 per 1000** (169 to 293)	**11 more per 1000** (43 fewer to 81 more)	⊕⊖⊖⊖ **Very low certainty** a,b,c
Sclerotherapy (5 RCTs, 320 participants)	**HR 1.35** (0.95 to 1.92) **Network estimate**	**212 per 1000**	**286 per 1000** (202 to 406)	**75 more per 1000** (10 fewer to 195 more)	⊕⊖⊖⊖ **Very low certainty** a,b,c
Beta-blockers + variceal band ligation (2 RCTs, 313 participants)	**HR 1.11** (0.56 to 2.19) **Network estimate**	**212 per 1000**	**235 per 1000** (119 to 464)	**23 more per 1000** (93 fewer to 252 more)	⊕⊖⊖⊖ **Very low certainty** a,b,c
Beta-blockers + nitrates (2 RCTs, 203 participants)	**HR 0.84** (0.44 to 1.64) **Network estimate**	**212 per 1000**	**178 per 1000** (92 to 347)	**34 fewer per 1000** (119 fewer to 135 more)	⊕⊖⊖⊖ **Very low certainty** a,b,c
Nitrates (3 RCTs, 298 participants)	**HR 1.19** (0.66 to 2.11) **Network estimate**	**212 per 1000**	**251 per 1000** (139 to 447)	**39 more per 1000** (72 fewer to 235 more)	⊕⊖⊖⊖ **Very low certainty** a,b,c
Beta-blockers + sclerotherapy (2 RCTs, 167 participants)	**HR 2.08** (1.03 to 4.08) **Network estimate**	**212 per 1000**	**440 per 1000** (218 to 864)	**228 more per 1000** (6 more to 652 more)	⊕⊕⊖⊖ **Low certainty** a,b
Portocaval shunt (No direct RCT)	**HR 0.51** (0.06 to 2.92) **Network estimate**	**212 per 1000**	**108 per 1000** (12 to 620)	**103 fewer per 1000** (200 fewer to 408 more)	⊕⊖⊖⊖ **Very low certainty** a,b,c

Health-related quality of life					
No trials reported health-related quality of life.					—
Serious adverse events (number of participants) **Total studies: 6** **Total participants: 457** **Follow-up: 11–55 months**					
Beta-blockers	**Reference**				—
Variceal band ligation (5 RCTs, 372 participants)	**OR 0.75** (0.02 to 23.24) **Network estimate**	**56 per 1000**	**42 per 1000** (1 to 578)	**13 fewer per 1000** (54 fewer to 522 more)	⊕⊖⊖⊖ **Very low certainty** a,c,d
Sclerotherapy (1 RCT, 85 participants)	**OR 0.55** (0.00 to 272.05) **Network estimate**	**56 per 1000**	**32 per 1000** (0 to 941)	**24 fewer per 1000** (55 fewer to 886 more)	⊕⊖⊖⊖ **Very low certainty** a,c,d
Serious adverse events (number of events) **Total studies: 1** **Total participants: 168** **Follow-up: 13 months**					
Beta-blockers	**Reference**				—
Variceal band ligation (1 RCT, 168 participants)	**RaR 10.49** (2.83 to 60.64) **Network estimate**	**24 per 1000**	**252 per 1000** (68 to 1455)	**228 more per 1000** (44 more to 1431 more)	⊕⊕⊖⊖ **Low certainty** a,d
Any adverse events (number of participants) **Total studies: 12** **Total participants: 1165** **Follow-up: 11–55 months**					
Beta-blockers	**Reference**				—
No active intervention (2 RCTs, 256 participants)	**OR 0.28** (0.02 to 2.91) **Network estimate**	**190 per 1000**	**62 per 1000** (6 to 407)	**128 fewer per 1000** (185 fewer to 216 more)	⊕⊖⊖⊖ **Very low certainty** a,c,e
Variceal band ligation	**OR 1.60**	**190 per 1000**	**273 per 1000**	**83 more per 1000**	⊕⊖⊖⊖

(7 RCTs, 728 participants)	(0.54 to 5.15) **Network estimate**		(113 to 548)	(78 fewer to 357 more)	**Very low certainty** a,c,e
Sclerotherapy (No direct RCT)	**OR 1.19** (0.02 to 80.24) **Network estimate**	**190 per 1000**	**219 per 1000** (5 to 950)	**28 more per 1000** (186 fewer to 759 more)	⊕⊖⊖⊖ **Very low certainty** a,c,e
Beta-blockers + nitrates (1 RCT, 57 participants)	**OR 3.41** (1.11 to 11.28) **Direct estimate**	**190 per 1000**	**445 per 1000** (207 to 726)	**255 more per 1000** (17 more to 536 more)	⊕⊕⊖⊖ **Low certainty** a,d
Any adverse events (number of events) **Total studies: 11** **Total participants: 1340** **Follow-up: 12–52 months**					
Beta-blockers	**Reference**				—
No active intervention (No direct RCT)	**RaR 0.97** (0.59 to 1.68) **Network estimate**	**610 per 1000**	**594 per 1000** (357 to 1024)	**16 fewer per 1000** (253 fewer to 415 more)	⊕⊖⊖⊖ **Very low certainty** a,c,e
Variceal band ligation (4 RCTs, 480 participants)	**RaR 0.77** (0.63 to 0.94) **Network estimate**	**610 per 1000**	**469 per 1000** (384 to 572)	**141 fewer per 1000** (226 fewer to 38 fewer)	⊕⊕⊖⊖ **Low certainty** a,e
Sclerotherapy (2 RCTs, 90 participants)	**RaR 2.49** (1.53 to 4.22) **Network estimate**	**610 per 1000**	**1518 per 1000** (934 to 2576)	**909 more per 1000** (325 more to 1966 more)	⊕⊕⊖⊖ **Low certainty** a,e
Beta-blockers + variceal band ligation (1 RCT, 140 participants)	**RaR 1.33** (0.93 to 1.92) **Network estimate**	**610 per 1000**	**812 per 1000** (567 to 1173)	**202 more per 1000** (43 fewer to 563 more)	⊕⊖⊖⊖ **Very low certainty** a,c,e
Liver transplantation **Total studies: 7** **Total participants: 681** **Follow-up: 11–52 months**					
Beta-blockers	**Reference**				—
No active intervention (1 RCT, 161 participants)	**HR 1.36** (0.35 to 5.80)	**48 per 1000**	**66 per 1000** (17 to 280)	**18 more per 1000** (31 fewer to 231 more)	⊕⊖⊖⊖

	Network estimate				**Very low certainty** a,c,d
Variceal band ligation (5 RCTs, 380 participants)	**HR 1.41** (0.83 to 2.43) **Network estimate**	**48 per 1000**	**68 per 1000** (40 to 117)	**20 more per 1000** (8 fewer to 69 more)	⊕⊖⊖⊖ **Very low certainty** a,c,d
Beta-blockers + variceal band ligation (1 RCT, 140 participants)	**HR 2.40** (0.19 to 77.48) **Network estimate**	**48 per 1000**	**116 per 1000** (9 to 1000)	**67 more per 1000** (39 fewer to 952 more)	⊕⊕⊖⊖ **Low certainty** a,c
Symptomatic variceal bleeding **Total studies: 7** **Total participants: 1007** **Follow-up: 15–44 months**					
Beta-blockers	**Reference**				—
No active intervention (1 RCT, 140 participants)	**HR 1.14** (0.56 to 2.40) **Network estimate**	**180 per 1000**	**204 per 1000** (101 to 431)	**24 more per 1000** (79 fewer to 251 more)	⊕⊖⊖⊖ **Very low certainty** a,c,d
Variceal band ligation (3 RCTs, 330 participants)	**HR 0.80** (0.47 to 1.36) **Network estimate**	**180 per 1000**	**144 per 1000** (84 to 244)	**36 fewer per 1000** (96 fewer to 64 more)	⊕⊖⊖⊖ **Very low certainty** a,c,d
Sclerotherapy (1 RCT, 141 participants)	**HR 0.91** (0.44 to 1.95) **Network estimate**	**180 per 1000**	**164 per 1000** (80 to 351)	**16 fewer per 1000** (100 fewer to 171 more)	⊕### **Very low certainty** a,c,d
Beta-blockers + variceal band ligation (1 RCT, 140 participants)	**HR 1.13** (0.45 to 2.87) **Network estimate**	**180 per 1000**	**203 per 1000** (81 to 517)	**23 more per 1000** (99 fewer to 337 more)	⊕⊖⊖⊖ **Very low certainty** a,c,d
Nitrates (1 RCT, 118 participants)	**HR 1.27** (0.61 to 2.66) **Network estimate**	**180 per 1000**	**228 per 1000** (110 to 478)	**48 more per 1000** (70 fewer to 298 more)	⊕⊖⊖⊖ **Very low certainty** a,c,d
Beta-blockers + sclerotherapy (1 RCT, 141 participants)	**HR 0.92** (0.41 to 2.08)	**180 per 1000**	**166 per 1000** (73 to 375)	**14 fewer per 1000** (107 fewer to 195 more)	⊕⊖⊖⊖

	Network estimate				**Very low certainty** a,c,d
Any variceal bleeding **Total studies: 27** **Total participants: 2460** **Follow-up: 6–55 months**					
Beta-blockers	**Reference**				—
No active intervention (2 RCTs, 208 participants)	**HR 2.71** (0.97 to 7.68) **Network estimate**	**97 per 1000**	**262 per 1000** (94 to 744)	**165 more per 1000** (3 fewer to 647 more)	⊕⊖⊖⊖ **Very low certainty** a,b,c
Variceal band ligation (9 RCTs, 879 participants)	**HR 0.72** (0.33 to 1.51) **Network estimate**	**97 per 1000**	**70 per 1000** (32 to 146)	**27 fewer per 1000** (65 fewer to 49 more)	⊕⊖⊖⊖ **Very low certainty** a,b,c
Sclerotherapy (3 RCTs, 175 participants)	**HR 1.02** (0.33 to 3.27) **Network estimate**	**97 per 1000**	**98 per 1000** (31 to 316)	**1 more per 1000** (65 fewer to 219 more)	⊕⊖⊖⊖ **Very low certainty** a,b,c
Beta-blockers + variceal band ligation (1 RCT, 173 participants)	**HR 0.21** (0.04 to 0.71) **Direct estimate**	**97 per 1000**	**21 per 1000** (4 to 69)	**76 fewer per 1000** (93 fewer to 28 fewer)	⊕⊕⊖⊖ **Low certainty** a,d
Beta-blockers + nitrates (1 RCT, 57 participants)	**HR 0.93** (0.16 to 5.32) **Network estimate**	**97 per 1000**	**90 per 1000** (16 to 515)	**7 fewer per 1000** (81 fewer to 418 more)	⊕⊖⊖⊖ **Very low certainty** a,b,c
Nitrates (1 RCT, 52 participants)	**HR 6.40** (1.58 to 47.42) **Direct estimate**	**97 per 1000**	**620 per 1000** (153 to 1000)	**523 more per 1000** (56 more to 903 more)	⊕⊕⊖⊖ **Low certainty** a,d
Other features of decompensation **Total studies: 4** **Total participants: 333** **Follow-up: 18–55 months**					
Beta-blockers	**Reference**				—
Variceal band ligation	**RaR 1.11**	**162 per 1000**	**180 per 1000**	**18 more per 1000**	⊕⊖⊖⊖

(2 RCTs, 130 participants)	(0.44 to 2.86) **Network estimate**		(72 to 464)	(90 fewer to 302 more)	**Very low certainty** a,c,d
Beta-blockers + nitrates (2 RCTs, 203 participants)	**RaR 1.16** (0.64 to 2.13) **Network estimate**	**162 per 1000**	**188 per 1000** (103 to 345)	**26 more per 1000** (59 fewer to 183 more)	⊕⊖⊖⊖ **Very low certainty** a,c,d

*Ranking was not provided because of the considerable uncertainty in the ranking.

CrI: credible interval; **HR:** hazard ratio; **OR:** odds ratio; **RaR:** rate ratio; **RCT:** randomised clinical trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

General comment: The GRADE classification was based on the main results.
[a]Downgraded one level for risk of bias because the trial(s) included in the analysis was/were at high risk of bias.
[b]Downgraded one level for inconsistency because there was evidence of statistical heterogeneity.
[c]Downgraded one level for imprecision because the credible intervals were wide (included clinical benefit and harms).
[d]Downgraded one level for imprecision because the sample size was small.
[e]Downgraded one level for indirectness because there was evidence of statistical inconsistency.

BACKGROUND

Description of the condition

Liver cirrhosis

The liver is a complex organ with multiple functions including carbohydrate, fat, protein, and drug metabolism; and synthetic, storage, digestive, excretory, and immunological functions (Read 1972). Liver cirrhosis is a disease in which the normal microcirculation, the gross vascular anatomy, and the hepatic architecture have been variably destroyed and altered with fibrous septa surrounding regenerated or regenerating parenchymal nodules (Tsochatzis 2014; NCBI 2018a). The major causes of liver cirrhosis include excessive alcohol consumption, viral hepatitis, non-alcohol-related fatty liver disease, autoimmune liver disease, and metabolic liver disease (Williams 2014; Ratib 2015; Setiawan 2016). The global prevalence of liver cirrhosis is difficult to estimate as most estimates correspond to chronic liver disease (which includes liver fibrosis and liver cirrhosis). In studies from the US, the prevalence of chronic liver disease varies between 0.3% and 2.1% (Scaglione 2015; Setiawan 2016); in the UK, the prevalence was 0.1% in one study (Fleming 2008). In 2010, liver cirrhosis was responsible for an estimated 2% of all global deaths, equivalent to one million deaths (Mokdad 2014). There is an increasing trend of cirrhosis-related deaths in some countries such as the UK, while there is a decreasing trend in other countries such as France (Mokdad 2014; Williams 2014). The major cause of complications and deaths in people with liver cirrhosis is the development of clinically significant portal hypertension (hepatic venous pressure gradient at least 10 mmHg) (de Franchis 2015). Some of the clinical features of decompensation include jaundice, coagulopathy, ascites, variceal bleeding, hepatic encephalopathy, and renal failure (de Franchis 2015; McPherson 2016; EASL 2018). Decompensated cirrhosis is the most common indication for liver transplantation (Merion 2010; Adam 2012).

Oesophageal varices

Oesophageal varices are dilated veins in the oesophagus, usually due to portal hypertension (NCBI 2018b), and are a feature of clinically significant portal hypertension. The prevalence of oesophageal varices varies between 40% and 95% in people with cirrhosis (Chawla 2012; McCarty 2017). The annual incidence of oesophageal varices in people with cirrhosis varies from 3% to 22% (Cales 1990a; Merli 2003; D'Amico 2014).

There are many classification systems available for assessing the risk of bleeding from oesophageal varices. The classification system that is followed from a management perspective is the Baveno I consensus definition, which classifies oesophageal varices as small and large (de Franchis 1992). The criteria for distinction between small and large oesophageal varices is variable (de Franchis 1992). The current UK guidelines and European Association for the Study of the Liver (EASL) guidelines on the management of variceal bleeding acknowledges this variability and suggests that small varices tend to be narrow, and they flatten easily with air during endoscopy as compared to medium/large varices, which are usually broader and flatten with difficulty, or do not flatten at all (Tripathi 2015; EASL 2018). Other definitions for small oesophageal varices include less than 5 mm in size and less than 25% of oesophageal lumen (Abby Philips 2016). Other risk factors for bleeding from oesophageal varices include the pressure within the varices (hepatic venous pressure gradient at least 12 mmHg), increased tension on the variceal wall as indicated by red spots or red wale markings (longitudinal red streaks on the varices) on endoscopy, and severity of the liver disease (Beppu 1981; NIEC 1988; de Franchis 2015; Tripathi 2015). Approximately 15% to 20% of people with oesophageal varices bleed in about one to three years (Gluud 2012; Qi 2015). The short-term mortality of an episode of acute variceal bleeding is about 15% to 30% (Ioannou 2003; Gøtzsche 2008; D'Amico 2010; Rios 2015). Five-year mortality in people with variceal bleeding is more than 80% (Liu 2016). In France, the mean in-hospital costs of treating an acute episode of bleeding was EUR 13,500 in 2007 (Thabut 2007); in the US, the mean six-month costs of treating people with variceal bleeding was USD 16,500 in 2000 (Zaman 2000).

Pathophysiology of oesophageal varices

In addition to causing arterial vasodilation of the splanchnic circulation (dilation of the blood vessels supplying the digestive organs in the abdomen such as the liver, pancreas, and intestines) (Gines 2009; Moore 2013), portal hypertension causes dilation of the collaterals between the portal venous system and systemic venous system (Sass 2009). One of the major locations of these collaterals is the lower end of the oesophagus and proximal part of the stomach. Therefore, portal hypertension leads to oesophageal varices (Sass 2009). According to Frank's modification of the 'Laplace law', the tension on the walls of blood vessels is dependent upon the diameter of the blood vessel and the pressure gradient across the walls (i.e. the difference in pressure inside the varices and the oesophageal lumen pressure) (Herman 2015). Since both the diameter of the vessels and the pressure at which the blood flows in the varices are increased due to portal hypertension, the tension on the wall increases leading to dilation of the blood vessels at the lower end of the oesophagus and proximal part of the stomach, which in turn increases the tension further (Herman 2015). This complex chain of events that reinforces itself through a feedback loop can eventually culminate in rupture of the varices (Sass 2009; Herman 2015).

Description of the intervention

Primary prevention of bleeding refers to treatment of oesophageal varices prior to their rupture and bleeding. The various treatments include non-cardioselective beta-blockers (referred to as 'beta-blockers' in the rest of this review; e.g. propranolol, carvedilol), endoscopic variceal band ligation, sclerotherapy, nitrates, transjugular intrahepatic portosystemic shunt (TIPS), and surgical portosystemic shunts (Gluud 2012; de Franchis 2015; Tripathi 2015; Garcia-Tsao 2017; EASL 2018). Of these, the UK guidelines, the EASL guidelines, the American Association for the Study of Liver Diseases (AASLD) guidelines, and the Baveno consensus VI conference position paper indicate that non-cardioselective beta-blockers or endoscopic band ligation should be considered for people with large oesophageal varices and small oesophageal varices at high risk of bleeding (e.g. those with red spots or red wale markings) (de Franchis 2015; Tripathi 2015; Garcia-Tsao 2017; EASL 2018). In addition, AASLD guidelines, EASL guidelines, and the Baveno consensus VI conference position paper suggest the use of non-cardioselective beta-blockers in people with decompensated cirrhosis and small oesophageal varices (de Franchis 2015; Garcia-Tsao 2017; EASL 2018). In addition, AASLD guidelines state that treatments such as sclerotherapy, nitrates, TIPS, and surgical portosystemic shunts have no role in the primary

prevention of bleeding in people with oesophageal varies (Garcia-Tsao 2017).

How the intervention might work

Non-cardioselective beta-blockers work by causing splanchnic vasoconstriction and decreasing cardiac output, leading to decreased portal pressure and decreased flow in the collaterals, which in turn decreases the pressure inside the oesophageal varices (Tripathi 2015). TIPS and surgical portosystemic shunts are aimed at diverting blood flow from the portal system to the systemic circulation, thereby decreasing portal pressure and reducing the oesophageal varices. Endoscopic variceal band ligation and sclerotherapy are local treatments aimed at obliteration of the oesophageal varices by reducing blood flow in them. Nitrates attempt to decrease the variceal pressure by vasodilation and decreased portal pressure (Tripathi 2015).

Why it is important to do this review

Considering the high mortality associated with variceal bleeding, it is important to provide optimal evidence-based treatment to prevent bleeding in people with oesophageal varices and to improve their survival. Several different treatments are available; however, their relative efficacy and optimal combinations are unknown. There has been one Cochrane Review on variceal band ligation versus beta-blockers for primary prevention of bleeding from oesophageal varices (Gluud 2012); another Cochrane Review attempted to evaluate the role of antacids in preventing bleeding from oesophagogastric varices (Guo 2008), but the main proposed mechanism was decreased gastric erosions, which may be relevant for sclerotherapy performed for oesophageal varices, but not for oesophageal varices per se. There had been no previous network meta-analyses on the different treatments in people with oesophageal varices secondary to decompensated cirrhosis with no history of bleeding. Network meta-analysis (NMA) allows for a combination of direct and indirect evidence and the ranking of different interventions for different outcomes (Salanti 2011; Salanti 2012). With this systematic review and NMA, we aimed to provide the best level of evidence for the benefits and harms of different treatments for the prevention of bleeding in people with oesophageal varices due to liver cirrhosis. We also presented results from direct comparisons whenever possible, as well as performing the NMA.

OBJECTIVES

To compare the benefits and harms of different treatments for prevention of first variceal bleeding from oesophageal varices in adults with liver cirrhosis through a network meta-analysis and to generate rankings of the different treatments for prevention of first variceal bleeding from oesophageal varices according to their safety and efficacy.

METHODS

Criteria for considering studies for this review

Types of studies

We considered only randomised clinical trials (including cross-over and cluster-randomised clinical trials) for this NMA irrespective of language, publication status, or date of publication. We excluded studies of other designs because of the risk of bias in such studies. Inclusion of indirect observational evidence could weaken our NMA, but this could also be viewed as a strength for assessing rare adverse events. It is well-established that exclusion of non-randomised studies increases the focus on potential benefits and reduces the focus on the risks of serious adverse events and those of any adverse events. However, we did not include these studies because of the findings of this review (i.e. the treatment decision should be driven by effects on mortality rather than treatment-related adverse events).

We also excluded trials that randomised participants without informed consent as we considered them unethical and trials in which the effect of randomisation was lost because of trial-related procedures effectively making such studies similar to observational studies.

Types of participants

We included randomised clinical trials in adults with oesophageal varices due to liver cirrhosis undergoing treatment for the prevention of first variceal bleeding. We included trials in which people with oesophageal varices also had gastric varices secondary to portal hypertension, but we did not include trials in which the treatment was targeted at the gastric varices rather than oesophageal varices. We excluded randomised clinical trials in which participants had current or a history of variceal bleeding. We also excluded trials in which the participants had previously undergone liver transplantation or previously received primary prophylaxis for oesophageal varices.

Types of interventions

We included any of the following treatments for comparison with one another, either alone or in combination:

- beta-blockers such as propranolol, carvedilol, and nadolol (we used the term 'beta-blockers' to refer to non-cardioselective beta-blockers);
- endoscopic variceal band ligation;
- endoscopic variceal sclerotherapy;
- nitrates;
- TIPS procedure;
- other forms of portosystemic shunts;
- no active intervention (no intervention or placebo).

We considered 'beta-blockers' as the reference group. Each of the above categories was considered as a 'treatment node.' We considered variations in endoscopic interventions or drugs within the same class, doses of drugs, frequency, and duration of interventions as the same treatment node. We treated each different combination of the categories as different treatment nodes. All the above interventions were considered 'decision set' (i.e. all the above interventions were of direct interest).

While we identified some additional interventions that are not listed above, we did not include such interventions as they are not currently used for primary preventive treatment of bleeding oesophageal varices.

We evaluated the plausibility of the NMA transitivity assumption by looking at the inclusion and exclusion criteria in the trials. The transitivity assumption means that participants included in the different trials with different treatments (in this case, for primary

prevention of oesophageal variceal bleeding) can be considered a part of a multi-arm randomised clinical trial and could potentially have been randomised to any of the interventions (Salanti 2012). In other words, any participant that meets the inclusion criteria is, in principle, equally likely to be randomised to any of the above eligible interventions or that potential effect-modifiers are not systematically different across comparisons. This necessitates that information on potential effect-modifiers, such as the size of the varices and risk of bleeding, and presence or absence of other features of decompensation, such as ascites, are similar across comparisons. As indicated in the Results section, there was no concern about the transitivity assumption related to the different types of varices (small or large) and those with and without other features of decompensation.

Types of outcome measures

Primary outcomes

- All-cause mortality at maximal follow-up (time-to-death).
- Health-related quality of life using a validated scale such as the EQ-5D or 36-Item Short Form Health Survey (SF-36) (EuroQol 2018; Optum 2018), at maximal follow-up.
- Serious adverse events (during or within six months after cessation of intervention). We defined a serious adverse event as any event that increased mortality; was life-threatening; required hospitalisation; resulted in persistent or significant disability; was a congenital anomaly/birth defect; or any important medical event that might have jeopardised the person or require intervention to prevent it (ICH-GCP 1997). However, none of the trial authors defined serious adverse events. Therefore, we used the list provided by trial authors for serious adverse events (as indicated in the protocol; Gurusamy 2018).
  * Proportion of people with one or more serious adverse events.
  * Number of serious adverse events per participant.

Secondary outcomes

- Any adverse events. We defined an adverse event as any untoward medical occurrence not necessarily having a causal relationship with the intervention but resulting in a dose reduction or discontinuation of intervention (any time after commencement of intervention) (ICH-GCP 1997). However, none of the trial authors defined 'adverse event'. Therefore, we used the list provided by trial authors for adverse events (as indicated in the protocol; Gurusamy 2018).
  * Proportion of people with one or more adverse events.
  * Number of any adverse events per participant.
- Liver transplantation (time to liver transplantation at maximal follow-up).
- Variceal bleeding (time to oesophageal variceal bleeding however defined by authors at maximal follow-up).
  * Symptomatic variceal bleeding (e.g. shortness of breath, shock).
  * Any variceal bleeding.
- Other features of decompensation (number of decompensation events per participant at maximal follow-up).

Exploratory outcomes

- Length of hospital stay (all hospital admissions until maximal follow-up).
- Number of days of lost work (in people who work) (maximal follow-up).
- Treatment costs (including the cost of the treatment and any resulting complications).

We chose the outcomes based on their importance to patients in a survey related to research priorities for people with liver diseases (Gurusamy 2019), based on feedback of the patient and public representative of this project, and based on an online survey about the outcomes promoted through Cochrane Consumer Network. Of these, the primary outcomes were considered critical outcomes, the secondary outcomes were considered important outcomes, and the exploratory outcomes were considered unimportant outcomes. We have presented the primary and secondary outcomes in the 'Summary of findings' tables.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 12) in the Cochrane Library, MEDLINE Ovid, Embase Ovid, and Science Citation Index Expanded (Web of Science) from inception to date of search for randomised clinical trials comparing two or more of the above interventions (see Types of interventions) without applying any language restrictions (Royle 2003). We searched for all possible comparisons formed by the interventions of interest. To identify further ongoing or completed trials, we also searched ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/), which searches various trial registers, including ISRCTN and ClinicalTrials.gov. We also searched the European Medical Agency (EMA) (www.ema.europa.eu/ema/) and USA Food and Drug Administration (FDA) (www.fda.gov) registries for randomised clinical trials. Appendix 1 provides the search strategies along with the time spans of the searches.

Searching other resources

We searched the references of the identified trials and the existing Cochrane Review on primary prevention of variceal bleeding in people with oesophageal varices due to liver cirrhosis (Gluud 2012) to identify additional trials for inclusion.

Data collection and analysis

Selection of studies

Two review authors (KG and Danielle R or MC) independently identified trials for inclusion by screening the titles and abstracts of articles identified by the literature search, and sought full-text articles of any records identified by at least one review author for potential inclusion. We selected trials for inclusion based on the full-text articles. We identified and excluded duplicates and collated multiple reports of the same study, so that each study, rather than each report, was the unit of interest in the review. We listed the records that we excluded and the reasons for their exclusion in the Characteristics of excluded studies table. We listed any ongoing trials identified primarily through the search of the clinical trial registers for further follow-up in the Characteristics of ongoing studies table. We resolved any discrepancies through

discussion. We illustrated the study selection process in a PRISMA diagram (Figure 1).

Figure 1. Study flow diagram. Date of search 17 December 2019. RCT: randomised clinical trial.

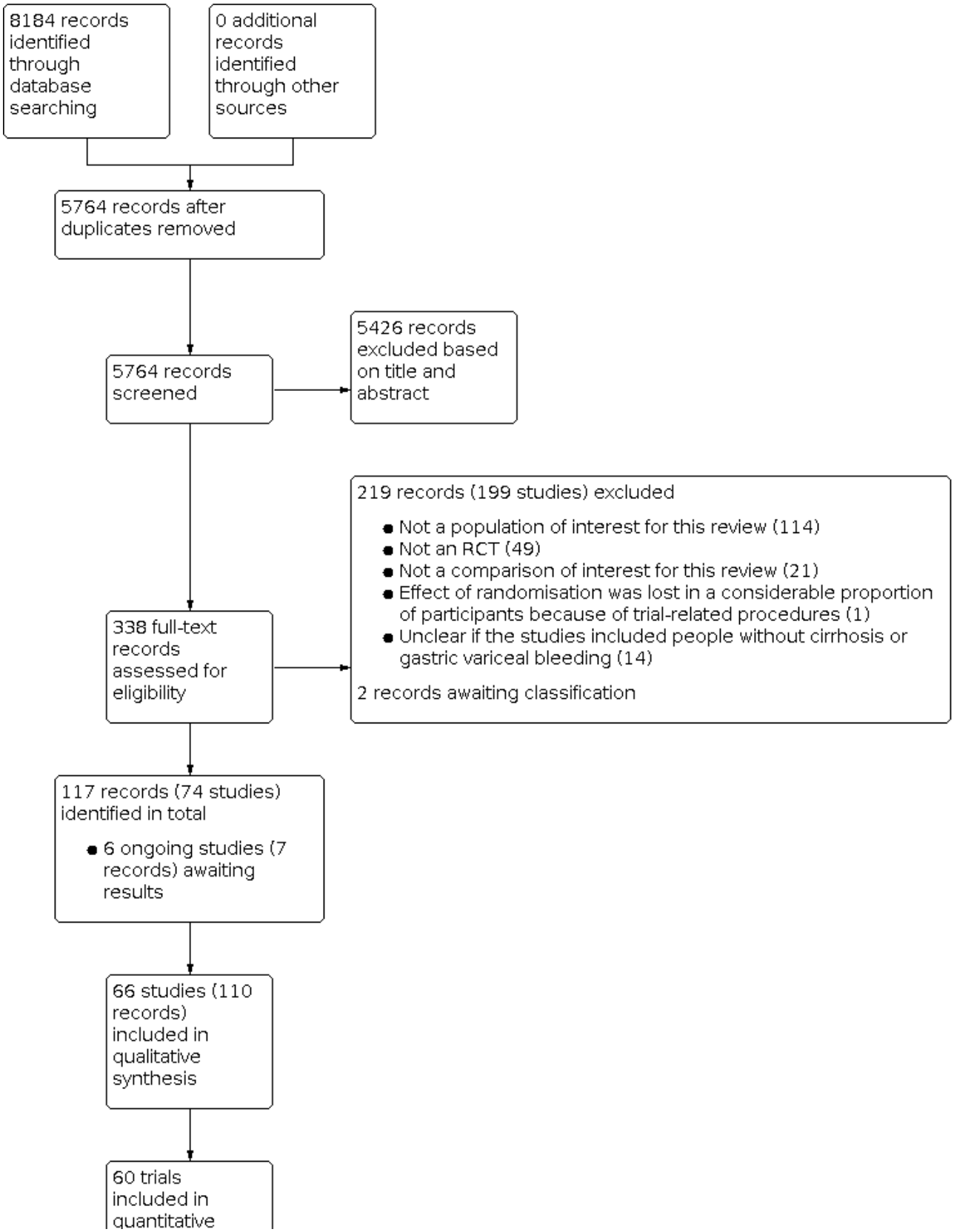
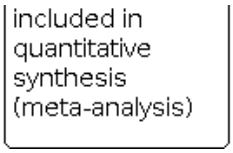


Figure 1. (Continued)



Data extraction and management

Two review authors (KG, MPT, LP, AB, Davide R, NW, LB, SA, TB, MC) independently extracted the data below in a prepiloted Microsoft Excel-based data extraction form (after translation of non-English articles).

- Outcome data (for each outcome and for each intervention group whenever applicable):
  - number of participants randomised;
  - number of participants included for the analysis;
  - number of participants with events for binary outcomes, mean and standard deviation for continuous outcomes, number of events and the mean follow-up period for count outcomes, and number of participants with events and the mean follow-up period for time-to-event outcomes;
  - natural logarithm of hazard ratio (HR) and its standard error if this was reported rather than the number of participants with events and the mean follow-up period for time-to-event outcomes;
  - definition of outcomes or scale used if appropriate.
- Data on potential effect modifiers:
  - participant characteristics such as age, sex, size of varices, presence of high-risk factors such as those with red spots or red wale markings, presence of other features of decompensation such as ascites, the aetiology for cirrhosis, and the interval between diagnosis of varices and prophylactic treatment;
  - details of the intervention and control (including dose, frequency, and duration);
  - length of follow-up;
  - information related to risk of bias assessment (see below).
- Other data:
  - year and language of publication;
  - country in which the participants were recruited;
  - year(s) in which the trial was conducted;
  - inclusion and exclusion criteria.

We collected data at maximum follow-up but also at short term (up to three months), and medium term (from three months to five years), if these were available.

We attempted to contact the trial authors to request unclear or missing information. If there was any doubt as to whether trials shared the same participants, completely or partially (by identifying common authors and centres), we planned to contact the trial authors to clarify whether the trial report was duplicated. We resolved any differences in opinion through discussion.

Assessment of risk of bias in included studies

We followed the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess the risk of bias in included trials (Higgins 2011). Specifically, we assessed sources of bias as defined below (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Savović 2012a; Savović 2012b; Savović 2018).

Allocation sequence generation

- Low risk of bias: sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were adequate if performed by an independent person not otherwise involved in the trial.
- Unclear risk of bias: the method of sequence generation was not specified.
- High risk of bias: the sequence generation method was not random or only quasi-randomised. We excluded such quasi-randomised studies.

Allocation concealment

- Low risk of bias: the allocation sequence was described as unknown to the investigators. Hence, the participants' allocations could not have been foreseen in advance of, or during, enrolment. Allocation was controlled by a central and independent randomisation unit, an onsite locked computer, identical-looking numbered sealed opaque envelopes, drug bottles or containers prepared by an independent pharmacist, or an independent investigator.
- Unclear risk of bias: it was unclear if the allocation was hidden or if the block size was relatively small and fixed so that intervention allocations may have been foreseen in advance of, or during, enrolment.
- High risk of bias: the allocation sequence was likely to be known to the investigators who assigned the participants. We excluded such quasi-randomised studies.

Blinding of participants and personnel

- Low risk of bias: blinding of participants and key study personnel ensured, and it was unlikely that the blinding could have been broken; or rarely no blinding or incomplete blinding, but the review authors judged that the outcome was not likely to be influenced by lack of blinding.
- Unclear risk of bias: any of the following: insufficient information to permit judgement of 'low risk' or 'high risk'; or the trial did not address this outcome.
- High risk of bias: any of the following: no blinding or incomplete blinding, and the outcome was likely to be influenced by lack of blinding; or blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome was likely to be influenced by lack of blinding.

Blinded outcome assessment

- Low risk of bias: blinding of outcome assessment ensured, and unlikely that the blinding could have been broken; or rarely no

blinding of outcome assessment, but the review authors judged that the outcome measurement was not likely to be influenced by lack of blinding.

- Unclear risk of bias: any of the following: insufficient information to permit judgement of 'low risk' or 'high risk'; or the trial did not address this outcome.
- High risk of bias: any of the following: no blinding of outcome assessment, and the outcome measurement was likely to be influenced by lack of blinding; or blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.

Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. The study used sufficient methods, such as multiple imputation, to handle missing data.
- Unclear risk of bias: there was insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias on the results.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk of bias: the trial reported the following predefined outcomes: all-cause mortality, adverse events, and variceal bleeding. If the original trial protocol was available, the outcomes should have been those called for in that protocol. If we obtained the trial protocol from a trial registry (e.g. ClinicalTrials.gov), the outcomes sought should have been those enumerated in the original protocol if the trial protocol was registered before or at the time that the trial was begun. If the trial protocol was registered after the trial was begun, we did not consider those outcomes to be reliable.
- Unclear risk of bias: not all predefined, or clinically relevant and reasonably expected, outcomes were reported fully, or it was unclear whether data on these outcomes were recorded or not.
- High risk of bias: one or more predefined or clinically relevant and reasonably expected outcomes were not reported, even though data on these outcomes should have been available and even recorded.

Other bias

- Low risk of bias: the trial appeared free of other components that could have put it at risk of bias (e.g. inappropriate control or dose or administration of control, baseline differences, early stopping).
- Unclear risk of bias: the trial may or may not have been free of other components that could have put it at risk of bias.
- High risk of bias: there were other factors in the trial that could have put it at risk of bias (e.g. baseline differences, early stopping).

We considered a trial at low risk of bias if it was at low risk across all listed bias domains. Otherwise, we considered trials at high risk of bias. At the outcome level, we classified an outcome at low risk of bias if the allocation sequence generation; allocation concealment; blinding of participants, healthcare professionals, and outcome assessors; incomplete outcome data; and selective outcome reporting (at the outcome level) were at low risk of bias for objective and subjective outcomes (Savović 2018).

Measures of treatment effect

Relative treatment effects

For dichotomous variables (e.g. proportion of participants with serious adverse events or any adverse events), we calculated the odds ratio (OR) with 95% credible interval (CrI) (or Bayesian confidence interval) (Severini 1993). For continuous variables (e.g. health-related quality of life reported on the same scale), we calculated the mean difference (MD) with 95% CrI. We planned to use standardised mean difference (SMD) values with 95% CrI for health-related quality of life if included trials used different scales. If we calculated the SMD, we planned to convert it to a common scale, for example, EQ-5D or SF-36 (using the standard deviation of the common scale) for the purpose of interpretation. For count outcomes (e.g. number of serious adverse events or number of any adverse events), we calculated the rate ratio (RaR) with 95% CrI. This assumes that the events were independent of each other (i.e. if a person had an event, they were not at an increased risk of further outcomes, which is the assumption in Poisson likelihood). For time-to-event data (e.g. all-cause mortality at maximal follow-up), we calculated HRs with 95% CrI.

Relative ranking

We estimated the ranking probabilities for all interventions of being at each possible rank for each intervention for each outcome when NMA was performed. We obtained the surface under the cumulative ranking curve (SUCRA) (cumulative probability), rankogram, and relative ranking table with 95% CrI for the ranking probabilities for each outcome when NMA was performed (Salanti 2011; Chaimani 2013).

Unit of analysis issues

The unit of analysis was the participant with oesophageal varices according to the intervention group to which the participant was randomly assigned.

Cluster-randomised clinical trials

If we identified any cluster-randomised clinical trials, we planned to include them if the effect estimate adjusted for cluster correlation was available or if there was sufficient information to calculate the design effect (which would allow us to take clustering into account). We also planned to assess additional domains of risk of bias for cluster-randomised trials according to guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Cross-over randomised clinical trials

If we had identified any cross-over randomised clinical trials, we planned to include only the outcomes of the period before crossover because the included treatments could have residual effects.

Trials with multiple intervention groups

We collected data for all trial intervention groups that met the inclusion criteria, and listed them in the 'Characteristics of included studies' table. The codes that we used for analysis accounted for the correlation between the effect sizes from studies with more than two groups.

Dealing with missing data

We performed an intention-to-treat analysis, whenever possible (Newell 1992); otherwise, we used the available data. When intention-to-treat analysis is not used and the data are not missing at random (e.g. treatment was withdrawn due to adverse events or duration of treatment was shortened because of lack of response and such participants were excluded from analysis), this could lead to biased results; therefore, we conducted best–worst case scenario analysis (assuming a good outcome in the intervention group and bad outcome in the control group) and worst–best case scenario analysis (assuming a bad outcome in the intervention group and good outcome in the control group) as sensitivity analyses, whenever possible, for binary and time-to-event outcomes, where binomial likelihood was used.

For continuous outcomes, we imputed the standard deviation from P values, according to guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If the data were likely to be normally distributed, we used the median for meta-analysis when the mean was not available; otherwise, we planned to simply provide a median and interquartile range of the difference in medians. If it was not possible to calculate the standard deviation from the P value or the confidence intervals, we planned to impute the standard deviation using the largest standard deviation in other trials for that outcome. This form of imputation can decrease the weight of the study for calculation of MDs and may bias the effect estimate to no effect for calculation of SMDs (Higgins 2011).

