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Secondary prevention of variceal bleeding in adults with previous oesophageal variceal bleeding due to decompensated liver cirrhosis: a network meta-analysis (Review)

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[Intervention Review]

Secondary prevention of variceal bleeding in adults with previous oesophageal variceal bleeding due to decompensated liver cirrhosis: a network meta-analysis

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Editorial note: An error was noted about the reason for exclusion of the study Sauerbruch 2015. Previously, it was erroneously indicated that the reason for exclusion was related to the population. The correct reason for exclusion is related to the comparison. Specifically, drug therapy with or without variceal band ligation guided by hepatic venous pressure gradient (HVPG) was not an intervention of interest for this review. The error is corrected in the review and table of excluded studies.

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 of diagnosis. Several different treatments are available, which include endoscopic sclerotherapy, variceal band ligation, beta-blockers, transjugular intrahepatic portosystemic shunt (TIPS), and surgical portocaval shunts, among others. However, there is uncertainty surrounding their individual and relative benefits and harms.

Objectives

To compare the benefits and harms of different initial treatments for secondary prevention of variceal bleeding in adults with previous oesophageal variceal bleeding due to decompensated liver cirrhosis through a network meta-analysis and to generate rankings of the different treatments for secondary prevention 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 until December 2019 to identify randomised clinical trials in people with cirrhosis and a previous history of bleeding from oesophageal varices.

Selection criteria

We included only randomised clinical trials (irrespective of language, blinding, or status) in adults with cirrhosis and previous history of bleeding from oesophageal varices. We excluded randomised clinical trials in which participants had no previous history of bleeding from oesophageal varices, previous history of bleeding only from gastric varices, those who failed previous treatment (refractory bleeding), those who had acute bleeding at the time of treatment, and those who had previously undergone liver transplantation.

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 of Health and Care Excellence Decision Support Unit guidance.

Main results

We included a total of 48 randomised clinical trials (3526 participants) in the review. Forty-six trials (3442 participants) were included in one or more comparisons. The trials that provided the information included people with cirrhosis due to varied aetiologies. The follow-up ranged from two months to 61 months. All the trials were at high risk of bias. A total of 12 interventions were compared in these trials (sclerotherapy, beta-blockers, variceal band ligation, beta-blockers plus sclerotherapy, no active intervention, TIPS (transjugular intrahepatic portosystemic shunt), beta-blockers plus nitrates, portocaval shunt, sclerotherapy plus variceal band ligation, beta-blockers plus nitrates plus variceal band ligation, beta-blockers plus variceal band ligation, sclerotherapy plus nitrates).

Overall, 22.5% of the trial participants who received the reference treatment (chosen because this was the commonest treatment compared in the trials) of sclerotherapy died during the follow-up period ranging from two months to 61 months. There was considerable uncertainty in the effects of interventions on mortality. Accordingly, none of the interventions showed superiority over another. None of the trials reported health-related quality of life. Based on low-certainty evidence, variceal band ligation may result in fewer serious adverse events (number of people) than sclerotherapy (OR 0.19; 95% CrI 0.06 to 0.54; 1 trial; 100 participants).

Based on low or very low-certainty evidence, the adverse events (number of participants) and adverse events (number of events) may be different across many comparisons; however, these differences are due to very small trials at high risk of bias showing large differences in some comparisons leading to many differences despite absence of direct evidence.

Based on low-certainty evidence, TIPS may result in large decrease in symptomatic rebleed than variceal band ligation (HR 0.12; 95% CrI 0.03 to 0.41; 1 trial; 58 participants). Based on moderate-certainty evidence, any variceal rebleed was probably lower in sclerotherapy than in no active intervention (HR 0.62; 95% CrI 0.35 to 0.99, direct comparison HR 0.66; 95% CrI 0.11 to 3.13; 3 trials; 296 participants), beta-blockers plus sclerotherapy than sclerotherapy alone (HR 0.60; 95% CrI 0.37 to 0.95; direct comparison HR 0.50; 95% CrI 0.07 to 2.96; 4 trials; 231 participants); TIPS than sclerotherapy (HR 0.18; 95% CrI 0.08 to 0.38; direct comparison HR 0.22; 95% CrI 0.01 to 7.51; 2 trials; 109 participants), and in portocaval shunt than sclerotherapy (HR 0.21; 95% CrI 0.05 to 0.77; no direct comparison) groups.

Based on low-certainty evidence, beta-blockers alone and TIPS might result in more, other compensation, events than sclerotherapy (rate ratio 2.37; 95% CrI 1.35 to 4.67; 1 trial; 65 participants and rate ratio 2.30; 95% CrI 1.20 to 4.65; 2 trials; 109 participants; low-certainty evidence).

The evidence indicates considerable uncertainty about the effect of the interventions including those related to beta-blockers plus variceal band ligation in the remaining comparisons.

Authors' conclusions

The evidence indicates considerable uncertainty about the effect of the interventions on mortality. Variceal band ligation might result in fewer serious adverse events than sclerotherapy. TIPS might result in a large decrease in symptomatic rebleed than variceal band ligation. Sclerotherapy probably results in fewer 'any' variceal rebleeding than no active intervention. Beta-blockers plus sclerotherapy and TIPS probably result in fewer 'any' variceal rebleeding than sclerotherapy. Beta-blockers alone and TIPS might result in more other compensation events than sclerotherapy. The evidence indicates considerable uncertainty about the effect of the interventions in the remaining comparisons. Accordingly, high-quality randomised comparative clinical trials are needed.

PLAIN LANGUAGE SUMMARY

Prevention of rebleeding from enlarged veins in the food pipe (oesophagus) resulting from advanced liver disease

What is the aim of this Cochrane Review?

To find out the best available preventive treatment for repeated bleeding from oesophageal varices (enlarged veins in the food pipe) in people with advanced liver disease (liver cirrhosis, or late-stage scarring of the liver with complications). People with cirrhosis who had previously bled from oesophageal varices are at significant risk of death from another episode of bleeding. Therefore, it is important to provide preventive treatment to prevent rebleeding in such people, but the benefits and harms of different treatments available are currently unclear. The authors of this review collected and analysed all relevant randomised clinical trials with the aim of finding out the best treatment. They found 48 randomised clinical trials (studies where participants are randomly assigned to one of two treatment groups). During analysis of data, authors used standard Cochrane methods, which allow comparison of only two treatments at a time. Authors also used advanced techniques that allow comparison of multiple treatments at the same time (usually referred as 'network (or indirect) meta-analysis').

Date of literature search
December 2019

Key messages
None of the studies were conducted without flaws, and because of this, there is moderate to very high uncertainty in the findings of this review. Approximately one in five trial participants with cirrhosis who received preventive treatment after control of initial bleeding from oesophageal varices died within five years of treatment with sclerotherapy.

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 previous bleeding from oesophageal varices. Participants were given different treatments for preventing further bleeding oesophageal varices. The authors excluded studies in people who had bleeding from the stomach, who had no previous bleeding from the oesophageal varices, those who failed to respond to another treatment before study entry, and those who had liver transplantation previously. The average age of participants, when reported, ranged from 40 to 63 years. The treatments used in the trials included endoscopic sclerotherapy (injecting into the enlarged veins by looking through a tube inserted through the mouth), variceal band ligation (inserting bands around the dilated veins by seeing through a tube inserted through the mouth), beta-blockers (drugs that slow the heart and decrease the force of heart pumping resulting in decrease pressure in the blood vessels), and TIPS (transjugular intrahepatic portosystemic shunt; an artificial channel that connects the different blood vessels that carry oxygen-depleted blood (venous system)) within the liver to reduce the pressure built-up in the portal venous system, one of the two venous systems draining the liver), portocaval shunt (performing surgery to create the artificial channel described for TIPS) among others. The review authors wanted to gather and analyse data on death, quality of life, serious and non-serious adverse events, recurrence of bleeding, and development of other complications of advanced liver disease.

What were the main results of the review?
The 48 studies included a small number of participants (3526 participants). Study data were sparse. Forty-six studies with 3442 participants provided data for analyses. The follow-up of the trial participants ranged from two months to five years.

The funding source for the research was unclear in 36 studies; commercial organisations funded five studies. There were no concerns regarding the source of funding for the remaining nine studies.

The review shows the following.
- The evidence indicates considerable uncertainty about the effect of the interventions on the risk of death
- Variceal band ligation might result in fewer serious adverse events than sclerotherapy
- The evidence indicates considerable uncertainty about the effect of the interventions on serious and non-serious adverse events
- Sclerotherapy probably results in decrease in further bleeding than no treatment
- Beta-blockers plus sclerotherapy and TIPS probably result in a decrease in further bleeding than sclerotherapy alone
- Portocaval shunt may result in a decrease in further bleeding than sclerotherapy
- 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
- Future well-designed trials are needed to find out the best treatment for people with cirrhosis and previous bleeding from oesophageal varices.

Summary of findings 1. Secondary prevention of bleeding in people with previous oesophageal variceal bleeding due to decompensated liver cirrhosis (common interventions)

Patient or population: people with liver cirrhosis and previous oesophageal variceal bleeding
Settings: secondary or tertiary care
Intervention: various interventions
Comparison: sclerotherapy
Follow-up period: 2 months to 65 months

Outcomes/Interventions	Beta-blockers		Variceal band ligation		Beta-blockers plus Sclerotherapy		No active intervention		TIPS		Beta-blockers plus Variceal band ligation	
Mortality												
Sclerotherapy 225 per 1000 (22.5%)	**HR 0.88** (0.66 to 1.18) **Network estimate**	**28 fewer per 1000** (77 fewer to 40 more)	**HR 0.95** (0.62 to 1.46) **Network estimate**	**12 fewer per 1000** (86 fewer to 103 more)	**HR 0.69** (0.43 to 1.09) **Network estimate**	**70 fewer per 1000** (128 fewer to 20 more)	**HR 1.20** (0.83 to 1.84) **Network estimate**	**44 more per 1000** (39 fewer to 189 more)	**HR 0.94** (0.56 to 1.59) **Network estimate**	**13 fewer per 1000** (100 fewer to 132 more)	**HR 0.83** (0.22 to 3.05) **Network estimate**	**21 fewer per 1000** (107 fewer to 131 more)
	Low certainty[1,2]		**Low certainty**[1,2]		**Low certainty**[1,2]		**Low certainty**[1,2]		**Low certainty**[1,2]		**Low certainty**[1,2]	
	Based on 493 participants (9 RCTs)		Based on 399 participants (5 RCTs)		Based on 370 participants (8 RCTs)		Based on 412 participants (4 RCTs)		Based on 189 participants (3 RCTs)		No direct RCT	
Health-related quality of life												
None of the trials reported heath-related quality of life.												
Serious adverse events (number of people)												
Sclerotherapy 360 per 1000 (36%)	**OR 0.47** (0.13 to 1.53) **Network estimate**	**150 fewer per 1000** (291 fewer to 103 more)	**OR 0.19** (0.06 to 0.53) **Network estimate**	**265 fewer per 1000** (330 fewer to 130 fewer)	**OR 1.29** (0.28 to 5.70) **Network estimate**	**61 more per 1000** (223 fewer to 402 more)	-		-		-	

	Very low certainty[1,2,3]		**Low certainty**[1,3]		**Very low certainty**[1,2,3]						
	Based on 91 participants (1 RCT)		Based on 100 participants (1 RCT)		No direct RCT						
Serious adverse events (number of events)											
None of the trials reported serious adverse events (number of events).											
Any adverse events (number of people)											
Sclerotherapy 380 per 1000 (38%)	**OR 11.86** (1.16 to 427.95) **Network estimate**	**499 more per 1000** (35 more to 616 more)	**OR 0.39** (0.16 to 1.09) **Network estimate**	**186 fewer per 1000** (292 fewer to 21 more)	**OR 1.46** (0.36 to 6.06) **Network estimate**	**92 more per 1000** (200 fewer to 408 more)	**OR 0.22** (0.05 to 0.86) **Direct estimate**	**261 fewer per 1000** (350 fewer to 34 fewer)	**OR 0.02** (0.00 to 0.17) **Network estimate**	**368 fewer per 1000** (379 fewer to 284 fewer)	-
	Low certainty[1,3]		**Very low certainty**[1,2,3]		**Very low certainty**[1,2,3]		**Low certainty**[1,3]		**Low certainty**[1,3]		
	No direct RCT		Based on 115 participants (2 RCTs)		Based on 71 participants (2 RCTs)		Based on 40 participants (1 RCT)		No direct RCT		
Any adverse events (number of events)											
Sclerotherapy 581 per 1000 (58.1 per 100 participants)	-	-	**Rate ratio 0.40** (0.26 to 0.61) **Network estimate**	**348 fewer per 1000** (431 fewer to 226 fewer)	**Rate ratio 0.93** (0.68 to 1.26) **Network estimate**	44 fewer per 1000 (186 fewer to 148 more)	-		**Rate ratio 1.10** (0.73 to 1.66) **Network estimate**	**57 more per 1000** (158 fewer to 382 more)	**Rate ratio 0.13** (0.06 to 0.28) **Network estimate**	**505 fewer per 1000** (547 fewer to 420 fewer)
			Moderate certainty[1]		**Low certainty**[1,2]				**Low certainty**[1,2]		**Moderate certainty**[1]	
			Based on 188 participants (2 RCTs)		Based on 128 participants (2 RCTs)				Based on 63 participants (1 RCT)		No direct RCT	
Liver transplantation												
Sclerotherapy	-	-	**HR 0.94**	**1 fewer per 1000**	**HR 1.26**	**5 more per 1000**	-		**HR 1.52**	**10 more per 1000**	-	

19 per 1000 (1.9%)			(0.03 to 35.27) **Network estimate**	(18 fewer to 635 more)	(0.17 to 10.10) **Network estimate**	(15 fewer to 169 more)		(0.39 to 6.60) **Network estimate**	(11 fewer to 104 more)	
			Very low certainty[1,2,3]		**Very low certainty**[1,2,3]			**Very low certainty**[1,2,3]		
			Based on 111 participants (1 RCT)		Based on 40 participants (1 RCT)			Based on 80 participants (1 RCT)		
Symptomatic variceal rebleed										
Sclerotherapy 56 per 1000 (5.6%)	**HR 0.46** (0.00 to 43.25) **Network estimate**	**30 fewer per 1000** (55 fewer to 944 more)	**HR 0.43** (0.00 to 50.40) **Network estimate**	**31 fewer per 1000** (55 fewer to 944 more)	-		**HR 1.19** (0.00 to 1726.76) **Network estimate**	**11 more per 1000** (56 fewer to 944 more)	**HR 0.05** (0.00 to 94.44) **Network estimate**	**53 fewer per 1000** (56 fewer to 944 more)	-
	Very low certainty[1,2,3,4,5]		**Very low certainty**[1,2,3,4,5]				**Very low certainty**[1,2,3,4,5]		**Very low certainty**[1,2,3,4,5]	
	Based on 28 participants (1 RCT)		Based on 111 participants (1 RCT)				No direct RCT		No direct RCT	
Any variceal rebleed										
Sclerotherapy 473 per 1000 (47.3%)	**HR 1.62** (1.14 to 2.38) **Network estimate**	**295 more per 1000** (67 more to 527 more)	**HR 1.61** (0.72 to 3.77) **Network estimate**	**287 more per 1000** (132 fewer to 527 more)	**HR 0.60** (0.37 to 0.95) **Network estimate**	**189 fewer per 1000** (300 fewer to 24 fewer)	**HR 1.61** (1.01 to 2.86) **Network estimate**	**288 more per 1000** (5 more to 527 more)	**HR 0.18** (0.08 to 0.38) **Network estimate**	**386 fewer per 1000** (434 fewer to 294 fewer)	-
	Moderate certainty[1]		**Low certainty**[1,2]		**Moderate certainty**[1]		**Moderate certainty**[1]		**Moderate certainty**[1]	
	Based on 420 participants (6 RCTs)		Based on 111 participants (2 RCTs)		Based on 231 participants (4 RCTs)		Based on 296 participants (3 RCTs)		Based on 109 participants (2 RCTs)	
Other features of decompensation at maximal follow-up										
Sclerotherapy 292 per 1000	**Rate ratio 2.40** (1.35 to 4.55)	**409 more per 1000**	**Rate ratio 1.92** (0.31 to 10.62)	**267 more per 1000** (201 fewer to 2807 more)	**Rate ratio 0.45** (0.09 to 1.75)	**160 fewer per 1000**	-		**Rate ratio 2.27** (1.19 to 4.59)	**369 more per 1000**	-

(29.2 per 100 participants)	**Network estimate**	(103 more to 1035 more)	**Network estimate**		**Network estimate**	(267 fewer to 218 more)		**Network estimate**	(56 more to 1046 more)
	Low certainty[1,3]		**Very low certainty**[1,2,3]		**Very low certainty**[1,2,3]			**Low certainty**[1,3]	
	Based on 65 participants (1 RCT)		No direct RCT		No direct RCT			Based on 109 participants (2 RCTs)	

*Ranking was not provided because of the considerable uncertainty in the ranking.
CrI: Credible interval; **HR:** Hazard ratio; **OR:** Odds 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.