Assessment of heterogeneity

We assessed clinical and methodological heterogeneity by carefully examining the characteristics and design of included trials. We also planned to assess the presence of clinical heterogeneity by comparing effect estimates (see Subgroup analysis and investigation of heterogeneity) in trial reports of different drug dosages, different regimens of endoscopic treatment, based on the size of varices (small versus large varices), based on the presence of features suggestive of high risk of bleeding (e.g. red spots or red wale markings), different aetiologies for cirrhosis (e.g. alcohol-related liver disease, viral liver diseases, autoimmune liver disease), and based on the co-interventions (e.g. both groups received prophylactic antibiotics). Different study designs and risk of bias can contribute to methodological heterogeneity.

We assessed statistical heterogeneity by comparing the results of the fixed-effect model meta-analysis and the random-effects model meta-analysis, lack of overlap of 95% CrIs of between-study variance (Tau^2) with zero, and by calculating the NMA-specific I^2 statistic (Jackson 2014) using Stata/SE 15.1. When possible, we explored substantial clinical, methodological, or statistical heterogeneity and addressed the heterogeneity in subgroup analysis (see Subgroup analysis and investigation of heterogeneity).

Assessment of transitivity across treatment comparisons

We assessed the transitivity assumption by comparing the distribution of the potential effect modifiers (clinical: small versus large, presence of features of high risk of bleeding; and methodological: risk of bias, year of randomisation, duration of follow-up) across the different pairwise comparisons.

Assessment of reporting biases

For the NMA, we planned to perform a comparison-adjusted funnel plot. However, to interpret a comparison-adjusted funnel plot, it is necessary to rank the studies in a meaningful way as asymmetry may be due to small sample sizes in newer studies (comparing newer treatments with older treatments) or higher risk of bias in older studies (Chaimani 2012). As there was no specific change in the risk of bias in the studies, sample size, or the control group used over time, we judged the reporting bias by the completeness of the search (Chaimani 2012). We also considered lack of reporting of outcomes as a form of reporting bias.

Data synthesis

We conducted NMAs to compare multiple interventions simultaneously for each of the primary and secondary outcomes. When two or more interventions were combined, we considered this as a separate intervention ('node'). NMA combines direct evidence within trials and indirect evidence across trials (Mills 2012). We obtained a network plot to ensure that the trials were connected by interventions using Stata/SE 15.1 (Chaimani 2013). We excluded any trials that were not connected to the network from the NMA, and we reported only the direct pairwise meta-analysis for such comparisons. We summarised the population and methodological characteristics of the trials included in the NMA in a table based on pairwise comparisons. We conducted a Bayesian NMA using the Markov chain Monte Carlo method in OpenBUGS 3.2.3, according to guidance from the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) documents (Dias 2016). We modelled the treatment contrast (i.e. log OR for binary outcomes, MD or SMD for continuous outcomes, log RaR for count outcomes, and log HR for time-to-event outcomes) for any two interventions ('functional parameters') as a function of comparisons between each individual intervention and the reference group ('basic parameters') using appropriate likelihood functions and links (Lu 2006). We used binomial likelihood and logit link for binary outcomes, Poisson likelihood and log link for count outcomes, binomial likelihood and complementary log-log link (a semiparametric model which excludes censored individuals from the denominator of 'at risk' individuals at the point when they are censored) for time-to-event outcomes, and normal likelihood and identity link for continuous outcomes. We used 'beta-blockers' as the reference group across the networks, as this was the most common intervention compared in the trials. We performed a fixed-effect model and random-effects model for the NMA. We reported both models for comparison with the reference group in a forest plot when the results were different between the models. For each pairwise comparison in a table, we reported the fixed-effect model if the two models reported similar results; otherwise, we reported the more conservative model (i.e. usually the random-effects model).

We used a hierarchical Bayesian model using three different sets of initial values to start the simulation-based parameter estimation to assist with the assessment of convergence, employing codes provided by NICE DSU (Dias 2016). We used a normal distribution with large variance (10,000) for treatment effect priors (vague or flat priors) centred at no effect. For the random-effects model, we used a prior distributed uniformly (limits: 0 to 5) for the between-trial standard deviation parameter and assumed this variability would be the same across treatment comparisons (Dias 2016). We used a 'burn-in' of 30,000 simulations, checked for convergence (of effect

estimates and between-study heterogeneity) visually (i.e. whether the values in different chains mixed very well by visualisation), and ran the models for another 10,000 simulations to obtain effect estimates. If we did not obtain convergence, we increased the number of simulations for the 'burn-in' and used the 'thin' and 'over relax' functions to decrease the autocorrelation. If we still did not obtain convergence, we used alternate initial values and priors employing methods suggested by van Valkenhoef 2012. We estimated the probability that each intervention ranked at each of the possible positions based on estimated effect sizes and their corresponding uncertainty using the NICE DSU codes (Dias 2016).

Assessment of inconsistency

We assessed inconsistency (statistical evidence of the violation of the transitivity assumption) by fitting both an inconsistency model and a consistency model. We used inconsistency models employed in the NICE DSU manual, as we used a common between-study standard deviation (Dias 2014). In addition, we used design-by-treatment full interaction model and inconsistency factor plots to assess inconsistency, when applicable (Higgins 2012; Chaimani 2013). We used Stata/SE 15.1 to create inconsistency factor plots. In the presence of inconsistency (model fit better with inconsistency models than consistency model, 95% CrI of 'between-design' variance did not overlap zero, and the 95% confidence intervals of inconsistency factor did not overlap zero), we assessed whether the inconsistency was due to clinical or methodological heterogeneity by performing separate analyses for each of the different subgroups mentioned in the Subgroup analysis and investigation of heterogeneity section or limited NMA to a more compatible subset of trials, when possible.

Direct comparison

We performed the direct comparisons using the same codes and the same technical details.

Subgroup analysis and investigation of heterogeneity

We planned to assess the differences in the effect estimates between the following subgroups and investigated heterogeneity and inconsistency using meta-regression with the help of the codes provided in NICE DSU guidance (Dias 2012a), if we included a sufficient number of trials (when there were at least two trials in at least two of the subgroups). We planned to use the following trial-level covariates for meta-regression.

- Trials at low risk of bias compared to trials at high risk of bias.
- Based on the size of varices (small versus large varices).
- Based on the presence of features suggestive of high risk of bleeding (e.g. red spots or red wale markings).
- Based on the presence of other features of decompensation (e.g. ascites).
- Based on the aetiology for cirrhosis (e.g. alcohol-related liver disease, viral liver diseases, autoimmune liver disease).
- Based on the interval between the diagnosis of varices and the start of prophylactic treatment.
- Based on the co-interventions (e.g. both groups received prophylactic antibiotics to decrease the risk of subacute bacterial peritonitis in people with low-protein ascites).
- Based on the period of follow-up (short term: up to three months, medium term: more than three months to five years, and long term: more than five years).
- Based on the definition used by authors for serious adverse events and any adverse events (ICH-GCP 1997 versus other definitions).

We planned to calculate a single common interaction term which assumes that each relative treatment effect compared to a common comparator treatment (i.e. beta-blockers) is impacted in the same way by the covariate in question, when applicable (Dias 2012a). If the 95% CrI of the interaction term did not overlap zero, we considered this statistically significant heterogeneity or inconsistency (depending upon the factor being used as covariate).

Sensitivity analysis

If there were postrandomisation dropouts, we reanalysed the results using the best–worst case scenario and worst–best case scenario analyses as sensitivity analyses whenever possible. We also performed a sensitivity analysis excluding the trials in which mean or standard deviation, or both, were imputed, and we used the median standard deviation in the trials to impute missing standard deviations.

Presentation of results

We followed the PRISMA-NMA statement while reporting (Hutton 2015). We presented the effect estimates with 95% CrI for each pairwise comparison calculated from the direct comparisons and NMA. We originally planned to present the cumulative probability of the treatment ranks (i.e. the probability that the intervention was within the top two, the probability that the intervention was within the top three, etc.), but we did not present these because of the sparse data that can lead to misinterpretation of results due to large uncertainty in the rankings (the CrI was zero to one for all the ranks) in graphs (SUCRA) (Salanti 2011). We plotted the probability that each intervention was best, second best, third best, etc. for each of the different outcomes (rankograms), which are generally considered more informative (Salanti 2011; Dias 2012b), but we did not present these because of the sparse data that can lead to misinterpretation of results due to large uncertainty in the rankings (the CrI was zero to one for all the ranks). We uploaded all the raw data and the codes used for analysis in the European Organization for Nuclear Research open source database (Zenodo): the link is: https://doi.org/10.5281/zenodo.4546239.

Recommendations for future research

We provided recommendations for future research in the population, intervention, control, outcomes, period of follow-up, and study design, based on the uncertainties that we identified from the existing research.

Summary of findings and assessment of the certainty of the evidence

Grading of evidence

We presented 'Summary of findings' tables for all the primary and secondary outcomes (see Primary outcomes; Secondary outcomes). We followed the approach suggested by the GRADE Working Group (Brignardello-Petersen 2018; Yepes-Nunez 2019). First, we calculated the direct and indirect effect estimates (when possible) and 95% CrI using the node-splitting approach (Dias 2010), that is, calculating the direct estimate for each comparison by including only trials in which there was direct comparison of interventions and the indirect estimate for each

comparison by excluding the trials in which there was direct comparison of interventions (and ensuring a connected network). Next, we rated the quality of direct and indirect effect estimates using GRADE methodology, which takes into account the risk of bias, inconsistency (heterogeneity), directness of evidence (including incoherence, the term used in GRADE methodology for inconsistency in NMA), imprecision, and publication bias (Guyatt 2011). We then presented the relative and absolute estimates of the meta-analysis with the best certainty of evidence (Yepes-Nunez 2019). For illustration of the absolute measures, we used weighted median (Edgeworth 1887) control group proportion or mean. We also presented the 'Summary of findings' tables in a second format presenting all the outcomes for selected interventions (Yepes-Nunez 2019): we selected the four interventions (no active intervention, variceal band ligation, sclerotherapy, and beta-blockers plus variceal band ligation) that most trials compared (Table 1).

RESULTS

Description of studies

Results of the search

We identified 8184 records through electronic searches of CENTRAL (1855 records), MEDLINE Ovid (2725 records), Embase Ovid (1034 records), Science Citation Index Expanded (1902 records), ClinicalTrials.gov (83 records), World Health Organization Trials register (110 records), FDA (36 records), and EMA (439 records). After removing duplicates, there were 5765 records. We excluded 5426 clearly irrelevant records through reading titles and abstracts. We retrieved 339 full-text records for further assessment in detail. We excluded 220 records (199 studies) for the reasons stated in the Characteristics of excluded studies table. Two records are awaiting classification (Buuren 2003; eudract2011-006208-11). Seven records (six studies) are ongoing trials (ChiCTR-IPR-15005816; NCT02066649; NCT03736265; NCT03776955; NCT04074473; Tripathi 2019). Thus, we included 66 trials described in 110 records (Characteristics of included studies table). The reference flow is shown in Figure 1.

Included studies

The searched identified 66 trials for inclusion (Conn 1969; Paquet 1982; Witzel 1985; Pascal 1987; Wordehoff 1987; Fleig 1988; Ideo 1988; Lebrec 1988; Piai 1988; Santangelo 1988; Sauerbruch 1988; Snady 1988; Cales 1989a; Cales 1989b; Russo 1989; Andreani 1990; Conn 1991; De Franchis 1991; PROVA study group 1991; Quer 1991; Rossi 1991; VA Coop. Variceal Sclerotherapy Group 1991; Angelico 1993; Fassio 1993; Kanazawa 1993; Duhamel 1994; Paquet 1994; Lay 1997; Piscaglia 1998; De 1999; Lo 1999; Song 1999; Strauss 1999; Svoboda 1999; Chen 2000; Merkel 2000; Agarwal 2001; Deplano 2001; Borroni 2002; D'Amico 2002; Lui 2002; Lo 2004; Merkel 2004; Schepke 2004; Tomikawa 2004; Jutabha 2005; Psilopoulos 2005; Thuluvath 2005; Lay 2006; Wang 2006; Mishra 2007; Norbeto 2007; Tripathi 2009; Lo 2010; Perez-Ayuso 2010; Drastich 2011; Feng 2012; Singh 2012; Sarin 2013; Shah 2014; Bonilha 2015; Bhardwaj 2017; Khan 2017; Seo 2017; NCT00337740; NCT00921349). Studies randomised 6653 participants to different interventions. The number of participants ranged from 16 to 286 per study. Sixty trials included 6212 participants in one or more outcomes (Conn 1969; Paquet 1982; Witzel 1985; Pascal 1987; Wordehoff 1987; Fleig 1988; Ideo 1988; Lebrec 1988; Piai 1988; Santangelo 1988; Sauerbruch 1988; Snady 1988; Russo 1989; Andreani 1990; Conn 1991; De Franchis 1991; PROVA study group 1991; Quer 1991; Rossi 1991; VA Coop. Variceal Sclerotherapy Group 1991; Angelico 1993; Fassio 1993; Kanazawa 1993; Duhamel 1994; Paquet 1994; Lay 1997; De 1999; Lo 1999; Song 1999; Strauss 1999; Svoboda 1999; Chen 2000; Merkel 2000; Agarwal 2001; Borroni 2002; D'Amico 2002; Lui 2002; Lo 2004; Merkel 2004; Schepke 2004; Tomikawa 2004; Jutabha 2005; Psilopoulos 2005; Thuluvath 2005; Lay 2006; Wang 2006; Mishra 2007; Norbeto 2007; Tripathi 2009; Lo 2010; Perez-Ayuso 2010; Drastich 2011; Feng 2012; Singh 2012; Sarin 2013; Shah 2014; Bonilha 2015; Bhardwaj 2017; Khan 2017; Seo 2017). The mean or median age of participants ranged from 40 years to 63 years in the trials that reported this information (Conn 1969; Witzel 1985; Pascal 1987; Wordehoff 1987; Ideo 1988; Lebrec 1988; Piai 1988; Santangelo 1988; Sauerbruch 1988; Cales 1989b; Russo 1989; Andreani 1990; Conn 1991; De Franchis 1991; PROVA study group 1991; Quer 1991; Rossi 1991; VA Coop. Variceal Sclerotherapy Group 1991; Angelico 1993; Fassio 1993; Kanazawa 1993; Duhamel 1994; Paquet 1994; Lay 1997; Piscaglia 1998; De 1999; Lo 1999; Song 1999; Strauss 1999; Svoboda 1999; Merkel 2000; Borroni 2002; D'Amico 2002; Lui 2002; Lo 2004; Merkel 2004; Schepke 2004; Tomikawa 2004; Jutabha 2005; Psilopoulos 2005; Thuluvath 2005; Lay 2006; Wang 2006; Norbeto 2007; Tripathi 2009; Lo 2010; Perez-Ayuso 2010; Drastich 2011; Feng 2012; Sarin 2013; Shah 2014; Bonilha 2015; Bhardwaj 2017; Khan 2017; Seo 2017). The proportion of women ranged from 0.0% to 58.8% in the trials that reported this information (Witzel 1985; Wordehoff 1987; Ideo 1988; Lebrec 1988; Piai 1988; Santangelo 1988; Sauerbruch 1988; Russo 1989; Andreani 1990; Conn 1991; De Franchis 1991; PROVA study group 1991; Quer 1991; Rossi 1991; VA Coop. Variceal Sclerotherapy Group 1991; Angelico 1993; Fassio 1993; Kanazawa 1993; Duhamel 1994; Paquet 1994; Lay 1997; Piscaglia 1998; De 1999; Lo 1999; Song 1999; Svoboda 1999; Merkel 2000; Borroni 2002; D'Amico 2002; Lui 2002; Lo 2004; Merkel 2004; Schepke 2004; Tomikawa 2004; Jutabha 2005; Psilopoulos 2005; Thuluvath 2005; Lay 2006; Wang 2006; Tripathi 2009; Lo 2010; Perez-Ayuso 2010; Drastich 2011; Feng 2012; Sarin 2013; Shah 2014; Bonilha 2015; Bhardwaj 2017; Khan 2017; Seo 2017). The follow-up period in the trials ranged from 0.15 months to 60 months. Three trials had short-term follow-up (Cales 1989a; Cales 1989b; Piscaglia 1998); 61 trials had medium-term follow-up (Conn 1969; Paquet 1982; Witzel 1985; Pascal 1987; Wordehoff 1987; Fleig 1988; Ideo 1988; Lebrec 1988; Piai 1988; Santangelo 1988; Sauerbruch 1988; Snady 1988; Russo 1989; Andreani 1990; Conn 1991; De Franchis 1991; PROVA study group 1991; Quer 1991; Rossi 1991; VA Coop. Variceal Sclerotherapy Group 1991; Angelico 1993; Fassio 1993; Kanazawa 1993; Duhamel 1994; Paquet 1994; Lay 1997; De 1999; Lo 1999; Song 1999; Strauss 1999; Svoboda 1999; Chen 2000; Merkel 2000; Agarwal 2001; Deplano 2001; Borroni 2002; D'Amico 2002; Lui 2002; Lo 2004; Merkel 2004; Schepke 2004; Tomikawa 2004; Jutabha 2005; Psilopoulos 2005; Thuluvath 2005; Lay 2006; Wang 2006; Mishra 2007; Norbeto 2007; Tripathi 2009; Lo 2010; Perez-Ayuso 2010; Drastich 2011; Feng 2012; Singh 2012; Sarin 2013; Shah 2014; Bonilha 2015; Bhardwaj 2017; Khan 2017; Seo 2017); the remaining two trials did not report the period of follow-up (NCT00337740; NCT00921349).

Participants

Forty-one trials reported the proportion of participants who had small varices: in 10 trials, none of the participants had small varices (Wordehoff 1987; Fleig 1988; Ideo 1988; Santangelo 1988; Sauerbruch 1988; Russo 1989; Paquet 1994; De 1999; D'Amico 2002; Singh 2012); in five trials, all participants had small varices

(Strauss 1999; Merkel 2004; Mishra 2007; Sarin 2013; Bhardwaj 2017); in the remaining 26 trials, the proportion of participants who had small varices ranged from 4.5% to 88.9% (Witzel 1985; Pascal 1987; Andreani 1990; Conn 1991; PROVA study group 1991; Quer 1991; VA Coop. Variceal Sclerotherapy Group 1991; Angelico 1993; Kanazawa 1993; Duhamel 1994; Piscaglia 1998; Lo 1999; Song 1999; Svoboda 1999; Merkel 2000; Lui 2002; Lo 2004; Schepke 2004; Jutabha 2005; Psilopoulos 2005; Wang 2006; Norbeto 2007; Lo 2010; Shah 2014; Bonilha 2015; Seo 2017). Twenty-six trials reported the proportion of participants who had high risk of bleeding: in one trial, none of the participants had high risk of bleeding (Merkel 2004); in 15 trials, all participants had high risk of bleeding (Piai 1988; Fassio 1993; Kanazawa 1993; Paquet 1994; Lay 1997; Lo 1999; D'Amico 2002; Lo 2004; Tomikawa 2004; Psilopoulos 2005; Lay 2006; Wang 2006; Norbeto 2007; Lo 2010; Perez-Ayuso 2010); in the remaining 10 trials, the proportion of participants who had high risk of bleeding ranged from 4.6% to 66.4% (Sauerbruch 1988; Quer 1991; Duhamel 1994; Merkel 2000; Lui 2002; Schepke 2004; Jutabha 2005; Tripathi 2009; Drastich 2011; Bonilha 2015). Thirty-eight trials reported the proportion of participants who had other features of decompensation: in two trials, all participants had other features of decompensation (Conn 1969; Borroni 2002); in the remaining 36 trials, the proportion of participants who had other features of decompensation ranged from 1.6% to 64.1% (Ideo 1988; Santangelo 1988; Sauerbruch 1988; Cales 1989b; Russo 1989; Andreani 1990; Conn 1991; PROVA study group 1991; Quer 1991; VA Coop. Variceal Sclerotherapy Group 1991; Angelico 1993; Fassio 1993; Kanazawa 1993; Duhamel 1994; Lay 1997; Piscaglia 1998; De 1999; Lo 1999; Song 1999; Merkel 2000; D'Amico 2002; Lui 2002; Lo 2004; Merkel 2004; Schepke 2004; Lay 2006; Wang 2006; Tripathi 2009; Lo 2010; Perez-Ayuso 2010; Drastich 2011; Feng 2012; Singh 2012; Sarin 2013; Shah 2014; Bhardwaj 2017). Fifty-one trials reported the proportion of participants who had alcohol-related cirrhosis: in five trials, all participants had alcohol-related cirrhosis (Conn 1969; Snady 1988; Cales 1989a; Cales 1989b; VA Coop. Variceal Sclerotherapy Group 1991); in the remaining 46 trials, the proportion of participants who had alcohol-related cirrhosis ranged from 1.8% to 90.0% (Witzel 1985; Pascal 1987; Wordehoff 1987; Ideo 1988; Lebrec 1988; Piai 1988; Santangelo 1988; Sauerbruch 1988; Andreani 1990; Conn 1991; De Franchis 1991; PROVA study group 1991; Quer 1991; Rossi 1991; Angelico 1993; Fassio 1993; Duhamel 1994; Paquet 1994; Lay 1997; Piscaglia 1998; De 1999; Lo 1999; Song 1999; Svoboda 1999; Merkel 2000; Borroni 2002; Lui 2002; Lo 2004; Merkel 2004; Schepke 2004; Tomikawa 2004; Jutabha 2005; Psilopoulos 2005; Thuluvath 2005; Lay 2006; Wang 2006; Tripathi 2009; Lo 2010; Perez-Ayuso 2010; Drastich 2011; Feng 2012; Singh 2012; Sarin 2013; Shah 2014; Bonilha 2015; Bhardwaj 2017). Forty-three trials reported the proportion of participants who had viral-related cirrhosis: in five trials, none of the participants had viral-related cirrhosis (Conn 1969; Snady 1988; Cales 1989a; Cales 1989b; VA Coop. Variceal Sclerotherapy Group 1991); in the remaining 38 trials, the proportion of participants who had viral-related cirrhosis ranged from 3.2% to 92.0% (Witzel 1985; Wordehoff 1987; Lebrec 1988; Piai 1988; Santangelo 1988; Sauerbruch 1988; Russo 1989; Rossi 1991; Kanazawa 1993; Duhamel 1994; Paquet 1994; Lay 1997; Piscaglia 1998; Lo 1999; Song 1999; Svoboda 1999; Merkel 2000; Borroni 2002; D'Amico 2002; Lo 2004; Merkel 2004; Schepke 2004; Tomikawa 2004; Jutabha 2005; Psilopoulos 2005; Thuluvath 2005; Lay 2006; Wang 2006; Norbeto 2007; Lo 2010; Perez-Ayuso 2010; Drastich 2011; Feng 2012; Singh 2012; Sarin 2013; Shah 2014; Bonilha 2015; Bhardwaj 2017). Nineteen trials reported the proportion of participants who had autoimmune disease-related cirrhosis: in eight trials, none of the participants had autoimmune disease-related cirrhosis (Conn 1969; Snady 1988; Cales 1989a; Cales 1989b; VA Coop. Variceal Sclerotherapy Group 1991; Piscaglia 1998; Svoboda 1999; Tomikawa 2004); in the remaining 11 trials, the proportion of participants who had autoimmune disease-related cirrhosis ranged from 2.6% to 25.8% (Lebrec 1988; Santangelo 1988; Duhamel 1994; Paquet 1994; Schepke 2004; Jutabha 2005; Psilopoulos 2005; Thuluvath 2005; Perez-Ayuso 2010; Drastich 2011; Singh 2012). Thirty-nine trials reported the proportion of participants who had other causes of cirrhosis: in eight trials, none of the participants had other causes of cirrhosis (Conn 1969; Snady 1988; Cales 1989a; Cales 1989b; VA Coop. Variceal Sclerotherapy Group 1991; Piscaglia 1998; Svoboda 1999; Tomikawa 2004); in the remaining 31 trials, the proportion of participants who had other causes of cirrhosis ranged from 2.7% to 56.0% (Witzel 1985; Wordehoff 1987; Lebrec 1988; Piai 1988; Santangelo 1988; Russo 1989; Rossi 1991; Duhamel 1994; Paquet 1994; Lay 1997; Lo 1999; Song 1999; Merkel 2000; Borroni 2002; Lo 2004; Merkel 2004; Schepke 2004; Jutabha 2005; Psilopoulos 2005; Thuluvath 2005; Lay 2006; Wang 2006; Lo 2010; Perez-Ayuso 2010; Drastich 2011; Feng 2012; Singh 2012; Sarin 2013; Shah 2014; Bonilha 2015; Bhardwaj 2017).

Interventions

Trials compared nine interventions (beta-blockers, no active intervention, variceal band ligation, sclerotherapy, beta-blockers plus variceal band ligation, beta-blockers plus nitrates, nitrates, beta-blockers plus sclerotherapy, portocaval shunt). Sixty trials reported one or more outcomes for this review (Conn 1969; Paquet 1982; Witzel 1985; Pascal 1987; Wordehoff 1987; Fleig 1988; Ideo 1988; Lebrec 1988; Piai 1988; Santangelo 1988; Sauerbruch 1988; Snady 1988; Russo 1989; Andreani 1990; Conn 1991; De Franchis 1991; PROVA study group 1991; Quer 1991; Rossi 1991; VA Coop. Variceal Sclerotherapy Group 1991; Angelico 1993; Fassio 1993; Kanazawa 1993; Duhamel 1994; Paquet 1994; Lay 1997; De 1999; Lo 1999; Song 1999; Strauss 1999; Svoboda 1999; Chen 2000; Merkel 2000; Agarwal 2001; Borroni 2002; D'Amico 2002; Lui 2002; Lo 2004; Merkel 2004; Schepke 2004; Tomikawa 2004; Jutabha 2005; Psilopoulos 2005; Thuluvath 2005; Lay 2006; Wang 2006; Mishra 2007; Norbeto 2007; Tripathi 2009; Lo 2010; Perez-Ayuso 2010; Drastich 2011; Feng 2012; Singh 2012; Sarin 2013; Shah 2014; Bonilha 2015; Bhardwaj 2017; Khan 2017; Seo 2017). The important characteristics, potential effect modifiers, and follow-up in each trial is reported in Table 1. Overall, there seemed to be no systematic differences between the comparisons.

Funding

Five trials were partly or fully funded by industrial organisations who would benefit from the results of the study (Pascal 1987; Conn 1991; PROVA study group 1991; D'Amico 2002; Shah 2014); 11 trials were funded by neutral organisations who had no vested interests in the results of the study (Lebrec 1988; Andreani 1990; VA Coop. Variceal Sclerotherapy Group 1991; Lay 1997; Svoboda 1999; Borroni 2002; Schepke 2004; Jutabha 2005; Wang 2006; Tripathi 2009; Drastich 2011); the source of funding for the remaining 50 trials was unclear (Conn 1969; Paquet 1982; Witzel 1985; Wordehoff 1987; Fleig 1988; Ideo 1988; Piai 1988; Santangelo 1988; Sauerbruch 1988; Snady 1988; Cales 1989a; Cales 1989b; Russo 1989; De Franchis 1991; Quer 1991; Rossi 1991; Angelico 1993; Fassio 1993; Kanazawa 1993; Duhamel 1994; Paquet 1994; Piscaglia 1998; De 1999; Lo 1999; Song 1999; Strauss 1999; Chen 2000; Merkel 2000;

Agarwal 2001; Deplano 2001; Lui 2002; Lo 2004; Merkel 2004; Tomikawa 2004; Psilopoulos 2005; Thuluvath 2005; Lay 2006; Mishra 2007; Norbeto 2007; Lo 2010; Perez-Ayuso 2010; Feng 2012; Singh 2012; Sarin 2013; Bonilha 2015; Bhardwaj 2017; Khan 2017; Seo 2017; NCT00337740; NCT00921349).

Transitivity assumption

We have summarised the potential effect modifiers in Table 1. There were no concerns about the transitivity assumption related to the different types of varices (small or large) and those with and without other features of decompensation.

Excluded studies

The reasons for exclusion of studies are listed in the Characteristics of excluded studies table. The summary of reasons for exclusion of studies are as follows.

- Not a population of interest for this review as all trial participants did not have cirrhosis or oesophageal varices or had history of variceal bleeding (114 studies: Resnick 1969; Callow 1970; Resnick 1974; Phillips 1975; Mastai 1986; Dunk 1988; Kanazawa 1988; Kitano 1989; Sotto 1989; Cestari 1990; Kobe 1990; McKee 1990; Santambrogio 1990; Taranto 1990; Braga 1991; Feu 1991; Garcia-Pagán 1991; Kleber 1991; Testa 1991; Kitano 1992; McCormick 1992; Feu 1993; Hashizume 1993; McCormick 1993; Bolognesi 1994; Koch 1994; Plevris 1994; Bolognesi 1995; Cirera 1995; Group Francais de la Prevention Pre-Primaire 1995; Li 1995; Albillos 1996; Escorsell 1996; Estevens 1996; Garcia-Pagán 1996; Iwao 1996; Nevens 1996a; Nevens 1996b; Nevens 1996c; Sarin 1996; Zironi 1996; Escorsell 1997a; Escorsell 1997b; Miyoshi 1997; Pang 1997; Sugano 1997; Bandi 1998; Barrioz 1998; Masumoto 1998; Banares 1999; Cales 1999; Gotoh 1999; Nishikawa 1999; Sarin 1999; Umehara 1999; Iwakiri 2000; Romero 2000; Abraczinskas 2001; Cheng 2001; Escorsell 2001; Garcia-Pagán 2001; Lee 2001; Schepke 2001; Sugano 2001; De 2002; Lin 2002; Schiedermaier 2002; Sen 2002; Vorobioff 2002; Bellis 2003; De 2003; Garcia-Pagán 2003; Schiedermaier 2003; Liu 2004; Silva 2004; Ferrari 2005; Groszmann 2005; Kalambokis 2005; Kuwayama 2005; Lin 2005; Pozzi 2005; Rosemurgy 2005; Sarin 2005; Triantos 2005; Bolondi 2006; Gheorghe 2006; Ohmoto 2006; Qi 2007; Vorobioff 2007; Fernandez Perez 2008; Zargar 2008; Bonilha 2010; Gong 2010; Sarin 2010; Shang 2010; Hidaka 2011; Santos 2011; Copaci 2012; Kong 2013; Sohn 2013; Mo 2014; Li 2016a; Hanno 2016; Kainth 2017; Dong 2018; Bhardwaj 2019; ChiCTR-PRRC-08000228; eudract2006-006393-14; eudract2014-000102-35; eudract2014-002018-21; NCT00006398; NCT00799851; NCT01059396; SLCTR/2007/001).
- Not a randomised clinical trial (49 studies: Orloff 1962; Berardi 1974; Orloff 1974; Hutteroth 1983; Paquet 1983; Adson 1984; Conn 1986; Conn 1987; Kleber 1987; Lashner 1988; Batenburg 1990; Cales 1990b; Fort 1990; Gilbert 1991; Gregory 1991; Korula 1991; Poynard 1991; Reynolds 1991; Triger 1991; Burroughs 1992; Gallant 1992; Vanruiswyk 1992; Conn 1993; Gupta 1993; Paquet 1993; Thiel 1993; Mino 1995; ASGE 1998; Gong 1998; Oberti 1999; Ramond 1999; Stiegmann 1999; Assi 2000; Deschenes 2000; Sheikh 2000; Zalepuga 2000; Taniai 2002; Okano 2003a; Okano 2003b; Sharara 2003; Sussman 2003; Mann 2004; Bosch 2005; Gawrieh 2005; Hua 2007; Orloff 2014; ElRahim 2018; Pfisterer 2018; NCT03583996).
- Not a comparison of interest for this review as the intervention was not listed in one of the ones mentioned and is not currently in common use for primary prophylaxis (21 studies: Jackson 1968; Italian Proj. Prop. Prev. Bleed. 1988; Pagliaro 1989; Inokuchi 1990; Tincani 1993; Avgerinos 1994; Lin 1994; Tincani 1995; Lin 1996a; Abecasis 2003; Agarwala 2011; Chandok 2012; Hamza 2012; Yattoo 2013; Bhardwaj 2014; Alvarado-Tapias 2016; Kim 2016; ChiCTR-IIR-15007655; NCT01188733; NCT00493480; NCT01383044).
- Effect of randomisation was lost in a considerable proportion of participants because of trial-related procedures (one study: Avgerinos 2000).
- Unclear if the studies included non-cirrhotic participants or the prophylaxis was primarily against gastric variceal bleeding (14 studies: Lin 1996b; Madwar 1998; Siqueira 1998; Helmy 2015; Pollo-Flores 2015; ChiCTR-TRC-12002148; eudract2012-000236-26; eudract2012-002489-11; eudract2014-005523-27; eudract2014-002300-24; eudract2017-001762-13; NCT00409084; NCT02646202; NCT02695732).

Risk of bias in included studies

The risk of bias is summarised in Figure 2, Figure 3, and Table 2. All the trials except one trial (D'Amico 2002) were at unclear or high risk of bias in at least one of the domains and were at high risk of bias overall.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

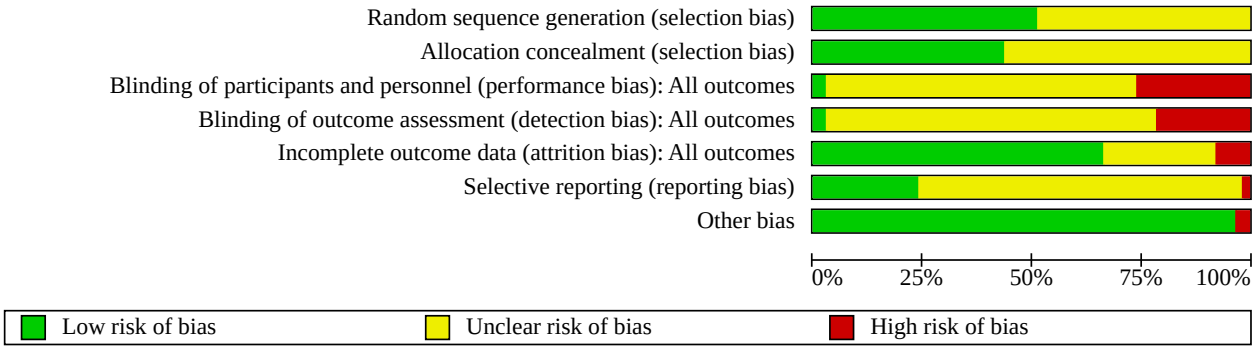


Figure 3.

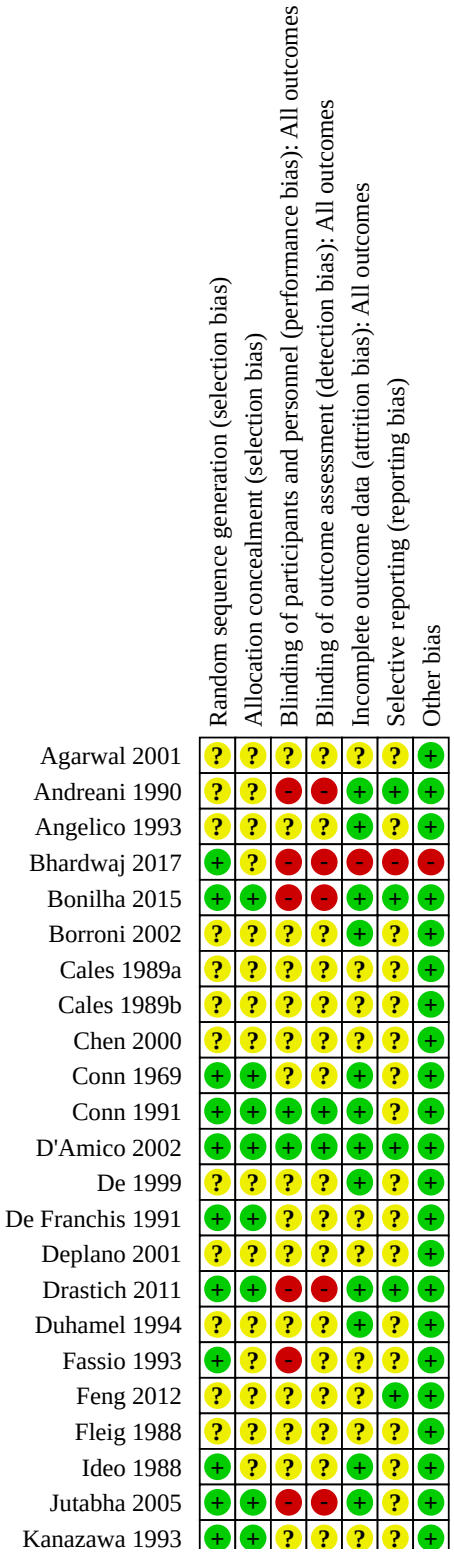
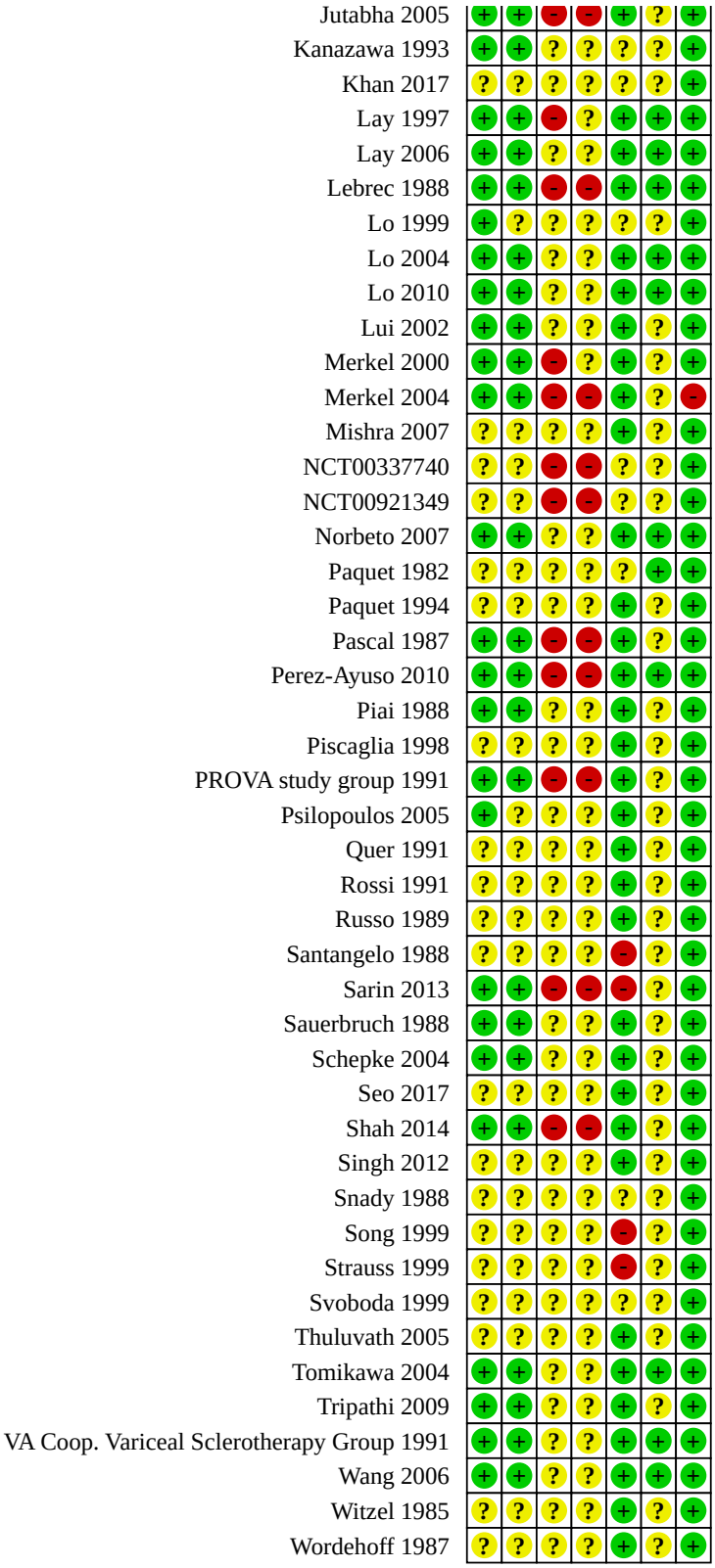


Figure 3. (Continued)



Allocation

Thirty-four trials were at low risk of sequence generation bias (Conn 1969; Pascal 1987; Ideo 1988; Lebrec 1988; Piai 1988; Sauerbruch 1988; Conn 1991; De Franchis 1991; PROVA study group 1991; VA Coop. Variceal Sclerotherapy Group 1991; Fassio 1993; Kanazawa 1993; Lay 1997; Lo 1999; Merkel 2000; D'Amico 2002; Lui 2002; Lo 2004; Merkel 2004; Schepke 2004; Tomikawa 2004; Jutabha 2005; Psilopoulos 2005; Lay 2006; Wang 2006; Norbeto 2007; Tripathi 2009; Lo 2010; Perez-Ayuso 2010; Drastich 2011; Sarin 2013; Shah 2014; Bonilha 2015; Bhardwaj 2017); the remaining 32 trials, which did not provide sufficient information, were at unclear risk of sequence generation bias (Paquet 1982; Witzel 1985; Wordehoff 1987; Fleig 1988; Santangelo 1988; Snady 1988; Cales 1989a; Cales 1989b; Russo 1989; Andreani 1990; Quer 1991; Rossi 1991; Angelico 1993; Duhamel 1994; Paquet 1994; Piscaglia 1998; De 1999; Song 1999; Strauss 1999; Svoboda 1999; Chen 2000; Agarwal 2001; Deplano 2001; Borroni 2002; Thuluvath 2005; Mishra 2007; Feng 2012; Singh 2012; Khan 2017; Seo 2017; NCT00337740; NCT00921349).