[1]Downgraded one level for risk of bias because the trial(s) included in the analysis was/were at high risk of bias
[2]Downgraded one level for imprecision because the credible intervals were wide (included clinical benefit and harms)
[3]Downgraded one level for imprecision because the sample size was small
[4]Downgraded one level for indirectness because this is based on indirect evidence only or these was evidence of statistical inconsistency
[5]Downgraded one level for inconsistency because there was evidence of statistical heterogeneity

Summary of findings 2. Secondary prevention of bleeding in people with previous oesophageal variceal bleeding due to decompensated liver cirrhosis (all interventions)

Patient or population: people with liver cirrhosis and previous oesophageal variceal bleeding
Settings: secondary or tertiary care
Intervention: various interventions
Comparison: sclerotherapy
Follow-up period: 2 months to 65 months
Network geometry plots: Figure 1

Interventions	Relative effect (95% CrI)	Anticipated absolute effect* (95% CrI)			Quality of evidence
		Sclerotherapy	Various interventions	Difference	
Mortality **Total studies: 45**					

Total participants: 3369					
Sclerotherapy	**Reference**				
Beta-blockers (9 RCTs; 493 participants)	**HR 0.88** (0.66 to 1.18) **Network estimate**	**225 per 1000**	**197 per 1000** (148 to 265)	**28 fewer per 1000** (77 fewer to 40 more)	**Low certainty**[1,2]
Variceal band ligation (5 RCTs; 399 participants)	**HR 0.95** (0.62 to 1.46) **Network estimate**	**225 per 1000**	**213 per 1000** (139 to 328)	**12 fewer per 1000** (86 fewer to 103 more)	**Low certainty**[1,2]
Beta-blockers plus Sclerotherapy (8 RCTs; 370 participants)	**HR 0.69** (0.43 to 1.09) **Network estimate**	**225 per 1000**	**155 per 1000** (97 to 245)	**70 fewer per 1000** (128 fewer to 20 more)	**Low certainty**[1,2]
No active intervention (4 RCTs; 412 participants)	**HR 1.20** (0.83 to 1.84) **Network estimate**	**225 per 1000**	**269 per 1000** (186 to 414)	**44 more per 1000** (39 fewer to 189 more)	**Low certainty**[1,2]
TIPS (3 RCTs; 189 participants)	**HR 0.94** (0.56 to 1.59) **Network estimate**	**225 per 1000**	**212 per 1000** (125 to 357)	**13 fewer per 1000** (100 fewer to 132 more)	**Low certainty**[1,2]
Beta-blockers plus Nitrates (No direct RCT)	**HR 0.91** (0.53 to 1.58) **Network estimate**	**225 per 1000**	**204 per 1000** (118 to 356)	**21 fewer per 1000** (107 fewer to 131 more)	**Low certainty**[1,2]
Portocaval shunt (2 RCTs; 100 participants)	**HR 1.21** (0.68 to 2.15) **Network estimate**	**225 per 1000**	**273 per 1000** (154 to 484)	**48 more per 1000** (71 fewer to 259 more)	**Low certainty**[1,2]
Sclerotherapy plus Variceal band ligation (No direct RCT)	**HR 0.78** (0.35 to 1.76) **Network estimate**	**225 per 1000**	**176 per 1000** (79 to 397)	**49 fewer per 1000** (146 fewer to 172 more)	**Low certainty**[1,2]
Beta-blockers plus Nitrates plus Variceal band ligation (No direct RCT)	**HR 0.89** (0.40 to 1.98) **Network estimate**	**225 per 1000**	**201 per 1000** (91 to 444)	**24 fewer per 1000** (134 fewer to 219 more)	**Low certainty**[1,2]
Beta-blockers plus Variceal band ligation (No direct RCT)	**HR 0.83** (0.22 to 3.05) **Network estimate**	**225 per 1000**	**188 per 1000** (50 to 686)	**37 fewer per 1000** (175 fewer to 461 more)	**Low certainty**[1,2]

Sclerotherapy plus Nitrates (1 RCT; 76 participants)	**HR 0.19** (0.02 to 0.86) **Network estimate**	**225 per 1000**	**42 per 1000** (5 to 194)	**183 fewer per 1000** (220 fewer to 31 fewer)	**Moderate certainty**[1]
Health-related quality of life					
None of the trials reported health-related quality of life.					
Serious adverse events (number of people) **Total studies: 3** **Total participants: 322**					
Sclerotherapy	**Reference**				
Beta-blockers (1 RCT; 91 participants)	**OR 0.47** (0.13 to 1.53) **Network estimate**	**360 per 1000**	**210 per 1000** (69 to 463)	**150 fewer per 1000** (291 fewer to 103 more)	**Very low certainty**[1,2,3]
Variceal band ligation (1 RCT; 100 participants)	**OR 0.19** (0.06 to 0.53) **Network estimate**	**360 per 1000**	**95 per 1000** (30 to 230)	**265 fewer per 1000** (330 fewer to 130 fewer)	**Low certainty**[1,3]
Beta-blockers plus Sclerotherapy (No direct RCT)	**OR 1.29** (0.28 to 5.70) **Network estimate**	**360 per 1000**	**421 per 1000** (137 to 762)	**61 more per 1000** (223 fewer to 402 more)	**Very low certainty**[1,2,3]
Serious adverse events (number of events)					
None of the trials reported serious adverse events (number of events).					
Any adverse events (number of people) **Total studies: 11** **Total participants: 859**					
Sclerotherapy	**Reference**				
Beta-blockers (No direct RCT)	**OR 11.86** (1.16 to 427.95) **Network estimate**	**380 per 1000**	**879 per 1000** (415 to 996)	**499 more per 1000** (35 more to 616 more)	**Low certainty**[1,3]
Variceal band ligation (3 RCTs; 215 participants)	**OR 0.39** (0.16 to 1.09) **Network estimate**	**380 per 1000**	**194 per 1000** (88 to 401)	**186 fewer per 1000** (292 fewer to 21 more)	**Low certainty**[1,3]

Beta-blockers plus Sclerotherapy (2 RCTs; 71 participants)	**OR 1.46** (0.36 to 6.06) **Network estimate**	**380 per 1000**	**472 per 1000** (180 to 788)	**92 more per 1000** (200 fewer to 408 more)	**Low certainty**[1,3]
No active intervention (1 RCT; 40 participants)	**OR 0.22** (0.05 to 0.86) **Direct estimate**	**380 per 1000**	**119 per 1000** (30 to 346)	**261 fewer per 1000** (350 fewer to 34 fewer)	**Low certainty**[1,3]
TIPS (No direct RCT)	**OR 0.02** (0.00 to 0.17) **Network estimate**	**380 per 1000**	**12 per 1000** (1 to 96)	**368 fewer per 1000** (379 fewer to 284 fewer)	**Low certainty**[1,3]
Beta-blockers plus Nitrates (No direct RCT)	**OR 27.58** (2.79 to 981.42) **Network estimate**	**380 per 1000**	**944 per 1000** (631 to 998)	**564 more per 1000** (251 more to 618 more)	**Low certainty**[1,3]
Sclerotherapy plus Variceal band ligation (No direct RCT)	**OR 2.46** (0.36 to 23.78) **Network estimate**	**380 per 1000**	**601 per 1000** (179 to 936)	**221 more per 1000** (201 fewer to 556 more)	**Very low certainty**[1,2,3]
Beta-blockers plus Nitrates plus Variceal band ligation (No direct RCT)	**OR 94.92** (6.85 to 4500.75) **Network estimate**	**380 per 1000**	**983 per 1000** (808 to 1000)	**603 more per 1000** (428 more to 620 more)	**Low certainty**[1,3]
Any adverse events (number of events) **Total studies: 8** **Total participants: 592**					
Sclerotherapy	**Reference**				
Variceal band ligation (2 RCTs; 188 participants)	**Rate ratio 0.40** (0.26 to 0.61) **Network estimate**	**581 per 1000**	**233 per 1000** (149 to 355)	**348 fewer per 1000** (431 fewer to 226 fewer)	**Moderate certainty**[1]
Beta-blockers plus Sclerotherapy (2 RCTs; 128 participants)	**Rate ratio 0.93** (0.68 to 1.26) **Network estimate**	**581 per 1000**	**537 per 1000** (395 to 729)	**44 fewer per 1000** (186 fewer to 148 more)	**Low certainty**[1,2]
TIPS (1 RCT; 63 participants)	**Rate ratio 1.10** (0.73 to 1.66) **Network estimate**	**581 per 1000**	**637 per 1000** (423 to 963)	**57 more per 1000** (158 fewer to 382 more)	**Low certainty**[1,2]
Portocaval shunt (1 RCT; 45 participants)	**Rate ratio 0.87** (0.34 to 2.28)	**581 per 1000**	**507 per 1000** (195 to 1327)	**74 fewer per 1000** (386 fewer to 746 more)	**Low certainty**[1,2]

	Network estimate				
Beta-blockers plus Variceal band ligation (No direct RCT)	**Rate ratio 0.13** (0.06 to 0.28) **Network estimate**	**581 per 1000**	**76 per 1000** (33 to 160)	**505 fewer per 1000** (547 fewer to 420 fewer)	**Moderate certainty**[1]
Liver transplantation **Total studies: 4** **Total participants: 314**					
Sclerotherapy	**Reference**				
Variceal band ligation (1 RCT; 111 participants)	**HR 0.94** (0.03 to 35.27) **Network estimate**	**19 per 1000**	**17 per 1000** (0 to 653)	**1 fewer per 1000** (18 fewer to 635 more)	**Very low certainty**[1,2,3]
Beta-blockers plus Sclerotherapy (1 RCT; 40 participants)	**HR 1.26** (0.17 to 10.10) **Network estimate**	**19 per 1000**	**23 per 1000** (3 to 187)	**5 more per 1000** (15 fewer to 169 more)	**Very low certainty**[1,2,3]
TIPS (1 RCT; 80 participants)	**HR 1.52** (0.39 to 6.60) **Network estimate**	**19 per 1000**	**28 per 1000** (7 to 122)	**10 more per 1000** (11 fewer to 104 more)	**Very low certainty**[1,2,3]
Symptomatic variceal rebleed **Total studies: 7** **Total participants: 550**					
Sclerotherapy	**Reference**				
Beta-blockers (1 RCT; 28 participants)	**HR 0.46** (0.00 to 43.25) **Network estimate**	**56 per 1000**	**25 per 1000** (0 to 1000)	**30 fewer per 1000** (55 fewer to 944 more)	**Very low certainty**[1,2,3,4,5]
Variceal band ligation (1 RCT; 111 participants)	**HR 0.43** (0.00 to 50.40) **Network estimate**	**56 per 1000**	**24 per 1000** (0 to 1000)	**31 fewer per 1000** (55 fewer to 944 more)	**Very low certainty**[1,2,3,4,5]
No active intervention (No direct RCT)	**HR 1.19** (0.00 to 1726.76) **Network estimate**	**56 per 1000**	**66 per 1000** (0 to 1000)	**11 more per 1000** (56 fewer to 944 more)	**Very low certainty**[1,2,3,4,5]
TIPS (No direct RCT)	**HR 0.05** (0.00 to 94.44) **Network estimate**	**56 per 1000**	**3 per 1000** (0 to 1000)	**53 fewer per 1000** (56 fewer to 944 more)	**Very low certainty**[1,2,3,4,5]

Beta-blockers plus Nitrates (No direct RCT)	**HR 0.31** (0.00 to 183.46) **Network estimate**	**56 per 1000**	**17 per 1000** (0 to 1000)	**38 fewer per 1000** (56 fewer to 944 more)	**Very low certainty**[1,2,3,4,5]
Portocaval shunt (2 RCTs; 100 participants)	**HR 0.17** (0.00 to 8.86) **Network estimate**	**56 per 1000**	**9 per 1000** (0 to 492)	**46 fewer per 1000** (55 fewer to 437 more)	**Very low certainty**[1,2,3,4,5]
Sclerotherapy plus Variceal band ligation (No direct RCT)	**HR 0.30** (0.00 to 524.27) **Network estimate**	**56 per 1000**	**17 per 1000** (0 to 1000)	**39 fewer per 1000** (56 fewer to 944 more)	**Very low certainty**[1,2,3,4,5]
Beta-blockers plus Nitrates plus Variceal band ligation (No direct RCT)	**HR 0.25** (0.00 to 154.01) **Network estimate**	**56 per 1000**	**14 per 1000** (0 to 1000)	**42 fewer per 1000** (56 fewer to 944 more)	**Very low certainty**[1,2,3,4,5]
Any variceal rebleed **Total studies: 23** **Total participants: 1713**					
Sclerotherapy	**Reference**				
Beta-blockers (6 RCTs; 420 participants)	**HR 1.62** (1.14 to 2.38) **Network estimate**	**473 per 1000**	**767 per 1000** (540 to 1000)	**295 more per 1000** (67 more to 527 more)	**Moderate certainty**[1]
Variceal band ligation (2 RCTs; 111 participants)	**HR 1.61** (0.72 to 3.77) **Network estimate**	**473 per 1000**	**760 per 1000** (341 to 1000)	**287 more per 1000** (132 fewer to 527 more)	**Low certainty**[1,2]
Beta-blockers plus sclerotherapy (4 RCTs; 231 participants)	**HR 0.60** (0.37 to 0.95) **Network estimate**	**473 per 1000**	**284 per 1000** (173 to 449)	**189 fewer per 1000** (300 fewer to 24 fewer)	**Moderate certainty**[1]
No active intervention (3 RCTs; 296 participants)	**HR 1.61** (1.01 to 2.86) **Network estimate**	**473 per 1000**	**761 per 1000** (478 to 1000)	**288 more per 1000** (5 more to 527 more)	**Moderate certainty**[1]
TIPS (2 RCTs; 109 participants)	**HR 0.18** (0.08 to 0.38) **Network estimate**	**473 per 1000**	**87 per 1000** (39 to 179)	**386 fewer per 1000** (434 fewer to 294 fewer)	**Moderate certainty**[1]
Beta-blockers plus nitrates (No direct RCT)	**HR 2.13** (0.79 to 5.86) **Network estimate**	**473 per 1000**	**1000 per 1000** (373 to 1000)	**527 more per 1000** (99 fewer to 527 more)	**Low certainty**[1,2]
Portocaval shunt (No direct RCT)	**HR 0.21** (0.05 to 0.77) **Network estimate**	**473 per 1000**	**98 per 1000** (22 to 366)	**374 fewer per 1000** (451 fewer to 107 fewer)	**Moderate certainty**[1]