Twenty-nine trials were at low risk of allocation concealment bias (Conn 1969; Pascal 1987; Lebrec 1988; Piai 1988; Sauerbruch 1988; Conn 1991; De Franchis 1991; PROVA study group 1991; VA Coop. Variceal Sclerotherapy Group 1991; Kanazawa 1993; Lay 1997; Merkel 2000; D'Amico 2002; Lui 2002; Lo 2004; Merkel 2004; Schepke 2004; Tomikawa 2004; Jutabha 2005; Lay 2006; Wang 2006; Norbeto 2007; Tripathi 2009; Lo 2010; Perez-Ayuso 2010; Drastich 2011; Sarin 2013; Shah 2014; Bonilha 2015); the remaining 37 trials, which did not provide sufficient information, were at unclear risk of allocation concealment bias (Paquet 1982; Witzel 1985; Wordehoff 1987; Fleig 1988; Ideo 1988; Santangelo 1988; Snady 1988; Cales 1989a; Cales 1989b; Russo 1989; Andreani 1990; Quer 1991; Rossi 1991; Angelico 1993; Fassio 1993; Duhamel 1994; Paquet 1994; Piscaglia 1998; De 1999; Lo 1999; Song 1999; Strauss 1999; Svoboda 1999; Chen 2000; Agarwal 2001; Deplano 2001; Borroni 2002; Thuluvath 2005; Psilopoulos 2005; Mishra 2007; Feng 2012; Singh 2012; Bhardwaj 2017; Khan 2017; Seo 2017; NCT00337740; NCT00921349).

Blinding

Two trials were at low risk of performance bias as the participants and healthcare providers were blinded (Conn 1991; D'Amico 2002); 47 trials, which did not provide sufficient information, were at unclear risk of performance bias (Conn 1969; Paquet 1982; Witzel 1985; Wordehoff 1987; Fleig 1988; Ideo 1988; Piai 1988; Santangelo 1988; Sauerbruch 1988; Snady 1988; Cales 1989a; Cales 1989b; Russo 1989; De Franchis 1991; Quer 1991; Rossi 1991; VA Coop. Variceal Sclerotherapy Group 1991; Angelico 1993; Kanazawa 1993; Duhamel 1994; Paquet 1994; Piscaglia 1998; De 1999; Lo 1999; Song 1999; Strauss 1999; Svoboda 1999; Chen 2000; Agarwal 2001; Deplano 2001; Borroni 2002; Lui 2002; Lo 2004; Schepke 2004; Tomikawa 2004; Psilopoulos 2005; Thuluvath 2005; Lay 2006; Wang 2006; Mishra 2007; Norbeto 2007; Tripathi 2009; Lo 2010; Feng 2012; Singh 2012; Khan 2017; Seo 2017); the remaining 17 trials were at high risk of performance bias (Pascal 1987; Lebrec 1988; Andreani 1990; PROVA study group 1991; Fassio 1993; Lay 1997; Merkel 2000; Merkel 2004; Jutabha 2005; Perez-Ayuso 2010; Drastich 2011; Sarin 2013; Shah 2014; Bonilha 2015; Bhardwaj 2017; NCT00337740; NCT00921349).

Two trials were at low risk of detection bias (Conn 1991; D'Amico 2002); 50 trials, which did not provide sufficient information, were at unclear risk of detection bias (Conn 1969; Paquet 1982; Witzel 1985; Wordehoff 1987; Fleig 1988; Ideo 1988; Piai 1988; Santangelo 1988; Sauerbruch 1988; Snady 1988; Cales 1989a; Cales 1989b; Russo 1989; De Franchis 1991; Quer 1991; Rossi 1991; VA Coop. Variceal Sclerotherapy Group 1991; Angelico 1993; Fassio 1993; Kanazawa 1993; Duhamel 1994; Paquet 1994; Lay 1997; Piscaglia 1998; De 1999; Lo 1999; Song 1999; Strauss 1999; Svoboda 1999; Chen 2000; Merkel 2000; Agarwal 2001; Deplano 2001; Borroni 2002; Lui 2002; Lo 2004; Schepke 2004; Tomikawa 2004; Psilopoulos 2005; Thuluvath 2005; Lay 2006; Wang 2006; Mishra 2007; Norbeto 2007; Tripathi 2009; Lo 2010; Feng 2012; Singh 2012; Khan 2017; Seo 2017); the remaining 15 trials were at high risk of detection bias (Pascal 1987; Lebrec 1988; Andreani 1990; PROVA study group 1991; Merkel 2004; Jutabha 2005; Perez-Ayuso 2010; Drastich 2011; Sarin 2013; Shah 2014; Bonilha 2015; Bhardwaj 2017; NCT00337740; NCT00921349).

Incomplete outcome data

Forty-four trials were at low risk of attrition bias as there were no postrandomisation dropouts, the postrandomisation outputs were very few, or an intention-to-treat analysis was used (Conn 1969; Witzel 1985; Pascal 1987; Wordehoff 1987; Ideo 1988; Lebrec 1988; Piai 1988; Sauerbruch 1988; Russo 1989; Andreani 1990; Conn 1991; Quer 1991; PROVA study group 1991; Rossi 1991; VA Coop. Variceal Sclerotherapy Group 1991; Angelico 1993; Duhamel 1994; Paquet 1994; Lay 1997; Piscaglia 1998; De 1999; Merkel 2000; Borroni 2002; D'Amico 2002; Lui 2002; Lo 2004; Merkel 2004; Schepke 2004; Tomikawa 2004; Jutabha 2005; Psilopoulos 2005; Thuluvath 2005; Lay 2006; Wang 2006; Mishra 2007; Norbeto 2007; Tripathi 2009; Lo 2010; Perez-Ayuso 2010; Drastich 2011; Singh 2012; Shah 2014; Bonilha 2015; Seo 2017); 17 trials were at unclear risk of attrition bias (Paquet 1982; Fleig 1988; Snady 1988; Cales 1989a; Cales 1989b; De Franchis 1991; Fassio 1993; Kanazawa 1993; Lo 1999; Svoboda 1999; Chen 2000; Agarwal 2001; Deplano 2001; Feng 2012; Khan 2017; NCT00337740; NCT00921349), because it was unclear whether there were postrandomisation dropouts or whether the postrandomisation dropouts were related to the outcomes (if there were postrandomisation dropouts); the remaining five trials were at high risk of attrition bias as the postrandomisation dropouts were probably related to the outcomes (Santangelo 1988; Song 1999; Strauss 1999; Sarin 2013; Bhardwaj 2017).

Selective reporting

Sixteen trials were at low risk of selective outcome reporting bias as the important clinical outcomes expected to be reported in such trials were reported (Paquet 1982; Lebrec 1988; Andreani 1990; VA Coop. Variceal Sclerotherapy Group 1991; Lay 1997; D'Amico 2002; Lo 2004; Tomikawa 2004; Lay 2006; Wang 2006; Norbeto 2007; Lo 2010; Perez-Ayuso 2010; Drastich 2011; Feng 2012; Bonilha 2015); 49 trials were at unclear risk of selective outcome reporting bias as a protocol published prior to recruitment was not available (Conn 1969; Witzel 1985; Pascal 1987; Wordehoff 1987; Fleig 1988; Ideo 1988; Piai 1988; Santangelo 1988; Sauerbruch 1988; Snady 1988; Cales 1989a; Cales 1989b; Russo 1989; Conn 1991; De Franchis 1991; PROVA study group 1991; Quer 1991; Rossi 1991; Angelico 1993; Fassio 1993; Kanazawa 1993; Duhamel 1994; Paquet 1994; Piscaglia 1998; De 1999; Lo 1999; Song 1999; Strauss 1999; Svoboda 1999; Chen 2000; Merkel 2000; Agarwal 2001; Deplano 2001; Borroni 2002; Lui 2002; Merkel 2004; Schepke 2004; Jutabha 2005; Psilopoulos 2005; Thuluvath 2005; Mishra 2007; Tripathi 2009; Singh 2012; Sarin 2013; Shah 2014; Khan 2017; Seo 2017;

NCT00337740; NCT00921349); the remaining one trial was at high risk of selective outcome reporting bias as the outcomes were changed from the protocol published prior to recruitment without sufficient justification (Bhardwaj 2017).

Other potential sources of bias

Sixty-four trials were at low risk of other bias (Conn 1969; Paquet 1982; Witzel 1985; Pascal 1987; Wordehoff 1987; Fleig 1988; Ideo 1988; Lebrec 1988; Piai 1988; Santangelo 1988; Sauerbruch 1988; Snady 1988; Cales 1989a; Cales 1989b; Russo 1989; Andreani 1990; Conn 1991; De Franchis 1991; PROVA study group 1991; Quer 1991; Rossi 1991; VA Coop. Variceal Sclerotherapy Group 1991; Angelico 1993; Fassio 1993; Kanazawa 1993; Duhamel 1994; Paquet 1994; Lay 1997; Piscaglia 1998; De 1999; Lo 1999; Song 1999; Strauss 1999; Svoboda 1999; Chen 2000; Merkel 2000; Agarwal 2001; Deplano 2001; Borroni 2002; D'Amico 2002; Lui 2002; Lo 2004; Schepke 2004; Tomikawa 2004; Jutabha 2005; Psilopoulos 2005; Thuluvath 2005; Lay 2006; Wang 2006; Mishra 2007; Norbeto 2007; Tripathi 2009; Lo 2010; Perez-Ayuso 2010; Drastich 2011; Feng 2012; Singh 2012; Sarin 2013; Shah 2014; Bonilha 2015; Khan 2017; Seo 2017; NCT00337740; NCT00921349); the remaining two trials were at high risk of other bias (Merkel 2004; Bhardwaj 2017), because of discrepancy in the participant flow between the abstracts and full texts (see Characteristics of included studies table for detailed information) (Bhardwaj 2017), or because participants in the control group received pharmacological prophylaxis against bleeding before the bleeding episode; this could have influenced the effect estimates for all outcomes (Merkel 2004).

Effects of interventions

See: **Summary of findings 1** Primary prevention of bleeding in people with oesophageal varices due to liver cirrhosis (common interventions); **Summary of findings 2** Primary prevention of bleeding in people with oesophageal varices due to liver cirrhosis (all interventions)

The network plots (where relevant) are available in Figure 4. The inconsistency factor plots (where relevant) are available in Figure 5. The NMA results for mortality, adverse events, and any variceal bleed and the differences in the fixed-effect versus random-effects model, where relevant, are available in Figure 6. The model fit is available in Table 3. The effect estimates are available in Table 4.

Figure 4. Network plots: a high resolution version of this image can be found at https://doi.org/10.5281/zenodo.4409371. The network plots showing the outcomes for which network meta-analysis was performed. The size of the node (circle) provides a measure of the number of trials in which the particular intervention was included as one of the intervention groups. The thickness of the line provides a measure of the number of direct comparisons between two nodes (interventions). BT: balloon tamponade; PC_shunt: portocaval shunt; Sclero: sclerotherapy;

Som: somatostatin analogues; TIPS: transjugular intrahepatic portosystemic shunt; Vas: vasopressin analogues; VBL: variceal band ligation.

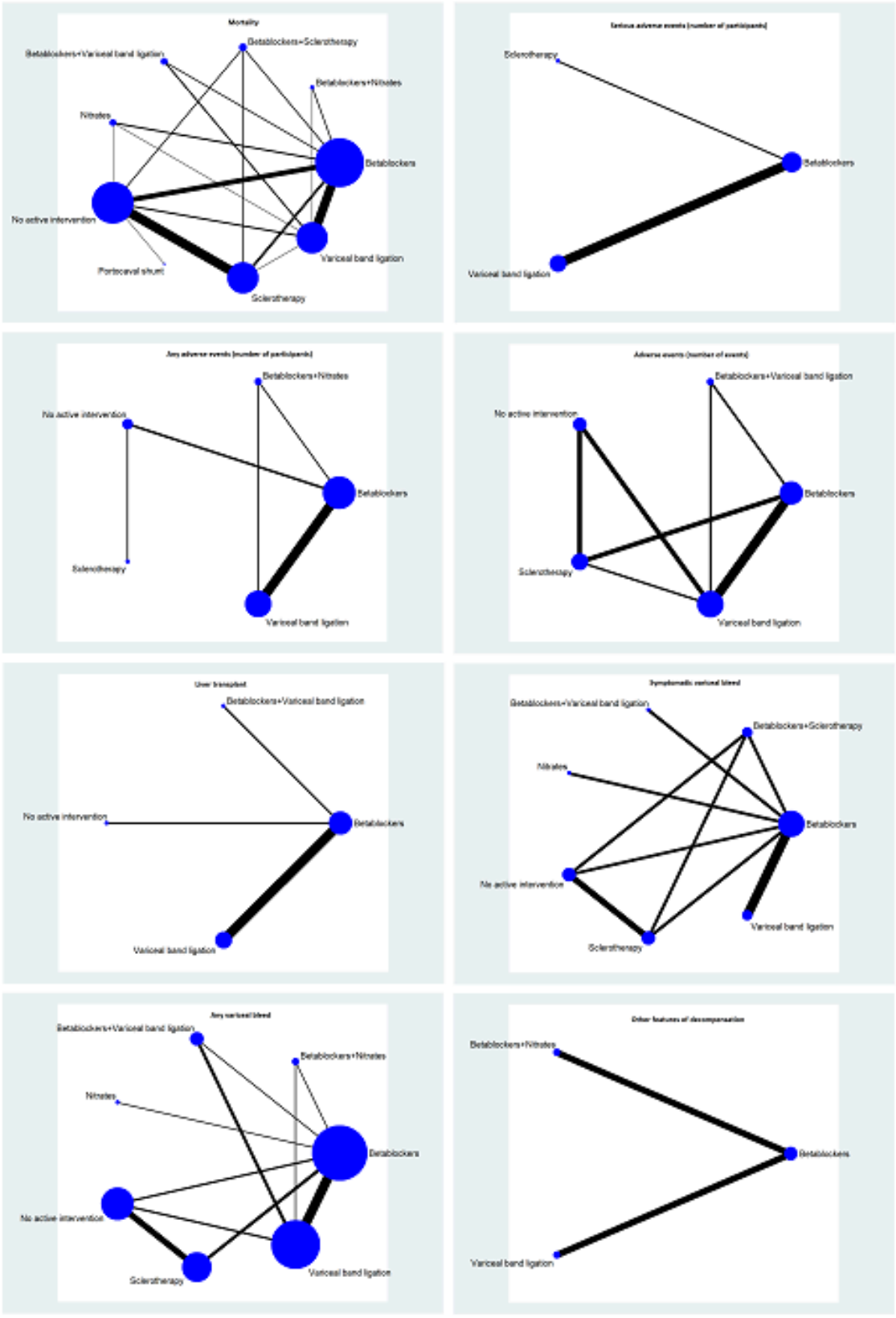
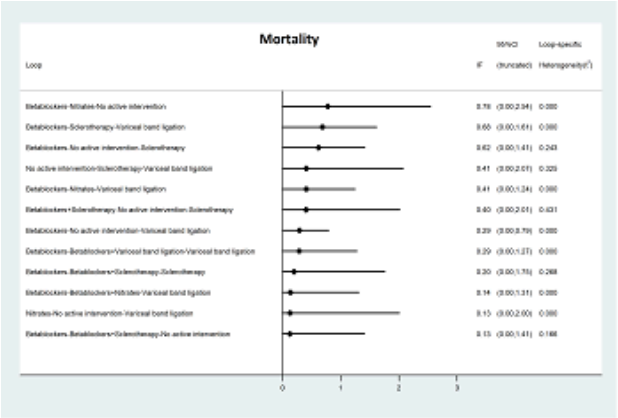
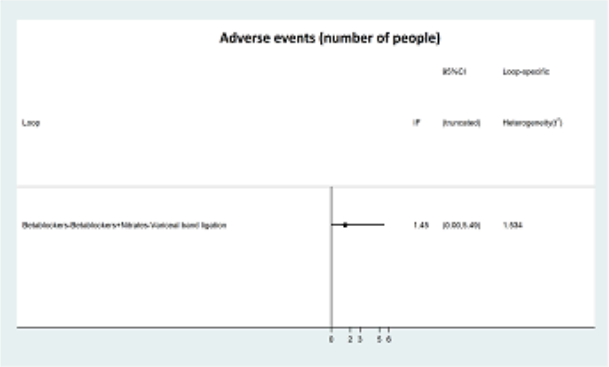
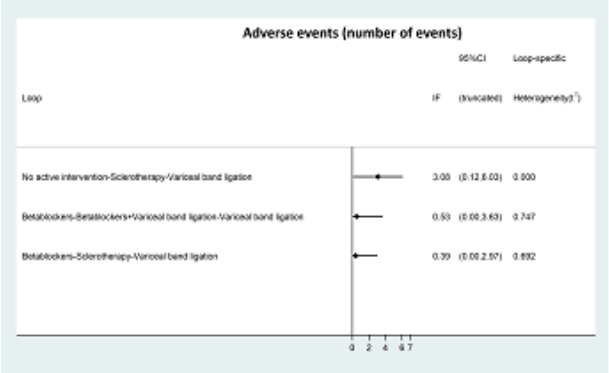
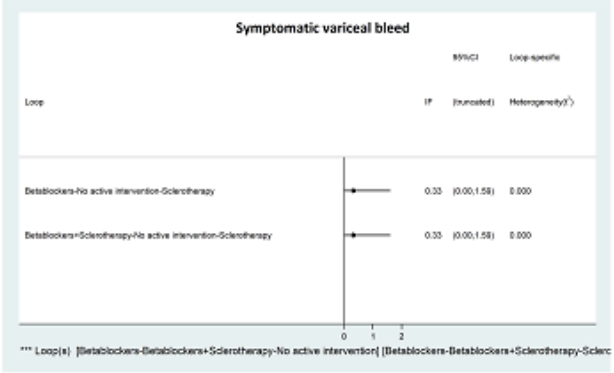


Figure 5. Inconsistency factor plots showing the inconsistency factors for the outcomes with direct and indirect evidence available for one or more comparisons. There was no evidence of inconsistency for any of the outcomes where this could be assessed (i.e. the confidence intervals of all the inconsistency factors for all outcomes overlap zero). A higher resolution image of this picture is available at https://doi.org/10.5281/zenodo.4441270. BT: balloon tamponade; PC_shunt: portocaval shunt; Sclero: sclerotherapy; Som: somatostatin analogues; TIPS: transjugular intrahepatic portosystemic shunt; Vas: vasopressin analogues; VBL: variceal band ligation.









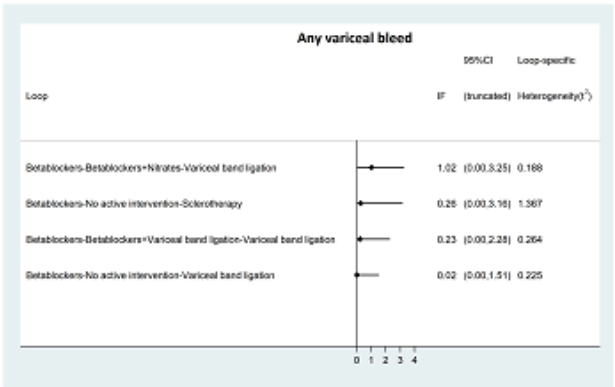
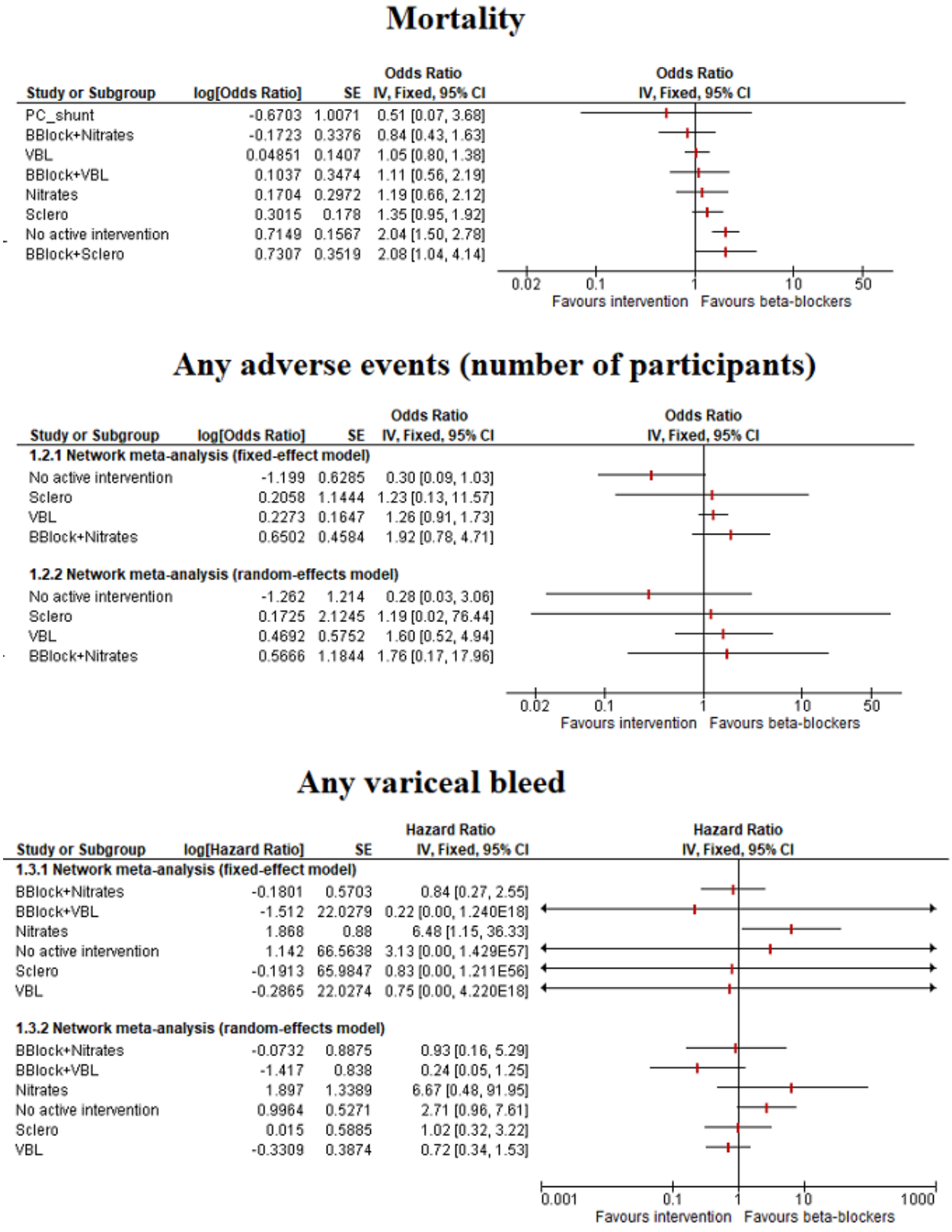


Figure 6. Forest plots showing mortality and the outcomes for which the random-effects model were different from the fixed-effect model. The more conservative random-effects model was used. BBlock: beta-blockers; Sclero: sclerotherapy; VBL: variceal band ligation.



We would like to note that no cluster- or cross-over randomised trials contributed to the effects of interventions. We would also like to note that there were several multiple arm trials. The codes that we used for analysis accounted for the correlation between the effect sizes from studies with more than two groups.

The 95% CrIs of the probability ranks were wide and included 0 and 1 in most comparisons for all the primary and secondary outcomes. This was probably because of the sparse data from small trials. Therefore, we did not present the ranking probabilities (in a table), rankograms, and SUCRA plots as we considered that presenting this information would be unhelpful and potentially misleading and would ignore the differences in systematic errors in the trials.

The certainty of evidence was low or very low for all the comparisons. This was because all the trials included in the comparison were at unclear or high risk of bias for at least one risk of bias domain at the outcome level (downgraded one level). For all direct comparisons, the number of events were fewer than 300, which resulted in downgrading of evidence one level for imprecision. For NMA, for outcomes other than mortality, any adverse events (number of participants), any adverse events (number of events), and any variceal bleed, the number of events were fewer than 300; therefore, we downgraded one level for imprecision. This resulted in low-certainty evidence for all the direct comparisons and for network estimates for the outcomes other than mortality, any adverse events (number of participants), any adverse events (number of events), and any variceal bleed. In comparisons where the wide CrIs overlapped significant clinical effect and no effect, we downgraded one more level for imprecision. There was also evidence of heterogeneity (called inconsistency in the GRADE system; not to be confused with inconsistency in direct and indirect estimates in the context of NMA) for mortality and any variceal bleed. For network meta-analyses in which there was inconsistency (any adverse events (number of participants) and any adverse events (number of events)), we downgraded one level for incongruence or indirectness of evidence.

Mortality

Fifty-seven trials (5911 participants) reported mortality (Conn 1969; Paquet 1982; Witzel 1985; Pascal 1987; Wordehoff 1987; Fleig 1988; Ideo 1988; Lebrec 1988; Piai 1988; Santangelo 1988; Sauerbruch 1988; Snady 1988; Russo 1989; Andreani 1990; Conn 1991; De Franchis 1991; PROVA study group 1991; Quer 1991; Rossi 1991; VA Coop. Variceal Sclerotherapy Group 1991; Angelico 1993; Fassio 1993; Kanazawa 1993; Duhamel 1994; Paquet 1994; Lay 1997; Lo 1999; Song 1999; Strauss 1999; Svoboda 1999; Chen 2000; Merkel 2000; Agarwal 2001; Borroni 2002; D'Amico 2002; Lui 2002; Lo 2004; Merkel 2004; Schepke 2004; Jutabha 2005; Psilopoulos 2005; Thuluvath 2005; Lay 2006; Wang 2006; Mishra 2007; Norbeto 2007; Tripathi 2009; Lo 2010; Perez-Ayuso 2010; Drastich 2011; Feng 2012; Singh 2012; Sarin 2013; Shah 2014; Bonilha 2015; Bhardwaj 2017; Seo 2017). The trials compared nine treatments. There were 1651 events in total (27.9%) over a mean or median follow-up period of eight months to 60 months. The weighted median control group proportion was 21.2%.

Direct comparisons

- Beta-blockers had lower mortality than no active intervention: HR 0.59 (95% CrI 0.42 to 0.83); 10 trials, 1200 participants; low-certainty evidence (because of the way information is presented in Table 4 and Summary of findings 1 where beta-blockers were used as the reference treatment, the HR of no active intervention versus beta-blockers was: HR 1.70 (95% CrI 1.21 to 2.39).
- Sclerotherapy had lower mortality than no active intervention: HR 0.61 (95% CrI 0.41 to 0.90); 18 trials, 1666 participants; low-certainty evidence.
- Sclerotherapy had higher mortality than beta-blockers: HR 1.88 (95% CrI 1.01 to 3.69); 5 trials, 320 participants; low-certainty evidence.

There was no evidence of differences between the treatments in the remaining direct comparisons (i.e. the remaining direct comparisons were not statistically significant) as shown in Table 4 (very low-certainty evidence).

Network meta-analysis

All the trials were connected to the network. All treatments were connected. There was no evidence of inconsistency according to model fit, inconsistency factor, and the 'between-design' variance. The random-effects model was used because we could not obtain convergence for the fixed-effect model despite various measures to achieve convergence. The 'between-study variance' was 0.16 (95% CrI 0.07 to 0.34).

In the NMA, in the following pairwise comparisons, the first intervention had lower mortality than the second intervention.

- Beta-blockers versus no active intervention: HR 0.49 (95% CrI 0.36 to 0.67); direct comparison: HR: 0.59 (95% CrI 0.42 to 0.83); 10 trials, 1200 participants; low-certainty evidence (because beta-blockers was the reference treatment, the HR of no active intervention versus beta-blockers in Table 4 and Summary of findings 1 was: HR 2.04 (95% CrI 1.50 to 2.78).
- Variceal band ligation versus no active intervention: HR 0.51 (95% CrI 0.35 to 0.74); direct comparison HR 0.49 (95% CrI 0.12 to 2.14); 3 trials, 355 participants; low-certainty evidence.
- Sclerotherapy versus no active intervention: HR 0.66 (95% CrI 0.51 to 0.85); direct comparison HR 0.61 (95% CrI 0.41 to 0.90); 18 trials, 1666 participants; low-certainty evidence.
- Beta-blockers plus nitrates versus no active intervention: HR 0.41 (95% CrI 0.20 to 0.85); no direct comparison; low-certainty evidence.

In the NMA, in the following pairwise comparisons, the first intervention had higher mortality than control.

- Beta-blockers plus sclerotherapy versus beta-blockers: HR 2.08 (95% CrI 1.03 to 4.08); direct comparison HR 2.03 (95% CrI 0.04 to 75.04); 2 trials, 167 participants; low-certainty evidence.

There was no evidence of differences between the treatments in the remaining comparisons in the NMA (very low-certainty evidence).

Health-related quality of life

No trials reported health-related quality of life.

Serious adverse events

No trials reported whether they used the ICH-GCP 1997 definition of serious adverse events. We used the description of events as

'serious' or 'severe' adverse events or complications as serious adverse events.

Serious adverse events (number of participants)

Nine trials (741 participants) reported serious adverse events (number of participants) (Andreani 1990; Svoboda 1999; Lo 2004; Jutabha 2005; Wang 2006; Norbeto 2007; Perez-Ayuso 2010; Drastich 2011; Bonilha 2015). The trials compared six treatments. There were 25 events in total (3.4%). The weighted median control group proportion was 5.6%.

Direct comparisons

There was no evidence of a difference in any of the direct comparisons (i.e. there was no statistically significant difference in any of the comparisons) (low-certainty evidence).

Network meta-analysis

Three trials were not connected to the network because they had zero events in both intervention groups (Svoboda 1999; Lo 2004; Wang 2006); one trial was not connected to the network because it was the only trial for the comparison and had zero events in one of the intervention groups (Bonilha 2015). The network had three connected treatments. There were no triangular or quadrangular loops; therefore, inconsistency was not checked. We used the fixed-effect model because it had equivalent results and model fit as random-effects model.

There was no evidence of difference in any of the NMA (i.e. there was no statistically significant difference in any of the comparisons) (very low-certainty evidence).

Serious adverse events (number of events)

Two trials (234 participants) reported serious adverse events (number of events) (Shah 2014; Bonilha 2015). The trials compared three treatments. There were 21 events in total (0.1 events per participant). The control event rate was 0.024 events per participant. One trial was not connected to the network because it was the only trial for the comparison and had zero events in one of the intervention groups (Bonilha 2015). As there was only one remaining trial, an NMA was not possible.

Beta-blockers plus variceal band ligation had 0/34 (0%) serious adverse events per participant and variceal band ligation had 1/32 (3.1%) serious adverse events per participant. Variceal band ligation had a higher number of serious adverse events (number of events) than beta-blockers (RaR 10.49, 95% CrI 2.83 to 60.64; 1 trial, 168 participants; low-certainty evidence).

Any adverse events

None of the trials reported whether they used the ICH-GCP 1997 definition of any adverse events. We used the description of events as 'adverse events' or 'complications' as any adverse events.

Any adverse events (number of participants)

Thirteen trials (1291 participants) reported any adverse events (number of participants) (Paquet 1982; Lebrec 1988; Lay 1997; D'Amico 2002; Lo 2004; Schepke 2004; Psilopoulos 2005; Lay 2006; Wang 2006; Perez-Ayuso 2010; Drastich 2011; Feng 2012; Sarin 2013). The trials compared five treatments. There were 314 events in total (24.3%). The weighted median control group proportion was 19.0%.

Direct comparisons

Beta-blockers plus nitrates had a higher number of 'any adverse events (number of participants)' than beta-blockers (OR 3.41, 95% CrI 1.11 to 11.28; 1 trial, 57 participants; low-certainty evidence).

There was no evidence of differences between the treatments in the remaining direct comparisons (i.e. the remaining direct comparisons were not statistically significant) as shown in Table 4.

Network meta-analysis

One trial was not connected to the network because it was the only trial for the comparison and had zero events in one of the intervention groups (Lay 1997). All treatments were connected. There was evidence of inconsistency according to the 'between-design' variance 2.91 (95% CrI 0.01 to 22.64), but not by inconsistency factor or model fit; therefore, there is uncertainty in the validity of NMA results. The direct comparisons are more reliable. The random-effects model was used because it was more conservative and had better model fit. The 'between-study variance' was 1.59 (95% CrI 0.47 to 6.72).

In the NMA, there was no evidence of differences in any of the comparisons (very low-certainty evidence).

Any adverse events (number of events)

Eleven trials (1340 participants) reported any adverse events (number of events) (VA Coop. Variceal Sclerotherapy Group 1991; Kanazawa 1993; Lay 1997; Svoboda 1999; Schepke 2004; Tomikawa 2004; Psilopoulos 2005; Lay 2006; Lo 2010; Shah 2014; Bonilha 2015). The trials compared five treatments. There were 1092 events in total (0.8 events per participant). The median control event rate was 0.61 per participant.

Direct comparisons

Variceal band ligation had lower any adverse events (number of events) than beta-blockers: RaR 0.73 (95% CrI 0.59 to 0.90); 4 trials, 480 participants; low-certainty evidence.

The first intervention had a higher number of any adverse events (number of events) than second intervention in the following direct comparisons.

- Sclerotherapy versus beta-blockers: RaR 2.47 (95% CrI 1.27 to 5.06); 2 trials, 90 participants; low-certainty evidence.
- Beta-blockers plus variceal band ligation versus beta-blockers: RaR 1.72 (95% CrI 1.08 to 2.76); 1 trial, 140 participants; low-certainty evidence.
- Sclerotherapy versus no active intervention: RaR 2.61 (95% CrI 2.18 to 3.18); 2 trials, 386 participants; low-certainty evidence.

There was no evidence of differences between the treatments in the remaining direct comparisons (i.e. the remaining direct comparisons were not statistically significant) as shown in Table 4 (very low-certainty evidence).

Network meta-analysis

All the trials were connected to the network. All treatments were connected. There was evidence of inconsistency according to

model fit, but not by the inconsistency factor. We could not obtain convergence for treatment-by-design model; therefore, there is uncertainty in the validity of NMA results. The direct comparisons are more reliable. We used the fixed-effect model because it had equivalent results and model fit as random-effects model.

In the NMA, in the following pairwise comparisons, the first intervention had lower any adverse events (number of events) than second intervention:

- Variceal band ligation versus beta-blockers: RaR 0.77 (95% CrI 0.63 to 0.94); direct comparison: RaR 0.73 (95% CrI 0.59 to 0.90); 4 trials, 480 participants; low-certainty evidence.
- Beta-blockers plus variceal band ligation versus sclerotherapy: RaR 0.53 (95% CrI 0.28 to 0.97); no direct comparison; very low-certainty evidence.

In the NMA, in the following pairwise comparisons, the first intervention had a higher number of any adverse events (number of events) than second intervention:

- Sclerotherapy versus beta-blockers: RaR 2.49 (95% CrI 1.53 to 4.22); direct comparison: RaR 2.47 (95% CrI 1.27 to 5.06); 2 trials, 90 participants; low-certainty evidence.
- Sclerotherapy versus no active intervention: RaR 2.56 (95% CrI 2.13 to 3.08); direct comparison: RaR 2.61 (95% CrI 2.18 to 3.18); 2 trials, 386 participants; low-certainty evidence.
- Sclerotherapy versus variceal band ligation: RaR 3.24 (95% CrI 1.99 to 5.49); direct comparison: RaR 1.99 (95% CrI 0.95 to 4.45); 1 trial, 107 participants; low-certainty evidence.
- Beta-blockers plus variceal band ligation versus variceal band ligation: RaR 1.73 (95% CrI 1.19 to 2.54); direct comparison: RaR 1.18 (95% CrI 0.66 to 2.06); 1 trial, 66 participants; low-certainty evidence.

There was no evidence of differences between the treatments in the remaining comparisons in the NMA (very low-certainty evidence).

Liver transplantation

Eight trials (766 participants) reported liver transplantation (Andreani 1990; Merkel 2004; Schepke 2004; Jutabha 2005; Thuluvath 2005; Norbeto 2007; Lo 2010; Drastich 2011). The trials compared five treatments. There were 68 events in total (8.9%). The weighted median control group proportion was 4.8%.

Direct comparisons

There was no evidence of differences in any of the direct comparisons (i.e. there was no statistically significant difference in any of the comparisons) (very low-certainty evidence).

Network meta-analysis

One trial was not connected to the network because it had zero events in both intervention groups (Andreani 1990). The network had four connected treatments. There were no triangular or quadrangular loops; therefore, inconsistency was not checked. We used the fixed-effect model because it had equivalent results and model fit as random-effects model. In the NMA, there was no evidence of differences in any of the comparisons (very low-certainty evidence).

Variceal bleeding

Symptomatic variceal bleeding

Seven trials (1007 participants) reported symptomatic variceal bleed (Sauerbruch 1988; PROVA study group 1991; Angelico 1993; Lo 2004; Jutabha 2005; Lo 2010; Feng 2012). The trials compared seven treatments. There were 198 events in total (19.7%). The weighted median control group proportion was 18%.

Direct comparisons

There was no evidence of differences in any of the direct comparisons (i.e. there was no statistically significant difference in any of the comparisons) (very low-certainty evidence).

Network meta-analysis

All the trials were connected to the network. All treatments were connected. There was no evidence of inconsistency according to the inconsistency factor or model fit. We could not obtain convergence for treatment-by-design model. We used the fixed-effect model because it had equivalent results and model fit as random-effects model. In the NMA, there was no evidence of differences in any of the comparisons.

Any variceal bleeding

Twenty-seven trials (2460 participants) reported any variceal bleeding (Paquet 1982; Witzel 1985; Lebrec 1988; Andreani 1990; Conn 1991; De Franchis 1991; Quer 1991; Kanazawa 1993; Duhamel 1994; Paquet 1994; Lay 1997; De 1999; Lo 1999; Song 1999; Chen 2000; Agarwal 2001; Borroni 2002; D'Amico 2002; Tomikawa 2004; Lay 2006; Wang 2006; Norbeto 2007; Perez-Ayuso 2010; Drastich 2011; Bonilha 2015; Khan 2017; Seo 2017). A total of seven treatments were compared in these trials. There were 430 events in total (17.5%). The weighted median control group proportion was 9.7%.

Direct comparisons

Beta-blockers plus variceal band ligation had lower 'any variceal bleeding' than beta-blockers (HR 0.21, 95% CrI 0.04 to 0.71; 1 trial, 173 participants; low-certainty evidence). Nitrates had a higher 'any variceal bleeding' than beta-blockers (HR 6.40, 95% CrI 1.58 to 47.42; 1 trial, 52 participants; low-certainty evidence).