Sclerotherapy plus variceal band ligation (No direct RCT)	**HR 1.83** (0.46 to 7.40) **Network estimate**	**473 per 1000**	**864 per 1000** (216 to 1000)	**391 more per 1000** (256 fewer to 527 more)	**Low certainty**[1,2]
Other features of decompensation **Total studies: 6** **Total participants: 349**					
Sclerotherapy	**Reference**				
Beta-blockers (1 RCT; 65 participants)	**Rate ratio 2.40** (1.35 to 4.55) **Network estimate**	**292 per 1000**	**701 per 1000** (395 to 1327)	**409 more per 1000** (103 more to 1035 more)	**Low certainty**[1,3]
Variceal band ligation (No direct RCT)	**Rate ratio 1.92** (0.31 to 10.62) **Network estimate**	**292 per 1000**	**559 per 1000** (90 to 3098)	**267 more per 1000** (201 fewer to 2807 more)	**Very low certainty**[1,2,3]
Beta-blockers plus Sclerotherapy (No direct RCT)	**Rate ratio 0.45** (0.09 to 1.75) **Network estimate**	**292 per 1000**	**131 per 1000** (25 to 509)	**160 fewer per 1000** (267 fewer to 218 more)	**Very low certainty**[1,2,3]
TIPS (2 RCTs; 109 participants)	**Rate ratio 2.27** (1.19 to 4.59) **Network estimate**	**292 per 1000**	**661 per 1000** (348 to 1338)	**369 more per 1000** (56 more to 1046 more)	**Low certainty**[1,3]
Sclerotherapy plus Variceal band ligation (No direct RCT)	**Rate ratio 2.18** (0.04 to 129.28) **Network estimate**	**292 per 1000**	**635 per 1000** (11 to 37707)	**344 more per 1000** (281 fewer to 37416 more)	**Very low certainty**[1,2,3]

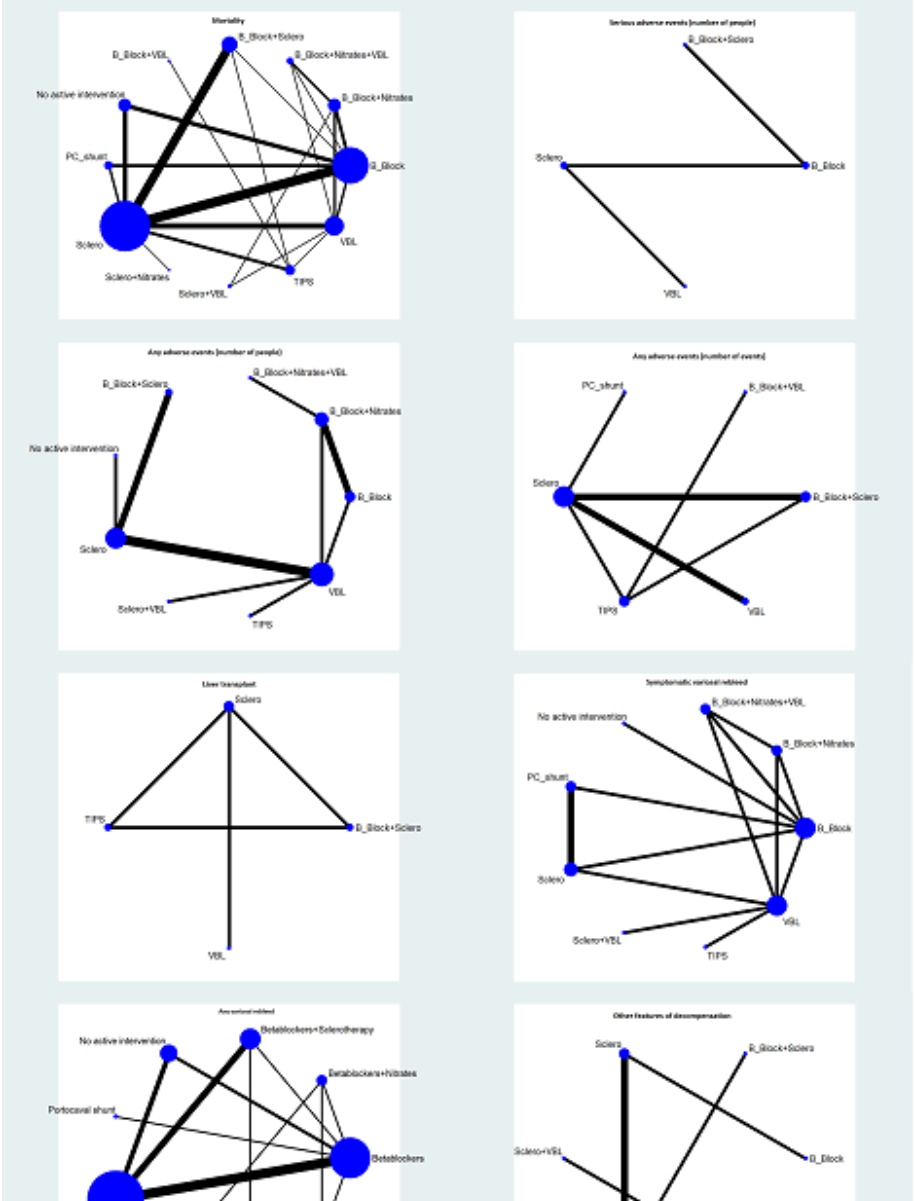
*Ranking was not provided because of the considerable uncertainty in the ranking.
CrI: Credible interval; **HR:** Hazard ratio; **OR:** Odds ratio; **RCT:** randomised clinical trial.

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.

[1]Downgraded one level for risk of bias because the trial(s) included in the analysis was/were at high risk of bias
[2]Downgraded one level for imprecision because the credible intervals were wide (included clinical benefit and harms)
[3]Downgraded one level for imprecision because the sample size was small
[4]Downgraded one level for indirectness because these was evidence of statistical inconsistency

[5]Downgraded one level for inconsistency because there was evidence of statistical heterogeneity

Figure 1. Network plots: A high resolution version of this image can be found here. 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). Abbreviations B_Block = Beta-blockers
PC_shunt = Portocaval shunt
Sclero = Sclerotherapy
TIPS = Transjugular intrahepatic portosystemic shunt
VBL = Variceal band ligation



BACKGROUND

Description of the condition

Liver cirrhosis

The liver is a complex organ with multiple functions including carbohydrate metabolism, fat metabolism, protein metabolism, drug metabolism, synthetic functions, storage functions, digestive functions, excretory functions, and immunological functions (Read 1972). Liver cirrhosis is a liver 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 USA, the prevalence of chronic liver disease varies between 0.3% to 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 due to 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 blood vessels in the oesophagus, usually due to portal hypertension (NCBI 2018b). Presence of oesophageal varices is 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 1990; 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 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 in the varices (hepatic venous pressure gradient greater than 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). Of those who survive, approximately 30% die in two years and approximately 20% have another episode of bleeding over two years (Qi 2016). In France, the mean in-hospital costs of treating acute episode of bleeding was EURO 13,500 in 2007 (Thabut 2007); in the USA, 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 are 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 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 vicious circle can eventually culminate in rupture of the varices (Sass 2009; Herman 2015).

Description of the intervention

Secondary prevention of bleeding refers to preventing re-bleeding once the initial variceal bleed has been stopped. The various treatments include non-cardioselective beta-blockers such as propranolol, endoscopic variceal band ligation, sclerotherapy, nitrates, transjugular intrahepatic portosystemic shunt (TIPS), and surgical portosystemic shunt (de Franchis 2015; Tripathi 2015; Qi 2016; Garcia-Tsao 2017; EASL 2018). Of these, the UK guidelines, the EASL guidelines, and the American Association for the Study of Liver Diseases (AASLD) guidelines indicate that non-cardioselective beta-blockers in combination with endoscopic band ligation should be considered as the first-line treatment to prevent rebleeding in people with a history of variceal bleeding (de Franchis 2015; Tripathi 2015; Garcia-Tsao 2017; EASL 2018). TIPS is considered a second-line treatment in people who rebleed despite having received secondary prevention treatment with beta-blockers plus endoscopic band ligation (de Franchis 2015; Tripathi 2015; Garcia-Tsao 2017); surgical portosystemic shunt is an alternative treatment in people who are not eligible for TIPS (Tripathi 2015).

How the intervention might work

Non-cardioselective beta-blockers work by causing splanchnic vasoconstriction and decreasing the 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 shunt are aimed at diverting blood flow from the portal system to the systemic circulation, thereby decreasing the portal pressure and reducing the pressure inside the oesophageal varices. Endoscopic variceal band ligation and sclerotherapy are local treatments aimed at obliteration of the oesophageal varices by reducing the blood flow in the oesophageal varices. 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 rebleeding in people with a history of variceal bleeding and also improve their survival. Several different treatments are available; however, their relative efficacy and optimal combination are not known. There has been one Cochrane Review on portosystemic shunts versus endoscopic therapy for variceal rebleeding in people with a history of variceal bleeding due to cirrhosis (Brand 2018). There have been no previous network meta-analyses on the topic. Network meta-analysis allows for a combination of direct and indirect evidence and ranking of different interventions for different outcomes (Salanti 2011; Salanti 2012). It also allows calculation of effect estimates when no direct evidence of relative effectiveness exists and allows inclusion of all relevant interventions in the population in a single analysis allowing the relative ranking of these interventions. With this systematic review and network meta-analysis, we aim 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 have also presented results from direct comparisons whenever possible, as well as performing the network meta-analysis.

OBJECTIVES

To compare the benefits and harms of different initial treatments for secondary prevention of variceal bleeding in adults with previous oesophageal variceal bleed due to decompensated liver cirrhosis through a network meta-analysis and to generate rankings of the different treatments for secondary prevention 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 network meta-analysis 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 network meta-analysis, 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 and other features of decompensation rather than treatment-related adverse events.

Types of participants

We included randomised clinical trials with adults with a history of oesophageal varices due to decompensated liver cirrhosis undergoing treatment for the prevention of rebleeding. We included trials in which people with oesophageal varices also had gastric varices, but we did not include trials in which the treatment was targeted at the gastric varices rather than oesophageal varices (as the pathophysiology and treatment for gastric only varices is different from oesophageal varices). We excluded randomised clinical trials in which participants had no previous history of bleeding or had an ongoing episode of variceal bleeding (considered in other reviews). We also excluded trials in which the participants had previously undergone liver transplantation (as the treatments used may be different in such patients compared to those who did not undergo liver transplantation). We also excluded participants who were refractory to secondary prevention treatments (as the treatments used as second line are different from those used for first line). We also excluded trials which included some participants who were eligible for this review and others who were not eligible for this review, unless separate data were available for the trial participants who were eligible for this review.

Types of interventions

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

- non-cardioselective beta-blockers such as propranolol, carvedilol, and nadolol;
- endoscopic variceal band ligation;
- endoscopic variceal sclerotherapy;
- nitrates;
- TIPS procedure;
- other forms of portosystemic shunt;
- no active intervention (no intervention or placebo).

We considered 'sclerotherapy' 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; therefore, we did not include trials comparing variations within treatment. 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 add these interventions to the list because they are no longer in use as initial treatment (first-line therapy) of secondary prevention of bleeding from oesophageal varices.

We evaluated the plausibility of the network meta-analysis transitivity assumption by looking at the inclusion and exclusion criteria in the studies. The transitivity assumption means

that participants included in the different trials with different treatments (in this case, for secondary prevention of oesophageal variceal bleeding) can be considered to be 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 presence or absence of other features of decompensation such as ascites are similar across comparisons.

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 would increase mortality; is life-threatening; requires hospitalisation; results in persistent or significant disability; is a congenital anomaly/birth defect; or any important medical event that might jeopardise 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).
  - Proportion of people with one or more serious adverse events.
  - Number of serious adverse events per participant.

Secondary outcomes

- Any adverse events (during or within six months after cessation of intervention). 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).
  - 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 rebleeding (time-to-oesophageal variceal bleeding however defined by authors at maximal follow-up).
  - Symptomatic variceal rebleeding (e.g. shortness of breath, shock, requiring blood transfusion).
  - Any variceal bleeding.
- Time-to-other features of decompensation (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) 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 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. We provided the search strategies along with the date of search in Appendix 1.

Searching other resources

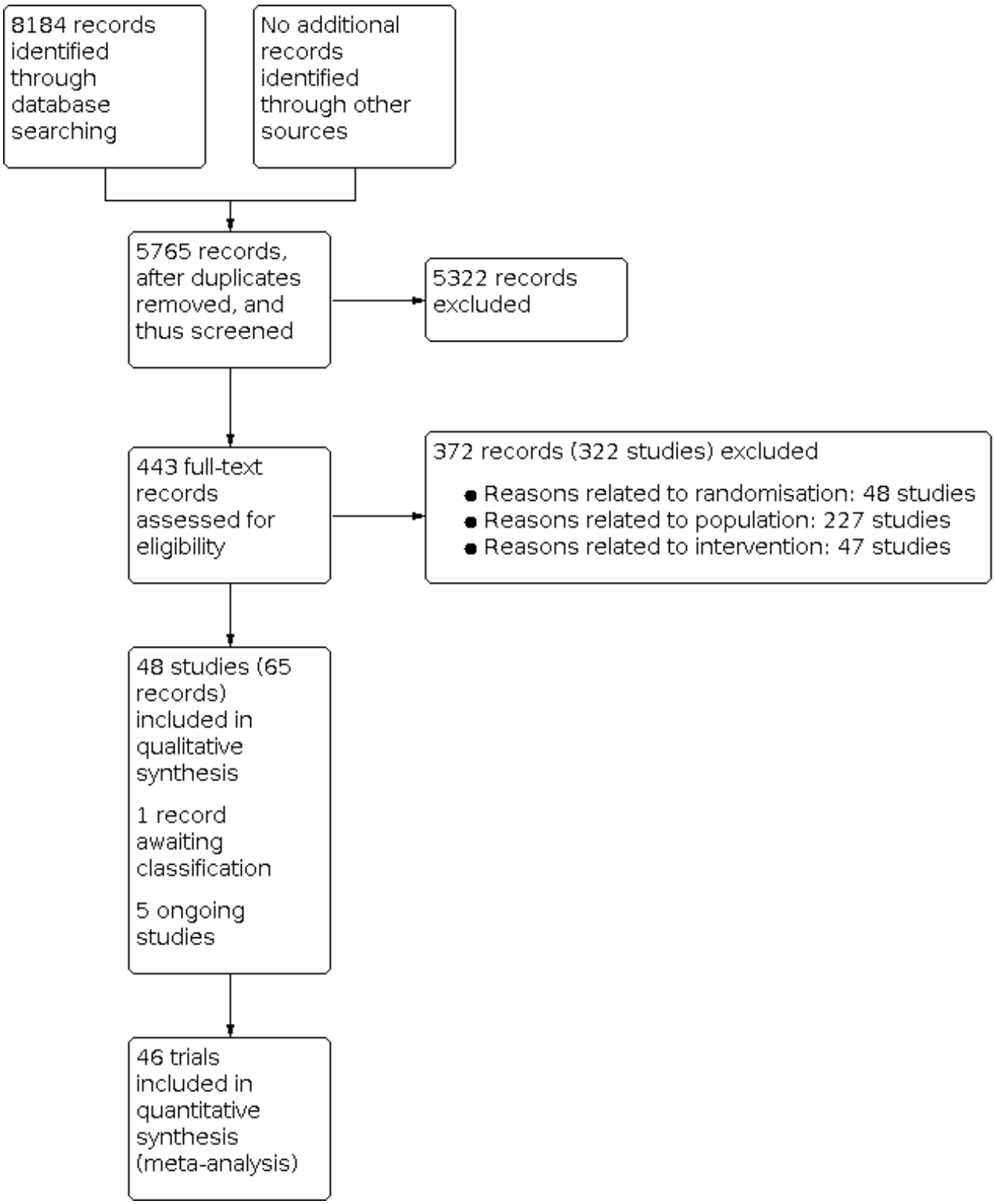
We searched the references of the identified trials and the existing Cochrane Review on secondary prevention of variceal bleeding in people with oesophageal varices due to liver cirrhosis (Brand 2018) to identify additional trials for inclusion.

Data collection and analysis

Selection of studies

Two review authors (KG and DRo 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 references identified by at least one review author for potential inclusion. We selected trials for inclusion based on the full-text articles. We listed the references that we excluded and the reasons for their exclusion in the Characteristics of excluded studies table. We also listed any ongoing trials identified primarily through the search of the clinical trial registers for further follow-up. We resolved any discrepancies through discussion. We illustrated the study selection process in a PRISMA diagram (Figure 2).

Figure 2. Study flow diagram
Date of search 17 December 2019



Data extraction and management

Two review authors (KG, MPT, IP, AB, DRa, NW, LB, SA, TB, MC, DF) 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 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, presence of other features of decompensation such as ascites, the aetiology for cirrhosis, and the interval between diagnosis of variceal bleeding 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 in the case of unclear or missing information. 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.

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.

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 rebleeding. 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, despite the fact that data on these outcomes should have been available and even recorded.

Other bias

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

We considered a trial to be at low risk of bias if we assessed the trial to be at low risk of bias across all listed bias risk domains. Otherwise, we considered the trial to be at high risk of bias. At the outcome level, we classified an outcome to be 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 are independent of each other, i.e. if a person has had an event, they are 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 hazard ratios (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 network meta-analysis was performed. We obtained the surface under the cumulative ranking curve (SUCRA) (cumulative probability), rankogram, and relative ranking table with CrI for the ranking probabilities for each outcome when network meta-analysis was performed (Salanti 2011; Chaimani 2013).

Unit of analysis issues

The unit of analysis was the participant with a history of oesophageal variceal bleeding according to the intervention group to which the participant was randomly assigned.

Cluster-randomised clinical trials

If we had identified any cluster-randomised clinical trials, we planned to include cluster-randomised clinical trials, provided that the effect estimate adjusted for cluster correlation was available, or if there was sufficient information available 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 identified any cross-over randomised clinical trials, we planned to include only the outcomes after the period of the first intervention 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. 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 data available to us. When intention-to-treat analysis was not used and the data were not missing at random (for example, 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 mean differences and may bias the effect estimate to no effect for calculation of standardised mean differences (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 (please see Subgroup analysis and investigation of heterogeneity) in trial reports of different drug dosages, presence of other features of decompensation, refractory or recurrent ascites, different aetiologies for cirrhosis (for example, alcohol-related liver disease, viral liver diseases, autoimmune liver disease), and based on the co-interventions (for example, both groups receive prophylactic antibiotics to decrease the risk of subacute bacterial peritonitis). 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% credible intervals of between-study variance (tau^2) with 0, and by calculating the network meta-analysis-specific I^2 statistic using Stata/SE 15.1 (Jackson 2014). 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: other features of decompensation and methodological: risk of bias, year of randomisation, duration of follow-up) across the different pairwise comparisons.

Assessment of reporting biases

For the network meta-analysis, 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 network meta-analyses 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'). Network meta-analysis 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 network meta-analysis, 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 network meta-analysis in a table based on pairwise comparisons. We conducted a Bayesian network meta-analysis 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 odds ratio for binary outcomes, mean difference or standardised mean difference for continuous outcomes, log rate ratio for count outcomes, and log hazard ratio 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 'sclerotherapy' as the reference group across the networks, as this was the commonest intervention compared in the trials. We performed a fixed-effect model and random-effects model for the network meta-analysis. 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 that 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 (IF) plots to assess inconsistency (Higgins 2012; Chaimani 2013) when applicable. We used Stata/SE 15.1 to create IF plots. In the presence of inconsistency (model fit better with inconsistency models than consistency model, 95% CrI of 'between-design' variance did not overlap 0, and the 95% confidence intervals of inconsistency factor did not overlap 0), 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 network meta-analysis to a more compatible subset of trials when possible.

Direct comparison

We performed the direct comparisons in the randomised clinical trials 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 planned to investigate 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 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 variceal bleed and the start of prophylactic treatment
- Based on the cointerventions (e.g. both groups receive 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 compared to 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. sclerotherapy) 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 post-randomisation 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-network meta-analysis statement while reporting (Hutton 2015). We presented the effect estimates with 95% CrI for each pairwise comparison calculated from the direct comparisons and network meta-analysis. 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, which can lead to misinterpretation of results due to large uncertainty in the rankings (the CrI was 0 to 1 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 which can lead to misinterpretation of results due to large uncertainty in the rankings (the CrI was 0 to 1 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) here.

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

We presented 'Summary of findings' tables for all the primary and secondary outcomes (see Primary outcomes; Secondary outcomes). We followed the approach suggested by Yepes-Nunez and colleagues (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 network meta-analysis), imprecision, and publication bias (Guyatt 2011a). 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 five interventions (beta-blockers, variceal band ligation, beta-blockers plus sclerotherapy, no active intervention, and TIPS) which were compared in the most trials (Table 1), and in addition selected beta-blockers plus variceal band ligation, currently recommended as standard of care by various clinical practice guidelines (de Franchis 2015; Tripathi 2015; Garcia-Tsao 2017; EASL 2018).

RESULTS

Description of studies

Results of the search

We identified 8184 records through electronic searches of CENTRAL (Wiley) (n = 1855), MEDLINE Ovid (n = 2725), Embase Ovid (n = 1034), Science Citation Index expanded (n = 1902), ClinicalTrials.gov (n = 83), WHO Trials register (n = 110), FDA (n = 36), and EMA (n = 439). After removing duplicate records, there were 5765 records. We excluded 5322 clearly irrelevant records through reading titles and abstracts. We retrieved a total of 443 full-text records for

further assessment in detail. We excluded 372 records (322 studies) for the reasons stated in the Characteristics of excluded studies. One record is awaiting classification and five records are ongoing trials. Thus, we included a total of 48 trials described in 65 records (Characteristics of included studies). The reference flow is shown in Figure 2.

Included studies

Fourty-eight trials were included (Esquivel Lopez 1984; Westaby 1985a; Ampelas 1987; Bader 1987; Alexandrino 1988; Fleig 1988; Bonkovsky 1989; Jensen 1989; Parelon 1989; Sheen 1989; Bertoni 1990; Fornaciari 1990; Henderson 1990; Lundell 1990; Andreani 1991; Kanazawa 1991; Martin 1991; Rossi 1991; Dasarathy 1992; Dwivedi 1992; Ink 1992; Vinel 1992; Avgerinos 1993; Jiron 1993; Anonymous 1994; Bertoni 1994; Mckee 1994; Villanueva 1994; Isaksson 1995; Baroncini 1996; Cabrera 1996; Urbistondo 1996; Avgerinos 1997; Baroncini 1997; Jalan 1997; Masliah 1997; Sanyal 1997; Sauer 1997; Cennamo 1998; Garcia-Villarreal 1999; Argonz 2000; Sauer 2002; Viazis 2002; Romero 2006; Ahmad 2009; García-Pagán 2009; Kong 2015; Kumar 2015). A total of 3526 participants were randomised to different interventions. The number of participants ranged from 14 to 204. A total of 3442 participants from 46 trials were included in one of more comparisons (Westaby 1985a; Ampelas 1987; Bader 1987; Alexandrino 1988; Fleig 1988; Bonkovsky 1989; Jensen 1989; Parelon 1989; Sheen 1989; Bertoni 1990; Fornaciari 1990; Henderson 1990; Lundell 1990; Andreani 1991; Kanazawa 1991; Martin 1991; Rossi 1991; Dasarathy 1992; Dwivedi 1992; Ink 1992; Vinel 1992; Avgerinos 1993; Jiron 1993; Anonymous 1994; Bertoni 1994; Mckee 1994; Villanueva 1994; Isaksson 1995; Cabrera 1996; Urbistondo 1996; Avgerinos 1997; Baroncini 1997; Jalan 1997; Masliah 1997; Sanyal 1997; Sauer 1997; Cennamo 1998; Garcia-Villarreal 1999; Argonz 2000; Sauer 2002; Viazis 2002; Romero 2006; Ahmad 2009; García-Pagán 2009; Kong 2015; Kumar 2015). We did not identify any cluster randomised clinical trials or cross-over randomised clinical trials that addressed the objectives of the review.

Participants

The mean or median age of the participants in the trials ranged from 40 to 63 years in the trials that reported this information (Esquivel Lopez 1984; Westaby 1985a; Bader 1987; Alexandrino 1988; Jensen 1989; Parelon 1989; Sheen 1989; Bertoni 1990; Lundell 1990; Kanazawa 1991; Martin 1991; Rossi 1991; Dasarathy 1992; Dwivedi 1992; Ink 1992; Vinel 1992; Avgerinos 1993; Jiron 1993; Bertoni 1994; Mckee 1994; Villanueva 1994; Isaksson 1995; Baroncini 1996; Cabrera 1996; Urbistondo 1996; Avgerinos 1997; Baroncini 1997; Jalan 1997; Sanyal 1997; Sauer 1997; Garcia-Villarreal 1999; Argonz 2000; Sauer 2002; Viazis 2002; Romero 2006; Ahmad 2009; García-Pagán 2009; Kong 2015; Kumar 2015). The proportion of females ranged from 0.0% to 80.4% in the trials that reported this information (Esquivel Lopez 1984; Westaby 1985a; Alexandrino 1988; Bonkovsky 1989; Jensen 1989; Parelon 1989; Sheen 1989; Bertoni 1990; Lundell 1990; Kanazawa 1991; Martin 1991; Rossi 1991; Dasarathy 1992; Dwivedi 1992; Ink 1992; Vinel 1992; Avgerinos 1993; Jiron 1993; Anonymous 1994; Bertoni 1994; Mckee 1994; Villanueva 1994; Isaksson 1995; Cabrera 1996; Urbistondo 1996; Avgerinos 1997; Baroncini 1997; Jalan 1997; Sanyal 1997; Sauer 1997; Cennamo 1998; Garcia-Villarreal 1999; Argonz 2000; Sauer 2002; Viazis 2002; Romero 2006; Ahmad 2009; García-Pagán 2009; Kong 2015). The follow-up period in the trials ranged from 1.8 to 65.2 months. Four trials had short-term follow-up (up to three months) (Bertoni 1990; Fornaciari 1990; Bertoni 1994; Viazis 2002); 42 trials had medium-term follow-up (three months to five years) (Esquivel Lopez 1984; Westaby 1985a; Ampelas 1987; Bader 1987; Alexandrino 1988; Fleig 1988; Bonkovsky 1989; Jensen 1989; Parelon 1989; Sheen 1989; Lundell 1990; Andreani 1991; Kanazawa 1991; Martin 1991; Rossi 1991; Dasarathy 1992; Dwivedi 1992; Ink 1992; Vinel 1992; Avgerinos 1993; Jiron 1993; Anonymous 1994; Mckee 1994; Villanueva 1994; Baroncini 1996; Cabrera 1996; Urbistondo 1996; Avgerinos 1997; Baroncini 1997; Jalan 1997; Masliah 1997; Sanyal 1997; Sauer 1997; Cennamo 1998; Garcia-Villarreal 1999; Argonz 2000; Sauer 2002; Romero 2006; Ahmad 2009; García-Pagán 2009; Kong 2015; Kumar 2015); and two trials had long-term follow-up (more than five years) (Henderson 1990; Isaksson 1995).

Nineteen trials reported the proportion of participants who had other features of decompensation: in one trial, none of the participants had other features of decompensation (Sheen 1989); in the remaining 18 trials, the proportion of participants who had other features of decompensation ranged from 11.1% to 67.2% (Henderson 1990; Rossi 1991; Dwivedi 1992; Ink 1992; Vinel 1992; Isaksson 1995; Cabrera 1996; Avgerinos 1997; Baroncini 1997; Jalan 1997; Sanyal 1997; Sauer 1997; Garcia-Villarreal 1999; Argonz 2000; Sauer 2002; Romero 2006; Ahmad 2009; García-Pagán 2009).