There was no evidence of differences between the treatments in the remaining direct comparisons (i.e. the remaining direct comparisons were not statistically significant) as shown in Table 4 (very low-certainty evidence).

Network meta-analysis

All the trials were connected to the network. All treatments were connected. There was no evidence of inconsistency according to model fit, inconsistency factor, and the 'between-design' variance. We used the random-effects model because it was more conservative and had better model fit. The 'between-study variance' was 0.92 (95% CrI 0.36 to 2.32).

In the NMA, in the following pairwise comparisons, the first intervention had lower 'any variceal bleeding' than second intervention.

- Variceal band ligation versus no active intervention: HR 0.27 (95% CrI 0.09 to 0.76); direct comparison: HR 0.33 (95% CrI 0.01 to 10.90); 2 trials, 253 participants; low-certainty evidence.
- Sclerotherapy versus no active intervention: HR 0.38 (95% CrI 0.16 to 0.88); direct comparison: HR 0.36 (95% CrI 0.05 to 2.45); 6 trials, 530 participants; low-certainty evidence.
- Beta-blockers plus variceal band ligation versus no active intervention: HR 0.09 (95% CrI 0.01 to 0.54); no direct comparison; low-certainty evidence.

In the NMA, nitrates had a higher number of any variceal bleeding than beta-blockers plus variceal band ligation (HR 28.02, 95% CrI 1.46 to 719.82; no direct comparison; low-certainty evidence).

There was no evidence of differences between the treatments in the remaining comparisons in the NMA (very low-certainty evidence).

Other features of decompensation

Five trials (362 participants) reported other features of decompensation (Conn 1969; De 1999; Merkel 2000; D'Amico 2002; Lay 2006). The other features of decompensation included hepatic encephalopathy, ascites, liver failure, hepatorenal syndrome, and spontaneous bacterial peritonitis (secondary to ascites). The trials compared five treatments. There were 70 events in total (0.193 per participant). The weighted median control group proportion was 0.162 per participant.

Direct comparisons

There was no evidence of differences in any of the direct comparisons (i.e. there was no statistically significant difference in any of the comparisons) (very low-certainty evidence; Table 4). There was also no evidence of differences in the trial not connected to the network (RaR 0.90, 95% CrI 0.16 to 4.24; 1 trial, 29 participants; very low-certainty evidence).

Network meta-analysis

One trial was not connected to the network because it had treatments unconnected to the network (Conn 1969). The network had three connected treatments. There were no triangular or quadrangular loops; therefore, inconsistency was not checked. We used the fixed-effect model because it had equivalent results and model fit as the random-effects model. In the NMA, there was no evidence of differences in any of the comparisons (very low-certainty evidence).

Exploratory outcomes

Length of hospital stay

One trial (95 participants) reported length of hospital stay (days) (all admissions until maximal follow-up) (Santangelo 1988). The trial compared two treatments. The trial did not report the standard deviation or other information to calculate the standard deviation. The mean length of hospital stay was 9.2 days in the sclerotherapy group versus 10.4 days in the no active intervention group.

Number of days of lost work

No trials reported number of days of lost work.

Treatment costs

Two trials (124 participants) reported treatment costs (Jutabha 2005; Norbeto 2007). The trials compared two treatments. Therefore, only direct comparisons were applicable. The weighted median control group mean was USD 2362.5.

Variceal band ligation had a higher treatment costs than beta-blockers (MD USD 480.10, 95% CrI 297.50 to 663.20; 2 trials, 124 participants).

Subgroup analysis

We did not perform any subgroup analyses. This is because only one of the trials was at low risk of bias, separate data based on clinical features such as high risk of bleeding, other features of decompensation, or aetiology for cirrhosis, and none of the trial authors clearly stated whether they used ICH-GCP 1997 for defining serious adverse events or any adverse events. Most trials that provided data fell under the category of medium-term follow-up; therefore, subgroup analysis based on follow-up was not performed. Several trials were available for small versus moderately large or large oesophageal varices for mortality; however, we could not obtain convergence for this analysis despite various measures.

Sensitivity analysis

'best–worst' and 'worst–best' scenario analyses

We performed the 'best–worst' and 'worst–best' scenario analyses for the sensitivity analysis related to missing outcome data. There were changes to interpretation of the results for the following analyses in the following outcomes. The 'main analysis' refers to results without any imputation of data.

Mortality

- Sclerotherapy versus beta-blockers:
  - main analysis: no evidence of difference between groups;
  - worst–best analysis: no evidence of difference between groups;
  - best–worst analysis: higher in sclerotherapy than beta-blockers.
- Beta-blockers plus sclerotherapy versus beta-blockers:
  - main analysis: higher in beta-blockers plus sclerotherapy than beta-blockers;
  - worst–best analysis: no evidence of difference between groups;
  - best–worst analysis: higher in beta-blockers plus sclerotherapy than beta-blockers.

Any variceal bleeding

- Sclerotherapy versus no active intervention:
  - main analysis: lower in sclerotherapy than no active intervention;
  - worst–best analysis: lower in sclerotherapy than no active intervention;
  - best–worst analysis: no evidence of difference between groups.

These results should be interpreted with caution, as they are susceptible to attrition bias resulting from postrandomisation dropouts. There were no changes to interpretation of the results

for the remaining analyses or outcomes. These outcomes and comparisons are, therefore, robust to postrandomisation dropouts.

Imputation of standard deviations

We did not perform any imputation of standard deviations.

Assessment of reporting biases

Since there was no meaningful way in which to rank these studies (i.e. there was no specific change in the risk of bias in the studies, sample size, or the control group used over time), we were unable to perform the comparison-adjusted funnel plot. Mortality was reported in most trials. However, other important outcomes such as adverse events were not reported in some trials indicating the possibility of reporting biases.

Post hoc analyses

Following comments from clinical experts who commented that the baseline risk in the control group would have changed over time, we attempted to perform the following analyses: baseline risk-adjusted network meta-analyses for mortality and any variceal bleeding, the two outcomes reported by most trials and the outcomes that determine whether an outcome should be used. Of these, we could not obtain convergence for the baseline risk-adjusted NMA for any variceal bleeding. The results of the baseline risk-adjusted NMA for mortality is available in Table 5 and the effect estimates of the NMA for mortality is available in Table 6.

The major differences in the interpretation of the results between the main analysis and the post hoc analyses were as follows.

Baseline risk-adjusted analysis

Mortality

Almost all the interventions including a combination of beta-blockers plus variceal band ligation had increased mortality compared to beta-blockers alone (Table 5). The model fit was similar to that of the model that did not include the baseline risk.

Subset of trials published from the year 2000 onwards

Mortality

There was no evidence of differences between most interventions. Endoscopic sclerotherapy had worse mortality than most interventions.

Any variceal bleeding

There was no evidence of differences in any of the comparisons.

DISCUSSION

Summary of main results

We performed a systematic review and NMA of the common treatments used for primary prevention of oesophageal variceal bleeding in people with oesophageal varices due to liver cirrhosis. The review included 66 trials, with 6653 participants. The trials compared nine interventions. A total of 60 trials (6212 participants) were included for one or more comparisons of this review (Conn 1969; Paquet 1982; Witzel 1985; Pascal 1987; Wordehoff 1987; Fleig 1988; Ideo 1988; Lebrec 1988; Piai 1988; Santangelo 1988; Sauerbruch 1988; Snady 1988; Russo 1989; Andreani 1990; Conn 1991; De Franchis 1991; PROVA study group 1991; Quer 1991; Rossi 1991; VA Coop. Variceal Sclerotherapy Group 1991; Angelico 1993; Fassio 1993; Kanazawa 1993; Duhamel 1994; Paquet 1994; Lay 1997; De 1999; Lo 1999; Song 1999; Strauss 1999; Svoboda 1999; Chen 2000; Merkel 2000; Agarwal 2001; Borroni 2002; D'Amico 2002; Lui 2002; Lo 2004; Merkel 2004; Schepke 2004; Tomikawa 2004; Jutabha 2005; Psilopoulos 2005; Thuluvath 2005; Lay 2006; Wang 2006; Mishra 2007; Norbeto 2007; Tripathi 2009; Lo 2010; Perez-Ayuso 2010; Drastich 2011; Feng 2012; Singh 2012; Sarin 2013; Shah 2014; Bonilha 2015; Bhardwaj 2017; Khan 2017; Seo 2017).

Overall, 21.2% of the trial participants who received beta-blockers died during the follow-up period ranging from eight months to 60 months. Based on low-certainty evidence, beta-blockers, variceal band ligation, sclerotherapy, and beta-blockers plus nitrates all had lower mortality than no active intervention (beta-blockers versus no active intervention: 0.49, 95% CrI 0.36 to 0.67; direct comparison: HR 0.59, 95% CrI 0.42 to 0.83; 10 trials, 1200 participants; variceal band ligation versus no active intervention: HR 0.51, 95% CrI 0.35 to 0.74; direct comparison: HR 0.49, 95% CrI 0.12 to 2.14; 3 trials, 355 participants; sclerotherapy versus no active intervention: HR 0.66, 95% CrI 0.51 to 0.85; direct comparison: HR 0.61, 95% CrI 0.41 to 0.90; 18 trials, 1666 participants; beta-blockers plus nitrates versus no active intervention: HR 0.41, 95% CrI 0.20 to 0.85; no direct comparison). In the baseline risk-adjusted model (which had a similar model fit as the model that did not include the baseline risk), almost all the interventions including a combination of beta-blockers plus variceal band ligation had increased mortality compared to beta-blockers alone (Table 5). When a subset of trials published from 2000 onwards revealed the sclerotherapy had increased mortality than most other interventions. None of the trials reported health-related quality of life. Based on low-certainty evidence, variceal band ligation had a higher number of serious adverse events (number of events) than beta-blockers (RaR 10.49; 95% CrI 2.83 to 60.64; 1 trial, 168 participants).

Based on low-certainty evidence, beta-blockers plus nitrates had a higher number of 'any adverse events (number of participants)' than beta-blockers (OR 3.41, 95% CrI 1.11 to 11.28; 1 trial, 57 participants). Based on low-certainty evidence, adverse events (number of events) were higher in sclerotherapy than beta-blockers (RaR 2.49, 95% CrI 1.53 to 4.22; direct comparison: RaR 2.47, 95% CrI 1.27 to 5.06; 2 trials, 90 participants), sclerotherapy than no active intervention (RaR 2.56, 95% CrI 2.13 to 3.08; direct comparison: RaR 2.61, 95% CrI 2.18 to 3.18; 2 trials, 386 participants), sclerotherapy than variceal band ligation (RaR 3.24, 95% CrI 1.99 to 5.49; direct comparison: RaR 1.99; 95% CrI 0.95 to 4.45; 1 trial, 107 participants), beta-blockers plus variceal band ligation than beta-blockers (direct comparison: RaR 1.72, 95% CrI 1.08 to 2.76; 1 trial, 140 participants), and beta-blockers plus variceal band ligation than variceal band ligation (RaR 1.73, 95% CrI 1.19 to 2.54; direct comparison: RaR 1.18, 95% CrI 0.66 to 2.06; 1 trial, 66 participants).

Based on low-certainty evidence, any variceal bleeding was lower in beta-blockers plus variceal band ligation than beta-blockers (direct comparison: HR 0.21, 95% CrI 0.04 to 0.71; 1 trial, 173 participants), variceal band ligation than no active intervention (HR 0.27, 95% CrI 0.09 to 0.76; direct comparison: HR 0.33, 95% CrI 0.01 to 10.90; 2 trials, 253 participants), sclerotherapy than no active intervention (HR 0.38, 95% CrI 0.16 to 0.88; direct comparison: HR 0.36, 95% CrI 0.05 to 2.45; 6 trials, 530 participants), and beta-blockers plus variceal band ligation than no active intervention (HR 0.09, 95% CrI 0.01 to 0.54; no direct comparison). Based on low-certainty

evidence, any variceal bleeding was higher in nitrates than beta-blockers (direct comparison: HR 6.40, 95% CrI 1.58 to 47.42; 1 trial, 52 participants) and in beta-blockers plus variceal band ligation (HR 28.02, 95% CrI 1.46 to 719.82; no direct comparison). When a subset of trials published from 2000 onwards were analysed, there was no evidence of differences in any of the comparisons.

The evidence indicates considerable uncertainty about the effect of the interventions in the remaining comparisons.

The weighted median mortality in the beta-blockers group was 21.2% up to five years. The sample size required to detect a relative risk reduction of 20% in the experimental group, with type I error of 5%, and type II error of 20% was 3834 participants. The prevalence of oesophageal varices varies between 10% and 60% people with cirrhosis and large oesophageal varices (Li 2016b). Therefore, it is possible to power studies in this population based on mortality.

Probably the most important questions to be answered are in which group of people should primary prophylaxis be considered, and which of variceal band ligation versus beta-blockers is better. Beta-blockers, variceal band ligation, and sclerotherapy all decrease mortality compared to no intervention, but beta-blockers and variceal band ligation are associated with fewer adverse events than sclerotherapy, which also decreases mortality. However, there is uncertainty as to whether beta-blockers or variceal band ligation are better. The major clinical practice guidelines also highlight this uncertainty in the comparison between variceal band ligation and beta-blockers (de Franchis 2015; Tripathi 2015; Garcia-Tsao 2017; EASL 2018).

Some of the major issues described above are being investigated in the current ongoing trials.

- NCT03776955 and NCT03736265 are comparing beta-blockers with placebo for people with small oesophageal varices (although NCT03736265 is including only hepatitis B virus-related cirrhosis and does not have mortality as one of its outcomes).
- NCT02066649 and Tripathi 2019 are comparing beta-blockers versus variceal band ligation in people with medium or large oesophageal varices.
- NCT03776955 and Tripathi 2019 plan to measure health-related quality of life and, therefore, can address the uncertainty around it.

The trials included in this systematic review used different criteria for selection of participants. The current clinical practice guidelines suggest that primary prophylaxis should be used for people with large oesophageal varices and small oesophageal varices at high risk of bleeding (e.g. those with red spots or red wale markings) (de Franchis 2015; Tripathi 2015; Garcia-Tsao 2017; EASL 2018). In addition, AASLD guidelines, EASL guidelines, and the Baveno consensus VI conference position paper suggest the use of non-cardioselective beta-blockers in people with decompensated cirrhosis and small oesophageal varices (de Franchis 2015; Garcia-Tsao 2017; EASL 2018). The ongoing trials appear to focus on the size of the varices for risk stratification. There are currently no systematic reviews of the risk prediction tools for mortality or bleeding from oesophageal varices. Such a systematic review will help in risk stratification of people with cirrhosis, so that primary prophylaxis can be started in people who are likely to benefit most.

Overall completeness and applicability of evidence

There did not seem to be any restrictions based on the aetiology or the presence of other features of decompensation in the trials that provided this information, particularly for the main interventions compared in this review. Therefore, the results of the study are applicable in people with cirrhosis resulting from varied aetiologies having oesophageal varices without history of bleeding.

The findings of this review are applicable only for adults with cirrhosis with oesophageal varices and are not applicable to children, people (of any age group) with gastric varices, or people with oesophageal varices due to non-cirrhotic causes of portal hypertension such as portal vein thrombosis or schistosomiasis. Moreover, the results are not applicable to people who have undergone liver transplantation. While many trials included participants with small varices, it is likely that most of these participants were at high risk of bleeding (although these were not stated using the definitions of the Baveno-Consensus VI conference. Similarly, although some trials included participants without features suggestive of high risk of bleeding, it is likely that most of these participants had medium or large varices. Therefore, the findings of this review are applicable only to people with medium or large oesophageal varices and those with small varices at high risk of bleeding.

Quality of the evidence

The overall certainty (quality) of evidence varied between low and very low. One of the main reasons for this was the unclear or high risk of bias in all but one trial. It is possible to perform trials at low risk of bias in certain comparisons: randomisation can be performed using standard methods, for example, web-based central randomisation; an intention-to-treat analysis can be performed; and a protocol should be published prior to recruitment. However, blinding of healthcare providers and participants may not be possible if endoscopic treatments are used as one of the interventions. It is possible to obtain low risk of performance bias by outlining the protocol clearly for additional treatments and hospital admissions. Outcome assessor blinding can be achieved for all comparisons by using placebo or a second team to assess the outcomes. If that is not possible, using clear, highly reproducible criteria for outcome definitions can decrease detection bias.

Another major reason for the decreased certainty of evidence was imprecision. While some network meta-analyses had sufficient number of events, none of the direct comparisons had an adequate sample size. As a result, the CrIs overlapped clinically significant benefits and clinically significant harms for most comparisons. Outcomes from ongoing trials can probably decrease the imprecision.

We used clinical outcomes; therefore, there is no issue of indirectness due to outcomes. There was no suggestion that the potential effect modifiers were systematically different across comparisons (i.e. there was no concern about the transitivity assumption) for most outcomes. However, it should be noted that some of the comparisons were downgraded as they were solely made up of indirect comparisons. One cannot rule out inconsistency ('incoherence' according to GRADE terminology) despite finding no evidence of this in most analyses.

There was no meaningful way to rank these studies (i.e. there was no specific change in the risk of bias in the studies, sample size, or the control group used over time); we have completed a thorough search for studies on effectiveness. However, different sets of trials were included for different outcomes: while 85% of trials reported mortality, only about 15% of trials reported serious adverse events adequately; only about 40% of trials reported variceal bleeding adequately; and less than 10% of trials described other decompensation events. These are outcomes that should have been recorded in trials of this nature, but were not reported. This may suggest reporting bias for these outcomes.

Potential biases in the review process

We selected a range of databases to search without using any language restrictions and conducted the NMA according to NICE DSU guidance. In addition, we analysed using the fixed-effect model and random-effects model and assessed and reported inconsistency whenever possible. These are the strengths of the review process.

We excluded studies that compared variations in duration or dose in the different interventions. Hence, this review does not provide information on whether one variation (e.g. drug dose or intervention frequency, or precise method of delivering an intervention) is better than another. We also considered drug classes as treatment nodes (as stated in the protocol). It is possible that some drugs in a drug class, for example, carvedilol, may be more effective than propranolol. However, there is no evidence to demonstrate that the treatment effects are different within the drug classes. If future trials demonstrate that carvedilol is more effective than propranolol, these must be considered as different treatment nodes in updates of this review.

All the trials were at high risk of bias and there was significant uncertainty in the ranking. Therefore, we could not rank the interventions in the order of effectiveness. The potential effect modifiers in the trials that reported them were broadly similar across comparisons. The results of direct comparisons and indirect comparisons were similar for most outcomes where we could assess this. Therefore, the concern about the transitivity assumption was low. However, this cannot be ruled out.

We included only randomised clinical trials, which are known to focus mostly on benefits and do not collect and report harms in a detailed manner. A significant effort is required to identify non-randomised studies that reported harms. It is also challenging to assess the risk of bias in those studies. If the ongoing trials result in adequate power to find meaningful differences in mortality, a systematic review on adverse events from observational studies will likely be unnecessary.

We included the trials without applying any restrictions based on publication date. The baseline risk may have changed over time. Therefore, we performed a post hoc analysis adjusting for baseline risk and performed an analysis including only trials published from 2000 onwards.

Agreements and disagreements with other studies or reviews

This is the first NMA of all the major interventions for initial management of oesophageal varices irrespective of size of varix and risk of bleeding. One NMA compared the different treatments for large oesophageal varices only and concluded that beta-blockers may decrease mortality. They also concluded that variceal band ligation may result in increased serious adverse events than beta-blockers. We agree with these findings (Sharma 2019). We also agree with Gluud 2012 that there was no evidence of a difference in mortality between beta-blockers and variceal band ligation. We are also broadly in agreement with the major guidelines that beta-blockers should be considered the first line treatment for primary prophylaxis and further research is necessary to determine whether variceal band ligation is better than beta-blockers (de Franchis 2015; Tripathi 2015; Garcia-Tsao 2017; EASL 2018).

AUTHORS' CONCLUSIONS

Implications for practice

Based on low-certainty evidence, beta-blockers, variceal band ligation, sclerotherapy, and beta-blockers plus nitrates may decrease mortality compared to no intervention in people with high-risk oesophageal varices, cirrhosis, and no history of bleeding. Based on low-certainty evidence, variceal band ligation may result in more serious adverse events than beta-blockers. The evidence indicates considerable uncertainty about the effect of beta-blockers versus variceal band ligation on variceal bleeding. The evidence also indicates considerable uncertainty about the effect of the interventions in most of the remaining comparisons.

Implications for research

For future randomised clinical trials within prevention of oesophageal variceal bleeding, it is noteworthy that only 85% of the included trials reported mortality; only about 15% of trials reported serious adverse events adequately; only about 40% of trials reported variceal bleeding adequately; and less than 10% of trials described other decompensation events. Moreover, the trials dealt with too small sample sizes. Furthermore, the trials did not adhere to the SPIRIT (www.spirit-statement.org) and CONSORT (www.consort-statement.org) statements and were seldom based on systematic reviews of previous trials.

The current ongoing trials may answer most of the uncertainties in this systematic review. These trials expect to recruit more than 4000 participants (approximately 6800 participants were included in this review) by 2024. There are currently no systematic reviews of the risk prediction tools for mortality or bleeding from oesophageal varices. Such a systematic review will help in risk stratification of people with cirrhosis, so that primary prophylaxis can be started in people who are likely to benefit most.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Agarwal 2001

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: India Period of recruitment: not stated Number randomised: 92 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 92 Mean age (years): not stated Females: not stated Small varices: not stated High risk of bleeding: not stated Other features of decompensation: not stated Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Other inclusion/exclusion criteria: not stated
Interventions	Group 1: beta-blockers and variceal band ligation (n = 46) Further details: propranolol (mean dose 92 mg/day) + variceal band ligation every 1–2 weeks until obliteration Group 2: variceal band ligation (n = 46) Further details: variceal band ligation every 1–2 weeks until obliteration
Outcomes	Mortality at maximal follow-up, variceal bleed at maximal follow-up (any) (number of participants) Follow-up (months): 8

Agarwal 2001 *(Continued)*

Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: no information of postrandomisation dropouts; authors stated that an intention to treat analysis was used.
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Andreani 1990

Study characteristics

Methods	Randomised clinical trial
Participants	Country: France Period of recruitment: 1985–1988 Number randomised: 85 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 85 Mean age (years): 56 Females: 32 (37.6%) Small varices: 72 (84.7%) High risk of bleeding: not stated Other features of decompensation: 5 (5.9%)

Andreani 1990 *(Continued)*

	Alcohol-related cirrhosis: 67 (78.8%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Other exclusion criteria: existence of hepatocellular carcinoma; contraindication to use of propranolol; serious associated illness reducing life expectancy to < 1 year; previous treatment with endoscopic sclerotherapy, propranolol, or surgery for portal hypertension
Interventions	Group 1: sclerotherapy (n = 42) Further details: sclerosant, 1% or 2% polidocanol 15–40 mL repeated every 1 or 2 weeks until complete disappearance Group 2: beta-blockers (n = 43) Further details: propranolol doses titrated to achieve a 25% reduction in resting heart rate Group 3: vitamin K. Excluded as vitamin K was not an intervention of interest – although the authors used this as placebo, vitamin K may have procoagulant properties
Outcomes	Mortality at maximal follow-up, serious adverse events (number of participants), liver transplantation at maximal follow-up, variceal bleed at maximal follow-up (any) (number of participants) Follow-up (months): 24
Notes	Source of funding (quote): "the study was funded by INSERM (Institut National de la Santé et de la Recherche Médicale) (author reply)." Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "the allocation was in sealed envelopes" (author reply).
Allocation concealment (selection bias)	Unclear risk	Quote: "the allocation was in sealed envelopes" (author reply). Comment: further details were not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "these treatments were not administered blindly."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "these treatments were not administered blindly."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts

Andreani 1990 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: no prepublished protocol available, but authors reported mortality, adverse events, and variceal bleed adequately.
Other bias	Low risk	Comment: no other bias noted

Angelico 1993

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: 1988–1990 Number randomised: 118 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 118 Mean age (years): 58 Females: 47 (39.8%) Small varices: 83 (70.3%) High risk of bleeding: not stated Other features of decompensation: 51 (43.2%) Alcohol-related cirrhosis: 32 (27.1%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Other inclusion/exclusion criteria: no history of previous bleeding, and a risk of bleeding more than 11% at 1 year and 16% at 2 years according to the North Italian Endoscopic Club (NIEC) predictive scoring system
Interventions	Group 1: nitrates (n = 57) Further details: isosorbide-5-mononitrate 3 times daily up to a maximum tolerated dose Group 2: beta-blockers (n = 61) Further details: propranolol up to a maximum tolerated dose (median 60 mg/day)
Outcomes	Mortality at maximal follow-up, variceal bleed at maximal follow-up (symptomatic recovery) (number of participants) Follow-up (months): 44
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Angelico 1993 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Using blocked randomization and sealed envelopes." Comment: no further details.
Allocation concealment (selection bias)	Unclear risk	Quote: "Using blocked randomization and sealed envelopes." Comment: no further details.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Bhardwaj 2017

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: India Period of recruitment: 2010–2012 Number randomised: 140 Postrandomisation dropouts: not stated Revised sample size: 140 Mean age (years): 49 Females: 21 (15.0%) Small varices: 140 (100.0%) High risk of bleeding: not stated Other features of decompensation: 17 (12.1%) Alcohol-related cirrhosis: 33 (23.6%) Viral-related cirrhosis: 35 (25.0%)

Bhardwaj 2017 *(Continued)*

	Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: 72 (51.4%) Other exclusion criteria: non-cirrhotic portal hypertension; Child-Turcotte-Pugh score > 12 or refractory ascites; acute kidney injury, significant cardiopulmonary comorbidity, uncontrolled diabetes, peripheral vascular disease; history of prior oesophageal variceal ligation or sclerotherapy or of surgery for portal hypertension; presence of any malignancy that significantly affects survival; evidence of alcoholic hepatitis or active alcohol abuse with last intake ≤ 1 month
Interventions	Group 1: no active intervention (n = 70) Further details: for 2 years Group 2: beta-blockers (n = 70) Further details: carvedilol 3.125–12.5 mg twice daily to ensure systolic blood pressure < 100 mmHg and heart rate < 55 bpm
Outcomes	Mortality at maximal follow-up Follow-up (months): 21
Notes	Source of funding: not stated Trial name/trial registry number: NCT01196507 Attempted to contact authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "An independent statistician generated allocation sequence." Comment: although the details on sequence generation were not reported, as an independent statistician generated allocation sequence, the sequence was probably random (and not based on hospital numbers, date of birth, alternation, or other quasi-random methods of sequence generation).
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "We decided, in agreement with the ethics committee, to use a single-blind design, also because it was considered unrealistic that blindness could be kept with a drug with an evident effect on heart rate." Comment: only the participant was blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "We decided, in agreement with the ethics committee, to use a single-blind design, also because it was considered unrealistic that blindness could be kept with a drug with an evident effect on heart rate."
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: although the participant flow was reported, an earlier abstract published 4 years previously had greater number of participants.
Selective reporting (reporting bias)	High risk	Comment: a prepublished protocol available prior to the start of the study showed that the authors had changed the timing of the primary outcome, removed important clinical outcomes as secondary endpoints, and replaced them with surrogate endpoints.

Bhardwaj 2017 *(Continued)*

Other bias	High risk	Comment: although the full text and abstract were linked to the same trial registry number and the period of recruitment was the same, and the abstract was published 4 years prior to the full text, the abstract mentioned randomising 175 participants (subsequent abstracts also refer to 175 participants), but the consort flow diagram showed only 140 participants without any reference about including or excluding the remaining 35 participants and an intention to treat analysis included only 140 participants.

Bonilha 2015

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Brazil Period of recruitment: 2008–2011 Number randomised: 66 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 66 Mean age (years): 54 Females: 19 (28.8%) Small varices: 58 (87.9%) High risk of bleeding: 34 (51.5%) Other features of decompensation: not stated Alcohol-related cirrhosis: 19 (28.8%) Viral-related cirrhosis: 37 (56.1%) Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: 12 (18.2%) Other exclusion criteria: contraindication for beta-blockers or previous and continued use of beta-blockers; previous shunt operation or TIPS; previous endoscopic band ligation or sclerotherapy for oesophageal varices; pregnancy; class IV or V according to the American Society of Anesthesiologists
Interventions	Group 1: beta-blockers and variceal band ligation (n = 34) Further details: variceal band ligation: multiband ligation device, maximum of 10 bands per session repeated at 3- to 4-week intervals until eradication of varices and propranolol 40 mg twice daily orally titrated at reduction in heart rate to 55 bpm or a 25% decrease in baseline heart rate Group 2: variceal band ligation (n = 32) Further details: variceal band ligation: multiband ligation device, maximum of 10 bands per session repeated at 3- to 4-week intervals until eradication of varices
Outcomes	Mortality at maximal follow-up, serious adverse events (number of participants), serious adverse events (number of events), any adverse events (number of events), variceal bleed at maximal follow-up (any) (number of participants)

Bonilha 2015 *(Continued)*

	Follow-up (months): 12
Notes	Source of funding: not stated Trial name/trial registry number: NCT01893541 Attempted to contact the authors in February 2020; received no additional information Individual participants had multiple cirrhosis aetiologies

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed by an independent physician by sequentially opening numbered opaque and sealed envelopes containing group allocation cards in a random sequence." Comment: although the details on sequence generation were not reported, the method of allocation concealment used made it highly likely that the sequence was random.
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed by an independent physician by sequentially opening numbered opaque and sealed envelopes containing group allocation cards in a random sequence."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The endoscopic diagnosis of oesophageal varices eradication or recurrence was always defined on the basis of the analysis of one physician who was blinded to patients' group assignments (only this physician was blinded)." Comment: participants and the healthcare providers were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "The endoscopic diagnosis of oesophageal varices eradication or recurrence was always defined on the basis of the analysis of one physician who was blinded to patients' group assignments (only this physician was blinded)." Comment: blinding was achieved only for an outcome that was not of interest for this review.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: a prepublished protocol was not available, but the authors reported mortality, adverse events, and variceal bleed adequately.
Other bias	Low risk	Comment: no other bias noted

Borroni 2002

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: 1994–1998

Borroni 2002 *(Continued)*

	Number randomised: 52 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 52 Mean age (years): 60 Females: 15 (28.8%) Small varices: not stated High risk of bleeding: not stated Other features of decompensation: 52 (100.0%) Alcohol-related cirrhosis: 23 (44.2%) Viral-related cirrhosis: 37 (71.2%) Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: 2 (3.8%) Other exclusion criteria: use of vasoactive drugs or other prophylactic treatments; hepatocellular carcinoma; renal failure; portal vein thrombosis; active alcohol drinking; refractory ascites defined according to the criteria of the International Ascites Club
Interventions	Group 1: nitrates (n = 27) Further details: isosorbide mononitrate 20 mg, increased to 40 mg twice daily Group 2: beta-blockers (n = 25) Further details: nadolol 40 mg increased until the resting heart rate fell by 25% or below 55 bpm
Outcomes	Mortality at maximal follow-up, variceal bleed at maximal follow-up (any) (number of participants) Follow-up (months): 18
Notes	Source of funding (quote): "A. Maggi and A. Panzeri received fellowship grants from the 'Istituto di Ricovero e Cura a Carattere Scientifico' (IRCCS) Ospedale Maggiore di Milano. This work was supported in part by a grant of the Ministero della Università Italiano." Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information Individual participants had multiple cirrhosis aetiologies

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: information not available

Borroni 2002 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Cales 1989a

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: France Period of recruitment: not stated Number randomised: 24 Postrandomisation dropouts: not stated Revised sample size: 24 Mean age (years): not stated Females: not stated Small varices: not stated High risk of bleeding: not stated Other features of decompensation: not stated Alcohol-related cirrhosis: 24 (100.0%) Viral-related cirrhosis: 0 (0.0%) Autoimmune disease-related cirrhosis: 0 (0.0%) Other causes of cirrhosis: 0 (0.0%) Other inclusion criteria: people with alcoholic cirrhosis and large oesophageal varices Other exclusion criteria: previous haemorrhage of gastrointestinal tract or hepatic encephalopathy
Interventions	Group 1: no active intervention (n = 8) Further details: placebo Group 2: beta-blockers (n = 16) Further details: propranolol 160 mg daily (conventional or long-acting) – no further details

Cales 1989a *(Continued)*

Outcomes	No outcomes of interest reported
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Cales 1989b

Study characteristics

Methods	Randomised clinical trial
Participants	Country: France Period of recruitment: not stated Number randomised: 16 Postrandomisation dropouts: not stated Revised sample size: 16 Mean age (years): 50 Females: not stated Small varices: not stated

Cales 1989b *(Continued)*

	High risk of bleeding: not stated Other features of decompensation: 6 (37.5%) Alcohol-related cirrhosis: 16 (100.0%) Viral-related cirrhosis: 0 (0.0%) Autoimmune disease-related cirrhosis: 0 (0.0%) Other causes of cirrhosis: 0 (0.0%) Other exclusion criteria: contraindication to beta-blockers; treatment with any cardiovascular drug in the 15 days before entry into the study; concomitant drugs apart from vitamins
Interventions	Group 1: no active intervention (n = 8) Further details: placebo Group 2: beta-blockers (n = 8) Further details: propranolol 160 mg daily (no further details)
Outcomes	No outcomes of interest reported
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Chen 2000

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Taiwan Period of recruitment: not stated Number randomised: 56 Postrandomisation dropouts: not stated Revised sample size: 56 Mean age (years): not stated Females: not stated Small varices: not stated High risk of bleeding: not stated Other features of decompensation: not stated Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Other exclusion criteria: prior gastrointestinal bleeding
Interventions	Group 1: variceal band ligation (n = 26) Further details: variceal band ligation (microvasive speedband ligator) every 2–3 weeks until eradication Group 2: beta-blockers (n = 30) Further details: propranolol to reduce heart rate by 25% (no further details)
Outcomes	Mortality at maximal follow-up, variceal bleed at maximal follow-up (any) (number of participants) Follow-up (months): 12
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available

Chen 2000 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Conn 1969

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: 1965–1968 Number randomised: 29 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 29 Mean age (years): 47 Females: not stated Small varices: not stated High risk of bleeding: not stated Other features of decompensation: 29 (100.0%) Alcohol-related cirrhosis: 29 (100.0%) Viral-related cirrhosis: 0 (0.0%) Autoimmune disease-related cirrhosis: 0 (0.0%) Other causes of cirrhosis: 0 (0.0%) Other exclusion criteria: aged > 65 years
Interventions	Group 1: portocaval shunt (n = 13) Further details: portocaval shunt Group 2: no active intervention (n = 16)

Conn 1969 *(Continued)*

	Further details: no treatment
Outcomes	Mortality at maximal follow-up, other features of decompensation at maximal follow-up, variceal bleed at maximal follow-up (any) (number of rebleeds) Follow-up (months): 19.1
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "sequentially numbered, sealed envelope." Comment: although the details on sequence generation were not reported, the method of allocation concealment used makes it highly likely that the sequence was random.
Allocation concealment (selection bias)	Low risk	Quote: "sequentially numbered, sealed envelope."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: although the authors excluded 1 participant who refused to undergo surgery from their analysis, they reported the outcomes of this person; therefore, we included them in our analysis.
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Conn 1991

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: multicentre; Spain, USA Period of recruitment: 1982–1986 Number randomised: 102 Postrandomisation dropouts: 0 (0.0%)

Conn 1991 *(Continued)*

	Revised sample size: 102 Mean age (years): 54 Females: 29 (28.4%) Small varices: 55 (53.9%) High risk of bleeding: not stated Other features of decompensation: 11 (10.8%) Alcohol-related cirrhosis: 80 (78.4%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Other inclusion criteria: well-established clinical diagnosis of cirrhosis, oesophageal varices on endoscopy and portal hypertension Other exclusion criteria: previous gastrointestinal bleed
Interventions	Group 1: no active intervention (n = 51) Further details: placebo Group 2: beta-blockers (n = 51) Further details: propranolol: dosage based on titration median dosage 80 mg; duration not stated clearly, but ≥ 6 months
Outcomes	Mortality at maximal follow-up, variceal bleed at maximal follow-up (any) (number of participants) Follow-up (months): 17
Notes	Source of funding (quote): "Supported by Ayerst Laboratories, New York, New York; Imperial Chemical industries, Spain; and the Veterans Administration Merit Review Program" Trial name/trial registry number: CT 06510-8056 Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the patients were randomly selected using a sealed envelope technique and computer-generated randomization to receive either placebo or propranolol therapy."
Allocation concealment (selection bias)	Low risk	Quote: "the patients were randomly selected using a sealed envelope technique and computer-generated randomization to receive either placebo or propranolol therapy."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The placebo and the propranolol tablets were identical in appearance. To maintain the double-blind nature of the investigation, the patients were examined on each visit by a nurse and the postdoctoral fellow assigned to the study."