Some 39 trials reported the proportion of participants who had alcohol-related cirrhosis: in three trials, all the participants had alcohol-related cirrhosis (Rossi 1991; Anonymous 1994; Urbistondo 1996); in the remaining 36 trials, the proportion of participants who had alcohol-related cirrhosis ranged from 0.7% to 97.4% (Esquivel Lopez 1984; Westaby 1985a; Alexandrino 1988; Bonkovsky 1989; Jensen 1989; Parelon 1989; Sheen 1989; Bertoni 1990; Henderson 1990; Lundell 1990; Kanazawa 1991; Martin 1991; Dasarathy 1992; Ink 1992; Vinel 1992; Avgerinos 1993; Jiron 1993; Bertoni 1994; Mckee 1994; Villanueva 1994; Isaksson 1995; Cabrera 1996; Avgerinos 1997; Baroncini 1997; Jalan 1997; Sanyal 1997; Sauer 1997; Garcia-Villarreal 1999; Argonz 2000; Sauer 2002; Viazis 2002; Romero 2006; Ahmad 2009; García-Pagán 2009; Kong 2015; Kumar 2015). Some 27 trials reported the proportion of participants who had viral-related cirrhosis: in four trials, none of the participants had viral-related cirrhosis (Martin 1991; Rossi 1991; Anonymous 1994; Urbistondo 1996); in the remaining 23 trials, the proportion of participants who had viral-related cirrhosis ranged from 1.8% to 99.3% (Westaby 1985a; Jensen 1989; Sheen 1989; Bertoni 1990; Henderson 1990; Kanazawa 1991; Dasarathy 1992; Avgerinos 1993; Jiron 1993; Bertoni 1994; Mckee 1994; Avgerinos 1997; Baroncini 1997; Jalan 1997; Sanyal 1997; Sauer 1997; Argonz 2000; Sauer 2002; Viazis 2002; Romero 2006; Ahmad 2009; García-Pagán 2009; Kong 2015). Some 16 trials reported the proportion of participants who had autoimmune disease-related cirrhosis: in five trials, none of the participants had autoimmune disease-related cirrhosis (Martin 1991; Rossi 1991; Anonymous 1994; Urbistondo 1996; Ahmad 2009); in the remaining 11 trials, the proportion of participants who had autoimmune disease-related cirrhosis ranged from 1.3% to 21.6% (Westaby 1985a; Jensen 1989; Henderson 1990; Avgerinos 1993; Jiron 1993; Mckee 1994; Avgerinos 1997; Baroncini 1997; Jalan 1997; Argonz 2000; Kong 2015). Some 27 trials reported the proportion of participants who had other-causes for cirrhosis: in four trials, none of the participants had other-causes for cirrhosis (Rossi 1991; Anonymous 1994; Urbistondo 1996; Ahmad 2009); in the remaining 23 trials, the proportion of participants who had other-causes for cirrhosis ranged from 0.9% to 47.3% (Westaby

1985a; Alexandrino 1988; Jensen 1989; Sheen 1989; Bertoni 1990; Henderson 1990; Martin 1991; Dasarathy 1992; Avgerinos 1993; Jiron 1993; Bertoni 1994; Mckee 1994; Avgerinos 1997; Baroncini 1997; Jalan 1997; Sanyal 1997; Sauer 1997; Argonz 2000; Sauer 2002; Viazis 2002; Romero 2006; García-Pagán 2009; Kong 2015).

Interventions

A total of 12 interventions were compared in these trials (sclerotherapy, beta-blockers, variceal band ligation, beta-blockers plus sclerotherapy, no active intervention, TIPS, beta-blockers plus nitrates, portocaval shunt, sclerotherapy plus variceal band ligation, beta-blockers plus nitrates plus variceal band ligation, beta-blockers plus variceal band ligation, sclerotherapy plus nitrates).

Forty-four trials had two interventions (Esquivel Lopez 1984; Westaby 1985a; Ampelas 1987; Bader 1987; Alexandrino 1988; Fleig 1988; Bonkovsky 1989; Jensen 1989; Parelon 1989; Sheen 1989; Bertoni 1990; Fornaciari 1990; Henderson 1990; Lundell 1990; Andreani 1991; Kanazawa 1991; Martin 1991; Dasarathy 1992; Dwivedi 1992; Ink 1992; Vinel 1992; Avgerinos 1993; Jiron 1993; Anonymous 1994; Bertoni 1994; Mckee 1994; Villanueva 1994; Isaksson 1995; Baroncini 1996; Cabrera 1996; Avgerinos 1997; Baroncini 1997; Jalan 1997; Masliah 1997; Sanyal 1997; Sauer 1997; Cennamo 1998; Garcia-Villarreal 1999; Argonz 2000; Sauer 2002; Viazis 2002; Romero 2006; García-Pagán 2009; Kong 2015), three trials had three interventions (Rossi 1991; Kumar 2015; Urbistondo 1996), and one trial had four interventions (Ahmad 2009) included for this review.

Some 46 trials reported one or more outcomes for this review (Westaby 1985a; Ampelas 1987; Bader 1987; Alexandrino 1988; Fleig 1988; Bonkovsky 1989; Jensen 1989; Parelon 1989; Sheen 1989; Bertoni 1990; Fornaciari 1990; Henderson 1990; Lundell 1990; Andreani 1991; Kanazawa 1991; Martin 1991; Rossi 1991; Dasarathy 1992; Dwivedi 1992; Ink 1992; Vinel 1992; Avgerinos 1993; Jiron 1993; Anonymous 1994; Bertoni 1994; Mckee 1994; Villanueva 1994; Isaksson 1995; Cabrera 1996; Urbistondo 1996; Avgerinos 1997; Baroncini 1997; Jalan 1997; Masliah 1997; Sanyal 1997; Sauer 1997; Cennamo 1998; Garcia-Villarreal 1999; Argonz 2000;Domagk 2000Sauer 2002; Viazis 2002; Romero 2006; Ahmad 2009; García-Pagán 2009; Kong 2015; Kumar 2015). The important characteristics, potential effect modifiers, and follow-up in each trial is reported in Table 1. Overall, there do not seem to be any systematic differences between the comparisons.

Funding

The source of funding for five trials was industrial organisations who would benefit from the results of the study (Fleig 1988; Bonkovsky 1989; Jensen 1989; Bertoni 1994; García-Pagán 2009); nine trials were funded by neutral organisations who have no vested interests in the results of the study (Westaby 1985a; Henderson 1990; Lundell 1990; Avgerinos 1993; Anonymous 1994; Sanyal 1997; Sauer 1997; Romero 2006; Kong 2015); the source of funding for the remaining 34 trials was unclear (Esquivel Lopez 1984; Ampelas 1987; Bader 1987; Alexandrino 1988; Parelon 1989; Sheen 1989; Bertoni 1990; Fornaciari 1990; Andreani 1991; Kanazawa 1991; Martin 1991; Rossi 1991; Dasarathy 1992; Dwivedi 1992; Ink 1992; Vinel 1992; Jiron 1993; Mckee 1994; Villanueva 1994; Isaksson 1995; Baroncini 1996; Cabrera 1996; Urbistondo 1996; Avgerinos 1997; Baroncini 1997; Jalan 1997; Masliah 1997; Cennamo 1998; Garcia-Villarreal 1999; Argonz 2000; Sauer 2002; Viazis 2002; Ahmad 2009; Kumar 2015).

Excluded studies

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

- Reasons related to randomisation: 48 studies (Orloff 1962; Berardi 1974; Orloff 1974; Paquet 1983; Adson 1984; Conn 1986; Conn 1987; Kleber 1987; Piai 1987; Terblanche 1988; Fort 1990; Gilbert 1991; Svoboda 1992; Conn 1993; Thiel 1993; Van Stiegmann 1993; Dwivedi 1995; Mino 1995; Benner 1996; Pereira 1997; Srinivasan 1997; Am. Soc. Gastro. Endo. 1998; Gong 1998; Sheikh 1998; Sung 1998; Khaitiyar 2000; Russo 2000; Shah 2001; Groszmann 2002; Maldonado 2002; Marrero 2002; Taniai 2002; Villanueva 2002; Wiest 2002; Okano 2003a; Okano 2003b; Yoshida 2004; Gonzalez-Suarez 2006; Kuran 2006; Hua 2007; D'Amico 2008; Evrard 2008; Bosch 2013; Zhou 2013; Orloff 2014; Chen 2018; NCT03583996; Pfisterer 2018)
- Reasons related to population: 226 studies (Resnick 1969; Callow 1970; Jackson 1971; Resnick 1974; Rikkers 1978; Terblanche 1979; Lebrec 1981; Reynolds 1981; Witzel 1982; Burroughs 1983; Otte 1983; Terblanche 1983; Westaby 1984; Korula 1985; Westaby 1985b; Mastai 1986; Villeneuve 1986; Westaby 1986; Gatta 1987; Queuniet 1987; Teres 1987; Dollet 1988; Dunk 1988; Johansson 1988; Kanazawa 1988; Prioton 1988; Colombo 1989; Jeng 1989; Kitano 1989; O'Connor 1989; Sotto 1989; Taupignon 1989; Tommasini 1989; Westaby 1989; Cestari 1990; Garden 1990; McKee 1990; Santambrogio 1990; Spina 1990; Taranto 1990; Braga 1991; Feu 1991; Garcia-Pagan 1991; Kleber 1991; Planas 1991; Testa 1991; Bhargava 1992; Kitano 1992; McCormick 1992; Acharya 1993; Feu 1993; Hashizume 1993; Lo 1993; McCormick 1993; Rikkers 1993; Saraya 1993; Teres 1993; Young 1993; Berner 1994; Bolognesi 1994; El-Tourabi 1994; Moreto 1994; Primignani 1994; Vickers 1994; Bolognesi 1995; Cirera 1995; Li 1995; Ministro 1995; Pontes 1995; Primignani 1995; Albillos 1996; Elsayed 1996; Escorsell 1996; Estevens 1996; Garcia-Pagan 1996; Iwao 1996; Lin 1996; Nakase 1996; Nevens 1996a; Nevens 1996b; Rosemurgy 1996; Villanueva 1996; Zironi 1996; Balatsos 1997; Bhargava 1997; Durdevic 1997; Escorsell 1997; Escorsell 1997a; Fakhry 1997; Iso 1997; Jenkins 1997; Pang 1997; Rossle 1997; Saeed 1997; Sarin 1997; Sugano 1997; Bandi 1998; Barrioz 1998; D'Amico 1998; Lo 1998; Masumoto 1998; Merli 1998; Shin 1998; Siqueira 1998; Zhao 1998; Al Traif 1999; Banares 1999; Buuren 1999; de la Pena 1999; Djurdjevic 1999; Garg 1999; Gotoh 1999; Gralnek 1999; Masci 1999; Nishikawa 1999; Pena 1999; Umehara 1999; Domagk 2000; Gournay 2000; Iwakiri 2000; NCT00006161; Romero 2000; Shigemitsu 2000; Van Buuren 2000; Cheng 2001; Escorsell 2001; Lee 2001; Nakamura 2001; Narahara 2001; Pomier-Layrargues 2001; Schepke 2001; Sugano 2001; Villanueva 2001; Bobadilla-Diaz 2002; De 2002; Escorsell 2002; Lin 2002; Lo 2002; Schiedermaier 2002; Sen 2002; Serwah 2002; Vorobioff 2002; Bellis 2003; De 2003; Evrard 2003; Schiedermaier 2003; Liu 2004; Silva 2004; Tripathi 2004; de la Pena 2005; Farag 2005; Ferrari 2005; Kalambokis 2005; Kuwayama 2005; Lin 2005; Pena 2005; Pozzi 2005; Sarin 2005; Lin 2006; Ohmoto 2006; Santambrogio 2006; Bhuiyan 2007; ISRCTN77521636; Morales 2007; NCT00570973; Qi 2007; Vorobioff 2007; ChiCTR08000228;

Fernandez 2008; Lo 2008; NCT00799851; Van Buuren 2008; Zargar 2008; Zhang 2008; Kumar 2009; Lo 2009a; Bonilha 2010; Gong 2010; Harras 2010; NCT01103154; Graupera 2011; Luo 2011; Priyadarshi 2011; Santos 2011; Copaci 2012; EUCTR2006-006393-14; EUCTR2012-002489-11; Lo 2012; NCT01640964; Wang 2012; Chen 2013; George 2013; Smith 2013; Sohn 2013; Sun 2013; Zhao 2013; EUCTR2014-002018-21; Mo 2014; NCT02119884; Stanley 2014; Abd Elmoety 2015; ChiCTR11001577; ChiCTR12002148; Geng 2015; Helmy 2015; ISRCTN14174793; Liao 2015; Luo 2015; NCT02508623; Chen 2016; Costa 2016; Hanno 2016; Harki 2016a; Holster 2016; Lacet 2016; Li 2016; NCT02646202; Zuckerman 2016; ChiCTR1800020322; Dong 2018; Lv 2018; NCT03687216; NCT03783065; Chen 2019; ChiCTR1900021212; Dunne 2019)

- Reasons related to intervention: 48 studies (Mikkelsen 1974; Goff 1986; Rhodes 1986; Bories 1987; Terabayashi 1987; Akriviadis 1989; Palazzi 1989; Triger 1992; Fiaccadori 1993; Dehesa 1994; Magnano 1994; Nos 1995; Sarin 1995; Krige 1996; Kim 1997; Eleftheriadis 1998; Escorsell 1998; Liu 1998; Nakamura 1998; Li 2000; Li 2000a; Lo 2000; Gonzalez-Abraldes 2001; Jiang 2001; Brensing 2002; Cipolletta 2002; Gulberg 2002; Patch 2002; Lu 2004; Zhu 2004; Baik 2005; EUCTR2005-003557-27; El-Saadany 2007; Lo 2009b; Villanueva 2009; Monici 2010; Agarwala 2011; ChiCTR11000192; Agarwal 2015; Rawat 2015; Sauerbruch 2015; Abraldes 2016; ChiCTR15007655; NCT02740166; Huang 2017; Kamal 2017; Villanueva 2017; ChiCTR1800018070).

Risk of bias in included studies

The risk of bias is summarised in Figure 3, Figure 4, and in Table 2. All the trials were at unclear or high risk of bias in at least one of the domains and were considered to be at high risk of bias overall.