Conn 1991 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The placebo and the propranolol tablets were identical in appearance. To maintain the double-blind nature of the investigation, the patients were examined on each visit by a nurse and the postdoctoral fellow assigned to the study."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

D'Amico 2002

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: 1992–1996 Number randomised: 57 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 57 Mean age (years): 56 Females: 27 (47.4%) Small varices: 0 (0.0%) High risk of bleeding: 57 (100.0%) Other features of decompensation: 9 (15.8%) Alcohol-related cirrhosis: not stated Viral-related cirrhosis: 49 (86.0%) Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Other exclusion criteria: large varices known for > 1 year; hepatocellular carcinoma; serum creatinine > 2 mg/dL; aged > 75 years; features of decompensation such as hepatic encephalopathy; contraindications to beta-blockers
Interventions	Group 1: beta-blockers + nitrates (n = 30) Further details: nadolol 20 mg daily increased by 20 mg until maximum tolerated dose (heart rate > 55 bpm) was reached + isosorbide mononitrate 10 mg twice daily increased to 40 mg twice daily until maximum tolerated dose (systolic blood pressure > 90 mmHg) was reached Group 2: beta-blockers (n = 27)

D'Amico 2002 *(Continued)*

	Further details: nadolol 20 mg daily increased by 20 mg until maximum tolerated dose (heart rate > 55 bpm) was reached + placebo
Outcomes	Mortality at maximal follow-up, any adverse events (number of participants), variceal bleed at maximal follow-up (any) (number of participants), other features of decompensation at maximal follow-up Follow-up (months): 31
Notes	Source of funding (quote): "The trial drug and placebo were kindly provided by Chiesi Farmaceutici, Florence, Italy" Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Treatment packages were consecutively numbered and contained active treatment or placebo according to a randomisation by permuted blocks of 10…Each patient in the included trial was assigned to the next treatment package (which randomly contained the active drug or placebo)." Comment: although details on sequence generation were not reported, the method of allocation concealment used makes it highly likely that the sequence was random.
Allocation concealment (selection bias)	Low risk	Quote: "Treatment packages were consecutively numbered and contained active treatment or placebo according to a randomisation by permuted blocks of 10…Each patient in the included trial was assigned to the next treatment package (which randomly contained the active drug or placebo)." Comment: although the precise method of sequence generation was not reported, the allocation was probably concealed to implement this method of blinding.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind placebo controlled trial." Comment: blinding was achieved using a placebo.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double-blind placebo controlled trial." Comment: blinding was achieved using a placebo.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: a prepublished protocol was not available, but the authors reported mortality, adverse events, and variceal bleed adequately.
Other bias	Low risk	Comment: no other bias noted

De 1999

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: India Period of recruitment: 1994–1996 Number randomised: 30 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 30 Mean age (years): 40 Females: 8 (26.7%) Small varices: 0 (0.0%) High risk of bleeding: not stated Other features of decompensation: 4 (13.3%) Alcohol-related cirrhosis: 5 (16.7%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Other inclusion criteria: hepatic venous pressure gradient ≥ 12 mmHg
Interventions	Group 1: variceal band ligation (n = 15) Further details: variceal band ligation: weekly to fortnightly until variceal eradication Group 2: beta-blockers (n = 15) Further details: propranolol to decrease heart rate by 25%
Outcomes	Variceal bleed at maximal follow-up (any) (number of participants), other features of decompensation at maximal follow-up Follow-up (months): 17.6
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available

De 1999 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

De Franchis 1991

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: 1985–1987 Number randomised: 126 Postrandomisation dropouts: 20 (15.9%) Revised sample size: 106 Reasons for postrandomisation dropouts: not high-risk varices, previous history of bleeding, prior treatment with beta-blockers, did not consent to treatment Mean age (years): 56 Females: 37 (34.9%) Small varices: not stated High risk of bleeding: not stated Other features of decompensation: not stated Alcohol-related cirrhosis: 40 (37.7%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Other exclusion criteria: life expectancy < 1 year, gastrointestinal ulcers at randomisation
Interventions	Group 1: sclerotherapy (n = 55)

De Franchis 1991 *(Continued)*

	Further details: sclerotherapy: ethanolamine oleate 5% or 1% polidocanol, repeated at 7 days, 30 days, and then monthly under eradication Group 2: no active intervention (n = 51) Further details: no treatment
Outcomes	Mortality at maximal follow-up, variceal bleed at maximal follow-up (any) (number of participants) Follow-up (months): 24
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "At the beginning of the study, each center was given a computer-generated randomization list, which was kept by physicians not directly involved in the study."
Allocation concealment (selection bias)	Low risk	Quote: "At the beginning of the study, each center was given a computer-generated randomization list, which was kept by physicians not directly involved in the study."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were postrandomisation dropouts, but it was unclear whether these were related to the outcomes. Our sensitivity analysis indicated the results of the network meta-analysis were sensitive to postrandomisation dropouts.
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Deplano 2001

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: not stated

Deplano 2001 *(Continued)*

	Number randomised: 36 Postrandomisation dropouts: not stated Revised sample size: 36 Mean age (years): not stated Females: not stated Small varices: not stated High risk of bleeding: not stated Other features of decompensation: not stated Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Other exclusion criteria: no previous bleeding
Interventions	Group 1: beta-blockers + nitrates (n = 14) Further details: nadolol + isosorbide mononitrates (no further details) Group 2: beta-blockers (n = 22) Further details: nadolol (no further details)
Outcomes	None of the outcomes of interest were reported.
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias)	Unclear risk	Comment: information not available

Deplano 2001 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Drastich 2011

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Czech Republic Period of recruitment: not stated Number randomised: 73 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 73 Mean age (years): 57 Females: 22 (30.1%) Small varices: not stated High risk of bleeding: 28 (38.4%) Other features of decompensation: 20 (27.4%) Alcohol-related cirrhosis: 46 (63.0%) Viral-related cirrhosis: 9 (12.3%) Autoimmune disease-related cirrhosis: 2 (2.7%) Other causes of cirrhosis: 16 (21.9%) Other exclusion criteria: congestive heart failure, renal failure, malignancy, history of sclerotherapy, endoscopic variceal band ligation or portosystemic shunt, gastric or duodenal ulcer
Interventions	Group 1: variceal band ligation (n = 40) Further details: variceal band ligation: 6 Shooter, Wilson-Cook; 2-weekly intervals until eradication of varices Group 2: beta-blockers (n = 33) Further details: propranolol started at 20 mg twice daily and increased to reduce heart rate by 25%, but not < 55 bpm
Outcomes	Mortality at maximal follow-up, serious adverse events (number of participants), any adverse events (number of participants), liver transplantation at maximal follow-up, variceal bleed at maximal follow-up (any) (number of participants) Follow-up (months): 11

Drastich 2011 *(Continued)*

Notes	Source of funding (quote): "Study was funded by Grant Agency of Ministry of Health of the Czech Republic" (author reply) Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated table of random numbers."
Allocation concealment (selection bias)	Low risk	Quote: "randomization was centralized" (author reply).
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Study was not blinded" (author reply).
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Study was not blinded" (author reply).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: a prepublished protocol was not available, but the authors reported mortality, adverse events, and variceal bleed adequately.
Other bias	Low risk	Comment: no other bias noted

Duhamel 1994

Study characteristics

Methods	Randomised clinical trial
Participants	Country: France Period of recruitment: 1985–1988 Number randomised: 117 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 117 Mean age (years): 56 Females: 29 (24.8%) Small varices: 103 (88.0%) High risk of bleeding: 32 (27.4%)

Duhamel 1994 *(Continued)*

	Other features of decompensation: 75 (64.1%) Alcohol-related cirrhosis: 94 (80.3%) Viral-related cirrhosis: 8 (6.8%) Autoimmune disease-related cirrhosis: 4 (3.4%) Other causes of cirrhosis: 10 (8.5%) Other exclusion criteria: aged > 80 years, hepatocellular carcinoma, heart failure, respiratory failure, previous variceal haemorrhage, previous gastrointestinal bleed of unknown cause, use of beta-blockers
Interventions	Group 1: sclerotherapy (n = 57) Further details: sclerotherapy: up to 30 mL of 1% polidocanol repeated every 3 weeks until obliteration of varices Group 2: no active intervention (n = 60) Further details: no treatment
Outcomes	Mortality at maximal follow-up, variceal bleed at maximal follow-up (any) (number of participants) Follow-up (months): 30
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Each centre was in possession of numbered sealed envelopes." Comment: further details were not available.
Allocation concealment (selection bias)	Unclear risk	Quote: "Each centre was in possession of numbered sealed envelopes." Comment: further details were not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: although the study authors excluded 1 participant, the outcome for this person was reported; therefore, we included them in the analysis.
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available

Duhamel 1994 *(Continued)*

Other bias	Low risk	Comment: no other bias noted

Fassio 1993

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Argentina Period of recruitment: 1989–1991 Number randomised: 42 Postrandomisation dropouts: not stated Revised sample size: 42 Mean age (years): 53 Females: 8 (19.0%) Small varices: not stated High risk of bleeding: 42 (100.0%) Other features of decompensation: 24 (57.1%) Alcohol-related cirrhosis: 35 (83.3%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Other exclusion criteria: hepatocellular carcinoma, renal failure, cardiac failure, treatments that could change survival (steroids for autoimmune hepatitis, interferon for hepatitis B virus/hepatitis C virus) or other disease limiting survival
Interventions	Group 1: nitrates (n = 23) Further details: isosorbide mononitrate 20 mg twice daily (duration not stated, probably until the follow-up) Group 2: no active intervention (n = 19) Further details: placebo
Outcomes	Mortality at maximal follow-up, variceal bleed at maximal follow-up (any) (number of rebleeds) Follow-up (months): 10.7
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information
Risk of bias	

Fassio 1993 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Random number table."
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The patients were not aware of the treatment received. In contrast, the treating doctors were not blind with respect to which patients received drugs or placebo."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Feng 2012

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: China Period of recruitment: 1998–2008 Number randomised: 168 Postrandomisation dropouts: not stated Revised sample size: 168 Mean age (years): 54 Females: 63 (37.5%) Small varices: not stated High risk of bleeding: not stated Other features of decompensation: 39 (23.2%) Alcohol-related cirrhosis: 14 (8.3%) Viral-related cirrhosis: 140 (83.3%) Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: 14 (8.3%)

Feng 2012 *(Continued)*

	Other exclusion criteria: aged > 75 years or < 18 years; with malignant tumours, uraemia, or other serious life-threatening diseases; complicated with refractory ascites, hepatic encephalopathy, and severe jaundice; previously treated with shunt or endoscopic treatment
Interventions	Group 1: variceal band ligation (n = 84) Further details: variceal band ligation (no further details) repeated every 2 weeks until eradication Group 2: beta-blockers (n = 84) Further details: propranolol 30–160 mg/day to maintain heart rate just above 25% from baseline, 60 bpm and systolic blood pressure at 90 mmHg; duration not reported, probably until follow-up
Outcomes	Mortality at maximal follow-up, any adverse events (number of participants), variceal bleed at maximal follow-up (symptomatic recovery) (number of participants) Follow-up (months): 23.8
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available
Selective reporting (reporting bias)	Low risk	Comment: a prepublished protocol was not available, but the authors reported mortality, adverse events, and variceal bleed adequately.
Other bias	Low risk	Comment: no other bias noted

Fleig 1988

Study characteristics

Methods	Randomised clinical trial

Fleig 1988 *(Continued)*

Participants	Country: Germany Period of recruitment: not stated Number randomised: 49 Postrandomisation dropouts: 9 (18.4%) Revised sample size: 40 Reasons for postrandomisation dropouts: protocol violations Mean age (years): not stated Females: not stated Small varices: 0 (0.0%) High risk of bleeding: not stated Other features of decompensation: not stated Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Other inclusion/exclusion criteria: not stated
Interventions	Group 1: sclerotherapy (n = 16) Further details: sclerotherapy: 1% polidocanol until the varices were eradicated or covered by fibrous tissue Group 2: no active intervention (n = 24) Further details: no active treatment until bleeding
Outcomes	Mortality at maximal follow-up Follow-up (months): 28.8
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: information not available

Fleig 1988 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were postrandomisation dropouts due to protocol violation; unclear whether this could be related to intervention and outcome. Our sensitivity analysis indicated the results of the network meta-analysis were sensitive to postrandomisation dropouts.
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Ideo 1988

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: 1982–1986 Number randomised: 57 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 57 Mean age (years): 53 Females: 15 (26.3%) Small varices: 0 (0.0%) High risk of bleeding: not stated Other features of decompensation: 4 (7.0%) Alcohol-related cirrhosis: 30 (52.6%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Other exclusion criteria: prior variceal bleed, not large varices, contraindication to beta-blockers, cardiopulmonary disease, erosive gastroduodenitis, peptic ulcer disease, hepatocellular carcinoma, other neoplasia, intractable ascites
Interventions	Group 1: no active intervention (n = 27) Further details: placebo Group 2: beta-blockers (n = 30)

Ideo 1988 *(Continued)*

	Further details: nadolol at doses that reduced resting heart rate by approximately 25%
Outcomes	Mortality at maximal follow-up, variceal bleed at maximal follow-up (any) (number of rebleeds) Follow-up (months): 22.8
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The admitted patients were randomly assigned to treatment by a system of random numbers."
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Jutabha 2005

Study characteristics

Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: 1996–2001 Number randomised: 62 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 62 Mean age (years): 55

Jutabha 2005 *(Continued)*

	Females: 18 (29.0%) Small varices: 4 (6.5%) High risk of bleeding: 21 (33.9%) Other features of decompensation: not stated Alcohol-related cirrhosis: 7 (11.3%) Viral-related cirrhosis: 47 (75.8%) Autoimmune disease-related cirrhosis: 6 (9.7%) Other causes of cirrhosis: 12 (19.4%) Clinical exclusion criteria: people who were unco-operative, unable to give written informed consent, or could not return for routine follow-up; serious recurrent or outgoing comorbid illness (e.g. severe renal, cardiac, or respiratory failure; peritonitis; or sepsis); contraindication to beta-blockers (e.g. severe congestive heart failure, severe chronic obstructive pulmonary disease, severe asthma, or severe insulin-dependent diabetes mellitus) Biochemical exclusion criteria: severe coagulopathy unresponsive to blood product transfusions (e.g. prothrombin time 3 seconds over control or international normalised ratio 1.6); severe thrombocytopenia, defined as a platelet count 40,000/μL; increased alpha-fetoprotein level; positive beta-human chorionic gonadotropin (women only) Diagnostic imaging exclusion criteria: documented hepatoma (by scanning and increased alpha-fetoprotein, histology, or both); portal or hepatic vein thrombosis; large-volume or tense ascites that could not be controlled with diuretics and sodium restriction and required repeated therapeutic paracentesis Endoscopic exclusion criteria: contraindication to therapeutic endoscopy; presence of moderate or large gastric or duodenal varices; severe erosive oesophagitis, oesophageal stricture requiring dilation, active duodenal or gastric ulceration, or upper gastrointestinal tumour; severe upper gastrointestinal angioma syndrome (watermelon stomach or upper gastrointestinal angiomas) or severe portal hypertensive gastropathy with spontaneous or contact bleeding, severe recurrent upper gastrointestinal bleeding, or severe anaemia with haemoccult-positive stools thought to be secondary to the upper gastrointestinal angioma syndrome or portal hypertensive gastropathy because of an otherwise negative gastrointestinal evaluation (including push enteroscopy, colonoscopy, and small-bowel x-ray) that excluded another source of gastrointestinal haemorrhage
Interventions	Group 1: variceal band ligation (n = 31) Further details: variceal band ligation using Saeed 6 Shooter, performed monthly until varices were eradicated Group 2: beta-blockers (n = 31) Further details: propranolol titrated to reducing resting pulse by ≥ 25%
Outcomes	Mortality at maximal follow-up, serious adverse events (number of participants), liver transplantation at maximal follow-up, variceal bleed at maximal follow-up (symptomatic recovery) (number of participants), treatment costs Follow-up (months): 15
Notes	Source of funding (quote): "The study and investigators were supported in part by the following grants: NIH Clinical Associate Physician Award (R.J.), American Society for Gastrointestinal Endoscopy Research Award (R.J.), NIH NIDDK IK24 DK 02650 Grant (D.M.J.), NIH NIDDK 41301 (CURE CORE grant), and NIH General Clinical Research Center-PHS Grant 5 MO1-RR00865825." Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Jutabha 2005 *(Continued)*

	Individual participants had multiple cirrhosis aetiologies

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Treatment assignment was by opening a sealed opaque envelope that designated 1 of 2 treatments." Comment: although the details on sequence generation was not reported, the method of allocation concealment used makes it highly likely that the sequence was random.
Allocation concealment (selection bias)	Low risk	Quote: "Treatment assignment was by opening a sealed opaque envelope that designated 1 of 2 treatments."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "not blinded" (author reply).
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "not blinded" (author reply).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Kanazawa 1993

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Japan Period of recruitment: 1987–1992 Number randomised: 65 Postrandomisation dropouts: 4 (6.2%) Revised sample size: 61 Reasons for postrandomisation dropouts: lost to follow-up Mean age (years): 58 Females: 19 (31.1%) Small varices: 36 (59.0%) High risk of bleeding: 65 (100.0%)

Kanazawa 1993 *(Continued)*

	Other features of decompensation: 8 (13.1%) Alcohol-related cirrhosis: not stated Viral-related cirrhosis: 39 (63.9%) Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Other inclusion criteria: liver cirrhosis; no history of vomiting blood; not having been treated for oesophageal varices; no liver cancer; oesophageal varices of ≥ F2 RC sign positive, Beppu score < 1.14; hepatovenous pressure gradient ≥ 12 mmHg; Child-Pugh score ≤ 13; aged < 75 years
Interventions	Group 1: sclerotherapy (n = 32) Further details: sclerotherapy: ethanolamine oleate, repeated weekly to reduce it to F1 Group 2: beta-blockers (n = 33) Further details: propranolol started at 30 mg titrated to reduce the heart rate by 25%
Outcomes	Mortality at maximal follow-up, any adverse events (number of events), variceal bleed at maximal follow-up (any) (number of participants) Follow-up (months): 31
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "subjects were divided into propranolol group or sclerotherapy group by envelope method." Comment: although details on sequence generation were not reported, the method of allocation concealment used makes it highly likely that the sequence was random.
Allocation concealment (selection bias)	Low risk	Quote: "subjects were divided into propranolol group or sclerotherapy group by envelope method." Comment: although details on allocation concealment were not reported (as sealed envelope technique or shuffled envelope technique), the authors are likely to have used a method that was likely to result in randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias)	Unclear risk	Comment: there were postrandomisation dropouts; unclear whether these were related to the intervention and outcomes. Our sensitivity analysis indi-

Kanazawa 1993 *(Continued)*

All outcomes		cated the results of the network meta-analysis were sensitive to postrandomisation dropouts.
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Khan 2017

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Pakistan Period of recruitment: not stated Number randomised: 250 Postrandomisation dropouts: not stated Revised sample size: 250 Mean age (years): 53 Females: 103 (41.2%) Small varices: not stated High risk of bleeding: not stated Other features of decompensation: not stated Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Other exclusion criteria: previous variceal bleed, pregnancy or lactating, allergy to carvedilol, already receiving beta-blocker, cancer, severe systemic illness, hypertension, diabetes, psychiatric disease, chronic obstructive pulmonary disease, asthma, mean arterial pressure < 55 mmHg, heart rate < 50 bpm, and portal vein thrombosis
Interventions	Group 1: variceal band ligation (n = 125) Further details: variceal band ligation (multiband device): unclear if it was repeated Group 2: beta-blockers (n = 125) Further details: carvedilol 12.5 mg once daily for 6 months
Outcomes	Variceal bleed at maximal follow-up (any) (number of participants) Follow-up (months): 6
Notes	Source of funding: not stated

Khan 2017 *(Continued)*

	Trial name/trial registry number: not stated
	Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Lay 1997

Study characteristics

Methods	Randomised clinical trial
Participants	Country: China
	Period of recruitment: 1993–1995
	Number randomised: 126
	Postrandomisation dropouts: 0 (0.0%)
	Revised sample size: 126
	Mean age (years): 55
	Females: 25 (19.8%)
	Small varices: not stated
	High risk of bleeding: 126 (100.0%)
	Other features of decompensation: 65 (51.6%)
	Alcohol-related cirrhosis: 23 (18.3%)

Lay 1997 *(Continued)*

	Viral-related cirrhosis: 96 (76.2%) Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: 7 (5.6%) Other inclusion criteria: no known previous bleeding from the upper gastrointestinal tract; presence of high-risk oesophageal varices; cirrhosis with no other diseases restricting life expectancy Other exclusion criteria: gastric or ectopic varices
Interventions	Group 1: variceal band ligation (n = 62) Further details: variceal band ligation using an endoscopic ligation device weekly for first 3 weeks and then every 2 weeks until obliteration of varices Group 2: no active intervention (n = 64) Further details: no treatment
Outcomes	Mortality at maximal follow-up, any adverse events (number of participants), any adverse events (number of events), variceal bleed at maximal follow-up (any) (number of participants) Follow-up (months): 13.5
Notes	Source of funding (quote): "Supported by grant NSC 83-0412-B-075A-011 from the National Science Council, R.O.C" Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "sealed-envelope method." Comment: although the details on sequence generation were not reported, the method of allocation concealment used makes it highly likely that the sequence was random.
Allocation concealment (selection bias)	Low risk	Quote: "sealed-envelope method."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "At the time of endoscopy, the patients in the EVL [endoscopic variceal ligation] group returned for visits more frequently than the non-EVL group. The follow-up was indeed different in these two groups of patients."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "At the time of endoscopy, the patients in the EVL group returned for visits more frequently than the non-EVL group. The follow-up was indeed different in these two groups of patients." Comment: although the follow-up was different between the groups, there is a possibility that outcome assessors were blinded. However, information on blinding or lack of blinding was not provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts

Lay 1997 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: prepublished protocol not available, but the authors reported mortality, adverse events, and variceal bleed adequately.
Other bias	Low risk	Comment: no other bias noted

Lay 2006

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: China Period of recruitment: 1998–2002 Number randomised: 100 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 100 Mean age (years): 56 Females: 22 (22.0%) Small varices: not stated High risk of bleeding: 100 (100.0%) Other features of decompensation: 17 (17.0%) Alcohol-related cirrhosis: 21 (21.0%) Viral-related cirrhosis: 73 (73.0%) Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: 6 (6.0%) Other inclusion criteria: no known previous bleeding from the upper gastrointestinal tract; presence of high-risk oesophageal varices; cirrhosis with no other diseases restricting life expectancy Other exclusion criteria: gastric or ectopic varices
Interventions	Group 1: variceal band ligation (n = 50) Further details: variceal band ligation using an endoscopic ligation device weekly for first 3 weeks and then every 2 weeks until obliteration of varices Group 2: beta-blockers (n = 50) Further details: propranolol initial dose 40 mg twice daily titrated to reduce the resting heart rate by 20%
Outcomes	Mortality at maximal follow-up, any adverse events (number of participants), any adverse events (number of events), variceal bleed at maximal follow-up (any) (number of participants), other features of decompensation at maximal follow-up Follow-up (months): 34.9
Notes	Source of funding: not stated

Lay 2006 *(Continued)*

	Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "sealed-envelope method." Comment: although the details on sequence generation were not reported, the method of allocation concealment used makes it highly likely that the sequence was random.
Allocation concealment (selection bias)	Low risk	Quote: "sealed-envelope method."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: prepublished protocol not available, but the authors reported mortality, adverse events, and variceal bleed adequately.
Other bias	Low risk	Comment: no other bias noted

Lebrec 1988

Study characteristics

Methods	Randomised clinical trial
Participants	Country: France Period of recruitment: 1982–1985 Number randomised: 106 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 106 Mean age (years): 56 Females: 27 (25.5%) Small varices: not stated High risk of bleeding: not stated

Lebrec 1988 *(Continued)*

	Other features of decompensation: not stated Alcohol-related cirrhosis: 78 (73.6%) Viral-related cirrhosis: 12 (11.3%) Autoimmune disease-related cirrhosis: 4 (3.8%) Other causes of cirrhosis: 12 (11.3%) Other inclusion criteria: no history of gastrointestinal bleeding; presence of ≥ 1 oesophageal varix measuring ≥ 4 mm; serum bilirubin < 100 µmol/L; absent or only mild and transient ascites; no hepatic encephalopathy Other exclusion criteria: Child-Pugh C; heart failure; asthma; hepatocellular carcinoma
Interventions	Group 1: no active intervention (n = 53) Further details: placebo Group 2: beta-blockers (n = 53) Further details: nadolol dose titrated to decrease the resting heart rate by approximately 25%
Outcomes	Mortality at maximal follow-up, any adverse events (number of participants), variceal bleed at maximal follow-up (any) (number of participants) Follow-up (months): 12
Notes	Source of funding (quote): "We had no special fund for the study" (author reply) Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computerized randomization software."
Allocation concealment (selection bias)	Low risk	Quote: "sealed envelopes."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The patients did not know whether they were receiving nadolol or placebo; the physicians caring for the patients did know."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "The patients did not know whether they were receiving nadolol or placebo; the physicians caring for the patients did know."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: prepublished protocol not available, but the authors reported mortality, adverse events, and variceal bleed adequately.

Lebrec 1988 *(Continued)*

Other bias	Low risk	Comment: no other bias noted

Lo 1999

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Taiwan Period of recruitment: 1992–1995 Number randomised: 133 Postrandomisation dropouts: 6 (4.5%) Revised sample size: 127 Reasons for postrandomisation dropouts: lost to follow-up Mean age (years): 56 Females: 20 (15.7%) Small varices: 57 (44.9%) High risk of bleeding: 127 (100.0%) Other features of decompensation: 43 (33.9%) Alcohol-related cirrhosis: 38 (29.9%) Viral-related cirrhosis: 82 (64.6%) Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: 7 (5.5%) Other exclusion criteria: aged > 70 years or < 20 years; malignancy, uraemia, other serious medical illness that may reduce life expectancy; presence of gastric varices on initial endoscopy; presence of refractory ascites, hepatic encephalopathy or marked jaundice (serum bilirubin > 10 mg/dL); history of shunt operation, TIPS, or endoscopic therapy; unable to co-operate
Interventions	Group 1: variceal band ligation (n = 64) Further details: variceal band ligation using Bard Interventional Products repeated every 3 weeks until variceal obliteration Group 2: no active intervention (n = 63) Further details: no treatment
Outcomes	Mortality at maximal follow-up, variceal bleed at maximal follow-up (any) (number of participants), variceal bleed at maximal follow-up (any) (number of rebleeds) Follow-up (months): 29
Notes	Source of funding: not stated Trial name/trial registry number: not stated

Lo 1999 *(Continued)*

	Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The method of randomization was based on a system of random numbers."
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were postrandomisation dropouts; it was unclear whether they were related to the intervention or outcomes. Our sensitivity analysis indicated the results of the network meta-analysis were sensitive to postrandomisation dropouts.
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Lo 2004

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Taiwan Period of recruitment: 1997–2000 Number randomised: 100 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 100 Mean age (years): 56 Females: 23 (23.0%) Small varices: 61 (61.0%) High risk of bleeding: 100 (100.0%) Other features of decompensation: 41 (41.0%) Alcohol-related cirrhosis: 20 (20.0%)

Lo 2004 *(Continued)*

	Viral-related cirrhosis: 73 (73.0%) Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: 7 (7.0%) Other exclusion criteria: aged > 75 years or < 20 years; presence of malignancy, uraemia, or other serious medical illness that could reduce life expectancy; refractory ascites, hepatic encephalopathy, or marked jaundice (bilirubinaemia > 10 mg/dL); history of shunt operation, TIPS, or endoscopic therapy (ligation or sclerotherapy); contraindication to treatment with beta-blockers
Interventions	Group 1: variceal band ligation (n = 50) Further details: variceal band ligation using multiband ligator repeated at 3- to 4-week intervals until obliteration Group 2: beta-blockers (n = 50) Further details: nadolol started at 40 mg once daily and titrated to reduce resting pulse rate to 25% or 55/minute
Outcomes	Mortality at maximal follow-up, serious adverse events (number of participants), any adverse events (number of participants), variceal bleed at maximal follow-up (symptomatic recovery) (number of participants) Follow-up (months): 22.2
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was by means of opaque, sealed envelopes numbered according to a table of random numbers."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was by means of opaque, sealed envelopes numbered according to a table of random numbers."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: prepublished protocol not available, but the authors reported mortality, adverse events, and variceal bleed adequately.
Other bias	Low risk	Comment: no other bias noted

Lo 2010

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Taiwan Period of recruitment: not stated Number randomised: 140 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 140 Mean age (years): 56 Females: 53 (37.9%) Small varices: 122 (87.1%) High risk of bleeding: 140 (100.0%) Other features of decompensation: 3 (2.1%) Alcohol-related cirrhosis: 24 (17.1%) Viral-related cirrhosis: 101 (72.1%) Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: 15 (10.7%) Other exclusion criteria: aged > 75 years or < 20 years; malignancy, uraemia, or other serious medical illness that may reduce life expectancy; refractory ascites, hepatic encephalopathy stage > 2 or deep jaundice (bilirubin > 10 mg/dL); history of shunt operation, TIPS, or endoscopic therapy; contraindications to beta-blockers; unable to co-operate; declined to participate
Interventions	Group 1: beta-blockers + variceal band ligation (n = 70) Further details: nadolol titrated to reduce pulse rate by 25%, duration until follow-up + variceal band ligation using multiband ligators repeated every 4 weeks until variceal obliteration Group 2: beta-blockers (n = 70) Further details: nadolol titrated to reduce pulse rate by 25%, until follow-up
Outcomes	Mortality at maximal follow-up, any adverse events (number of events), liver transplantation at maximal follow-up, variceal bleed at maximal follow-up (symptomatic recovery) (number of participants) Follow-up (months): 26
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Lo 2010 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "The method of randomization was based on opaque, sealed, envelopes numbered according to a table of random numbers."
Allocation concealment (selection bias)	Low risk	Quote: "The method of randomization was based on opaque, sealed, envelopes numbered according to a table of random numbers."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: prepublished protocol not available, but the authors reported mortality, adverse events, and variceal bleed adequately.
Other bias	Low risk	Comment: no other bias noted

Lui 2002

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Scotland Period of recruitment: 1994–1999 Number randomised: 172 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 172 Mean age (years): 55 Females: 75 (43.6%) Small varices: 144 (83.7%) High risk of bleeding: 8 (4.7%) Other features of decompensation: 5 (2.9%) Alcohol-related cirrhosis: 112 (65.1%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Other exclusion criteria: aged < 18 years or > 75 years; failure or inability to provide informed consent; advanced systemic illness; non-cirrhotic portal hypertension; person receiving existing vasoactive

Lui 2002 *(Continued)*

	agents; contraindications to beta-blockers; systolic blood pressure < 100 mmHg or diastolic < 50 mmHg or pulse rate < 56/minute; allergy to either trial medication
Interventions	Group 1: beta-blockers (n = 66) Further details: propranolol started at 40 mg twice daily and increased to 80 mg twice daily after 3 days if well tolerated, systolic blood pressure was > 100 mmHg, and pulse rate was > 50/minute Group 2: nitrates (n = 62) Further details: isosorbide mononitrate started at 20 mg twice daily and increased to 40 mg twice daily after 3 days if well tolerated and systolic blood pressure was > 100 mmHg Group 3: variceal band ligation (n = 44) Further details: variceal band ligation, initially by single band device later by multiband device every 2 weeks until variceal obliteration
Outcomes	Mortality at maximal follow-up, variceal bleed at maximal follow-up (any) (number of rebleeds) Follow-up (months): 19.7
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Serially numbered opaque envelopes containing cards with randomly assigned treatment arms were used." Comment: although the details on sequence generation were not reported, the method of allocation concealment used makes it highly likely that the sequence was random.
Allocation concealment (selection bias)	Low risk	Quote: "Serially numbered opaque envelopes containing cards with randomly assigned treatment arms were used."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Merkel 2000

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: 1991–1994 Number randomised: 146 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 146 Mean age (years): 57 Females: 55 (37.7%) Small varices: 101 (69.2%) High risk of bleeding: 97 (66.4%) Other features of decompensation: 16 (11.0%) Alcohol-related cirrhosis: 79 (54.1%) Viral-related cirrhosis: 53 (36.3%) Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: 4 (2.7%) Other exclusion criteria: previous treatment for portal hypertension; Child-Pugh score > 11; presence of any malignancy; inability to attend follow-up; contraindications to beta-blockers or long acting nitrates; concomitant or recent treatment with interferon for hepatitis B virus or hepatitis C virus
Interventions	Group 1: beta-blockers + nitrates (n = 72) Further details: nadolol dose titrated to achieve a 20–25% decrease in resting heart rate + isosorbide mononitrate starting with 10 mg twice daily, which was increased to 20 mg twice daily, unless hypotension (systolic blood pressure < 85 mmHg) or severe headache occurred Group 2: beta-blockers (n = 74) Further details: nadolol dose titrated to achieve a 20–25% decrease in resting heart rate
Outcomes	Mortality at maximal follow-up, other features of decompensation at maximal follow-up Follow-up (months): 55
Notes	Source of funding (quote): "Supported in part by a grant from the Italian Ministry of University and Scientific Research (National Project "Liver Cirrhosis and Virus Hepatitis")" Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Merkel 2000 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "tables of random numbers."
Allocation concealment (selection bias)	Low risk	Quote: "sealed, opaque, and consecutively numbered envelopes."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "single-blind, randomized, multicenter study."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "single-blind, randomized, multicenter study." Comment: the group blinded was not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Merkel 2004

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: 1996–2000 Number randomised: 161 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 161 Mean age (years): 56 Females: 78 (48.4%) Small varices: 161 (100.0%) High risk of bleeding: 0 (0.0%) Other features of decompensation: 41 (25.5%) Alcohol-related cirrhosis: 92 (57.1%) Viral-related cirrhosis: 62 (38.5%) Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: 7 (4.3%)

Merkel 2004 *(Continued)*

	Other exclusion criteria: previous variceal bleeding; previous medical, surgical, or endoscopic treatment for portal hypertension; Child-Pugh score > 11; neoplastic disease in any site; inability to perform follow-up; contraindications to beta-blockers
Interventions	Group 1: no active intervention (n = 78) Further details: placebo Group 2: beta-blockers (n = 83) Further details: nadolol, target of a 25% decrease or a heart rate of 50 bpm
Outcomes	Mortality at maximal follow-up, liver transplantation at maximal follow-up Follow-up (months): 36
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was generated by tables of random numbers."
Allocation concealment (selection bias)	Low risk	Quote: "opaque sealed and consecutively numbered envelopes containing randomization."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The single-blind study design was chosen because it was considered unrealistic that blindness could be kept using a drug with evident clinical effects and because dose adjustments during follow-up were expected to be necessary to maintain the requested effect on heart rate."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "The single-blind study design was chosen because it was considered unrealistic that blindness could be kept using a drug with evident clinical effects and because dose adjustments during follow-up were expected to be necessary to maintain the requested effect on heart rate…Endoscopists were kept unaware of the treatment arm to which the patients were randomized." Comment: blinding of endoscopists refers only to an outcome not included for this review.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	High risk	Quote: "After the diagnosis of aggravation of esophageal varices, all patients in the 2 arms were given pharmacologic prophylaxis." Comment: participants in control group received pharmacological prophylaxis against bleeding before the bleeding episode; this could have influenced the effect estimates for all outcomes.

Mishra 2007

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: India Period of recruitment: not stated Number randomised: 85 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 85 Mean age (years): not stated Females: not stated Small varices: 85 (100.0%) High risk of bleeding: not stated Other features of decompensation: not stated Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Other inclusion criteria: cirrhosis; small varices; no previous bleeding
Interventions	Group 1: no active intervention (n = 42) Further details: placebo Group 2: beta-blockers (n = 43) Further details: propranolol dose titrated to decrease resting heart rate to 55 bpm
Outcomes	Mortality at maximal follow-up Follow-up (months): 18
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available

Mishra 2007 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

NCT00337740

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: not stated Number randomised: not stated Postrandomisation dropouts: not stated Revised sample size: not stated Mean age (years): not stated Females: not stated Small varices: not stated High risk of bleeding: not stated Other features of decompensation: not stated Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Other inclusion criteria: evaluated for liver transplantation
Interventions	Group 1: variceal band ligation (n = not stated) Further details: no further details Group 2: beta-blockers (n = not stated)

NCT00337740 *(Continued)*

	Further details: no further details
Outcomes	None of the outcomes of interest were reported.
Notes	Source of funding: not stated Trial name/trial registry number: NCT00337740 Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open label."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open label."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available
Selective reporting (reporting bias)	Unclear risk	Comment: a prepublished protocol was not available.
Other bias	Low risk	Comment: no other bias noted

NCT00921349

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Taiwan Period of recruitment: 2004–2009 Number randomised: 140 Postrandomisation dropouts: not stated Revised sample size: 140 Mean age (years): not stated Females: not stated

NCT00921349 *(Continued)*

	Small varices: not stated High risk of bleeding: not stated Other features of decompensation: not stated Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated
Interventions	Group 1: beta-blockers + variceal band ligation (n = not stated) Further details: variceal band ligation: multiband ligation device, repeated at intervals of 3–4 weeks until all varices were obliterated + nadolol (no further details) Group 2: beta-blockers (n = not stated) Further details: nadolol (no further details)
Outcomes	None of the outcomes of interest were reported.
Notes	Source of funding: not stated Trial name/trial registry number: NCT00921349 Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open label."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open label."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available
Selective reporting (reporting bias)	Unclear risk	Comment: prepublished protocol not available.
Other bias	Low risk	Comment: no other bias noted

Norbeto 2007

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: 2001–2005 Number randomised: 62 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 62 Mean age (years): 53 Females: not stated Small varices: 53 (85.5%) High risk of bleeding: 62 (100.0%) Other features of decompensation: not stated Alcohol-related cirrhosis: not stated Viral-related cirrhosis: 32 (51.6%) Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Other exclusion criteria: oesophageal varices not less than F3 or F2 with red signs; presence of gastric varices; previous endoscopic, radiological, surgical, treatment of oesophageal varices; hepatocellular carcinoma; severe heart, respiratory, or renal failure; portal vein thrombosis; contraindications to beta-blockers; treatment with nitrates, calcium antagonists, or other antiarrhythmic drugs; pregnancy; neoplasias; an unco-operative attitude or suspicion for non-compliance to follow-up
Interventions	Group 1: variceal band ligation (n = 31) Further details: variceal band ligation multiband ligator, repeated every 2 weeks until the varices were completely eradicated Group 2: beta-blockers (n = 31) Further details: propranolol titrated to ensure systolic blood pressure ≥ 90 mmHg and heart rate ≥ 50 bpm
Outcomes	Mortality at maximal follow-up, serious adverse events (number of participants), liver transplantation at maximal follow-up, variceal bleed at maximal follow-up (any) (number of participants), treatment costs Follow-up (months): 14.6
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Norbeto 2007 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Randomization of numbers was assigned by a statistical software package."
Allocation concealment (selection bias)	Low risk	Quote: "sealed opaque envelope."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: prepublished protocol not available, but the authors reported mortality, adverse events, and variceal bleed adequately.
Other bias	Low risk	Comment: no other bias noted

Paquet 1982

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Germany Period of recruitment: 1978–1980 Number randomised: 71 Postrandomisation dropouts: 8 (11.3%) Revised sample size: 63 Reasons for postrandomisation dropouts: lost to follow-up Mean age (years): not stated Females: not stated Small varices: not stated High risk of bleeding: not stated Other features of decompensation: not stated Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated

Paquet 1982 *(Continued)*

	Other inclusion criteria: liver cirrhosis confirmed histologically; degree III or IV varices bearing telangiectasias on top and degree II-IV varices without telangiectasias but coagulation factors < 30%, or both
Interventions	Group 1: sclerotherapy (n = 31) Further details: sclerotherapy: aethoxysclerol 30–50 mL, 2–4 sessions at an interval of 6–7 days Group 2: no active intervention (n = 32) Further details: no treatment
Outcomes	Mortality at maximal follow-up, any adverse events (number of participants), variceal bleed at maximal follow-up (any) (number of participants) Follow-up (months): 18
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were postrandomisation dropouts; unclear whether these were related to interventions or outcomes. Our sensitivity analysis indicated the results of the network meta-analysis were sensitive to postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: prepublished protocol not available, but the authors reported mortality, adverse events, and variceal bleed adequately.
Other bias	Low risk	Comment: no other bias noted

Paquet 1994

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Germany

Paquet 1994 *(Continued)*

	Period of recruitment: 1987–1992 Number randomised: 89 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 89 Mean age (years): 51 Females: 32 (36.0%) Small varices: 0 (0.0%) High risk of bleeding: 89 (100.0%) Other features of decompensation: not stated Alcohol-related cirrhosis: 63 (70.8%) Viral-related cirrhosis: 15 (16.9%) Autoimmune disease-related cirrhosis: 4 (4.5%) Other causes of cirrhosis: 7 (7.9%) Other inclusion criteria: no history of upper gastrointestinal bleeding; no previous endoscopic evidence of oesophageal varices degrees III and IV with telangiectasias (minivarices); hepatovenous pressure gradient > 16 mmHg; liver cirrhosis histologically confirmed with no other disease reducing life expectancy to < 1 year; full consent to participate in the study
Interventions	Group 1: sclerotherapy (n = 44) Further details: sclerotherapy: 0.5–1% aethoxysclerol repeated every week until varices were reduced in size and covered by fibrous tissue Group 2: no active intervention (n = 45) Further details: no treatment
Outcomes	Mortality at maximal follow-up, variceal bleed at maximal follow-up (any) (number of participants) Follow-up (months): 33
Notes	Source of funding (quote): "Dr. Gad received grants from the Egyptian Government (1988 – 90 and 1994)." Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: information not available

Paquet 1994 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Pascal 1987

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: France Period of recruitment: 1983–1984 Number randomised: 230 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 230 Mean age (years): 54 Females: not stated Small varices: 171 (74.3%) High risk of bleeding: not stated Other features of decompensation: not stated Alcohol-related cirrhosis: 207 (90.0%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Other inclusion criteria: adults aged < 75 years; cirrhosis with Child-Pugh score < 14; grade II or III oesophageal varices Other exclusion criteria: contraindications to beta-blockers; history of upper gastrointestinal bleed; evidence of gastroduodenal ulcer, hepatocellular carcinoma; receiving treatment that altered portal haemodynamics
Interventions	Group 1: no active intervention (n = 112) Further details: placebo Group 2: beta-blockers (n = 118)

Pascal 1987 *(Continued)*

	Further details: propranolol to reduce the heart rate by 20–25%
Outcomes	Mortality at maximal follow-up Follow-up (months): 14.3
Notes	Source of funding (quote): "We are indebted to … Dr C Dupont (ICI Pharma, France) for her help." Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Consecutively numbered series of sealed individual opaque envelopes." Comment: although the details on sequence generation were not reported, the method of allocation concealment used makes it highly likely that the sequence was random.
Allocation concealment (selection bias)	Low risk	Quote: "Consecutively numbered series of sealed individual opaque envelopes."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The patients were unaware of which treatment they received. The physicians and evaluators were not blinded."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "The patients were unaware of which treatment they received. The physicians and evaluators were not blinded."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Perez-Ayuso 2010

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Chile Period of recruitment: 1998–2007 Number randomised: 75 Postrandomisation dropouts: 0 (0.0%)

Perez-Ayuso 2010 *(Continued)*

	Revised sample size: 75 Mean age (years): 59 Females: 38 (50.7%) Small varices: not stated High risk of bleeding: 75 (100.0%) Other features of decompensation: 8 (10.7%) Alcohol-related cirrhosis: 18 (24.0%) Viral-related cirrhosis: 11 (14.7%) Autoimmune disease-related cirrhosis: 13 (17.3%) Other causes of cirrhosis: 42 (56.0%) Other inclusion criteria: cirrhosis; no history of haemorrhage from oesophageal varices; high-risk varices; non-current treatment with beta-blocker Other exclusion criteria: aged < 18 years or > 70 years; evidence of portal thrombosis, malignancy, contraindication to beta-blockers; previous variceal endoscopic treatment, TIPS, surgical shunt, renal failure, or denial to participate in the study
Interventions	Group 1: variceal band ligation (n = 39) Further details: variceal band ligation using a multiband ligator, repeated every 3 weeks until eradication of varices Group 2: beta-blockers (n = 36) Further details: propranolol increased to achieve a reduction of 25% of the pretreatment resting heart rate, heart rate was 55 bpm or systolic blood pressure was < 90 mmHg
Outcomes	Mortality at maximal follow-up, serious adverse events (number of participants), any adverse events (number of participants), variceal bleed at maximal follow-up (any) (number of participants) Follow-up (months): 55
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Stratified randomization was centrally performed according to Child-Pugh classification (Child-Pugh score <9 or ≥9)."
Allocation concealment (selection bias)	Low risk	Quote: "Random allocation sequence was generated using numerated sealed envelopes."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "After the randomization the patient and physicians were informed."

Perez-Ayuso 2010 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "After the randomization the patient and physicians were informed."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: prepublished protocol not available, but the authors reported mortality, adverse events, and variceal bleed adequately.
Other bias	Low risk	Comment: no other bias noted

Piai 1988

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: 1983–1985 Number randomised: 140 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 140 Mean age (years): 56 Females: 41 (29.3%) Small varices: not stated High risk of bleeding: 140 (100.0%) Other features of decompensation: not stated Alcohol-related cirrhosis: 47 (33.6%) Viral-related cirrhosis: 57 (40.7%) Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: 19 (13.6%) Other inclusion criteria: no known previous bleeding from the upper gastrointestinal tract; oesophageal varices at high risk of bleeding; liver cirrhosis with no other disease reducing life expectancy
Interventions	Group 1: sclerotherapy (n = 71) Further details: sclerotherapy: polidocanol 1% maximum 20–40 mL, 7- to 10-day interval between sessions Group 2: no active intervention (n = 69) Further details: no treatment
Outcomes	Mortality at maximal follow-up

Piai 1988 *(Continued)*

	Follow-up (months): 13
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly allocated either to a treatment group or to a control group (using a sealed envelope method)." Comment: although the details on sequence generation was not reported, the method of allocation concealment used makes it highly likely that the sequence was random.
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomly allocated either to a treatment group or to a control group (using a sealed envelope method)."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Piscaglia 1998

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: not stated Number randomised: 18 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 18 Mean age (years): 58 Females: 7 (38.9%)

Piscaglia 1998 *(Continued)*

	Small varices: 16 (88.9%) High risk of bleeding: not stated Other features of decompensation: 3 (16.7%) Alcohol-related cirrhosis: 4 (22.2%) Viral-related cirrhosis: 14 (77.8%) Autoimmune disease-related cirrhosis: 0 (0.0%) Other causes of cirrhosis: 0 (0.0%) Other inclusion criteria: absence of previous episodes of gastrointestinal bleeding; no previous prophylaxis of variceal bleeding by sclerotherapy, banding ligation, or TIPS; exclusion of any cardiovascular disease; absence of portal vein thrombosis or portal vein hepatofugal flow; technical feasibility of duplex-Doppler
Interventions	Group 1: beta-blockers and nitrates (n = 10) Further details: propranolol 40 mg once daily increased to 40 mg twice daily for 1 month + single dose of isosorbide mononitrate 20 mg Group 2: no active intervention (n = 8) Further details: placebo
Outcomes	None of the outcomes of interest were reported.
Notes	Source of funding (quote): "This study was supported by 60% Funds of Ministero dell'Universita e Ricerca Scientifica e Tecnologica (MURST)." Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: placebo used, but it was unclear whether blinding was achieved.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: placebo used, but it was unclear whether blinding was achieved.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts

Piscaglia 1998 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

PROVA study group 1991

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Norway Period of recruitment: 1985–1989 Number randomised: 286 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 286 Mean age (years): 54 Females: 86 (30.1%) Small varices: 245 (85.7%) High risk of bleeding: not stated Other features of decompensation: 23 (8.0%) Alcohol-related cirrhosis: 235 (82.2%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Other exclusion criteria: previous sclerotherapy of oesophageal varices, current beta-blocker treatment or impossibility for it to be replaced by another medication, repeated sclerotherapy not technically feasible, and permanent beta-blocker treatment not feasible
Interventions	Group 1: beta-blockers (n = 68) Further details: propranolol: starting dose 160 mg adjusted to decrease heart rate by 25% Group 2: sclerotherapy (n = 73) Further details: sclerotherapy: polidocanol 10 mg/mL, maximum of 30 mL repeated in 1- to 2-week intervals Group 3: beta-blockers and sclerotherapy (n = 73) Further details: sclerotherapy: polidocanol 10 mg/mL, maximum of 30 mL repeated in 1- to 2-week intervals + propranolol: starting dose 160 mg adjusted to decrease heart rate by 25% Group 4: no active intervention (n = 72) Further details: no active treatment

PROVA study group 1991 *(Continued)*

Outcomes	Mortality at maximal follow-up, variceal bleed at maximal follow-up (symptomatic recovery) (number of participants) Follow-up (months): 15.4
Notes	Source of funding (quote): "The study was supported by the Danish Medical Research Council (grant no. 12-55991, ICI Pharmaceuticals Inc. and Kreussler Inc." Trial name/trial registry number: PROVA study group Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization was generated from tables of random numbers, stratified by participating hospitals and administered by sealed, opaque and consecutively numbered envelopes."
Allocation concealment (selection bias)	Low risk	Quote: "The randomization was generated from tables of random numbers, stratified by participating hospitals and administered by sealed, opaque and consecutively numbered envelopes."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "No placebo medication and no sham endoscopy were used…In our trial, administration of the treatments and assessment of treatment effects were not blinded either for either patients or physicians."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "No placebo medication and no sham endoscopy were used…In our trial, administration of the treatments and assessment of treatment effects were not blinded either for either patients or physicians."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Psilopoulos 2005

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Greece Period of recruitment: 1999–2003 Number randomised: 60 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 60

Psilopoulos 2005 *(Continued)*

	Mean age (years): 60 Females: 18 (30.0%) Small varices: 46 (76.7%) High risk of bleeding: 60 (100.0%) Other features of decompensation: not stated Alcohol-related cirrhosis: 15 (25.0%) Viral-related cirrhosis: 36 (60.0%) Autoimmune disease-related cirrhosis: 4 (6.7%) Other causes of cirrhosis: 5 (8.3%) Other inclusion criteria: portal hypertension caused by cirrhosis, irrespectively of aetiology and Child–Pugh class; grade II or grade III oesophageal varices (F2, F3 according to Beppu classification), with ≥ 1 sign of increased risk of bleeding (red wale markings, cherry red spots, haematocystic spots); no history of variceal bleeding; no treatment with beta-blockers or nitrates; written informed consent Other exclusion criteria: aged > 70 years or < 20 years; gastric or ectopic varices; severe comorbidity that could substantially reduce life expectancy; refractory ascites, hepatic encephalopathy, or marked jaundice (serum bilirubin > 10 mg/dL); known contraindications to propranolol treatment such as heart failure, obstructive airway disease, hypotension (systolic pressure < 90 mmHg), bradycardia (pulse rate < 60/minute), diabetes mellitus, severe peripheral vascular disease; history of endoscopic sclerotherapy, endoscopic variceal ligation, TIPSs, or surgical portacaval shunt
Interventions	Group 1: variceal band ligation (n = 30) Further details: variceal band ligation using a multiband ligator repeated Group 2: beta-blockers (n = 30) Further details: propranolol, adjusted to achieve a 25% maximal reduction of the pretreatment pulse rate
Outcomes	Mortality at maximal follow-up, any adverse events (number of participants), any adverse events (number of events) Follow-up (months): 27.5
Notes	Source of funding (quote): "The study was partially funded by a grant of the Hellenic Society of Gastroenterology." Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "table of random numbers."
Allocation concealment (selection bias)	Unclear risk	Quote: "A resident doctor gave a number from the table to each patient entering the study." Comment: further details were not available.

Psilopoulos 2005 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Quer 1991

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Spain Period of recruitment: not stated Number randomised: 47 Postrandomisation dropouts: 1 (2.1%) Revised sample size: 46 Reasons for postrandomisation dropouts: refused therapy Mean age (years): 56 Females: 16 (34.8%) Small varices: 30 (65.2%) High risk of bleeding: 7 (15.2%) Other features of decompensation: 4 (8.7%) Alcohol-related cirrhosis: 31 (67.4%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Other inclusion criteria: hepatic cirrhosis and varices type B or greater Other exclusion criteria: previous episodes of digestive haemorrhage
Interventions	Group 1: sclerotherapy (n = 22)

Quer 1991 *(Continued)*

	Further details: sclerotherapy: 1% polidocanol 30–50 mL per session, every 2 weeks to start with and later every 4 weeks until obliteration Group 2: no active intervention (n = 24) Further details: no treatment
Outcomes	Mortality at maximal follow-up, variceal bleed at maximal follow-up (any) (number of participants) Follow-up (months): 16
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there was a postrandomisation dropout, unclear if this was related to the intervention, but was unlikely to alter the effect estimates considerably.
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Rossi 1991

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: 1984–1988 Number randomised: 37 Postrandomisation dropouts: 0 (0.0%)

Rossi 1991 *(Continued)*

	Revised sample size: 37 Mean age (years): 63 Females: 20 (54.1%) Small varices: not stated High risk of bleeding: not stated Other features of decompensation: not stated Alcohol-related cirrhosis: 18 (48.6%) Viral-related cirrhosis: 11 (29.7%) Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: 8 (21.6%) Other inclusion criteria: cirrhosis; high-risk varices; partial thromboplastin time > 50%; platelet count > 70,000/µL Other exclusion criteria: previous haemorrhage; peptic ulcer; neoplasia
Interventions	Group 1: sclerotherapy (n = 18) Further details: sclerotherapy 1% polidocanol at weekly intervals until obliteration of varices Group 2: no active intervention (n = 19) Further details: no treatment
Outcomes	Mortality at maximal follow-up Follow-up (months): 36.6
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available

Rossi 1991 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Russo 1989

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: 1984–1985 Number randomised: 41 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 41 Mean age (years): 62 Females: 17 (41.5%) Small varices: 0 (0.0%) High risk of bleeding: not stated Other features of decompensation: not stated Alcohol-related cirrhosis: 0 (0.0%) Viral-related cirrhosis: 31 (75.6%) Autoimmune disease-related cirrhosis (e.g. primary sclerosing cholangitis, primary biliary cirrhosis, autoimmune hepatitis): not stated Other causes for cirrhosis: 10 (24.3%) Other inclusion criteria: only non-alcoholic liver cirrhosis Other exclusion criteria: alcohol intake > 80 g/day
Interventions	Group 1: sclerotherapy (n = 21) Further details: sclerotherapy: 1% polidocanol mean 22.5 mL per session repeated every 7–10 days until obliteration of varices Group 2: no active intervention (n = 20) Further details: no treatment
Outcomes	Mortality at maximal follow-up Follow-up (months): 18

Russo 1989 *(Continued)*

Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Santangelo 1988

Study characteristics

Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: 1985–1987 Number randomised: 101 Postrandomisation dropouts: 6 (5.9%) Revised sample size: 95 Reasons for postrandomisation dropouts: did not want to continue sclerotherapy or lost to follow-up Mean age (years): 42 Females: 25 (26.3%) Small varices: 0 (0.0%) High risk of bleeding: not stated

Santangelo 1988 *(Continued)*

	Other features of decompensation: 22 (23.0%) Alcohol-related cirrhosis: 85 (89.5%) Viral-related cirrhosis: 3 (3.2%) Autoimmune disease-related cirrhosis: 4 (4.2%) Other causes of cirrhosis: 3 (3.2%) Other exclusion criteria: ≤ grade 2 or lower varices, or no varices
Interventions	Group 1: sclerotherapy (n = 49) Further details: sclerotherapy: 1% sodium tetradecyl 10–20 mL per treatment session, repeated every 10–14 days until varices decrease markedly in size or were obliterated Group 2: no active intervention (n = 46) Further details: no treatment
Outcomes	Mortality at maximal follow-up, length of hospital stay (days) (all admissions until maximal follow-up) Follow-up (months): 13
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts, which were probably related to the intervention and outcome.
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Sarin 2013

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: India Period of recruitment: 2004–2007 Number randomised: 164 Postrandomisation dropouts: 14 (8.5%) Revised sample size: 150 Reasons for postrandomisation dropouts: dropped out before the completion of 6 months of study Mean age (years): 43 Females: 30 (20.0%) Small varices: 150 (100.0%) High risk of bleeding: not stated Other features of decompensation: 3 (2.0%) Alcohol-related cirrhosis: 53 (35.3%) Viral-related cirrhosis: 80 (53.3%) Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: 17 (11.3%) Other inclusion criteria: cirrhosis; aged 18–70 years, grade 1 or 2 varices or small per Bavano classification Other exclusion criteria: history of variceal bleeding
Interventions	Group 1: no active intervention (n = 73) Further details: placebo Group 2: beta-blockers (n = 77) Further details: propranolol titrated to achieve a target heart rate of 55 bpm or maximal dose 360 mg/day, if the medication was well tolerated and the systolic blood pressure remained at least 90 mmHg
Outcomes	Mortality at maximal follow-up, any adverse events (number of participants) Follow-up (months): 25
Notes	Source of funding: not stated Trial name/trial registry number: NCT00772057 Attempted to contact the authors in February 2020; received no additional information

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Sarin 2013 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "All randomizations were done by computer-generated random numbers."
Allocation concealment (selection bias)	Low risk	Quote: "The randomization sequence remained with the statistician, and the sequence remained concealed from the investigators until the intervention was assigned."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Single blind…The endoscopists were blinded to the treatment protocol." Comment: the primary outcome of this trial was growth of oesophageal varices, which an endoscopist assessed.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Single blind…The endoscopists were blinded to the treatment protocol." Comment: the primary outcome of this trial was growth of oesophageal varices, which an endoscopist assessed. However, the endoscopist assessed none of the outcomes of interest for this review.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts that were probably related to the intervention and outcome.
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Sauerbruch 1988

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Germany Period of recruitment: 1982–1986 Number randomised: 133 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 133 Mean age (years): 56 Females: 44 (33.1%) Small varices: 0 (0.0%) High risk of bleeding: 48 (36.1%) Other features of decompensation: 63 (47.4%) Alcohol-related cirrhosis: 88 (66.2%) Viral-related cirrhosis: 34 (25.6%) Autoimmune disease-related cirrhosis: not stated

Sauerbruch 1988 *(Continued)*

	Other causes of cirrhosis: not stated Other inclusion criteria: liver cirrhosis; ≥ 2 varices in the distal part of the oesophagus, each with a diameter ≥ 5 mm; no previous intestinal bleeding; no extrahepatic disease; no gastrointestinal ulcer at the time of randomisation; a Child-Pugh score < 12; no current treatment with steroids, beta-blockers, and penicillamine; aged 18–75 years
Interventions	Group 1: sclerotherapy (n = 68) Further details: sclerotherapy: 1% polidocanol repeated every 7–10 days until obliteration Group 2: no active intervention (n = 65) Further details: no treatment
Outcomes	Mortality at maximal follow-up, variceal bleed at maximal follow-up (symptomatic recovery) (number of participants) Follow-up (months): 22
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was subsequently carried out by a Central trial secretariat according to the Efron biased coin method."
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was subsequently carried out by a Central trial secretariat according to the Efron biased coin method."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Schepke 2004

Study characteristics

Schepke 2004 *(Continued)*

Methods	Randomised clinical trial
Participants	Country: Germany Period of recruitment: 1996–2001 Number randomised: 157 Postrandomisation dropouts: 5 (3.2%) Revised sample size: 152 Reasons for postrandomisation dropouts: wrongly included despite meeting exclusion criteria Mean age (years): 56 Females: 48 (31.6%) Small varices: 67 (44.1%) High risk of bleeding: 59 (38.8%) Other features of decompensation: 19 (12.5%) Alcohol-related cirrhosis: 78 (51.3%) Viral-related cirrhosis: 47 (30.9%) Autoimmune disease-related cirrhosis: 8 (5.3%) Other causes of cirrhosis: 18 (11.8%) Other inclusion criteria: ≥ 2 oesophageal varices with diameter > 5 mm; confirmed liver cirrhosis; Child-Pugh score < 12; aged 18–75 years Other exclusion criteria: previous variceal bleeding; prehepatic portal hypertension; heart rate < 64 bpm; systolic blood pressure < 100 mmHg; contraindications to propranolol; severe comorbidity reducing life expectancy; being listed for liver transplantation; long-term anticoagulant treatment; treatment with beta-blockers or nitrates 30 days before randomisation; existing transjugular intrahepatic porto-systemic or surgical shunt; non-compliance with the study protocol
Interventions	Group 1: variceal band ligation (n = 75) Further details: variceal band ligation using multiband ligator at weekly sessions until obliteration Group 2: beta-blockers (n = 77) Further details: propranolol, until a reduction of the resting heart rate of 20% compared to the pre-treatment heart rate
Outcomes	Mortality at maximal follow-up, any adverse events (number of participants), any adverse events (number of events), liver transplantation at maximal follow-up Follow-up (months): 51.8
Notes	Source of funding (quote): "Supported by the German Association for the Study of the Liver (GASL) and the Ernst und Berta Grimmke Stiftung, Dusseldorf, Germany" Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information
Risk of bias	

Schepke 2004 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were centrally assigned to the 2 treatment arms at the Institute of Medical Biometry, University of Bonn, Germany, by a block randomization with blocks of 6 patients for each centre." Comment: although the details on sequence generation were not reported, the method of allocation concealment used makes it highly likely that the sequence was random.
Allocation concealment (selection bias)	Low risk	Quote: "Patients were centrally assigned to the 2 treatment arms at the Institute of Medical Biometry, University of Bonn, Germany, by a block randomization with blocks of 6 patients for each centre."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: although there were postrandomisation dropouts, these did not appear to be related to the intervention or outcome.
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Seo 2017

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: South Korea Period of recruitment: not stated Number randomised: 260 Postrandomisation dropouts: 1 (0.4%) Revised sample size: 259 Reasons for postrandomisation dropouts: not stated Mean age (years): 53 Females: 70 (27.0%) Small varices: 146 (56.4%) High risk of bleeding: not stated Other features of decompensation: not stated

Seo 2017 *(Continued)*

	Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated
Interventions	Group 1: beta-blockers + variceal band ligation (n = 87) Further details: propranolol started at 20 mg twice daily and increased until reduction of heart rate to 55 bpm or 25% reduction from baseline (duration not stated) + variceal band ligation was performed at 4-week intervals until oesophageal varices were eradicated Group 2: variceal band ligation (n = 86) Further details: variceal band ligation performed at 4-week intervals until oesophageal varices were eradicated Group 3: beta-blockers (n = 86) Further details: propranolol started at 20 mg twice daily and increased until reduction of heart rate to 55 bpm or 25% reduction from baseline (duration not stated)
Outcomes	Mortality at maximal follow-up, variceal bleed at maximal follow-up (any) (number of participants) Follow-up (months): 24
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 1 participant was excluded from analysis; unclear whether this was related to the outcomes, but was unlikely to alter the effect estimates considerably.
Selective reporting (reporting bias)	Unclear risk	Comment: prepublished protocol not available.
Other bias	Low risk	Comment: no other bias noted

Shah 2014

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Pakistan Period of recruitment: 2007–2011 Number randomised: 168 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 168 Mean age (years): 48 Females: 46 (27.4%) Small varices: 91 (54.2%) High risk of bleeding: not stated Other features of decompensation: 65 (38.7%) Alcohol-related cirrhosis: 3 (1.8%) Viral-related cirrhosis: 151 (89.9%) Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: 14 (8.3%) Other inclusion criteria: liver cirrhosis; large size oesophageal varices Other exclusion criteria: pregnant or lactating; allergy to carvedilol or reactive airway disease; already on beta-blocker treatment; presence of any hepatic or other malignancy; people with psychiatric or mental disabilities that would prevent them giving informed consent and refusal to give consent; gastric varices alone
Interventions	Group 1: variceal band ligation (n = 86) Further details: variceal band ligation using multiband ligator, repeated every 3 weeks until obliteration of varices Group 2: beta-blockers (n = 82) Further details: carvedilol 6.25 mg once daily increased to 6.25 mg twice daily after 1 week
Outcomes	Mortality at maximal follow-up, serious adverse events (number of events), any adverse events (number of events) Follow-up (months): 13.3
Notes	Source of funding (quote): "The research team acknowledges the unconditional support of Ferozsons Laboratories (BF Bio-Sciences)" Trial name/trial registry number: NCT01070641 Attempted to contact the authors in February 2020; received no additional information
Risk of bias	

Shah 2014 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Each of the three study sites were provided with the serially labelled sealed opaque envelopes containing treatment assignment information. These envelopes were opened in a consecutive manner to receive either carvedilol or EVL [endoscopic variceal ligation] depending on the randomization assignment." Comment: although the details on sequence generation was not reported, the method of allocation concealment used makes it highly likely that the sequence was random.
Allocation concealment (selection bias)	Low risk	Quote: "Each of the three study sites were provided with the serially labelled sealed opaque envelopes containing treatment assignment information. These envelopes were opened in a consecutive manner to receive either carvedilol or EVL [endoscopic variceal ligation] depending on the randomization assignment."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open label."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open label."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Singh 2012

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: India Period of recruitment: not stated Number randomised: 38 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 38 Mean age (years): not stated Females: not stated Small varices: 0 (0.0%)

Singh 2012 *(Continued)*

	High risk of bleeding: not stated Other features of decompensation: 23 (60.5%) Alcohol-related cirrhosis: 19 (50.0%) Viral-related cirrhosis: 15 (39.5%) Autoimmune disease-related cirrhosis: 1 (2.6%) Other causes of cirrhosis: 3 (7.9%) Other inclusion criteria: liver cirrhosis; large size varices (grade 3–4) Other exclusion criteria: receiving antiviral therapy; concomitant hepatoma or another tumour; severe cardio-pulmonary or renal disease; bradycardia; bronchial asthma; diabetes mellitus; heart failure; peripheral vascular disease; a psychiatric disorder; glaucoma; prostatic hypertrophy
Interventions	Group 1: variceal band ligation (n = 18) Further details: variceal band ligation using multiband ligator every week until the varices were obliterated Group 2: beta-blockers (n = 20) Further details: propranolol, at a dose sufficient to decrease the baseline heart rate by 25%, until the varices were obliterated
Outcomes	Mortality at maximal follow-up Follow-up (months): 12
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts

Singh 2012 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Snady 1988

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: US Period of recruitment: 1982–1986 Number randomised: 56 Postrandomisation dropouts: not stated Revised sample size: 56 Mean age (years): not stated Females: not stated Small varices: not stated High risk of bleeding: not stated Other features of decompensation: not stated Alcohol-related cirrhosis: 56 (100.0%) Viral-related cirrhosis: 0 (0.0%) Autoimmune disease-related cirrhosis: 0 (0.0%) Other causes of cirrhosis: 0 (0.0%) Other inclusion criteria: people with cirrhosis with alcoholic liver disease and oesophageal varices that never bled
Interventions	Group 1: beta-blockers (n = 14) Further details: propranolol (no further details) Group 2: no active intervention (n = 15) Further details: placebo Group 3: sclerotherapy (n = 15) Further details: sclerotherapy (no further details) Group 4: beta-blockers + sclerotherapy (n = 12) Further details: propranolol (no further details) + sclerotherapy (no further details)
Outcomes	Mortality at maximal follow-up Follow-up (months): 12

Snady 1988 *(Continued)*

Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Song 1999

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Korea Period of recruitment: 1996–1998 Number randomised: 64 Postrandomisation dropouts: 3 (4.7%) Revised sample size: 61 Reasons for postrandomisation dropouts: transferred to different hospital or discontinued therapy after complications Mean age (years): 55 Females: 6 (9.8%) Small varices: 39 (63.9%)

Song 1999 *(Continued)*

	High risk of bleeding: not stated Other features of decompensation: 7 (11.5%) Alcohol-related cirrhosis: 22 (36.1%) Viral-related cirrhosis: 35 (57.4%) Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: 4 (6.6%) Other inclusion criteria: high-risk varices Other exclusion criteria: previous bleeding, cardiopulmonary disease, hepatocellular carcinoma
Interventions	Group 1: variceal band ligation (n = 31) Further details: variceal band ligation using Stiegmann-Goff endoscopic ligator kit, repeated at 2-week to 3-month intervals until obliteration of varices Group 2: beta-blockers (n = 30) Further details: propranolol titrated to decrease the heart rate to 25% of the participant's basal heart rate
Outcomes	Mortality at maximal follow-up, variceal bleed at maximal follow-up (any) (number of participants) Follow-up (months): 12
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts, which were probably related to the intervention and outcomes.
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available

Song 1999 *(Continued)*

Other bias	Low risk	Comment: no other bias noted

Strauss 1999

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Brazil Period of recruitment: 1984–1989 Number randomised: 43 Postrandomisation dropouts: 3 (7.0%) Revised sample size: 40 Reasons for postrandomisation dropouts: lost to follow-up or did not complete sclerotherapy Mean age (years): 51 Females: not stated Small varices: 40 (100.0%) High risk of bleeding: not stated Other features of decompensation: not stated Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Other inclusion criteria: liver cirrhosis, no previous bleeding, small oesophageal varices
Interventions	Group 1: sclerotherapy (n = 19) Further details: sclerotherapy: ethanolamine oleate up to 20 mL per session, repeated every 30 days until obliteration Group 2: no active intervention (n = 21) Further details: no treatment
Outcomes	Mortality at maximal follow-up Follow-up (months): 60
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information
Risk of bias	

Strauss 1999 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts that were related to the intervention and likely to be related to outcomes.
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Svoboda 1999

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Czech Republic Period of recruitment: 1994–1997 Number randomised: 186 Postrandomisation dropouts: 29 (15.6%) Revised sample size: 157 Reasons for postrandomisation dropouts: lost to follow-up Mean age (years): 46 Females: 35 (22.3%) Small varices: 7 (4.5%) High risk of bleeding: not stated Other features of decompensation: not stated Alcohol-related cirrhosis: 109 (69.4%) Viral-related cirrhosis: 48 (30.6%) Autoimmune disease-related cirrhosis: 0 (0.0%)

Svoboda 1999 *(Continued)*

	Other causes of cirrhosis: 0 (0.0%) Other inclusion criteria: people with cirrhosis with alcoholic liver disease and oesophageal varices that never bled
Interventions	Group 1: sclerotherapy (n = 55) Further details: sclerotherapy: 1% polidocanol, maximum of 20 mL per session initially every 2 weeks, and then every month until eradication of varices Group 2: variceal band ligation (n = 52) Further details: variceal band ligation using multiband ligator until eradication of varices Group 3: no active intervention (n = 50) Further details: no treatment
Outcomes	Mortality at maximal follow-up, serious adverse events (number of participants), any adverse events (number of events) Follow-up (months): 25
Notes	Source of funding (quote): "This work was supported by grant IGA MZ CR 5187 of Internal Grant Agency of Ministry of Health of the Czech Republic ND5 187-3" Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were postrandomisation dropouts; it is unclear whether these are related to the intervention and outcomes. Our sensitivity analysis indicated the results of the network meta-analysis were sensitive to postrandomisation dropouts.
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Thuluvath 2005

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Brazil Period of recruitment: 2000–2002 Number randomised: 31 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 31 Mean age (years): 52 Females: 14 (45.2%) Small varices: not stated High risk of bleeding: not stated Other features of decompensation: not stated Alcohol-related cirrhosis: 6 (19.4%) Viral-related cirrhosis: 13 (41.9%) Autoimmune disease-related cirrhosis: 8 (25.8%) Other causes of cirrhosis: 4 (12.9%) Other inclusion criteria: liver cirrhosis, no previous bleeding, small oesophageal varices
Interventions	Group 1: variceal band ligation (n = 16) Further details: variceal band ligation using multiband ligator every 2–3 weeks until obliteration Group 2: beta-blockers (n = 15) Further details: propranolol dose was titrated to achieve a resting heart rate < 60 bpm, or a 25% reduction from baseline, or until the maximum tolerated dose was achieved
Outcomes	Mortality at maximal follow-up, liver transplantation at maximal follow-up Follow-up (months): 27.4
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "using sealed envelopes." Comment: further details were not available

Thuluvath 2005 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Quote: "using sealed envelopes." Comment: further details were not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Tomikawa 2004

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Japan Period of recruitment: 1999–2000 Number randomised: 25 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 25 Mean age (years): 59 Females: 10 (40.0%) Small varices: not stated High risk of bleeding: 25 (100.0%) Other features of decompensation: not stated Alcohol-related cirrhosis: 2 (8.0%) Viral-related cirrhosis: 23 (92.0%) Autoimmune disease-related cirrhosis: 0 (0.0%) Other causes of cirrhosis: 0 (0.0%) Other inclusion criteria: cirrhosis with large varices and sign of high risk of bleeding
Interventions	Group 1: sclerotherapy (n = 13)

Tomikawa 2004 *(Continued)*

	Further details: sclerotherapy: 5% ethanolamine oleate at weekly intervals until the whole lower oesophageal mucosa was replaced with an iatrogenic shallow ulcer Group 2: beta-blockers (n = 12) Further details: propranolol, dose titrated until the heart rate at rest was reduced by approximately 25%
Outcomes	Any adverse events (number of events), variceal bleed at maximal follow-up (any) (number of participants) Follow-up (months): 13.5
Notes	Source of funding (quote): "This study was supported in part by health research grants from the “Health Science Research Including Drug Innovation” from the Japan Health Sciences Foundation." Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to groups A or B by their drawing an envelope that enclosed a slip on which either 'A' or 'B' was written."
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomly assigned to groups A or B by their drawing an envelope that enclosed a slip on which either 'A' or 'B' was written."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: prepublished protocol not available, but the authors reported mortality, adverse events, and variceal bleed adequately.
Other bias	Low risk	Comment: no other bias noted

Tripathi 2009

Study characteristics

Methods	Randomised clinical trial
Participants	Country: UK Period of recruitment: 2000–2006

Tripathi 2009 *(Continued)*

	Number randomised: 152 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 152 Mean age (years): 54 Females: 43 (28.3%) Small varices: not stated High risk of bleeding: 7 (4.6%) Other features of decompensation: 78 (51.3%) Alcohol-related cirrhosis: 111 (73.0%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Other inclusion criteria: presence of cirrhosis and oesophageal varices grade II or larger in size without previous variceal bleeding Other exclusion criteria: aged < 18 years or > 75 years; pregnant or lactating women; people of child-bearing age not receiving contraception; allergy to carvedilol; already on beta-blockers or nitrates; presence of malignancy that significantly affects survival; presence of severe systemic illness (cardiorespiratory, active sepsis); psychiatric disease or learning difficulty that will prevent the granting of informed consent; presence of obstructive airways disease; mean arterial pressure 55 mmHg or pulse 50 bpm at baseline; and portal vein thrombosis
Interventions	Group 1: variceal band ligation (n = 75) Further details: variceal band ligation using multibander devices every 2 weeks until eradication of varices Group 2: beta-blockers (n = 77) Further details: carvedilol 12.5 mg once daily (initial dose 6.25 mg and increased to 12.5 mg per day if systolic blood pressure did not fall below 90 mmHg)
Outcomes	Mortality at maximal follow-up Follow-up (months): 20
Notes	Source of funding (quote): "Supported by the University of Edinburgh" Trial name/trial registry number: ISRCTN26269039 Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed separately in each centre using serially numbered sealed envelopes." Comment: although the details on sequence generation were not reported, the method of allocation concealment used makes it highly likely that the sequence was random.

Tripathi 2009 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed separately in each centre using serially numbered sealed envelopes."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

VA Coop. Variceal Sclerotherapy Group 1991

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: 1985–1986 Number randomised: 281 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 281 Mean age (years): 58 Females: 0 (0.0%) Small varices: 181 (64.4%) High risk of bleeding: not stated Other features of decompensation: 140 (49.8%) Alcohol-related cirrhosis: 281 (100.0%) Viral-related cirrhosis: 0 (0.0%) Autoimmune disease-related cirrhosis: 0 (0.0%) Other causes of cirrhosis: 0 (0.0%) Other exclusion criteria: hepatitis B surface antigen positivity; hepatocellular carcinoma; previous sclerotherapy or shunt surgery; history of malignancies or cardiovascular disease
Interventions	Group 1: sclerotherapy (n = 143)

VA Coop. Variceal Sclerotherapy Group 1991 *(Continued)*

	Further details: sclerotherapy: 1.5% sodium tetradecyl sulphate up to 20 mL per session until obliteration; frequency unclear Group 2: no active intervention (n = 138) Further details: placebo
Outcomes	Mortality at maximal follow-up, any adverse events (number of events), variceal bleed at maximal follow-up (any) (number of rebleeds) Follow-up (months): 47
Notes	Source of funding (quote): "Supported by the Cooperative Services Program of the Medical Research Service, Department of Veterans Affairs" Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was carried out according to permuted-blocks design." Comment: the details of randomisation were not reported, but combined with the fact that a permuted-block design was used and blinding was achieved means that randomisation was probably performed.
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was carried out according to permuted-blocks design." Comment: the details of randomisation were not reported, but combined with the fact that a permuted-block design was used and blinding was achieved means that randomisation was probably performed.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Only the members of the endoscopy-sclerotherapy team were aware of the patient's assignments; all other care givers remained unaware of the treatment assignment." Comment: unclear whether the participants were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Only the members of the endoscopy-sclerotherapy team were aware of the patient's assignments; all other care givers remained unaware of the treatment assignment." Comment: unclear whether the outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: prepublished protocol not available, but the authors reported mortality, adverse events, and variceal bleed adequately.
Other bias	Low risk	Comment: no other bias noted

Wang 2006

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Taiwan Period of recruitment: 2002–2004 Number randomised: 61 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 61 Mean age (years): 61 Females: 23 (37.7%) Small varices: 39 (63.9%) High risk of bleeding: 61 (100.0%) Other features of decompensation: 1 (1.6%) Alcohol-related cirrhosis: 11 (18.0%) Viral-related cirrhosis: 47 (77.0%) Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: 3 (4.9%) Other inclusion criteria: portal hypertension caused by cirrhosis; oesophageal varices of moderate or severe grade, associated with any red colour signs (red wale marking, cherry red spots, haematocystic spots); no history of haemorrhage from oesophageal varices; no current treatment with beta-blockers or nitrates, diagnosis of cirrhosis was based on liver biopsy or clinical examination, biochemical tests, and imaging studies Other exclusion criteria: aged > 75 years or < 20 years; presence of malignancy, uraemia, or other serious medical illness that could reduce life expectancy; refractory ascites, hepatic encephalopathy, or marked jaundice (serum bilirubin > 10 mg/dL); history of shunt operation, transjugular intrahepatic portosystemic stent shunt, or endoscopic therapy (sclerotherapy or endoscopic variceal ligation); contraindications to beta-blockers or nitrates, e.g. asthma, chronic obstructive airway disease, diabetes mellitus with documented hypoglycaemic episodes, congestive heart failure, peripheral vascular disease, hypotension (systolic blood pressure < 90 mmHg) and bradycardia
Interventions	Group 1: beta-blockers + nitrates (n = 31) Further details: nadolol to reduce the pulse rate by 25% and isosorbide mononitrate 20 mg once or twice daily Group 2: variceal band ligation (n = 30) Further details: variceal band ligation using multiband ligator repeated at 4-weekly intervals until obliteration
Outcomes	Mortality at maximal follow-up, serious adverse events (number of participants), any adverse events (number of participants), variceal bleed at maximal follow-up (any) (number of participants) Follow-up (months): 23.3

Wang 2006 *(Continued)*

Notes	Source of funding (quote): "The study was supported by a grant from the Medical Research and Advancement Foundation in Memory of Dr Chi-Shuen Tsou in Taiwan." Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was by means of opaque, sealed envelopes numbered according to a table of random numbers."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was by means of opaque, sealed envelopes numbered according to a table of random numbers."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: prepublished protocol not available, but the authors reported mortality, adverse events, and variceal bleed adequately.
Other bias	Low risk	Comment: no other bias noted

Witzel 1985

Study characteristics

Methods	Randomised clinical trial
Participants	Country: West Germany Period of recruitment: 1978–1983 Number randomised: 109 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 109 Mean age (years): 53 Females: 37 (33.9%) Small varices: 75 (68.8%) High risk of bleeding: not stated

Witzel 1985 *(Continued)*

	Other features of decompensation: not stated Alcohol-related cirrhosis: 88 (80.7%) Viral-related cirrhosis: 16 (14.7%) Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: 5 (4.6%) Other inclusion criteria: liver cirrhosis, no previous bleeding
Interventions	Group 1: sclerotherapy (n = 56) Further details: sclerotherapy 1% polidocanol repeated monthly until variceal obliteration Group 2: no active intervention (n = 53) Further details: no treatment
Outcomes	Mortality at maximal follow-up, variceal bleed at maximal follow-up (any) (number of participants) Follow-up (months): 25
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

Wordehoff 1987

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Germany Period of recruitment: 1978–1983 Number randomised: 49 Postrandomisation dropouts: 0 (0.0%) Revised sample size: 49 Mean age (years): 54 Females: 12 (24.5%) Small varices: 0 (0.0%) High risk of bleeding: not stated Other features of decompensation: not stated Alcohol-related cirrhosis: 22 (44.9%) Viral-related cirrhosis: 18 (36.7%) Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: 9 (18.4%) Other inclusion criteria: people with stage III or IV varices with confirmed liver cirrhosis and no previous bleeding
Interventions	Group 1: sclerotherapy (n = 25) Further details: sclerotherapy using 1% polidocanol, maximum 30 mL per session, repeated every 8–10 days until obliteration Group 2: no active intervention (n = 24) Further details: no treatment
Outcomes	Mortality at maximal follow-up Follow-up (months): 44
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempted to contact the authors in February 2020; received no additional information

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available

Wordehoff 1987 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol available
Other bias	Low risk	Comment: no other bias noted

bpm: beats per minute; n: number of participants; TIPS: transjugular intrahepatic portosystemic shunt.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abecasis 2003	Not a comparison of interest for this review.
Abraczinskas 2001	Not a population of interest for this review.
Adson 1984	Not an RCT.
Agarwala 2011	Not a comparison of interest for this review.
Albillos 1996	Not a population of interest for this review.
Alvarado-Tapias 2016	Not a comparison of interest for this review.
ASGE 1998	Not an RCT.
Assi 2000	Not an RCT.
Avgerinos 1994	Not a comparison of interest for this review.
Avgerinos 2000	Compared endoscopic sclerotherapy + propranolol vs propranolol alone. Measured intraoesophageal variceal pressure. During this procedure, a considerable proportion of the control group who were randomised to propranolol received endoscopic sclerotherapy because of bleeding during measurement of intraoesophageal variceal pressure. Therefore, the effect of randomisation was lost.
Banares 1999	Not a population of interest for this review.
Bandi 1998	Not a population of interest for this review.
Barrioz 1998	Not a population of interest for this review.
Batenburg 1990	Not an RCT.