Figure 3. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

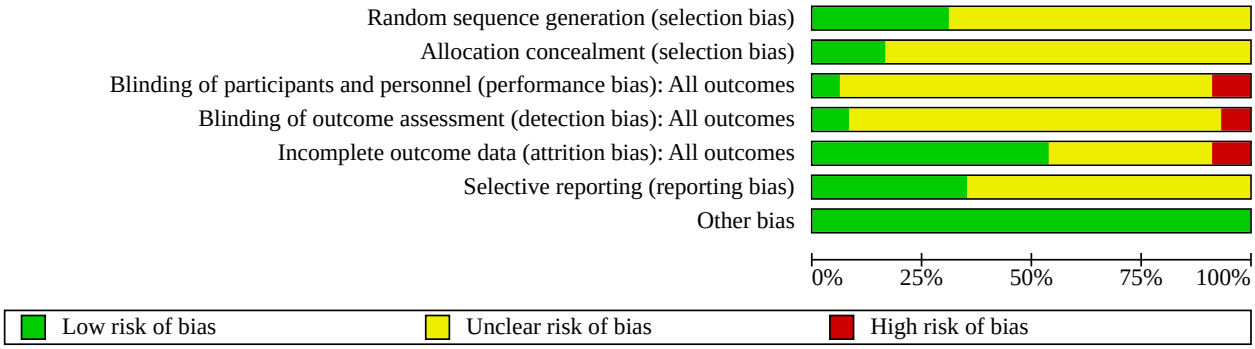


Figure 4. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

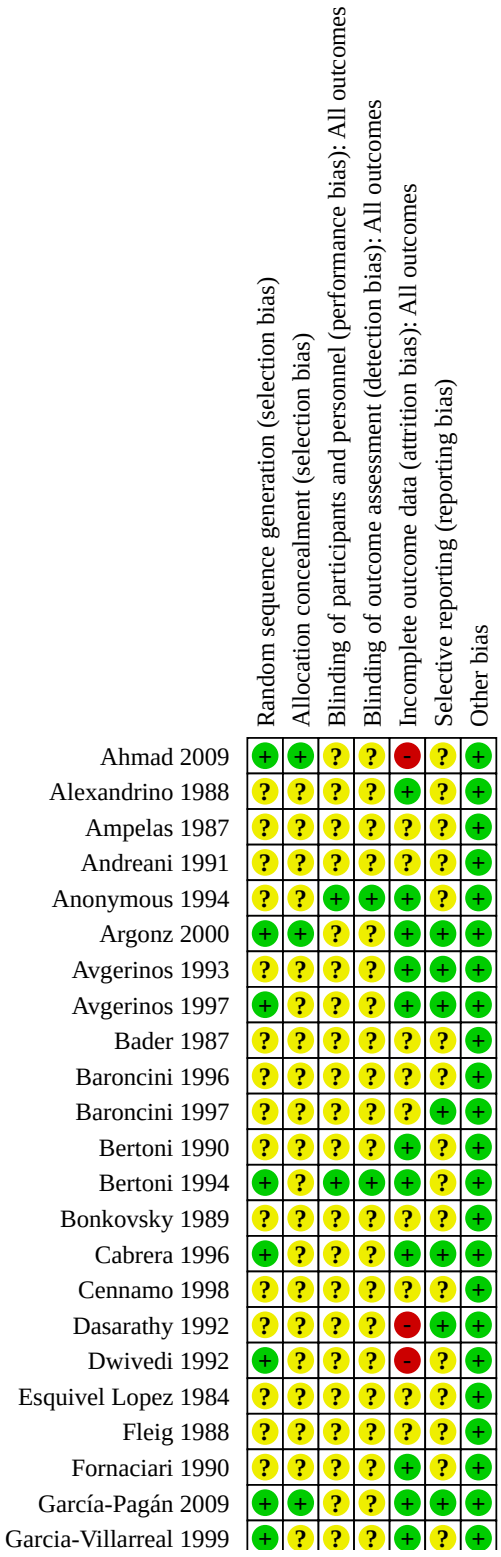
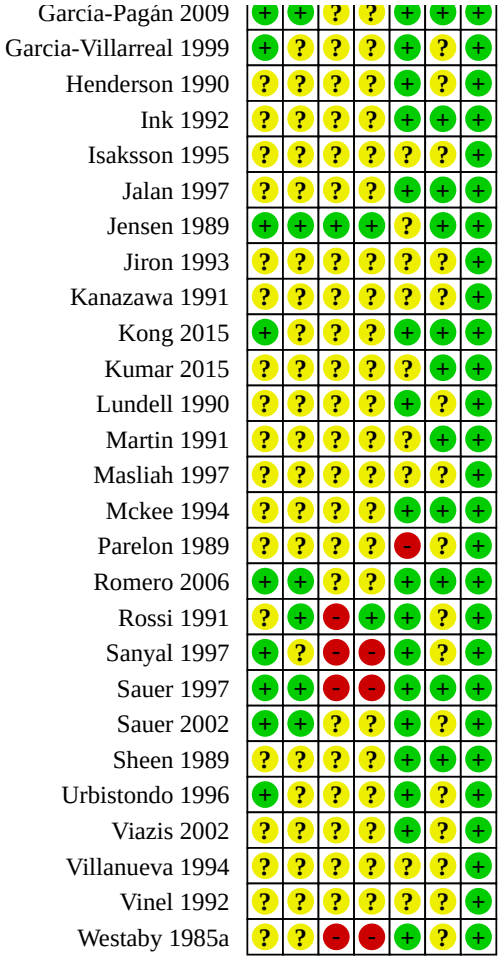


Figure 4. (Continued)



Allocation

Some 15 trials were at low risk of sequence generation bias (Jensen 1989; Dwivedi 1992; Bertoni 1994; Cabrera 1996; Urbistondo 1996; Avgerinos 1997; Sanyal 1997; Sauer 1997; Garcia-Villarreal 1999; Argonz 2000; Sauer 2002; Romero 2006; Ahmad 2009; García-Pagán 2009; Kong 2015); the remaining 33 trials, which did not provide sufficient information, were at unclear risk of sequence generation bias (Westaby 1985a; Alexandrino 1988; Fleig 1988; Bonkovsky 1989; Esquivel Lopez 1984; Ampelas 1987; Bader 1987; Parelon 1989; Sheen 1989; Bertoni 1990; Henderson 1990; Fornaciari 1990; Lundell 1990; Andreani 1991; Kanazawa 1991; Martin 1991; Rossi 1991; Dasarathy 1992; Ink 1992; Avgerinos 1993; Jiron 1993; Vinel 1992; Anonymous 1994; Mckee 1994; Villanueva 1994; Isaksson 1995; Baroncini 1996; Baroncini 1997; Jalan 1997; Masliah 1997; Cennamo 1998; Viazis 2002; Kumar 2015).

Some eight trials were at low risk of allocation concealment bias (Jensen 1989; Rossi 1991; Sauer 1997; Argonz 2000; Sauer 2002; Romero 2006; Ahmad 2009; García-Pagán 2009); the remaining 40 trials, which did not provide sufficient information, were at unclear risk of allocation concealment bias (Esquivel Lopez 1984; Westaby 1985a; Ampelas 1987; Bader 1987; Alexandrino 1988; Fleig 1988; Bonkovsky 1989; Parelon 1989; Sheen 1989; Bertoni 1990; Fornaciari 1990; Henderson 1990; Lundell 1990; Andreani 1991; Kanazawa 1991; Martin 1991; Dasarathy 1992; Dwivedi 1992; Ink 1992; Vinel 1992; Avgerinos 1993; Jiron 1993; Anonymous 1994; Bertoni 1994; Mckee 1994; Villanueva 1994; Isaksson 1995; Baroncini 1996; Cabrera 1996; Urbistondo 1996; Avgerinos 1997; Baroncini 1997; Jalan 1997; Masliah 1997; Sanyal 1997; Cennamo 1998; Garcia-Villarreal 1999; Viazis 2002; Kong 2015; Kumar 2015).

Blinding

Three trials were at low risk of performance bias as the participants and healthcare providers were blinded (Jensen 1989; Anonymous 1994; Bertoni 1994); 41 trials, which did not provide sufficient information, were at unclear risk of performance bias (Esquivel Lopez 1984; Ampelas 1987; Bader 1987; Alexandrino 1988; Fleig 1988; Bonkovsky 1989; Parelon 1989; Sheen 1989; Bertoni 1990; Fornaciari 1990; Henderson 1990; Lundell 1990; Andreani 1991; Kanazawa 1991; Martin 1991; Dasarathy 1992; Dwivedi 1992; Ink 1992; Vinel 1992; Avgerinos 1993; Jiron 1993; Mckee 1994; Villanueva 1994; Isaksson 1995; Baroncini 1996; Cabrera 1996; Urbistondo 1996; Avgerinos 1997; Baroncini 1997; Jalan 1997; Masliah 1997; Cennamo 1998; Garcia-Villarreal 1999; Argonz 2000; Sauer 2002; Viazis 2002; Romero 2006; Ahmad 2009; García-Pagán 2009; Kong 2015; Kumar 2015); the remaining four trials were at high risk of performance bias (Westaby 1985a; Rossi 1991; Sanyal 1997; Sauer 1997).

Four trials were at low risk of detection bias (Jensen 1989; Rossi 1991; Anonymous 1994; Bertoni 1994); 41 trials, which did not provide sufficient information, were at unclear risk of detection bias (Esquivel Lopez 1984; Ampelas 1987; Bader 1987; Alexandrino 1988; Fleig 1988; Bonkovsky 1989; Parelon 1989; Sheen 1989; Bertoni 1990; Fornaciari 1990; Henderson 1990; Lundell 1990; Andreani 1991; Kanazawa 1991; Martin 1991; Dasarathy 1992; Dwivedi 1992; Ink 1992; Vinel 1992; Avgerinos 1993; Jiron 1993; Mckee 1994; Villanueva 1994; Isaksson 1995; Baroncini 1996; Cabrera 1996; Urbistondo 1996; Avgerinos 1997; Baroncini 1997; Jalan 1997; Masliah 1997; Cennamo 1998; Garcia-Villarreal 1999; Argonz 2000; Sauer 2002; Viazis 2002; Romero 2006; Ahmad 2009; García-Pagán 2009; Kong 2015; Kumar 2015); the remaining three trials were at high risk of detection bias (Westaby 1985a; Sanyal 1997; Sauer 1997).

Incomplete outcome data

Some 26 trials were at low risk of attrition bias as there were no post-randomisation dropouts or an intention-to-treat analysis was used (Westaby 1985a; Alexandrino 1988; Sheen 1989; Bertoni 1990; Fornaciari 1990; Henderson 1990; Lundell 1990; Rossi 1991; Ink 1992; Avgerinos 1993; Anonymous 1994; Bertoni 1994; Mckee 1994; Cabrera 1996; Urbistondo 1996; Avgerinos 1997; Jalan 1997; Sanyal 1997; Sauer 1997; Garcia-Villarreal 1999; Argonz 2000; Sauer 2002; Viazis 2002; Romero 2006; García-Pagán 2009; Kong 2015); 18 trials were at unclear risk of attrition bias (Esquivel Lopez 1984; Ampelas 1987; Bader 1987; Fleig 1988; Bonkovsky 1989; Jensen 1989; Andreani 1991; Kanazawa 1991; Martin 1991; Vinel 1992; Jiron 1993; Villanueva 1994; Isaksson 1995; Baroncini 1996; Baroncini 1997; Masliah 1997; Cennamo 1998; Kumar 2015) because it was not clear whether there were post-randomisation drop-outs or whether the post-randomisation dropouts were related to the outcomes (if there were post-randomisation dropouts); the remaining four trials were at high risk of attrition bias (Parelon 1989; Dasarathy 1992; Dwivedi 1992; Ahmad 2009), as the post-randomisation dropouts were probably related to the outcomes.

Selective reporting

Some 17 trials were at low risk of selective outcome reporting bias (Jensen 1989; Sheen 1989; Martin 1991; Dasarathy 1992; Ink 1992; Avgerinos 1993; Mckee 1994; Cabrera 1996; Avgerinos 1997; Baroncini 1997; Jalan 1997; Sauer 1997; Argonz 2000; Romero 2006; García-Pagán 2009; Kong 2015; Kumar 2015), as the outcomes were reported or the important clinical outcomes expected to be reported in such trials were reported; the remaining 31 trials were at unclear risk of selective outcome reporting bias (Esquivel Lopez 1984; Westaby 1985a; Ampelas 1987; Bader 1987; Alexandrino 1988; Fleig 1988; Bonkovsky 1989; Parelon 1989; Bertoni 1990; Fornaciari 1990; Henderson 1990; Lundell 1990; Andreani 1991; Kanazawa 1991; Rossi 1991; Dwivedi 1992; Vinel 1992; Jiron 1993; Anonymous 1994; Bertoni 1994; Villanueva 1994; Isaksson 1995; Baroncini 1996; Urbistondo 1996; Masliah 1997; Sanyal 1997; Cennamo 1998; Garcia-Villarreal 1999; Sauer 2002; Viazis 2002; Ahmad 2009), as a protocol published prior to recruitment was not available.

Other potential sources of bias

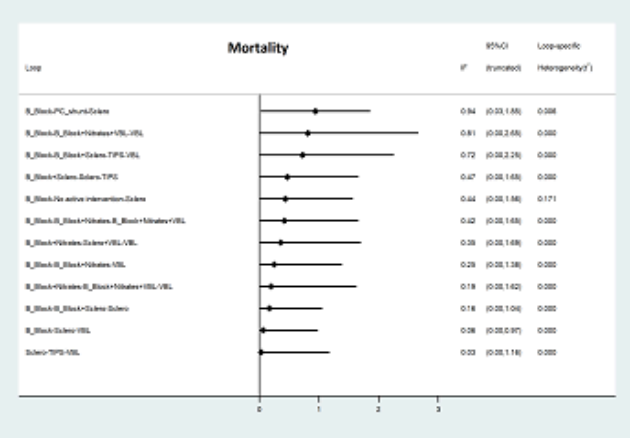
No other potential source of bias was noted in any of the trials.

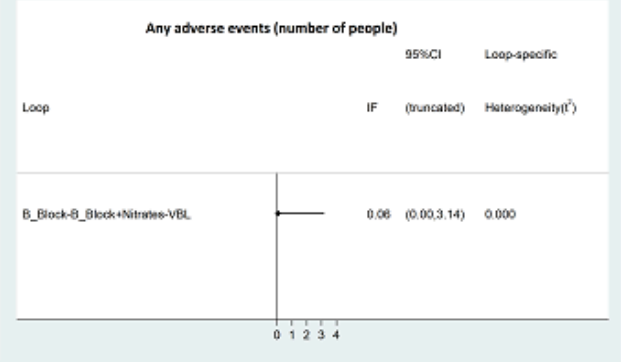
Effects of interventions

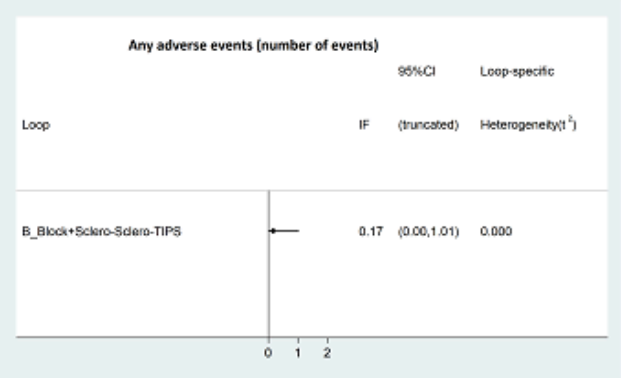
See: **Summary of findings 1** Secondary prevention of bleeding in people with previous oesophageal variceal bleeding due to decompensated liver cirrhosis (common interventions); **Summary of findings 2** Secondary prevention of bleeding in people with previous oesophageal variceal bleeding due to decompensated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

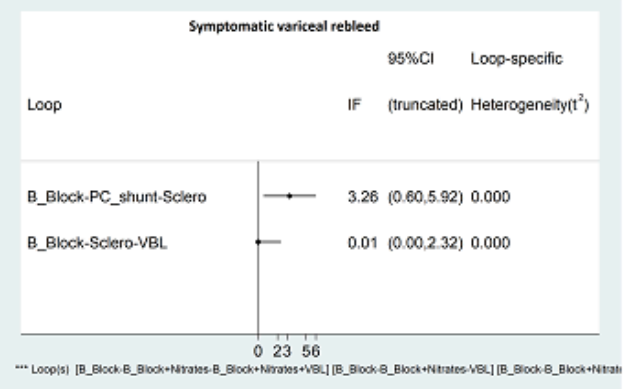
The network plots (where relevant) are available in Figure 1. The inconsistency factor plots (where relevant) are available in Figure 5. The differences in the fixed-effect versus random-effects model, where relevant, are available in Figure 6. The model fit is available in Table 3. The effect estimates are available in Table 4.