Study	Reason for exclusion
Bellis 2003	Not a population of interest for this review.
Berardi 1974	Not an RCT.
Bhardwaj 2014	Not a comparison of interest for this review.
Bhardwaj 2019	Not a population of interest for this review.
Bolognesi 1994	Not a population of interest for this review.
Bolognesi 1995	Not a population of interest for this review.
Bolondi 2006	Not a population of interest for this review.
Bonilha 2010	Not a population of interest for this review.
Bosch 2005	Not an RCT.
Braga 1991	Not a population of interest for this review.
Burroughs 1992	Not an RCT.
Cales 1990b	Not an RCT.
Cales 1999	Not a population of interest for this review.
Callow 1970	Not a population of interest for this review.
Cestari 1990	Not a population of interest for this review.
Chandok 2012	Not a comparison of interest for this review.
Cheng 2001	Not a population of interest for this review.
ChiCTR-IIR-15007655	Not a comparison of interest for this review.
ChiCTR-PRRC-08000228	Not a population of interest for this review.
ChiCTR-TRC-12002148	Unclear if the studies included non-cirrhotic participants or gastric variceal bleeding.
Cirera 1995	Not a population of interest for this review.
Conn 1986	Not an RCT.
Conn 1987	Not an RCT.
Conn 1993	Not an RCT.
Copaci 2012	Not a population of interest for this review.
De 2002	Not a population of interest for this review.
De 2003	Not a population of interest for this review.
Deschenes 2000	Not an RCT.

Study	Reason for exclusion
Dong 2018	Not a population of interest for this review.
Dunk 1988	Not a population of interest for this review.
ElRahim 2018	Not an RCT.
Escorsell 1996	Not a population of interest for this review.
Escorsell 1997a	Not a population of interest for this review.
Escorsell 1997b	Not a population of interest for this review.
Escorsell 2001	Not a population of interest for this review.
Estevens 1996	Not a population of interest for this review.
eudract2006-006393-14	Not a population of interest for this review.
eudract2012-000236-26	Unclear if the studies included people without cirrhosis or gastric variceal bleeding.
eudract2012-002489-11	Unclear if the studies included people without cirrhosis or gastric variceal bleeding.
eudract2014-000102-35	Not a population of interest for this review.
eudract2014-002018-21	Not a population of interest for this review.
eudract2014-002300-24	Unclear if the studies included people without cirrhosis or gastric variceal bleeding.
eudract2014-005523-27	Unclear if the studies included people without cirrhosis or gastric variceal bleeding.
eudract2017-001762-13	Unclear if the studies included people without cirrhosis or gastric variceal bleeding.
Fernandez Perez 2008	Not a population of interest for this review.
Ferrari 2005	Not a population of interest for this review.
Feu 1991	Not a population of interest for this review.
Feu 1993	Not a population of interest for this review.
Fort 1990	Not an RCT.
Gallant 1992	Not an RCT.
Garcia-Pagán 1991	Not a population of interest for this review.
Garcia-Pagán 1996	Not a population of interest for this review.
Garcia-Pagán 2001	Not a population of interest for this review.
Garcia-Pagán 2003	Not a population of interest for this review.
Gawrieh 2005	Not an RCT.
Gheorghe 2006	Not a population of interest for this review.

Study	Reason for exclusion
Gilbert 1991	Not an RCT.
Gong 1998	Not an RCT.
Gong 2010	Not a population of interest for this review.
Gotoh 1999	Not a population of interest for this review.
Gregory 1991	Not an RCT.
Groszmann 2005	Not a population of interest for this review.
Group Francais de la Prevention Pre-Primaire 1995	Not a population of interest for this review.
Gupta 1993	Not an RCT.
Hamza 2012	Not a comparison of interest for this review.
Hanno 2016	Not a population of interest for this review.
Hashizume 1993	Not a population of interest for this review.
Helmy 2015	Unclear if the studies included people without cirrhosis or gastric variceal bleeding.
Hidaka 2011	Not a population of interest for this review.
Hua 2007	Not an RCT.
Hutteroth 1983	Not an RCT.
Inokuchi 1990	Not a comparison of interest for this review.
Italian Proj. Prop. Prev. Bleed. 1988	Not a comparison of interest for this review.
Iwakiri 2000	Not a population of interest for this review.
Iwao 1996	Not a population of interest for this review.
Jackson 1968	Not a comparison of interest for this review.
Kainth 2017	Not a population of interest for this review.
Kalambokis 2005	Not a population of interest for this review.
Kanazawa 1988	Not a population of interest for this review.
Kim 2016	Not a comparison of interest for this review.
Kitano 1989	Not a population of interest for this review.
Kitano 1992	Not a population of interest for this review.
Kleber 1987	Not an RCT.

Study	Reason for exclusion
Kleber 1991	Not a population of interest for this review.
Kobe 1990	Not a population of interest for this review.
Koch 1994	Not a population of interest for this review.
Kong 2013	Not a population of interest for this review.
Korula 1991	Not an RCT.
Kuwayama 2005	Not a population of interest for this review.
Lashner 1988	Not an RCT.
Lee 2001	Not a population of interest for this review.
Li 1995	Not a population of interest for this review.
Li 2016a	Not a population of interest for this review.
Lin 1994	Not a comparison of interest for this review.
Lin 1996a	Not a comparison of interest for this review.
Lin 1996b	Unclear if the studies included people without cirrhosis or gastric variceal bleeding.
Lin 2002	Not a population of interest for this review.
Lin 2005	Not a population of interest for this review.
Liu 2004	Not a population of interest for this review.
Madwar 1998	Unclear if the studies included people without non-cirrhosis or gastric variceal bleeding.
Mann 2004	Not an RCT.
Mastai 1986	Not a population of interest for this review.
Masumoto 1998	Not a population of interest for this review.
McCormick 1992	Not a population of interest for this review.
McCormick 1993	Not a population of interest for this review.
McKee 1990	Not a population of interest for this review.
Mino 1995	Not an RCT.
Miyoshi 1997	Not a population of interest for this review.
Mo 2014	Not a population of interest for this review.
NCT00006398	Not a population of interest for this review.
NCT00409084	Unclear if the studies included people without cirrhosis or gastric variceal bleeding.

Study	Reason for exclusion
NCT00493480	Not a comparison of interest for this review.
NCT00799851	Not a population of interest for this review.
NCT01059396	Not a population of interest for this review.
NCT01188733	Not a comparison of interest for this review.
NCT01383044	Not a comparison of interest for this review.
NCT02646202	Unclear if the studies included people without cirrhosis or gastric variceal bleeding.
NCT02695732	Unclear if the studies included people without cirrhosis or gastric variceal bleeding.
NCT03583996	Not an RCT.
Nevens 1996a	Not a population of interest for this review.
Nevens 1996b	Not a population of interest for this review.
Nevens 1996c	Not a population of interest for this review.
Nishikawa 1999	Not a population of interest for this review.
Oberti 1999	Not an RCT.
Ohmoto 2006	Not a population of interest for this review.
Okano 2003a	Not an RCT.
Okano 2003b	Not an RCT.
Orloff 1962	Not an RCT.
Orloff 1974	Not an RCT.
Orloff 2014	Not an RCT.
Pagliaro 1989	Not a comparison of interest for this review.
Pang 1997	Not a population of interest for this review.
Paquet 1983	Not an RCT.
Paquet 1993	Not an RCT.
Pfisterer 2018	Not an RCT.
Phillips 1975	Not a population of interest for this review.
Plevris 1994	Not a population of interest for this review.
Pollo-Flores 2015	Unclear if the studies included people without cirrhosis or gastric variceal bleeding.
Poynard 1991	Not an RCT.

Study	Reason for exclusion
Pozzi 2005	Not a population of interest for this review.
Qi 2007	Not a population of interest for this review.
Ramond 1999	Not an RCT.
Resnick 1969	Not a population of interest for this review.
Resnick 1974	Not a population of interest for this review.
Reynolds 1991	Not an RCT.
Romero 2000	Not a population of interest for this review.
Rosemurgy 2005	Not a population of interest for this review.
Santambrogio 1990	Not a population of interest for this review.
Santos 2011	Not a population of interest for this review.
Sarin 1996	Not a population of interest for this review.
Sarin 1999	Not a population of interest for this review.
Sarin 2005	Not a population of interest for this review.
Sarin 2010	Not a population of interest for this review.
Schepke 2001	Not a population of interest for this review.
Schiedermaier 2002	Not a population of interest for this review.
Schiedermaier 2003	Not a population of interest for this review.
Sen 2002	Not a population of interest for this review.
Shang 2010	Not a population of interest for this review.
Sharara 2003	Not an RCT.
Sheikh 2000	Not an RCT.
Silva 2004	Not a population of interest for this review.
Siqueira 1998	Unclear if the studies included people without cirrhosis or gastric variceal bleeding.
SLCTR/2007/001	Not a population of interest for this review.
Sohn 2013	Not a population of interest for this review.
Sotto 1989	Not a population of interest for this review.
Stiegmann 1999	Not an RCT.
Sugano 1997	Not a population of interest for this review.

Study	Reason for exclusion
Sugano 2001	Not a population of interest for this review.
Sussman 2003	Not an RCT.
Taniai 2002	Not an RCT.
Taranto 1990	Not a population of interest for this review.
Testa 1991	Not a population of interest for this review.
Thiel 1993	Not an RCT.
Tincani 1993	Not a comparison of interest for this review.
Tincani 1995	Not a comparison of interest for this review.
Triantos 2005	Not a population of interest for this review.
Triger 1991	Not an RCT.
Umehara 1999	Not a population of interest for this review.
Vanruiswyk 1992	Not an RCT.
Vorobioff 2002	Not a population of interest for this review.
Vorobioff 2007	Not a population of interest for this review.
Yattoo 2013	Not a comparison of interest for this review.
Zalepuga 2000	Not an RCT.
Zargar 2008	Not a population of interest for this review.
Zironi 1996	Not a population of interest for this review.

RCT: randomised clinical trial.

Characteristics of studies awaiting classification *[ordered by study ID]*

Buuren 2003

Methods	Randomised clinical trial
Participants	People with cirrhosis and oesophageal varices
Interventions	Endoscopic sclerotherapy
Outcomes	Mortality, bleeding (unclear whether this was from oesophageal varices), adverse events
Notes	Randomisation performed before the consent from participants were obtained. The ethics of including this trial in systematic reviews is an ongoing debate.

eudract2011-006208-11

Methods	Randomised clinical trial
Participants	Adults with oesophageal variceal bleeding with cirrhosis
Interventions	Group 1: endoscopic band ligation Further details: no further details Group 2: oral carvedilol Further details: no further details
Outcomes	Not stated
Notes	No published data

Characteristics of ongoing studies *[ordered by study ID]*

ChiCTR-IPR-15005816

Study name	Multicenter, randomized, comparative, prospective study on efficacy of EVL-EVS sequential therapy in preventing esophageal variceal hemorrhage
Methods	Randomised clinical trial
Participants	Inclusion criteria: written informed consent; aged 18–65 years; history of liver cirrhosis, endoscopy confirmed by gastroesophageal varices exist and have indication of endoscopic therapy; percutaneous transluminal angioplasty ≥ 40%; without other complications of liver cirrhosis Exclusion criteria: with light to moderate oesophageal varices; with gastric varices; percutaneous transluminal angioplasty < 40%; combined with malignant tumour of liver or other organs; cannot give written informed consent
Interventions	Group 1: control group Further details: no further details Group 2: EVL Further details: no further details Group 3: EVS Further details: no further details Group 4: EVL + EVS Further details: no further details
Outcomes	Outcomes planned: 5 year survival rate, oesophageal varices bleeding, rebleeding, oesophageal varices elimination
Starting date	July 2017
Contact information	Bin Wu: binwu001@hotmail.com Department of Gastroenterology, The Third Affiliated Hospital of Sun Yat-sen University. No. 600, Tianhe Rd, Tianhe District, Guangzhou, Guangdong, China

ChiCTR-IPR-15005816 *(Continued)*

Notes	Planned sample size: 50 Planned study time: July 2017 to October 2017

NCT02066649

Study name	Carvedilol vs band ligation vs combination therapy for primary prophylaxis of variceal bleeding
Methods	Randomised clinical trial
Participants	Inclusion criteria: aged > 18 years with diagnosis of cirrhosis (by history, serology, or imaging), with medium or large oesophageal varices on variceal screening oesophagogastroduodenoscopy, and no history of gastrointestinal bleeding, as related to portal hypertension Exclusion criteria: pregnant women; receiving beta-blockers or nitrates for any underlying condition; allergies to carvedilol; mean arterial pressure < 55 mmHg or heart rate < 55 beats per minute at baseline; presence of hepatocellular carcinoma; presence of portal vein thrombosis; severe, uncontrolled respiratory disease (asthma, chronic obstructive pulmonary disease); complete heart block or other significant arrhythmias; significant renal disease (Chronic Kidney Disease stage III or higher); unable to provide consent; and people who in the opinion of the principal investigator are not suitable for participation in the trial
Interventions	Group 1: beta-blocker Further details: initiating participant on carvedilol after diagnosis of varices made on endoscopy Group 2: variceal band ligation Further details: performing variceal band ligation during endoscopy on participant after diagnosis of oesophageal varices made on endoscopy Group 3: beta-blocker + variceal band ligation Further details: once participant has confirmed large oesophageal varices on endoscopy, he/she will be started on carvedilol (postprocedure) in addition to having variceal band ligation performed during endoscopy
Outcomes	Planned primary outcomes: incidence of first variceal bleed (time frame: within 2-year follow-up) Planned secondary outcomes: bleed-related mortality; overall mortality; recurrence of varices (time frame: within 2-year follow-up)
Starting date	Estimated study start date: July 2018
Contact information	Nikolaos T Pyrsopoulos Rutgers, The State University of New Jersey
Notes	Planned sample size: not stated Planned study time: July 2018 to September 2021

NCT03736265

Study name	Carvedilol for prevention of oesophageal varices progression

NCT03736265 *(Continued)*

Methods	Randomised clinical trial
Participants	Inclusion criteria: males or females; people with hepatitis B virus-related liver cirrhosis with ≥ 2 years of antiviral therapy; presence of small or medium oesophageal varices without red colour sign; hepatitis B virus-DNA < 1×10^3 IU/mL; signature of informed consent Exclusion criteria: previous presence of decompensated cirrhosis including ascites, bleeding and hepatic encephalopathy; any contraindications to beta-blockers including asthma, chronic obstructive pulmonary disease, allergic rhinitis, New York Heart Association class IV heart failure, atrioventricular block, sinus bradycardia (heart rate < 50 beats per minute), cardiogenic shock, hypotension (systolic blood pressure < 90 mmHg), sick sinus syndrome, insulin dependent diabetes, peripheral vascular disease; allergy to carvedilol; any malignancy that affects survival; renal dysfunction; history of beta-blockers within last 3 months; history of surgery for portal hypertension; history of prior EVL or sclerotherapy, history of surgery for portal hypertension including portosystemic shunts, disconnection and spleen resection and TIPS; severe systemic diseases; refusal to participate in the study
Interventions	Group 1: beta-blocker + nucleos(t)ide analogue Further details: based on nucleoside analogue, carvedilol will be given to the participants. Carvedilol started at 6.25 mg once per day. After 1 week, will be increased to 6.25 mg twice daily. Target dose 12.5 mg twice daily will be started after 2 weeks if systolic blood pressure does not fall below 90 mmHg and heart rate 55 beats per minute. Group 2: nucleos(t)ide analogues Further details: continuing take nucleoside analogue including lamivudine, adefovir dipivoxil, entecavir, telbivudine, tenofovir disoproxil fumarate and tenofovir alafenamide
Outcomes	Planned primary outcomes: progression incidence of oesophageal varices (time frame: 2 years) (defined as varices developed from small (F1) to medium or large (F2/F3); varices developed from medium (F2) to large (F3); bleeding from oesophageal varices) Planned secondary outcomes: cumulative rate of liver decompensation (including ascites, hepatic encephalopathy) after 2 years; cumulative rate of hepatic cellular carcinoma, death, or liver transplantation after 2 year; progression rate of non-invasive scores (Child-Pugh, Model for End-Stage Liver Disease, aspartate transaminase to platelet ratio index, Fibrosis-4 score) after 2 years; dynamic change of liver stiffness quantified by transient elastography after 2 years; dynamic change of haemodynamics parameter (heart rate and mean arterial pressure) after 2 years
Starting date	Study start date: 26 August 2017
Contact information	Xiaojuan Ou, Beijing Friendship Hospital
Notes	Planned sample size: 240 participants Planned study time: August 2017 to December 2021

NCT03776955

Study name	Beta-blockers for oesophageal varices
Methods	Randomised clinical trial
Participants	Inclusion criteria: aged > 18 years; cirrhosis and portal hypertension (defined by any 2 of the following: 1. characteristic clinical examination findings (≥ 1 of liver function tests, haematological panel, coagulation profile abnormalities); 2. characteristic radiological findings (≥ 1 of heterogeneous, small liver with irregular contour, splenomegaly, ascites, varices, recanalised umbilical vein); 3. fi-

NCT03776955 *(Continued)*

	brosis score > stage 4 on liver biopsy; 4. Fibroscan liver stiffness measurement > 15 kilopascal without other explanation); small oesophageal varices diagnosed within the last 3 months (defined as < 5 mm in diameter or varices which completely disappear on moderate insufflation at gastroscopy); not received a beta-blocker in the last week; capacity to provide informed consent Exclusion criteria: non-cirrhotic portal hypertension; medium/large oesophageal varices (current or history of; (defined as > 5 mm in diameter); isolated gastric, duodenal, rectal varices with or without evidence of recent bleeding; previous variceal haemorrhage; red signs accompanying varices at endoscopy; known intolerance to beta-blockers; contraindication to beta-blocker (heart rate < 50 bpm, known 2nd degree or higher heart block, sick sinus syndrome, systolic blood pressure < 85 mmHg, chronic airways obstruction (asthma/chronic obstructive pulmonary disease), floppy iris syndrome, CYP2D6 poor metaboliser, history of cardiogenic shock, history of severe hypersensitivity reaction to beta-blockers, untreated phaeochromocytoma, severe peripheral vascular disease, prinzmetal angina, New York Heart Association IV heart failure); unable to provide informed consent; Child-Pugh C cirrhosis; already receiving a beta-blocker for another reason that cannot be discontinued; graft cirrhosis after liver transplantation; evidence of active malignancy without curative therapy planned; pregnant or lactating women; women of child bearing potential unwilling to use adequate contraception during the trial; people who have been on another clinical trial within the previous 3 months
Interventions	Group 1: beta-blocker Further details: 6.25 mg or 12.5 mg if tolerated Group 2: placebo Further details: oral placebo
Outcomes	Planned primary outcomes: time to first variceal haemorrhage; assessment of the cost effectiveness of early intervention with non-specific beta-blockers in this patient population Planned secondary outcomes: variceal bleed rate (time frame: 1 and 3 years); variceal bleeding needing intervention (time frame: 3 years; number of participants that progress to medium/large varices requiring clinical intervention); composite of variceal bleed rate and bleeding needing intervention (time frame: 3 years; i.e. unit less measure of rate of ((number of participants who bled) + (number of participants who progressed without bleeding))/(number of participants in that arm at randomisation) at 3 years ranging from 0 to 1; clinical decompensation (time frame: 3 years; spontaneous bacterial peritonitis, new ascites, new hepatic encephalopathy); Child-Pugh Score for Cirrhosis mortality (time frame: 3 years; range 5–15; higher scores represent worse outcomes); model for end-stage liver disease score (time frame: 3 years; range 6–40; higher scores represent worse outcomes); survival (overall, liver-related, cardiovascular-related; time frame: 3 years); quality of life assessment (time frame: 3 years; using EQ5D-5L; range 5–25; higher scores represent worse outcomes)
Starting date	Actual study start date: 17 June 2019
Contact information	Vishal Patel: vishal.patel@nhs.net Kieran Brack: kch-tr.boppptrial@nhs.net
Notes	Planned sample size: 1200 participants Planned study time: June 2019 to December 2024

NCT04074473

Study name	Impact of nonselective beta-blocker on acute kidney injury in cirrhotic patients with oesophageal varices

NCT04074473 *(Continued)*

Methods	Randomised clinical trial
Participants	Inclusion criteria: aged 20–85 years; people with cirrhosis with oesophageal varices regardless of bleeding event or not will be enrolled in this study Exclusion criteria: terminal stage hepatocellular carcinoma; other malignancy; stroke; active sepsis; chronic kidney disease stage 4 under renal replacement therapy; contraindications to non-selective beta-blockers; history of non-selective beta-blockers use, sclerotherapy, banding ligation, transjugular intrahepatic porto-systemic shunt, or shunt surgery; serum total bilirubin > 10 mg/dL; refractory ascites; hepato-renal syndrome; pregnancy; severe heart failure (New York Heart Association (Fc III/IV); bronchial asthma or chronic obstructive pulmonary disease; second or third degree atrioventricular block; severe hypotension; refusal to participate
Interventions	Group 1: beta-blocker Further details: propranolol 10 mg twice daily initially and titrated every week to achieve 25% reduction in heart rate (heart rate > 55 bpm or systemic blood pressure > 90 mmHg) Group 2: oesophageal variceal ligation Further details: oesophageal variceal ligation every 3–4 weeks to achieve variceal eradication under endoscopy. After eradication, follow-up endoscopy every 3 months and variceal ligation again if recurrence Group 3: oesophageal variceal ligation (discontinue propranolol after oesophageal variceal eradication) Further details: participants randomised to banding ligation group discontinue propranolol after eradication of oesophageal varices
Outcomes	Planned primary outcomes: acute kidney injury; hepatorenal syndrome; overall survival (time frame for all: 3 years) Planned secondary outcomes: oesophageal varices bleeding/rebleeding; infection rate (time frame for both: 3 years)
Starting date	Actual study start date: 13 April 2015
Contact information	Ming-Chih Hou: mchou@vghtpe.gov.tw Han-Chieh Lin: hclin@vghtpe.gov.tw
Notes	Planned sample size: 170 participants Planned study time: April 2015 to July 2020

Tripathi 2019

Study name	Study protocol for a randomised controlled trial of carvedilol vs variceal band ligation in primary prevention of variceal bleeding in liver cirrhosis (CALIBRE trial)
Methods	Randomised clinical trial
Participants	Inclusion criteria: person with cirrhosis and medium varices (Grade II varices that do not flatten on air insufflation and do not occlude the lumen) or large varices (Grade III varices which are larger than Grade II varices and occupy the whole lumen) that have never bled as defined in the British Society of Gastroenterology guidelines

Tripathi 2019 *(Continued)*

	Exclusion criteria: receiving propranolol, carvedilol, or nadolol for primary prevention or have had band ligation
Interventions	Group 1: beta-blocker Further details: carvedilol 12.5 mg once daily Group 2: oesophageal variceal ligation Further details: as per the British Society of Gastroenterology guidelines
Outcomes	Planned primary outcomes: any variceal bleeding within 1 year of randomisation (first variceal bleed defined as haematemesis or melena (or both) with either endoscopic evidence of variceal bleeding or stigmata of recent haemorrhage and ≥ 2 g/L reduction in haemoglobin within 24 hours of admission or massive upper gastrointestinal bleeding leading to death. The definition includes bleeding from banding ulceration Planned secondary outcomes: time to first variceal bleed in days (from randomisation); mortality at 1 year (from randomisation; all-cause mortality, liver-related mortality, cardiovascular mortality); transplant free survival at 1 year (from randomisation); adverse events related to treatment (up to 12 months after randomisation; dysphagia requiring discontinuation of treatment, symptomatic hypotension requiring change in treatment, dyspnoea, gastrointestinal upset); other complications of cirrhosis (new onset ascites confirmed clinically or on imaging and graded as per International Club of Ascites recommendations, new onset encephalopathy defined using West Haven Criteria, spontaneous bacterial peritonitis, hepatocellular carcinoma, any renal dysfunction as per International Club of Ascites – Acute Kidney Injury definitions; health-related quality of life (EQ-5D-5L) from randomisation to 6 and 12 months; use of healthcare resources (costs and cost-effectiveness based on the outcomes of cost per variceal bleeding avoided within 1 year of randomisation, cost per quality-adjusted life-year estimated using the EQ-5D-5L, and cost per death avoided at 1 year); patient preference (qualitative interviews with patients and staff during the pilot phase that will explore patients' experience of and preferences related to treatment (carvedilol or oesophageal variceal ligation); use of alternative therapies; cross-over therapies
Starting date	Quote: "Patient enrollment is expected to start in early 2019"
Contact information	Dr Dhiraj Tripathi: d.tripathi@bham.ac.uk
Notes	Planned sample size: 2630 participants Planned study time: early 2019 to end 2022

EVL: endoscopic variceal ligation; EVS: endoscopic variceal sclerotherapy.

ADDITIONAL TABLES

Table 1. Characteristics of included studies (ordered by comparisons)

Study name	Intervention 1 (number of participants) vs intervention 2 (number of participants)	Small varices	High risk of bleeding	Included participants with other features of decompensation	Aetiology of cirrhosis	Period of recruitment	Follow-up in months	Overall risk of bias
PROVA study group 1991	No active intervention (72) vs beta-blockers (68)	Not stated	Not stated	Yes (encephalopathy)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: not stated Autoimmune-related: not stated Other: not stated	1985–1989	15.4	High
Bhardwaj 2017	No active intervention (70) vs beta-blockers (70)	All participants had small varices	Participants with and without high risk of bleeding	Yes (ascites)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: not stated Other: participants with and without other causes of cirrhosis	2010–2012	21	High
Cales 1989a	No active intervention (8) vs beta-blockers (16)	Not stated	Not stated	Not stated	Alcohol-related: all participants had alcohol-related cirrhosis Viral-related: no participants had viral-related cirrhosis Autoimmune-related: no participants had autoimmune disease-related cirrhosis Other: no participants had other causes of cirrhosis	Not stated	0.15	High
Cales 1989b	No active intervention (8) vs beta-blockers (8)	Not stated	Not stated	Yes (ascites)	Alcohol-related: all participants had alcohol-related cirrhosis Viral-related: no participants had viral-related cirrhosis	Not stated	0.25	High

Table 1. Characteristics of included studies (ordered by comparisons) *(Continued)*

					Autoimmune-related: no participants had autoimmune disease-related cirrhosis Other: no participants had other causes of cirrhosis			
Conn 1991	No active intervention (51) vs beta-blockers (51)	Not stated	Not stated	Yes (encephalopathy)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: not stated Autoimmune-related: not stated Other: not stated	1982–1986	17	High
Ideo 1988	No active intervention (27) vs beta-blockers (30)	No participants had small varices	Not stated	Yes (encephalopathy)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: not stated Autoimmune-related: not stated Other: not stated	1982–1986	22.8	High
Lebrec 1988	No active intervention (53) vs beta-blockers (53)	Not stated	Not stated	Yes (not stated)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: participants with and without autoimmune disease-related cirrhosis Other: participants with and without other causes of cirrhosis	1982–1985	12	High
Merkel 2004	No active intervention (78) vs beta-blockers (83)	All participants had small varices	No participants had high risk of bleeding	Yes (ascites)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: not stated Other: participants with and without other causes of cirrhosis	1996–2000	36	High

Table 1. Characteristics of included studies (ordered by comparisons) *(Continued)*

Mishra 2007	No active intervention (42) vs beta-blockers (43)	All participants had small varices	Not stated	Not stated	Alcohol-related: not stated Viral-related: not stated Autoimmune-related: not stated Other: not stated	Not stated	18	High
Pascal 1987	No active intervention (112) vs beta-blockers (118)	Not stated	Not stated	Not stated	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: not stated Autoimmune-related: not stated Other: not stated	1983–1984	14.3	High
Sarin 2013	No active intervention (73) vs beta-blockers (77)	All participants had small varices	Participants with and without high risk of bleeding	Yes (encephalopathy)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: not stated Other: participants with and without other causes of cirrhosis	2004–2007	25	High
Snady 1988	No active intervention (15) vs beta-blockers (14)	Not stated	Not stated	Not stated	Alcohol-related: all participants had alcohol-related cirrhosis Viral-related: no participants had viral-related cirrhosis Autoimmune-related: no participants had autoimmune disease-related cirrhosis Other: no participants had other causes of cirrhosis	1982–1986	12	High
Chen 2000	Variceal band ligation (26) vs beta-blockers (30)	Not stated	Not stated	Not stated	Alcohol-related: not stated Viral-related: not stated Autoimmune-related: not stated Other: not stated	Not stated	12	High

Table 1. Characteristics of included studies (ordered by comparisons) *(Continued)*

De 1999	Variceal band ligation (15) vs beta-blockers (15)	No participants had small varices	Not stated	Yes (encephalopathy)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: not stated Autoimmune-related: not stated Other: not stated	1994–1996	17.6	High
Drastich 2011	Variceal band ligation (40) vs beta-blockers (33)	Not stated	Participants with and without high risk of bleeding	Yes (ascites)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: participants with and without autoimmune disease-related cirrhosis Other: participants with and without other causes of cirrhosis	Not stated	11	High
Feng 2012	Variceal band ligation (84) vs beta-blockers (84)	Not stated	Not stated	Yes (ascites)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: not stated Other: participants with and without other causes of cirrhosis	1998–2008	23.8	High
Jutabha 2005	Variceal band ligation (31) vs beta-blockers (31)	Not stated	Participants with and without high risk of bleeding	Not stated	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: participants with and without autoimmune disease-related cirrhosis Other: participants with and without other causes of cirrhosis	1996–2001	15	High

Table 1. Characteristics of included studies (ordered by comparisons) *(Continued)*

Khan 2017	Variceal band ligation (125) vs beta-blockers (125)	Not stated	Not stated	Not stated	Alcohol-related: not stated Viral-related: not stated Autoimmune-related: not stated Other: not stated	Not stated	6	High
Lay 2006	Variceal band ligation (50) vs beta-blockers (50)	Not stated	All participants had high risk of bleeding	Yes (ascites)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: participants with and without autoimmune disease-related cirrhosis Other: participants with and without other causes of cirrhosis	1998–2002	34.9	High
Lo 2004	Variceal band ligation (50) vs beta-blockers (50)	Not stated	All participants had high risk of bleeding	Yes (ascites)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: not stated Other: participants with and without other causes of cirrhosis	1997–2000	22.2	High
Lui 2002	Variceal band ligation (44) vs beta-blockers (66)	Not stated	Participants with and without high risk of bleeding	Yes (encephalopathy)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: not stated Autoimmune-related: not stated Other: not stated	1994–1999	19.7	High
NCT00337740	Variceal band ligation (not stated) vs beta-blockers (not stated)	Not stated	Not stated	Not stated	Alcohol-related: not stated Viral-related: not stated Autoimmune-related: not stated	not stated	not stated	High

Table 1. Characteristics of included studies (ordered by comparisons) *(Continued)*

					Other: not stated			
Norbeto 2007	Variceal band ligation (31) vs beta-blockers (31)	Not stated	All participants had high risk of bleeding	Not stated	Alcohol-related: not stated Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: not stated Other: not stated	2001–2005	14.6	High
Perez-Ayuso 2010	Variceal band ligation (39) vs beta-blockers (36)	Not stated	All participants had high risk of bleeding	Yes (encephalopathy)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: participants with and without autoimmune disease-related cirrhosis Other: participants with and without other causes of cirrhosis	1998–2007	55	High
Psilopoulos 2005	Variceal band ligation (30) vs beta-blockers (30)	Not stated	All participants had high risk of bleeding	Not stated	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: participants with and without autoimmune disease-related cirrhosis Other: participants with and without other causes of cirrhosis	1999–2003	27.5	High
Schepke 2004	Variceal band ligation (75) vs beta-blockers (77)	Not stated	Participants with and without high risk of bleeding	Yes (encephalopathy)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: participants with and without autoimmune disease-related cirrhosis	1996–2001	51.8	High

Table 1. Characteristics of included studies (ordered by comparisons) *(Continued)*

					Other: participants with and without other causes of cirrhosis			
Seo 2017	Variceal band ligation (86) vs beta-blockers (86)	Not stated	Not stated	Not stated	Alcohol-related: not stated Viral-related: not stated Autoimmune-related: not stated Other: not stated	Not stated	24	High
Shah 2014	Variceal band ligation (86) vs beta-blockers (82)	Not stated	Not stated	Yes (ascites)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: participants with and without autoimmune disease-related cirrhosis Other: participants with and without other causes of cirrhosis	2007–2011	13.3	High
Singh 2012	Variceal band ligation (18) vs beta-blockers (20)	No participants had small varices	Not stated	Yes (ascites)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: participants with and without autoimmune disease-related cirrhosis Other: participants with and without other causes of cirrhosis	Not stated	12	High
Song 1999	Variceal band ligation (31) vs beta-blockers (30)	Not stated	Not stated	Yes (encephalopathy)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: not stated Other: participants with and without other causes of cirrhosis	1996–1998	12	High

Table 1. Characteristics of included studies (ordered by comparisons) *(Continued)*

Thuluvath 2005	Variceal band ligation (16) vs beta-blockers (15)	Not stated	Not stated	Not stated	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: participants with and without autoimmune disease-related cirrhosis Other: participants with and without other causes of cirrhosis	2000–2002	27.4	High
Tripathi 2009	Variceal band ligation (75) vs beta-blockers (77)	Not stated	Participants with and without high risk of bleeding	Yes (ascites)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: not stated Autoimmune-related: not stated Other: not stated	2000–2006	20	High
Lay 1997	Variceal band ligation (62) vs no active intervention (64)	Not stated	All participants had high risk of bleeding	Yes (ascites)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: participants with and without autoimmune disease-related cirrhosis Other: participants with and without other causes of cirrhosis	1993–1995	13.5	High
Lo 1999	Variceal band ligation (64) vs no active intervention (63)	Not stated	All participants had high risk of bleeding	Yes (ascites)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: not stated Other: participants with and without other causes of cirrhosis	1992–1995	29	High

Table 1. Characteristics of included studies (ordered by comparisons) *(Continued)*

Svoboda 1999	Variceal band ligation (52) vs no active intervention (50)	Not stated	Not stated	Not stated	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: no participants had autoimmune disease-related cirrhosis Other: no participants had other causes of cirrhosis	1994–1997	25	High
Andreani 1990	Sclerotherapy (42) vs beta-blockers (43)	Not stated	Not stated	Yes (encephalopathy)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: not stated Autoimmune-related: not stated Other: not stated	1985–1988	24	High
PROVA study group 1991	Sclerotherapy (73) vs beta-blockers (68)	Not stated	Not stated	Yes (encephalopathy)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: not stated Autoimmune-related: not stated Other: not stated	1985–1989	15.4	High
Kanazawa 1993	Sclerotherapy (32) vs beta-blockers (33)	Not stated	Not stated	Yes (encephalopathy)	Alcohol-related: not stated Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: not stated Other: not stated	1987–1992	31	High
Snady 1988	Sclerotherapy (15) vs beta-blockers (14)	Not stated	Not stated	Not stated	Alcohol-related: all participants had alcohol-related cirrhosis Viral-related: no participants had viral-related cirrhosis Autoimmune-related: no participants had autoimmune disease-related cirrhosis	1982–1986	12	High

Table 1. Characteristics of included studies (ordered by comparisons) *(Continued)*

					Other: no participants had other causes of cirrhosis			
Tomikawa 2004	Sclerotherapy (13) vs beta-blockers (12)	Not stated	All participants had high risk of bleeding	Not stated	Alcohol-related: participants with alcohol-related cirrhosis and without alcohol relate Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: no participants had autoimmune disease-related cirrhosis Other: no participants had other causes of cirrhosis	1999–2000	13.5	High
VA Coop. Variceal Sclerotherapy Group 1991	Sclerotherapy (143) vs no active intervention (138)	Not stated	Not stated	Yes (ascites)	Alcohol-related: all participants had alcohol-related cirrhosis Viral-related: no participants had viral-related cirrhosis Autoimmune-related: no participants had autoimmune disease-related cirrhosis Other: no participants had other causes of cirrhosis	1985–1986	47	High
PROVA study group 1991	Sclerotherapy (73) vs no active intervention (72)	Not stated	Not stated	Yes (encephalopathy)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: not stated Autoimmune-related: not stated Other: not stated	1985–1989	15.4	High
De Franchis 1991	Sclerotherapy (55) vs no active intervention (51)	Not stated	Not stated	Not stated	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: not stated Autoimmune-related: not stated Other: not stated	1985–1987	24	High
Duhamel 1994	Sclerotherapy (57) vs no ac-	Not stated	Participants with and	Yes (ascites)	Alcohol-related: participants with and without alcohol-related cirrhosis	1985–1988	30	High

Table 1. Characteristics of included studies (ordered by comparisons) *(Continued)*

	tive intervention (60)		without high risk of bleeding		Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: participants with and without autoimmune disease-related cirrhosis Other: participants with and without other causes of cirrhosis			
Fleig 1988	Sclerotherapy (16) vs no active intervention (24)	No participants had small varices	Not stated	Not stated	Alcohol-related: not stated Viral-related: not stated Autoimmune-related: not stated Other: not stated	Not stated	28.8	High
Paquet 1982	Sclerotherapy (31) vs no active intervention (32)	Not stated	Not stated	Not stated	Alcohol-related: not stated Viral-related: not stated Autoimmune-related: not stated Other: not stated	1978–1980	18	High
Paquet 1994	Sclerotherapy (44) vs no active intervention (45)	No participants had small varices	All participants had high risk of bleeding	Not stated	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: participants with and without autoimmune disease-related cirrhosis Other: participants with and without other causes of cirrhosis	1987–1992	33	High
Piai 1988	Sclerotherapy (71) vs no active intervention (69)	Not stated	All participants had high risk of bleeding	Not stated	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: not stated	1983–1985	13	High

Table 1. Characteristics of included studies (ordered by comparisons) *(Continued)*

					Other: participants with and without other causes of cirrhosis			
Quer 1991	Sclerotherapy (22) vs no active intervention (24)	Not stated	Participants with and without high risk of bleeding	Yes (encephalopathy)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: not stated Autoimmune-related: not stated Other: not stated	Not stated	16	High
Rossi 1991	Sclerotherapy (18) vs no active intervention (19)	Not stated	Not stated	Not stated	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: not stated Other: participants with and without other causes of cirrhosis	1984–1988	36.6	High
Russo 1989	Sclerotherapy (21) vs no active intervention (20)	No participants had small varices	Not stated	Yes (not stated)	Alcohol-related: not stated Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: not stated Other: participants with and without other causes of cirrhosis	1984–1985	18	High
Santangelo 1988	Sclerotherapy (49) vs no active intervention (46)	No participants had small varices	Not stated	Yes (encephalopathy)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: participants with and without autoimmune disease-related cirrhosis Other: participants with and without other causes of cirrhosis	1985–1987	13	High
Sauerbruch 1988	Sclerotherapy (68) vs no ac-	No participants	Participants with and	Yes (ascites)	Alcohol-related: participants with and without alcohol-related cirrhosis	1982–1986	22	High

Table 1. Characteristics of included studies (ordered by comparisons) *(Continued)*

	tive intervention (65)	had small varices	without high risk of bleeding		Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: not stated Other: not stated			
Snady 1988	Sclerotherapy (15) vs no active intervention (15)	Not stated	Not stated	Not stated	Alcohol-related: all participants had alcohol-related cirrhosis Viral-related: no participants had viral-related cirrhosis Autoimmune-related: no participants had autoimmune disease-related cirrhosis Other: no participants had other causes of cirrhosis	1982–1986	12	High
Strauss 1999	Sclerotherapy (19) vs no active intervention (21)	All participants had small varices	Not stated	Not stated	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: not stated Other: not stated	1984–1989	60	High
Svoboda 1999	Sclerotherapy (55) vs no active intervention (50)	Not stated	Not stated	Not stated	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: no participants had autoimmune disease-related cirrhosis Other: no participants had other causes of cirrhosis	1994–1997	25	High
Witzel 1985	Sclerotherapy (56) vs no active intervention (53)	Not stated	Not stated	Not stated	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: not stated	1978–1983	25	High

Table 1. Characteristics of included studies (ordered by comparisons) *(Continued)*

					Other: participants with and without other causes of cirrhosis			
Wordehoff 1987	Sclerotherapy (25) vs no active intervention (24)	No participants had small varices	Not stated	Not stated	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: not stated Other: participants with and without other causes of cirrhosis	1978–1983	44	High
Svoboda 1999	Sclerotherapy (55) vs variceal band ligation (52)	Not stated	Not stated	Not stated	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: no participants had autoimmune disease-related cirrhosis Other: no participants had other causes of cirrhosis	1994–1997	25	High
Lo 2010	Beta-blockers + variceal band ligation (70) vs beta-blockers (70)	Not stated	All participants had high risk of bleeding	Yes (encephalopathy)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: not stated Other: participants with and without other causes of cirrhosis	Not stated	26	High
NCT00921349	Beta-blockers + variceal band ligation (Not stated) vs beta-blockers (not stated)	Not stated	Not stated	Not stated	Alcohol-related: not stated Viral-related: not stated Autoimmune-related: not stated Other: not stated	2004–2009	Not stated	High
Seo 2017	Beta-blockers + variceal band ligation (87) vs	Not stated	Not stated	Not stated	Alcohol-related: not stated Viral-related: not stated	Not stated	24	High

Table 1. Characteristics of included studies (ordered by comparisons) *(Continued)*

	beta-blockers (86)				Autoimmune-related: not stated Other: not stated			
Agarwal 2001	Beta-blockers + Variceal band ligation (46) vs variceal band ligation (46)	Not stated	Not stated	Not stated	Alcohol-related: not stated Viral-related: not stated Autoimmune-related: not stated Other: not stated	Not stated	8	High
Bonilha 2015	Beta-blockers + Variceal band ligation (34) vs variceal band ligation (32)	Not stated	Participants with and without high risk of bleeding	Not stated	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: not stated Other: participants with and without other causes of cirrhosis	2008–2011	12	High
Seo 2017	Beta-blockers + Variceal band ligation (87) vs variceal band ligation (86)	Not stated	Not stated	Not stated	Alcohol-related: not stated Viral-related: not stated Autoimmune-related: not stated Other: not stated	Not stated	24	High
D'Amico 2002	Beta-blockers + nitrates (30) vs beta-blockers (27)	No	All participants had high risk of bleeding	Yes (ascites)	Alcohol-related: not stated Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: not stated Other: not stated	1992–1996	31	Low
Deplano 2001	Beta-blockers + nitrates (14) vs beta-blockers (22)	Not stated	Not stated	Not stated	Alcohol-related: not stated Viral-related: not stated Autoimmune-related: not stated Other: not stated	Not stated	14	High

Table 1. Characteristics of included studies (ordered by comparisons) *(Continued)*

Merkel 2000	Beta-blockers + nitrates (72) vs beta-blockers (74)	Not stated	Participants with and without high risk of bleeding	Yes (encephalopathy)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: not stated Other: participants with and without other causes of cirrhosis	1991–1994	55	High
Piscaglia 1998	Beta-blockers + nitrates (10) vs no active intervention (8)	Not stated	Not stated	Yes (not stated)	Alcohol-related: all participants had alcohol-related cirrhosis Viral-related: all participants had viral-related cirrhosis Autoimmune-related: no participants had autoimmune disease-related cirrhosis Other: no participants had other causes of cirrhosis	Not stated	1	High
Wang 2006	Beta-blockers + nitrates (31) vs variceal band ligation (30)	Not stated	All participants had high risk of bleeding	Yes (encephalopathy)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: not stated Other: participants with and without other causes of cirrhosis	2002–2004	23.3	High
Angelico 1993	Nitrates (57) vs beta-blockers (61)	Not stated	Not stated	Yes (ascites)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: not stated Autoimmune-related: not stated Other: not stated	1988–1990	44	High
Borroni 2002	Nitrates (27) vs beta-blockers (25)	Not stated	Not stated	Yes (ascites)	Alcohol-related: participants with and without alcohol-related cirrhosis	1994–1998	18	High

Table 1. Characteristics of included studies (ordered by comparisons) *(Continued)*

					Viral-related: participants with and without viral-related cirrhosis Autoimmune-related: not stated Other: participants with and without other causes of cirrhosis			
Lui 2002	Nitrates (62) vs beta-blockers (66)	Not stated	Participants with and without high risk of bleeding	Yes (encephalopathy)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: not stated Autoimmune-related: not stated Other: not stated	1994–1999	19.7	High
Fassio 1993	Nitrates (23) vs No active intervention (19)	Not stated	All participants had high risk of bleeding	Yes (ascites)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: not stated Autoimmune-related: not stated Other: not stated	1989–1991	10.7	High
Lui 2002	Nitrates (62) vs Variceal band ligation (44)	Not stated	Participants with and without high risk of bleeding	Yes (encephalopathy)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: not stated Autoimmune-related: not stated Other: not stated	1994–1999	19.7	High
PROVA study group 1991	Beta-blockers + sclerotherapy (73) vs beta-blockers (68)	Not stated	Not stated	Yes (encephalopathy)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: not stated Autoimmune-related: not stated Other: not stated	1985–1989	15.4	High
Snady 1988	Beta-blockers + sclerotherapy (12) vs beta-blockers (14)	Not stated	Not stated	Not stated	Alcohol-related: all participants had alcohol-related cirrhosis Viral-related: no participants had viral-related cirrhosis	1982–1986	12	High

Table 1. Characteristics of included studies (ordered by comparisons) *(Continued)*

					Autoimmune-related: no participants had autoimmune disease-related cirrhosis Other: no participants had other causes of cirrhosis			
PROVA study group 1991	Beta-blockers + Sclerotherapy (73) vs no active intervention (72)	Not stated	Not stated	Yes (encephalopathy)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: not stated Autoimmune-related: not stated Other: not stated	1985–1989	15.4	High
Snady 1988	Beta-blockers + sclerotherapy (12) vs no active intervention (15)	Not stated	Not stated	Not stated	Alcohol-related: all participants had alcohol-related cirrhosis Viral-related: no participants had viral-related cirrhosis Autoimmune-related: no participants had autoimmune disease-related cirrhosis Other: no participants had other causes of cirrhosis	1982–1986	12	High
PROVA study group 1991	Beta-blockers + sclerotherapy (73) vs sclerotherapy (73)	Not stated	Not stated	Yes (encephalopathy)	Alcohol-related: participants with and without alcohol-related cirrhosis Viral-related: not stated Autoimmune-related: not stated Other: not stated	1985–1989	15.4	High
Snady 1988	Beta-blockers + sclerotherapy (12) vs sclerotherapy (15)	Not stated	Not stated	Not stated	Alcohol-related: all participants had alcohol-related cirrhosis Viral-related: no participants had viral-related cirrhosis Autoimmune-related: no participants had autoimmune disease-related cirrhosis Other: no participants had other causes of cirrhosis	1982–1986	12	High

Table 1. Characteristics of included studies (ordered by comparisons) *(Continued)*

Conn 1969	Portocaval shunt (13) vs no active intervention (16)	Not stated	Not stated	Yes (ascites)	Alcohol-related: all participants had alcohol-related cirrhosis Viral-related: no participants had viral-related cirrhosis Autoimmune-related: no participants had autoimmune disease-related cirrhosis Other: no participants had other causes of cirrhosis	1965–1968	19.1		High

Table 2. Risk of bias (ordered by comparison)

Study name	Intervention 1 (number of participants) vs intervention 2 (number of participants	Sequence generation	Allocation concealment	Blinding of participants and health-care providers	Blinding of outcome assessors	Missing outcome bias	Selective outcome reporting	Other bias	Overall risk of bias
PROVA study group 1991	No active intervention (72) vs beta-blockers (68)	Low	Low	High	High	Low	Unclear	Low	High
Bhardwaj 2017	No active intervention (70) vs beta-blockers (70)	Low	Unclear	High	High	High	High	High	High
Cales 1989a	No active intervention (8) vs beta-blockers (16)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
Cales 1989b	No active intervention (8) vs beta-blockers (8)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
Conn 1991	No active intervention (51) vs beta-blockers (51)	Low	Low	Low	Low	Low	Unclear	Low	High
Ideo 1988	No active intervention (27) vs beta-blockers (30)	Low	Unclear	Unclear	Unclear	Low	Unclear	Low	High
Lebrec 1988	No active intervention (53) vs beta-blockers (53)	Low	Low	High	High	Low	Low	Low	High

Table 2. Risk of bias (ordered by comparison) *(Continued)*

Merkel 2004	No active intervention (78) vs beta-blockers (83)	Low	Low	High	High	Low	Unclear	High	High
Mishra 2007	No active intervention (42) vs beta-blockers (43)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	High
Pascal 1987	No active intervention (112) vs beta-blockers (118)	Low	Low	High	High	Low	Unclear	Low	High
Sarin 2013	No active intervention (73) vs beta-blockers (77)	Low	Low	High	High	High	Unclear	Low	High
Snady 1988	No active intervention (15) vs beta-blockers (14)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
Chen 2000	Variceal band ligation (26) vs beta-blockers (30)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
De 1999	Variceal band ligation (15) vs beta-blockers (15)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	High
Drastich 2011	Variceal band ligation (40) vs beta-blockers (33)	Low	Low	High	High	Low	Low	Low	High
Feng 2012	Variceal band ligation (84) vs beta-blockers (84)	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	High
Jutabha 2005	Variceal band ligation (31) vs beta-blockers (31)	Low	Low	High	High	Low	Unclear	Low	High
Khan 2017	Variceal band ligation (125) vs beta-blockers (125)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
Lay 2006	Variceal band ligation (50) vs beta-blockers (50)	Low	Low	Unclear	Unclear	Low	Low	Low	High
Lo 2004	Variceal band ligation (50) vs beta-blockers (50)	Low	Low	Unclear	Unclear	Low	Low	Low	High
Lui 2002	Variceal band ligation (44) vs beta-blockers (66)	Low	Low	Unclear	Unclear	Low	Unclear	Low	High

Table 2. Risk of bias (ordered by comparison) *(Continued)*

NCT00337740	Variceal band ligation (not stated) vs beta-blockers (not stated)	Unclear	Unclear	High	High	Unclear	Unclear	Low	High
Norbeto 2007	Variceal band ligation (31) vs beta-blockers (31)	Low	Low	Unclear	Unclear	Low	Low	Low	High
Perez-Ayuso 2010	Variceal band ligation (39) vs beta-blockers (36)	Low	Low	High	High	Low	Low	Low	High
Psilopoulos 2005	Variceal band ligation (30) vs beta-blockers (30)	Low	Unclear	Unclear	Unclear	Low	Unclear	Low	High
Schepke 2004	Variceal band ligation (75) vs beta-blockers (77)	Low	Low	Unclear	Unclear	Low	Unclear	Low	High
Seo 2017	Variceal band ligation (86) vs beta-blockers (86)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	High
Shah 2014	Variceal band ligation (86) vs beta-blockers (82)	Low	Low	High	High	Low	Unclear	Low	High
Singh 2012	Variceal band ligation (18) vs beta-blockers (20)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	High
Song 1999	Variceal band ligation (31) vs beta-blockers (30)	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low	High
Thuluvath 2005	Variceal band ligation (16) vs beta-blockers (15)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	High
Tripathi 2009	Variceal band ligation (75) vs beta-blockers (77)	Low	Low	Unclear	Unclear	Low	Unclear	Low	High
Lay 1997	Variceal band ligation (62) vs no active intervention (64)	Low	Low	High	Unclear	Low	Low	Low	High
Lo 1999	Variceal band ligation (64) vs no active intervention (63)	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
Svoboda 1999	Variceal band ligation (52) vs no active intervention (50)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High

Table 2. Risk of bias (ordered by comparison) *(Continued)*

Andreani 1990	Sclerotherapy (42) vs beta-blockers (43)	Unclear	Unclear	High	High	Low	Low	Low	High
PROVA study group 1991	Sclerotherapy (73) vs beta-blockers (68)	Low	Low	High	High	Low	Unclear	Low	High
Kanazawa 1993	Sclerotherapy (32) vs beta-blockers (33)	Low	Low	Unclear	Unclear	Unclear	Unclear	Low	High
Snady 1988	Sclerotherapy (15) vs beta-blockers (14)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
Tomikawa 2004	Sclerotherapy (13) vs beta-blockers (12)	Low	Low	Unclear	Unclear	Low	Low	Low	High
VA Coop. Variceal Sclerotherapy Group 1991	Sclerotherapy (143) vs no active intervention (138)	Low	Low	Unclear	Unclear	Low	Low	Low	Low
PROVA study group 1991	Sclerotherapy (73) vs no active intervention (72)	Low	Low	High	High	Low	Unclear	Low	High
De Franchis 1991	Sclerotherapy (55) vs no active intervention (51)	Low	Low	Unclear	Unclear	Unclear	Unclear	Low	High
Duhamel 1994	Sclerotherapy (57) vs no active intervention (60)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	High
Fleig 1988	Sclerotherapy (16) vs no active intervention (24)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
Paquet 1982	Sclerotherapy (31) vs no active intervention (32)	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	High
Paquet 1994	Sclerotherapy (44) vs no active intervention (45)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	High
Piai 1988	Sclerotherapy (71) vs no active intervention (69)	Low	Low	Unclear	Unclear	Low	Unclear	Low	High

Table 2. Risk of bias (ordered by comparison) *(Continued)*

Quer 1991	Sclerotherapy (22) vs no active intervention (24)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	High
Rossi 1991	Sclerotherapy (18) vs no active intervention (19)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	High
Russo 1989	Sclerotherapy (21) vs no active intervention (20)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	High
Santangelo 1988	Sclerotherapy (49) vs no active intervention (46)	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low	High
Sauerbruch 1988	Sclerotherapy (68) vs no active intervention (65)	Low	Low	Unclear	Unclear	Low	Unclear	Low	High
Snady 1988	Sclerotherapy (15) vs no active intervention (15)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
Strauss 1999	Sclerotherapy (19) vs no active intervention (21)	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low	High
Svoboda 1999	Sclerotherapy (55) vs no active intervention (50)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
Witzel 1985	Sclerotherapy (56) vs no active intervention (53)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	High
Wordehoff 1987	Sclerotherapy (25) vs no active intervention (24)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	High
Svoboda 1999	Sclerotherapy (55) vs variceal band ligation (52)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
Lo 2010	Beta-blockers + variceal band ligation (70) vs beta-blockers (70)	Low	Low	Unclear	Unclear	Low	Low	Low	High
NCT00921349	Beta-blockers + variceal band ligation (not stated) vs beta-blockers (not stated)	Unclear	Unclear	High	High	Unclear	Unclear	Low	High
Seo 2017	Beta-blockers + variceal band ligation (87) vs beta-blockers (86)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High

Table 2. Risk of bias (ordered by comparison) *(Continued)*

Agarwal 2001	Beta-blockers + variceal band ligation (46) vs variceal band ligation (46)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
Bonilha 2015	Beta-blockers + variceal band ligation (34) vs variceal band ligation (32)	Low	Low	High	High	Low	Low	Low	High
Seo 2017	Beta-blockers + variceal band ligation (87) vs variceal band ligation (86)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
D'Amico 2002	Beta-blockers + nitrates (30) vs beta-blockers (27)	Low	Low	Low	Low	Low	Low	Low	Low
Deplano 2001	Beta-blockers + nitrates (14) vs beta-blockers (22)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
Merkel 2000	Beta-blockers + nitrates (72) vs beta-blockers (74)	Low	Low	High	Unclear	Low	Unclear	Low	High
Piscaglia 1998	Beta-blockers + nitrates (10) vs no active intervention (8)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	High
Wang 2006	Beta-blockers + nitrates (31) vs variceal band ligation (30)	Low	Low	Unclear	Unclear	Low	Low	Low	High
Angelico 1993	Nitrates (57) vs beta-blockers (61)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	High
Borroni 2002	Nitrates (27) vs beta-blockers (25)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	High
Lui 2002	Nitrates (62) vs beta-blockers (66)	Low	Low	Unclear	Unclear	Low	Unclear	Low	High
Fassio 1993	Nitrates (23) vs no active intervention (19)	Low	Unclear	High	Unclear	Unclear	Unclear	Low	High
Lui 2002	Nitrates (62) vs variceal band ligation (44)	Low	Low	Unclear	Unclear	Low	Unclear	Low	High
PROVA study group 1991	Beta-blockers + sclerotherapy (73) vs beta-blockers (68)	Low	Low	High	High	Low	Unclear	Low	High
Snady 1988	Beta-blockers + sclerotherapy (12) vs beta-blockers (14)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High

Table 2. Risk of bias (ordered by comparison) *(Continued)*

PROVA study group 1991	Beta-blockers + sclerotherapy (73) vs no active intervention (72)	Low	Low	High	High	Low	Unclear	Low	High
Snady 1988	Beta-blockers + sclerotherapy (12) vs no active intervention (15)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
PROVA study group 1991	Beta-blockers + sclerotherapy (73) vs sclerotherapy (73)	Low	Low	High	High	Low	Unclear	Low	High
Snady 1988	Beta-blockers + sclerotherapy (12) vs sclerotherapy (15)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
Conn 1969	Portocaval shunt (13) vs no active intervention (16)	Low	Low	Unclear	Unclear	Low	Unclear	Low	High

Table 3. Model fit

Mortality	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	—	572.7	573
DIC	—	662.4	666.2
pD	—	89.69	93.15
Serious adverse events (number of participants)	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	36.58	33.38	—
DIC	43.39	42.12	—
pD	6.814	8.737	—
Any adverse events (number of participants)	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	156.2	110.9	111.1
DIC	172.2	133.5	134
pD	15.99	22.61	22.94
Any adverse events (number of events)	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	185.9	185.9	135.1
DIC	200.8	200.9	157.6
pD	14.92	14.95	22.51
Liver transplantation	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	47.89	48.85	—
DIC	56.61	58.62	—
pD	8.717	9.773	—
Symptomatic variceal bleeding	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	81.84	78.92	78.21
DIC	94.73	94.48	93.86
pD	12.88	15.55	15.65
Any variceal bleeding	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	—	225.6	226.3

Table 3. Model fit *(Continued)*

DIC	—	270.7	273.3
pD	—	45.1	46.95
Other features of decompensation	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	36.98	37.02	—
DIC	42.85	42.93	—
pD	5.875	5.916	—

Dbar: posterior mean of deviance; DIC: deviance information criteria; pD: effective number of parameters or leverage.

Table 4. Effect estimates [a]

Mortality	Beta-blockers	No active intervention	Variceal band ligation	Sclerotherapy	Beta-blockers + variceal band ligation	Beta-blockers + nitrates	Nitrates	Beta-blockers + sclerotherapy	Portocaval shunt
Beta-blockers	—	*1.70 (1.21 to 2.39)*	1.06 (0.82 to 1.36)	*1.88 (1.01 to 3.69)*	1.05 (0.04 to 26.55)	0.88 (0.04 to 22.35)	1.37 (0.27 to 6.48)	2.03 (0.04 to 75.04)	—
No active intervention	*2.04 (1.50 to 2.78)*	—	0.49 (0.12 to 2.14)	*0.61 (0.41 to 0.90)*	—	—	0.34 (0.04 to 1.99)	1.02 (0.02 to 51.47)	0.25 (0.03 to 1.15)
Variceal band ligation	1.05 (0.80 to 1.38)	*0.51 (0.35 to 0.74)*	—	0.84 (0.36 to 1.97)	1.21 (0.11 to 11.26)	0.69 (0.22 to 2.06)	0.90 (0.44 to 1.86)	—	—
Sclerotherapy	1.35 (0.95 to 1.92)	*0.66 (0.51 to 0.85)*	1.29 (0.86 to 1.94)	—	—	—	—	1.19 (0.02 to 43.38)	—
Beta-blockers + variceal band ligation	1.11 (0.56 to 2.19)	0.54 (0.26 to 1.12)	1.06 (0.53 to 2.09)	0.82 (0.39 to 1.73)	—	—	—	—	—
Beta-blockers + nitrates	0.84 (0.44 to 1.64)	*0.41 (0.20 to 0.85)*	0.80 (0.40 to 1.62)	0.62 (0.30 to 1.32)	0.76 (0.30 to 1.97)	—	—	—	—
Nitrates	1.19 (0.66 to 2.11)	0.58 (0.30 to 1.10)	1.13 (0.60 to 2.08)	0.88 (0.45 to 1.69)	1.07 (0.44 to 2.58)	1.41 (0.59 to 3.37)	—	—	—
Beta-blockers + sclerotherapy	*2.08 (1.03 to 4.08)*	1.02 (0.52 to 1.93)	1.98 (0.95 to 4.00)	1.54 (0.77 to 2.94)	1.86 (0.72 to 4.80)	2.45 (0.94 to 6.29)	1.75 (0.71 to 4.22)	—	—
Portocaval shunt	0.51 (0.06 to 2.92)	0.25 (0.03 to 1.38)	0.49 (0.05 to 2.80)	0.38 (0.04 to 2.14)	0.46 (0.05 to 2.93)	0.61 (0.06 to 3.90)	0.43 (0.05 to 2.71)	0.25 (0.03 to 1.57)	—

Serious adverse events (number of participants)	Beta-blockers	Variceal band ligation	Sclerotherapy
Beta-blockers	—	0.71 (0.24 to 1.98)	0.56 (0.10 to 2.55)
Variceal band ligation	0.70 (0.23 to 2.01)	—	—

Table 4. Effect estimates [a] *(Continued)*

Sclerotherapy	0.56 (0.10 to 2.54)	0.79 (0.11 to 5.11)	—			

Any adverse events (number of participants)	**Beta-blockers**	**No active intervention**	**Variceal band ligation**	**Sclerotherapy**	**Beta-blockers + nitrates**	—
Beta-blockers	—	0.28 (0.01 to 10.28)	1.48 (0.38 to 6.13)	—	*3.41 (1.11 to 11.28)*	
No active intervention	0.28 (0.02 to 2.91)	—	—	4.08 (0.79 to 32.85)	—	
Variceal band ligation	1.60 (0.54 to 5.15)	5.71 (0.43 to 84.18)	—	—	0.51 (0.09 to 2.40)	
Sclerotherapy	1.19 (0.02 to 80.24)	4.21 (0.15 to 144.32)	0.73 (0.01 to 55.26)	—	—	
Beta-blockers + nitrates	1.76 (0.17 to 17.83)	6.25 (0.23 to 178.22)	1.10 (0.10 to 10.82)	1.48 (0.01 to 168.51)	—	

Any adverse events (number of events)	**Beta-blockers**	**No active intervention**	**Variceal band ligation**	**Sclerotherapy**	**Beta-blockers + variceal band ligation**	—
Beta-blockers	—	—	*0.73 (0.59 to 0.90)*	*2.47 (1.27 to 5.06)*	*1.72 (1.08 to 2.76)*	
No active intervention	0.97 (0.59 to 1.68)	—	0.65 (0.29 to 1.45)	*2.61 (2.18 to 3.18)*	—	
Variceal band ligation	*0.77 (0.63 to 0.94)*	0.79 (0.46 to 1.31)	—	1.99 (0.95 to 4.45)	1.18 (0.66 to 2.06)	
Sclerotherapy	*2.49 (1.53 to 4.22)*	*2.56 (2.13 to 3.08)*	*3.24 (1.99 to 5.49)*	—	—	

Table 4. Effect estimates [a] *(Continued)*

Beta-blockers + variceal band ligation	1.33 (0.93 to 1.92)	1.36 (0.72 to 2.53)	*1.73 (1.19 to 2.54)*	*0.53 (0.28 to 0.97)*	—			
Liver transplantation	**Beta-blockers**	**No active intervention**	**Variceal band ligation**	**Beta-blockers + variceal band ligation**	—			
Beta-blockers	—	1.37 (0.34 to 5.64)	1.40 (0.84 to 2.34)	2.46 (0.19 to 80.40)				
No active intervention	1.36 (0.35 to 5.80)	—	—	—				
Variceal band ligation	1.41 (0.83 to 2.43)	1.03 (0.22 to 4.54)	—	—				
Beta-blockers + variceal band ligation	2.40 (0.19 to 77.48)	1.79 (0.09 to 70.11)	1.71 (0.12 to 56.32)	—				
Symptomatic variceal bleed	**Beta-blockers**	**No active intervention**	**Variceal band ligation**	**Sclerotherapy**	**Beta-blockers + variceal band ligation**	**Nitrates**	**Beta-blockers + sclerotherapy**	—
Beta-blockers	—	1.03 (0.46 to 2.29)	0.79 (0.47 to 1.34)	1.01 (0.46 to 2.27)	1.13 (0.45 to 2.87)	1.27 (0.61 to 2.66)	0.92 (0.41 to 2.10)	
No active intervention	1.14 (0.56 to 2.40)	—	—	0.81 (0.50 to 1.32)	—	—	0.90 (0.40 to 2.00)	
Variceal band ligation	0.80 (0.47 to 1.36)	0.70 (0.28 to 1.71)	—	—	—	—	—	
Sclerotherapy	0.91 (0.44 to 1.95)	0.80 (0.49 to 1.29)	1.15 (0.46 to 2.89)	—	—	—	0.91 (0.41 to 2.03)	
Beta-blockers + variceal band ligation	1.13 (0.45 to 2.87)	0.99 (0.30 to 3.20)	1.42 (0.49 to 4.15)	1.24 (0.38 to 4.00)	—	—	—	

Table 4. Effect estimates [a] *(Continued)*

Nitrates	1.27 (0.61 to 2.66)	1.12 (0.39 to 3.11)	1.59 (0.64 to 3.96)	1.39 (0.49 to 3.90)	1.12 (0.34 to 3.62)	—	—
Beta-blockers + sclerotherapy	0.92 (0.41 to 2.08)	0.81 (0.38 to 1.65)	1.15 (0.44 to 3.04)	1.01 (0.47 to 2.09)	0.81 (0.24 to 2.79)	0.72 (0.24 to 2.18)	—

Any variceal bleeding	**Beta-blockers**	**No active intervention**	**Variceal band ligation**	**Sclerotherapy**	**Beta-blockers + variceal band ligation**	**Beta-blockers + nitrates**	**Nitrates**	—
Beta-blockers	—	3.03 (0.05 to 211.66)	0.77 (0.33 to 1.55)	1.39 (0.02 to 86.57)	*0.21 (0.04 to 0.71)*	0.59 (0.16 to 1.84)	*6.40 (1.58 to 47.42)*	
No active intervention	2.71 (0.97 to 7.68)	—	0.33 (0.01 to 10.90)	0.36 (0.05 to 2.45)	—	—	—	
Variceal band ligation	0.72 (0.33 to 1.51)	*0.27 (0.09 to 0.76)*	—	—	0.30 (0.00 to 4.57)	2.12 (0.54 to 9.83)	—	
Sclerotherapy	1.02 (0.33 to 3.27)	*0.38 (0.16 to 0.88)*	1.41 (0.42 to 4.99)	—	—	—	—	
Beta-blockers + variceal band ligation	0.24 (0.04 to 1.18)	*0.09 (0.01 to 0.54)*	0.34 (0.07 to 1.53)	0.24 (0.03 to 1.55)	—	—	—	
Beta-blockers + nitrates	0.93 (0.16 to 5.32)	0.34 (0.05 to 2.47)	1.30 (0.23 to 7.62)	0.92 (0.12 to 7.04)	3.85 (0.40 to 40.73)	—	—	
Nitrates	6.67 (0.56 to 105.85)	2.49 (0.17 to 46.67)	9.34 (0.70 to 166.00)	6.63 (0.41 to 126.98)	*28.02 (1.46 to 719.82)*	7.19 (0.35 to 187.17)	—	

Other features of decompensation	**Beta-blockers**	**Variceal band ligation**	**Beta-blockers + nitrates**	—
Beta-blockers	—	1.11 (0.45 to 2.80)	1.16 (0.64 to 2.12)	
Variceal band ligation	1.11 (0.44 to 2.86)	—	—	

Table 4. Effect estimates [a] *(Continued)*

Beta-blockers + nitrates	1.16 (0.64 to 2.13)	1.04 (0.34 to 3.16)	—

The table provides the effect estimates with 95% credible intervals of each pairwise comparison for the different outcomes. The top half of the table indicates the effect estimates from the direct comparisons. The bottom half of the table indicates the effect estimates from the network meta-analysis. For network meta-analysis, to identify the effect estimate of a comparison, for example A versus B, use the cell that occupies the row corresponding to intervention A and the column corresponding to intervention B. If that cell is empty (indicated by '—'), use the row corresponding to intervention B and the column corresponding to intervention A. Take the inverse of this number (i.e. 1/number) to arrive at the treatment effect of A versus B. For direct comparisons, this is the opposite; use the cell that occupies the column corresponding to intervention A and the row corresponding to intervention B. If that cell is empty, use the column corresponding to intervention B and the row corresponding to intervention A. Take the inverse of this number to arrive at the treatment effect of A versus B. If the cell corresponding to B versus A is also missing in direct comparisons, this means that there was no direct comparison.
Statistically significant results are shown in italics.

[a] **Effect measures**
The effect measure was hazard ratio for all outcomes except serious adverse events (number of participants), adverse events (number of participants), for which we used odds ratio as the effect measure and serious adverse events (number of events), adverse events (number of events), and other features of decompensation, for which we used rate ratio as the effect measure.

Table 5. Effect estimates (baseline risk-adjusted) [a]

Mortality	Beta-blockers	No active intervention	Variceal band ligation	Sclerotherapy	Beta-blockers + variceal band ligation	Beta-blockers + nitrates	Nitrates	Beta-blockers + sclerotherapy
Beta-blockers	—	—	—	—	—	—	—	—
No active intervention	*4.24 (2.39 to 8.04)*	—	—	—	—	—	—	—
Variceal band ligation	*2.33 (1.28 to 4.51)*	*0.55 (0.38 to 0.80)*	—	—	—	—	—	—
Sclerotherapy	*2.65 (1.50 to 4.95)*	*0.63 (0.48 to 0.81)*	1.14 (0.75 to 1.73)	—	—	—	—	—
Beta-blockers + variceal band ligation	*2.57 (1.06 to 6.61)*	0.61 (0.28 to 1.30)	1.11 (0.55 to 2.23)	0.97 (0.44 to 2.13)	—	—	—	—
Beta-blockers + nitrates	1.88 (0.79 to 4.78)	0.45 (0.21 to 0.95)	0.81 (0.39 to 1.67)	0.71 (0.33 to 1.56)	0.73 (0.28 to 1.94)	—	—	—
Nitrates	*2.56 (1.18 to 5.92)*	0.61 (0.31 to 1.16)	1.10 (0.58 to 2.08)	0.97 (0.49 to 1.92)	1.00 (0.40 to 2.47)	1.36 (0.54 to 3.37)	—	—
Beta-blockers + sclerotherapy	*4.17 (1.80 to 10.01)*	0.99 (0.49 to 1.91)	1.80 (0.84 to 3.71)	1.58 (0.79 to 3.07)	1.62 (0.59 to 4.29)	2.22 (0.81 to 5.84)	1.63 (0.65 to 4.02)	—

Table 5. Effect estimates (baseline risk-adjusted) [a] *(Continued)*

Portocaval shunt	1.06 (0.11 to 6.77)	0.25 (0.03 to 1.42)	0.46 (0.05 to 2.69)	0.40 (0.04 to 2.31)	0.41 (0.04 to 2.75)	0.56 (0.06 to 3.75)	0.41 (0.04 to 2.66)	0.25 (0.03 to 1.66)

[a]The table provides the effect estimates (hazard ratio) with 95% credible intervals of each pairwise comparison for mortality. The top half of the table is empty because this is the location for effect estimates from the direct comparisons, which we have presented in the main analysis (Table 4). The bottom half of the table indicates the effect estimates from the network meta-analysis adjusted for baseline risk. For network meta-analysis, to identify the effect estimate of a comparison, for example A versus B, use the cell that occupies the row corresponding to intervention A and the column corresponding to intervention B. If that cell is empty (indicated by '—'), use the row corresponding to intervention B and the column corresponding to intervention A. Take the inverse of this number (i.e. 1/number) to arrive at the treatment effect of A versus B.
Statistically significant results are shown in italics.

Table 6. Effect estimates (published from 2000 onwards) [a]

Mortality	**Beta-blockers**	**Variceal band ligation**	**Beta-blockers + variceal band ligation**	**No active intervention**	**Beta-blockers + nitrates**	**Nitrates**	**Sclerotherapy**
Beta-blockers	—	—	—	—	—	—	—
Variceal band ligation	1.09 (0.87 to 1.37)	—	—	—	—	—	—
Beta-blockers + variceal band ligation	1.12 (0.65 to 1.90)	1.03 (0.56 to 1.75)	—	—	—	—	—
No active intervention	1.57 (0.94 to 2.68)	1.44 (0.82 to 2.57)	1.40 (0.67 to 3.00)	—	—	—	—
Beta-blockers + nitrates	0.85 (0.53 to 1.35)	0.78 (0.47 to 1.29)	0.76 (0.37 to 1.54)	0.54 (0.26 to 1.09)	—	—	—
Nitrates	1.21 (0.67 to 2.16)	1.11 (0.61 to 2.02)	1.09 (0.50 to 2.36)	0.78 (0.35 to 1.66)	1.42 (0.68 to 3.02)	—	—
Sclerotherapy	*4.31 (1.41 to 12.94)*	*3.96 (1.27 to 12.17)*	*3.87 (1.12 to 13.09)*	2.76 (0.80 to 9.27)	*5.11 (1.52 to 16.88)*	*3.55 (1.02 to 12.28)*	—

Any variceal bleeding	**Beta-blockers**	**Variceal band ligation**	**Beta-blockers + variceal band ligation**	**Beta-blockers + nitrates**	—
Beta-blockers	—	—	—	—	
Variceal band ligation	0.73 (0.29 to 1.61)	—	—	—	

Table 6. Effect estimates (published from 2000 onwards) [a] *(Continued)*

Beta-blockers + variceal band ligation	0.25 (0.04 to 1.09)	0.35 (0.07 to 1.40)	—	—
Beta-blockers + nitrates	0.92 (0.18 to 4.83)	1.26 (0.25 to 7.15)	3.65 (0.46 to 37.23)	—
Nitrates	6.65 (0.63 to 100.69)	9.21 (0.79 to 165.50)	*27.09 (1.70 to 688.83)*	7.32 (0.41 to 172.95)

[a]The table provides the effect estimates (hazard ratio) with 95% credible intervals of each pairwise comparison for mortality and any variceal bleeding. The top half of the table is empty because this is the location for effect estimates from the direct comparisons, which we have presented in the main analysis (Table 4). The bottom half of the table indicates the effect estimates from the network meta-analysis including trials published from 2000 onwards. For network meta-analysis, to identify the effect estimate of a comparison, for example A versus B, use the cell that occupies the row corresponding to intervention A and the column corresponding to intervention B. If that cell is empty (indicated by '—'), use the row corresponding to intervention B and the column corresponding to intervention A. Take the inverse of this number (i.e. 1/number) to arrive at the treatment effect of A versus B.
Statistically significant results are shown in italics.

APPENDICES

Appendix 1. Search strategies

Database	Time span	Search strategy
Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	2019, Issue 12	#1 MeSH descriptor: [Esophageal and Gastric Varices] explode all trees #2 *esophageal varic* #3 #1 or #2
MEDLINE Ovid	1947 to December 2019	1. exp "Esophageal and Gastric Varices"/ 2. *esophageal varic*/.ti,ab. 3. 1 or 2 4. randomized controlled trial.pt. 5. controlled clinical trial.pt. 6. randomized.ab. 7. placebo.ab. 8. drug therapy.fs. 9. randomly.ab. 10. trial.ab. 11. groups.ab. 12. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 13. exp animals/ not humans.sh. 14. 12 not 13 15. 3 and 14
Embase Ovid	1974 to December 2019	1. exp esophagus varices/ 2. *esophageal varic*/.ti,ab. 3. 1 or 2 4. exp crossover-procedure/ or exp double-blind procedure/ or exp randomized controlled trial/ or single-blind procedure/ 5. (((((random* or factorial* or crossover* or cross over* or cross-over* or placebo* or double*) adj blind*) or single*) adj blind*) or assign* or allocat* or volunteer*).af. 6. 4 or 5 7. 3 and 6
Science Citation Index Expanded (Web of Science)	1945 to December 2019	#1 TS= (*esophageal varic*)

(Continued)

		#2 TS=(random* OR rct* OR crossover OR masked OR blind* OR placebo* OR meta-analysis OR systematic review* OR meta-analys*)
World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/Default.aspx)	December 2019	Condition: Esophageal Varices
ClinicalTrials.gov	December 2019	Interventional Studies | Esophageal Varices
European Medical Agency (www.ema.europa.eu/ema/) and US Food and Drug Administration (www.fda.gov)	March 2020	Esophageal Varices AND random

Appendix 2. Data

This table is too wide to be displayed in Review Manager 5. This table can be found at https://doi.org/10.5281/zenodo.4288489 (last accessed 22 March 2021).

HISTORY

Protocol first published: Issue 9, 2018
Review first published: Issue 4, 2021

CONTRIBUTIONS OF AUTHORS

Protocol

Conceiving the protocol: KG

Designing the protocol: KG

Co-ordinating the protocol: KG

Designing search strategies: KG

Writing the protocol: KG

Providing general advice on the protocol: ET

Securing funding for the protocol: KG

Both authors approved of the current protocol version

Performing previous work that was the foundation of the current study: not applicable

Review

Co-ordinating the review: KG

Study selection: KG, Danielle R, MC

Data extraction: KG, Davide R, MPT, AB, LP, NW, LB, SA, TB, MC

Writing the review: KG, LB

Providing advice on the review: SF, AJS, NC, EJM, MT, CSP, BRD, ET

Securing funding for the review: KG

All authors approved of the review for publication.

DECLARATIONS OF INTEREST

Davide R: none.

LB: none.

SF: none.

Danielle R: none.

NC: none.

AJS: none.

AB: none.

MPT: none.

LP: none.

MC: none.

SA: none.

TB: none.

EJM: none.

MT: none.

CSP: none.

BRD: none.

ET: none.

NW: none.

KG: none.

SOURCES OF SUPPORT

Internal sources

- University College London, UK

  Writing equipment, software, etc.

External sources

- National Institute for Health Research, UK

  Payment for writing reviews, writing equipment, and software.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- In the protocol, we stated: "However, because of the exponentially increased amount of work required for non-randomised studies, we will register and perform a new systematic review and meta-analysis of non-randomised studies for adverse events if there is uncertainty in the balance of benefits and harms of effective treatment(s)." In the discussion of this review, we stated: "A significant effort is required to identify non-randomised studies that reported harms. It is also challenging to assess the risk of bias in those studies. If the ongoing trials result in adequate power to find meaningful differences in mortality, a systematic review on adverse events from observational studies will likely be unnecessary." This is because we do not consider it good value for money to perform extremely resource-consuming research about the adverse events of treatments (over and above what is noted in randomised clinical trials) when we are not certain that the treatment works. We anticipate that the new trials to address the uncertainty in effectiveness will measure and report adverse events sufficiently to allow meaningful conclusions about the relative benefits and harms of treatments.

- We also excluded studies in which the effect of randomisation was lost because of trial-related procedures as the risk of bias in such studies becomes similar to that in observational studies.
- At the protocol stage, we did not expect any studies where randomisation was performed without informed consent; therefore, we did not specify that we would exclude such trials. However, during the systematic review process, we identified one trial in which randomisation was performed without informed consent. Therefore, we excluded this trial.
- We added information about the definition of treatment nodes and added clarification of the 'decision set.'
- We indicated how we planned to interpret standardised mean differences (SMD) if we calculated the SMD.
- We did not perform Trial Sequential Analysis because the risk of false-positive results with Bayesian meta-analysis is usually less or at least equivalent to Trial Sequential Analysis.
- We used the latest guidance from the GRADE Working group (Brignardello-Petersen 2018; Yepes-Nunez 2019), rather than the previous guidance (Puhan 2014), for presenting the 'Summary of Findings' tables.
- The trials did not report the proportion of people with other episodes of decompensation but reported the number of episodes of decompensation. Therefore, we treated this as a count outcome and used the Poisson likelihood to calculate the rate ratio.
- In the absence of a protocol published prior to the start of the study, we classified the risk of bias as low for selective reporting bias only when mortality, adverse events, and bleeding were reported, as we anticipated these outcomes to be routinely measured in clinical trials of this nature.
- We used 30,000 iterations (instead of 10,000 iterations) as a minimum for burn-in of the simulation sampler used to estimate quantities in the statistical models to ensure convergence of the simulation sampler.
- We did not present some information such as ranking probability tables, rankograms, and surface area under the curve (SUCRA plots) because of the concern about the misinterpretation of the results. We highlighted this clearly within the text of the review along with the reasons for not presenting them.
- We performed additional meta-regression analyses based on baseline risk and presented results from trials published since 2000 to account for the change in baseline risk over time.

NOTES

The methods section of this protocol was based on a standard Cochrane Hepato-Biliary Group template incorporating advice by the Complex Reviews Support Unit for a network meta-analysis protocol (Best 2018).