Figure 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 except for mortality and symptomatic variceal bleed (where the confidence intervals of the inconsistency factors do not overlap 0). A higher resolution image of this picture is available here. Abbreviations B_Block = Beta-blockers
PC_shunt = Portocaval shunt
Sclero = Sclerotherapy
TIPS = Transjugular intrahepatic portosystemic shunt
VBL = Variceal band ligation









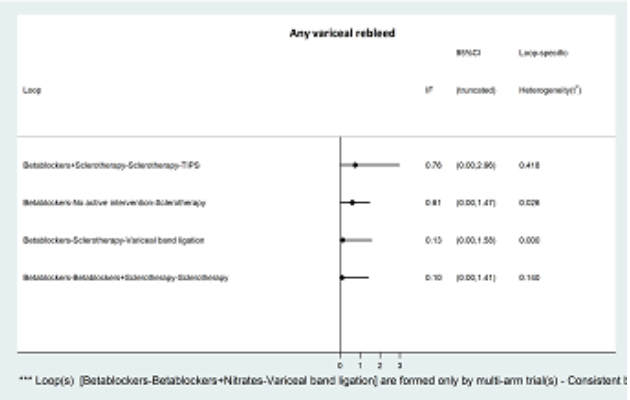
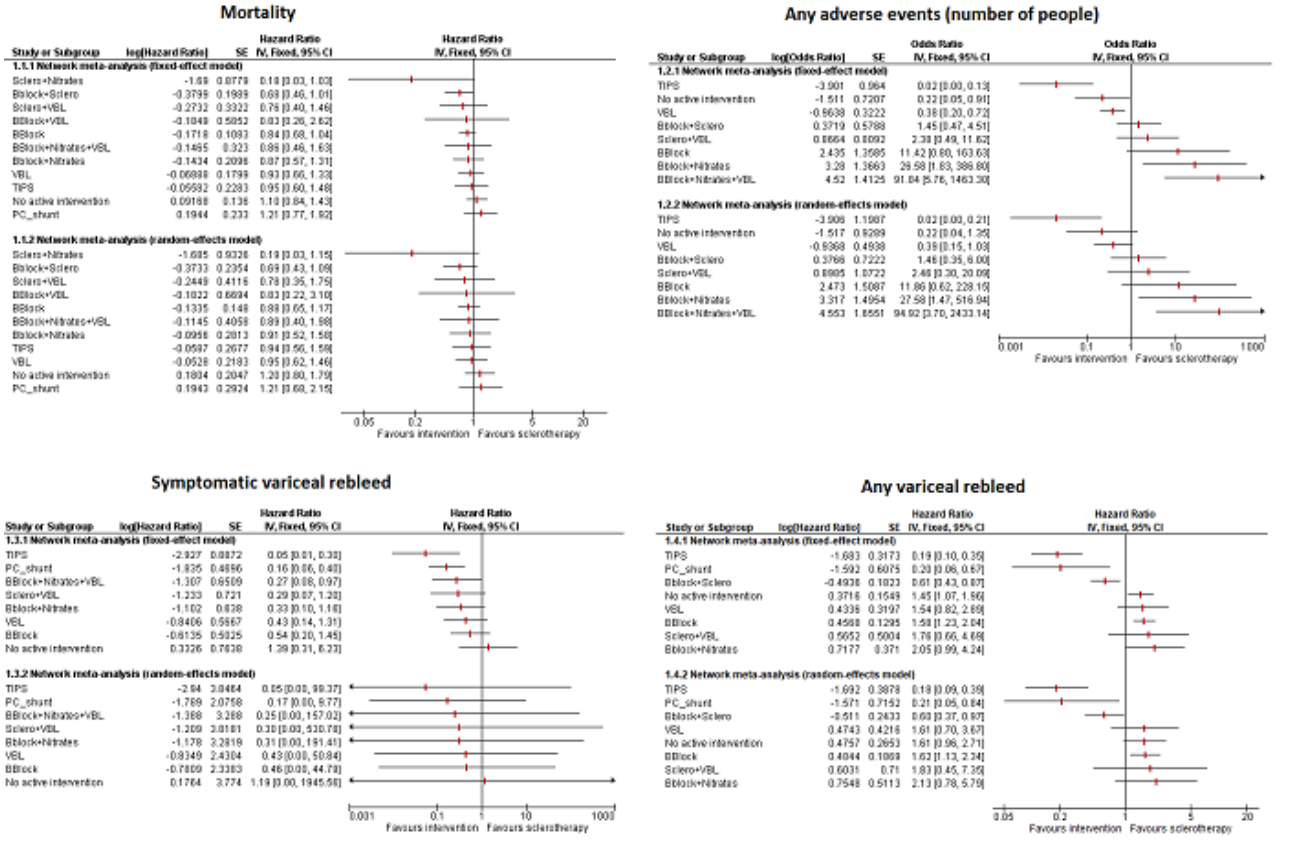


Figure 6. Forest plots showing the outcomes for which the random-effects model were different from the fixed-effect model. The more conservative random-effects model was used. A higher resolution image of this picture is available here. Abbreviations BBlock = Beta-blockers
PC_shunt = Portocaval shunt
Sclero = Sclerotherapy
TIPS = Transjugular intrahepatic portosystemic shunt
VBL = Variceal band ligation



The 95% credible intervals 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 (surface under the cumulative ranking curve) plots as we considered that presenting this information would be unhelpful and potentially misleading, and it would ignore the differences in systematic errors in the trials.

The certainty of evidence was moderate, 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 events and we downgraded one level for imprecision. For network meta-analysis, for outcomes other than mortality, any adverse events (number of events), and any variceal rebleed, the number of events were fewer than 300 and we downgraded one level for imprecision. In comparisons where the wide credible intervals 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 network meta-analysis) for symptomatic variceal rebleed. We downgraded one level for indirectness for symptomatic variceal rebleed as they may be incongruence for this outcome.

Mortality

Forty-two trials (3369 participants) reported mortality (Westaby 1985a; Ampelas 1987; Bader 1987; Fleig 1988; Bonkovsky 1989; Jensen 1989; Parelon 1989; Sheen 1989; Bertoni 1990; Fornaciari 1990; Henderson 1990; Lundell 1990; Andreani 1991; Kanazawa 1991; Martin 1991; Rossi 1991; Dasarathy 1992; Dwivedi 1992; Ink 1992; Vinel 1992; Avgerinos 1993; Jiron 1993; Anonymous 1994; Bertoni 1994; Mckee 1994; Villanueva 1994; Cabrera 1996; Urbistondo 1996; Avgerinos 1997; Baroncini 1997; Jalan 1997; Sanyal 1997; Sauer 1997; Garcia-Villarreal 1999; Argonz 2000; Sauer 2002; Viazis 2002; Romero 2006; Ahmad 2009; García-Pagán 2009; Kong 2015; Kumar 2015). A total of 12 treatments were compared in these trials. There were 853 (25.8%) events in total. The median control group (endoscopic sclerotherapy) proportion was 22.5%.

Direct comparisons

Sclerotherapy plus nitrates had lower mortality than sclerotherapy: hazard ratio (HR) 0.18 (95% credible interval (CrI) 0.02 to 0.79; 1 trial; 76 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. There was no evidence of inconsistency according to model fit and the 'between-design' variance. However, there was evidence of inconsistency in one loop (made up of the three-way comparison between beta-blockers, portocaval shunt, and sclerotherapy) in the inconsistency factor plot. The random-effects model was used because it was more conservative than the fixed-effect model, even though the model fit was similar as fixed-effect model. The 'between-study variance' was 0.07 (95% CrI 0.00 to 0.27).

In the network meta-analysis, in the following pairwise comparisons, the first intervention had lower mortality than the second intervention.

- Sclerotherapy plus nitrates versus sclerotherapy: HR 0.19 (95% CrI 0.02 to 0.86); direct comparison HR 0.18 (95% CrI 0.02 to 0.79); 1 trial; 76 participants; moderate-certainty evidence
- Sclerotherapy plus nitrates versus variceal band ligation: HR 0.19 (95% CrI 0.02 to 0.97); no direct comparison; moderate-certainty evidence
- Sclerotherapy plus nitrates versus no active intervention: HR 0.15 (95% CrI 0.02 to 0.75); no direct comparison; moderate-certainty evidence
- Sclerotherapy plus nitrates versus portocaval shunt: HR 0.15 (95% CrI 0.02 to 0.79); no direct comparison; moderate-certainty evidence

There was no evidence of differences between the treatments in the remaining comparisons in the network meta-analysis (low-certainty evidence). After excluding the trials including surgical portocaval shunt as one of their treatments (to assess whether the inconsistency in the inconsistency factor plot was due to the loop between beta-blockers, portocaval shunt, and sclerotherapy), the network meta-analysis results did not change. There was no further inconsistency in the inconsistency factor plot.

Health-related quality of life

None of the trials reported health-related quality of life.

Serious adverse events

None of the 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)

Four trials (467 participants) reported serious adverse events (number of participants) (Sheen 1989; Dasarathy 1992; Ink 1992; Romero 2006). A total of six treatments were compared in these trials. There were 80 events in total (17.1%). The median control group proportion was 36.0%.

Direct comparisons

Variceal band ligation had lower serious adverse events (number of people) than sclerotherapy: odds ratio (OR) 0.19 (95% CrI 0.06 to 0.54; 1 trial; 100 participants; low-certainty evidence).

Beta-blockers plus sclerotherapy had higher serious adverse events (number of participants) than beta-blockers: OR 2.75 (95% CrI 1.18 to 6.82; 1 trial; 131 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) (very low-certainty evidence).

Network meta-analysis

One trial was not connected to the network because it had treatments unconnected to network (Romero 2006); one trial was not connected to the network because it was the only trial for the comparison and had zero-event in one of the intervention groups (Sheen 1989). The network had four connected treatments. There were no triangular or quadrangular loops; therefore, inconsistency was not checked. The fixed-effect model was used because there was only one trial for each of the comparisons.

In the network meta-analysis, variceal band ligation had lower serious adverse events (number of people) than sclerotherapy: OR 0.19 (95% CrI 0.06 to 0.53); direct comparison OR 0.19 (95% CrI 0.06 to 0.54); 1 trial; 100 participants; low-certainty evidence; and beta-blockers plus sclerotherapy had higher serious events (number of participants) than beta-blockers: OR 2.74 (95% CrI 1.18 to 6.70); direct comparison OR 2.75 (95% CrI 1.18 to 6.82); 1 trial; 131 participants; very low-certainty evidence.

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

Serious adverse events (number of events)

None of the trials reported serious adverse events (number of events).

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)

Eleven trials (895 participants) reported any adverse events (number of participants) (Jensen 1989; Sheen 1989; Mckee 1994; Villanueva 1994; Avgerinos 1997; Jalan 1997; Masliah 1997; Argonz 2000; García-Pagán 2009; Kong 2015; Kumar 2015). A total of nine treatments were compared in these trials. There were 274 events in total (30.6%). The median control group proportion was 38.0%.

Direct comparisons

In the following direct comparisons, the first intervention had lower any adverse events (number of participants) than the second intervention.

- Sclerotherapy versus no active intervention: OR 4.55 (95% CrI 1.16 to 20.00); 1 trial; 40 participants; low-certainty evidence
- Variceal band ligation versus beta-blockers: OR 0.03 (95% CrI 0.00 to 0.21); 1 trial; 103 participants; low-certainty evidence
- TIPS versus variceal band ligation: OR 0.05 (95% CrI 0.01 to 0.25); 1 trial; 58 participants; low-certainty evidence

In the following direct comparisons, the first intervention had higher any adverse events (number of participants) than the second intervention.

- Beta-blockers plus nitrates versus beta-blockers: OR 2.34 (95% CrI 1.16 to 4.75); 2 trials; 181 participants; low-certainty evidence
- Beta-blockers plus nitrates versus variceal band ligation: OR 68.37 (95% CrI 10.79 to 2071.44); 1 trial; 95 participants; low-certainty evidence
- Sclerotherapy plus variceal band ligation versus variceal band ligation: OR 6.27 (95% CrI 1.70 to 31.63); 1 trial; 80 participants; low-certainty evidence
- Beta-blockers plus nitrates plus variceal band ligation versus beta-blockers plus nitrates: OR 3.40 (95% CrI 1.78 to 6.71); 1 trial; 158 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

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 (Sheen 1989). All treatments were connected. There was no evidence of inconsistency according to model fit or inconsistency factor plot. We were unable to obtain convergence for the 'between-design' variance despite various measures (probably because of the sparse data). The random-effects model was used because it was more conservative, even though the model fit was similar as fixed-effect model. The 'between-study variance' was 0.09 (95% CrI 0.00 to 2.71).

In the network meta-analysis, in the following pairwise comparisons, the first intervention had lower any adverse events (number of participants) than the second intervention.

- TIPS versus sclerotherapy: OR 0.02 (95% CrI 0.00 to 0.17); no direct comparison; low-certainty evidence
- Variceal band ligation versus beta-blockers: OR 0.03 (95% CrI 0.00 to 0.29); direct comparison OR 0.03 (95% CrI 0.00 to 0.21); 1 trial; 103 participants; low-certainty evidence
- Beta-blockers versus no active intervention: 56.49 (95% CrI 2.83 to 3016.94); no direct comparison; low-certainty evidence
- TIPS versus beta-blockers: OR 0.00 (95% CrI 0.00 to 0.03); no direct comparison; low-certainty evidence
- TIPS versus variceal band ligation: OR 0.05 (95% CrI 0.00 to 0.35); direct comparison OR 0.05 (95% CrI 0.01 to 0.25); 1 trial; 58 participants; low-certainty evidence
- TIPS versus beta-blockers plus sclerotherapy: OR 0.01 (95% CrI 0.00 to 0.19); no direct comparison; lo- certainty evidence

In the network meta-analysis, in the following pairwise comparisons, the first intervention had higher any adverse events (number of participants) than the second intervention.

- Beta-blockers versus sclerotherapy: OR 11.86 (95% CrI 1.16 to 427.95); no direct comparison; low-certainty evidence
- Beta-blockers plus nitrates versus sclerotherapy: OR 27.58 (95% CrI 2.79 to 981.42); no direct comparison; low-certainty evidence
- Beta-blockers plus nitrates versus beta-blockers plus sclerotherapy: OR 19.28 (95% CrI 1.26 to 920.58); no direct comparison; low-certainty evidence
- Beta-blockers plus nitrates versus no active intervention: OR 133.4 (95% CrI 6.86 to 7215.6); no direct comparison; low-certainty evidence
- Beta-blockers plus nitrates versus TIPS: OR 1474.4 (95% CrI 76.6 to 84120.0); no direct comparison; low-certainty evidence
- Beta-blockers plus nitrates versus variceal band ligation: OR 69.76 (95% CrI 8.65 to 2199.53); direct comparison: OR 68.37 (95% CrI 10.79 to 2071.44); 1 trial; 95 participants; low-certainty evidence
- Beta-blockers plus nitrates plus variceal band ligation versus sclerotherapy: OR 94.92 (95% CrI 6.85 to 4500.75); no direct comparison; low-certainty evidence
- Beta-blockers plus nitrates plus variceal band ligation versus beta-blockers: OR 7.96 (95% CrI 1.44 to 44.57); no direct comparison; low-certainty evidence
- Beta-blockers plus nitrates plus variceal band ligation versus variceal band ligation: OR 239.61 (95% CrI 20.47 to 9701.15); no direct comparison; low-certainty evidence
- Beta-blockers plus nitrates plus variceal band ligation versus beta-blockers plus sclerotherapy: OR 66.22 (95% CrI 3.19 to 3944.19); no direct comparison; low-certainty evidence
- Beta-blockers plus nitrates plus variceal band ligation versus no active intervention: OR 454.86 (95% CrI 17.78 to 31888.48); no direct comparison; low-certainty evidence
- Beta-blockers plus nitrates plus variceal band ligation versus TIPS: OR 5084.74 (95% CrI 208.51 to 362217.45); no direct comparison; low-certainty evidence
- Beta-blockers plus nitrates plus variceal band ligation versus sclerotherapy plus variceal band ligation: OR 38.40 (95% CrI 1.61 to 2221.64); no direct comparison; low-certainty evidence
- Sclerotherapy plus variceal band ligation versus variceal band ligation: OR 6.30 (95% CrI 1.11 to 47.18); direct comparison: OR 6.27 (95% CrI 1.70 to 31.63); 1 trial; 80 participants; low-certainty evidence
- Sclerotherapy plus variceal band ligation versus TIPS: OR 125.59 (95% CrI 9.11 to 2754.52); no direct comparison; low-certainty evidence

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

Any adverse events (number of events)

Eleven trials (935 participants) reported any adverse events (number of events) (Kanazawa 1991; Martin 1991; Avgerinos 1993; Isaksson 1995; Cabrera 1996; Avgerinos 1997; Baroncini 1997; Sauer 1997; Sauer 2002; Romero 2006; García-Pagán 2009). A total of 10 treatments were compared in these trials. There were 634 events

in total (0.7 events per participant). The median control event rate was 0.581 events per participant.

Direct comparisons

In the following direct comparisons, the first intervention had lower any adverse events (number of events) than the second intervention.

- Variceal band ligation versus sclerotherapy: rate ratio 0.40 (95% CrI 0.26 to 0.61); 2 trials; 188 participants; low-certainty evidence
- Beta-blockers plus variceal band ligation versus TIPS: rate ratio 0.12 (95% CrI 0.06 to 0.22); 1 trial; 85 participants; low-certainty evidence

Beta-blockers plus nitrates plus variceal band ligation had higher any adverse events (number of events) than beta-blockers plus nitrates: rate ratio 2.39 (95% CrI 1.51 to 3.89); 1 trial; 158 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). There was no evidence of differences in the remaining comparison not connected to the network: sclerotherapy plus variceal band ligation versus beta-blockers plus nitrates: rate ratio 0.97 (95% CrI 0.55 to 1.70); 1 trial; 109 participants (very low-certainty evidence).

Network meta-analysis

Two trials were not connected to the network because they had treatments unconnected to network (Romero 2006; García-Pagán 2009); 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 arms (Martin 1991). The network had six connected treatments. There was no evidence of inconsistency according to the inconsistency factor plot, but there was evidence was inconsistency according to model fit. We could not obtain convergence by design-by-treatment model. Fixed-effect model was used as it had similar model fit and equivalent results as random-effects model.

In the network meta-analysis, in the following pairwise comparisons, the first intervention had lower any adverse events (number of events) than the second intervention.

- Variceal band ligation versus sclerotherapy: rate ratio 0.40 (95% CrI 0.26 to 0.61); direct comparison: rate ratio 0.40 (95% CrI 0.26 to 0.61); 2 trials; 188 participants; moderate-certainty evidence
- Beta-blockers plus variceal band ligation versus sclerotherapy: rate ratio 0.13 (95% CrI 0.06 to 0.28); no direct comparison; moderate-certainty evidence
- Beta-blockers plus variceal band ligation versus variceal band ligation: rate ratio 0.33 (95% CrI 0.13 to 0.78); no direct comparison;moderate-certainty evidence
- Beta-blockers plus variceal band ligation versus beta-blockers plus sclerotherapy: rate ratio 0.14 (95% CrI 0.06 to 0.29); no direct comparison; moderate-certainty evidence
- Beta-blockers plus variceal band ligation versus TIPS: rate ratio 0.12 (95% CrI 0.06 to 0.22); direct comparison: rate ratio 0.12 (95% CrI 0.06 to 0.22); 1 trial; 85 participants; moderate-certainty evidence
- Beta-blockers plus variceal band ligation versus portocaval shunt: rate ratio 0.15 (95% CrI 0.04 to 0.51); no direct comparison; moderate-certainty evidence.

In the network meta-analysis, in the following pairwise comparisons, the first intervention had higher any adverse events (number of events) than the second intervention.

- Beta-blockers plus sclerotherapy versus variceal band ligation: rate ratio 2.30 (95% CrI 1.37 to 3.97); no direct comparison; moderate-certainty evidence
- TIPS versus variceal band ligation: rate ratio 2.74 (95% CrI 1.52 to 5.02); no direct comparison; moderate-certainty evidence

There was no evidence of differences between the treatments in the remaining comparisons in the network meta-analysis (low-certainty evidence).

Liver transplantation

Six trials (588 participants) reported liver transplantation (Westaby 1985a; Villanueva 1994; Baroncini 1997; Sanyal 1997; Sauer 1997; García-Pagán 2009). A total of seven treatments were compared in these trials. There were 21 events in total (3.6%). The median control group proportion was 1.9%.

Direct comparisons

There was no evidence of difference in any of the direct comparisons (i.e. there was no statistically significant difference in any of the comparisons) as shown in Table 4 (very low-certainty evidence). There was no evidence of differences in the remaining comparison not connected to the network: beta-blockers plus nitrates plus variceal band ligation versus beta-blockers plus nitrates: HR 0.61 (95% CrI 0.07 to 3.90; 1 trial; 158 participants; very low-certainty evidence).

Network meta-analysis

One trial was not connected to the network because it had zero-events in both arms (Westaby 1985a); one trial was not connected to the network because it had treatments unconnected to network (García-Pagán 2009).The network had four connected treatments. There was no evidence of inconsistency according to model fit, inconsistency factor, and the 'between-design' variance. The fixed-effect model was used because there was only one trial for each of the comparisons. In the network meta-analysis, there was no evidence of difference in any of the comparisons (very low-certainty evidence).

Variceal rebleed

Symptomatic variceal rebleed

Seven trials (550 participants) reported symptomatic variceal rebleed (Sheen 1989; Henderson 1990; Urbistondo 1996; Baroncini 1997; Jalan 1997; Argonz 2000; Ahmad 2009). A total of nine treatments were compared in these trials. There were 141 (25.6%) events in total. The median control group proportion was 5.6%.

Direct comparisons

TIPS had lower symptomatic variceal rebleed than variceal band ligation: HR 0.12 (95% CrI 0.03 to 0.41; 1 trial; 58 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 and the 'between-design' variance. However, there was evidence of inconsistency in one loop (made up of the three-way comparison between beta-blockers, portocaval shunt, and sclerotherapy in the inconsistency factor plot. The random-effects model was used because it was more conservative and had better model fit. The 'between-study variance' was 5.06 (95% CrI 0.30 to 22.71).

In the network meta-analysis, there was no evidence of differences in any of the comparisons (very low-certainty evidence). After excluding the trials including portocaval shunt as one of their treatments (to assess whether the inconsistency in the inconsistency factor plot was due to the loop between beta-blockers, portocaval shunt, and sclerotherapy), the network meta-analysis results did not change. We could not obtain an inconsistency factor plot since there was only study in each closed loop after the exclusion of the trials including portocaval shunt as one of their treatments.

Any variceal rebleed

Twenty-two trials (1676 participants) reported any variceal rebleed (Ampelas 1987; Alexandrino 1988; Fleig 1988; Bonkovsky 1989; Jensen 1989; Lundell 1990; Martin 1991; Rossi 1991; Dasarathy 1992; Dwivedi 1992; Ink 1992; Vinel 1992; Avgerinos 1993; Anonymous 1994; Mckee 1994; Cabrera 1996; Sauer 1997; Garcia-Villarreal 1999; Viazis 2002; Romero 2006; Kong 2015; Kumar 2015). A total of nine treatments were compared in these trials. There were 692 events in total (40.4%). The median control group proportion was 47.3%.

Direct comparisons

In the following direct comparisons, the first intervention had lower any variceal rebleed than the second intervention.

- Beta-blockers plus sclerotherapy versus beta-blockers: HR 0.36 (95% CrI 0.18 to 0.70); 1 trial; 131 participants; low-certainty evidence
- Portocaval shunt versus beta-blockers: HR 0.13 (95% CrI 0.03 to 0.37); 1 trial; 50 participants; low-certainty evidence
- TIPS versus beta-blockers plus sclerotherapy: HR 0.20 (95% CrI 0.07 to 0.49); 1 trial; 83 participants; low-certainty evidence

Beta-blockers had higher any variceal rebleed than sclerotherapy: HR 1.68 (95% CrI 1.06 to 2.83); 6 trials; 420 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 plot, and the 'between-design' variance. The random-effects model was used because it was more conservative than the fixed-effect model, even though the model fit was similar as fixed-effect model. The 'between-study variance' was 0.09 (95% CrI 0.00 to 0.48).

In the network meta-analysis, in the following pairwise comparisons, the first intervention had lower any variceal rebleed than the second intervention.

- Sclerotherapy versus no active intervention: HR: 0.62 (95% CrI 0.35 to 0.99); direct comparison HR 0.66 (95% CrI 0.11 to 3.13) 3 trials; 296 participants; moderate-certainty evidence
- Beta-blockers plus sclerotherapy versus sclerotherapy: HR 0.60 (95% CrI 0.37 to 0.95); direct comparison HR 0.50 (95% CrI 0.07 to 2.96); 4 trials; 231 participants; moderate-certainty evidence
- TIPS versus sclerotherapy: HR 0.18 (95% CrI 0.08 to 0.38); direct comparison HR 0.22 (95% CrI 0.01 to 7.51); 2 trials; 109 participants; moderate-certainty evidence
- Portocaval shunt versus sclerotherapy: HR 0.21 (95% CrI 0.05 to 0.77); no direct comparison; moderate-certainty evidence
- Beta-blockers plus sclerotherapy versus beta-blockers: HR 0.37 (95% CrI 0.21 to 0.62); direct comparison HR 0.36 (95% CrI 0.18 to 0.70); 1 trial; 131 participants; moderate-certainty evidence
- TIPS versus beta-blockers: HR 0.11 (95% CrI 0.05 to 0.25); no direct comparison; moderate-certainty evidence
- Portocaval shunt versus beta-blockers: HR 0.13 (95% CrI 0.03 to 0.45); direct comparison HR 0.13 (95% CrI 0.03 to 0.37); 1 trial; 50 participants; moderate-certainty evidence
- Beta-blockers plus sclerotherapy versus variceal band ligation: HR 0.37 (95% CrI 0.14 to 0.91); no direct comparison; moderate-certainty evidence
- Beta-blockers plus sclerotherapy versus no active intervention: HR 0.37 (95% CrI 0.17 to 0.70); no direct comparison; moderate-certainty evidence
- TIPS versus variceal band ligation: HR 0.11 (95% CrI 0.04 to 0.33); no direct comparison; moderate-certainty evidence
- Portocaval shunt versus variceal band ligation: HR 0.13 (95% CrI 0.02 to 0.57); no direct comparison; moderate-certainty evidence
- TIPS versus beta-blockers plus sclerotherapy: HR 0.31 (95% CrI 0.14 to 0.65); direct comparison HR 0.20 (95% CrI 0.07 to 0.49); 1 trial; 83 participants; moderate-certainty evidence
- TIPS versus no active intervention: HR 0.11 (95% CrI 0.04 to 0.27); no direct comparison; moderate-certainty evidence
- Portocaval shunt versus no active intervention: HR 0.13 (95% CrI 0.03 to 0.50); no direct comparison; moderate-certainty evidence
- Portocaval shunt versus beta-blockers plus nitrates: HR 0.10 (95% CrI 0.02 to 0.47); no direct comparison; moderate-certainty evidence

In the network meta-analysis, in the following pairwise comparisons, the first intervention had higher any variceal rebleed than the second intervention.

- Beta-blockers versus sclerotherapy: HR 1.62 (95% CrI 1.14 to 2.38); direct comparison HR 1.68 (95% CrI 1.06 to 2.83); 6 trials; 420 participants; moderate-certainty evidence
- Beta-blockers plus nitrates versus beta-blockers plus sclerotherapy: HR 3.54 (95% CrI 1.23 to 10.82); no direct comparison; moderate-certainty evidence
- Beta-blockers plus nitrates versus TIPS: HR 11.57 (95% CrI 3.43 to 41.93); no direct comparison; moderate-certainty evidence
- Sclerotherapy plus variceal band ligation versus TIPS: HR 9.98 (95% CrI 2.11 to 50.00); no direct comparison; moderate-certainty evidence
- Sclerotherapy plus variceal band ligation versus portocaval shunt: HR 8.88 (95% CrI 1.37 to 63.43); no direct comparison; moderate-certainty evidence

There was no evidence of differences between the treatments in the remaining comparisons in the network meta-analysis (low-certainty evidence).

Other features of decompensation

Eight trials (416 participants) reported other features of decompensation (Alexandrino 1988; Jensen 1989; Sheen 1989; Cabrera 1996; Jalan 1997; Sauer 1997; Cennamo 1998; Garcia-Villarreal 1999). A total of seven treatments were compared in these trials. There were 123 events in total (0.3 events per participant). The decompensation events included liver failure, hepatic encephalopathy, and spontaneous bacterial peritonitis (secondary to ascites). The median control event rate was 0.292 events per participant.

Direct comparisons

In the following direct comparisons, the first intervention had lower other features of decompensation than the second intervention.

- Beta-blockers versus sclerotherapy: rate ratio 2.37 (95% CrI 1.35 to 4.67); 1 trial; 65 participants; low-certainty evidence
- TIPS versus sclerotherapy: rate ratio 2.30 (95% CrI 1.20 to 4.65); 2 trials; 109 participants; low-certainty evidence
- TIPS versus beta-blockers plus sclerotherapy: rate ratio 4.79 (95% CrI 1.53 to 18.82); 1 trial; 83 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

Two trials were not connected to the network because they were the only trials for the comparison and had zero-events in one of the arms (Jensen 1989; Sheen 1989). The network had six connected treatments. There were no triangular or quadrangular loops; therefore, inconsistency was not checked. The fixed-effect model was used because it had equivalent results and model fit as random-effects model.

- Beta-blockers plus sclerotherapy had lower other features of decompensation than beta-blockers: rate ratio 0.18 (95% CrI 0.03 to 0.82); no direct comparison; low-certainty evidence

In the network meta-analysis, in the following pairwise comparisons, the first intervention had higher other features of decompensation than the second intervention.

- Beta-blockers versus sclerotherapy: rate ratio 2.40 (95% CrI 1.35 to 4.55); direct comparison rate ratio 2.37 (95% CrI 1.35 to 4.67); 1 trial; 65 participants; low-certainty evidence
- TIPS versus sclerotherapy: rate ratio 2.27 (95% CrI 1.19 to 4.59); direct comparison rate ratio 2.30 (95% CrI 1.20 to 4.65); 2 trials; 109 participants; low-certainty evidence
- TIPS versus beta-blockers plus sclerotherapy: rate ratio 5.01 (95% CrI 1.57 to 23.45); direct comparison rate ratio 4.79 (95% CrI 1.53 to 18.82); 1 trial; 83 participants; low-certainty evidence

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

Exploratory outcomes

Length of hospital stay

Six trials (413 participants) reported length of hospital stay for all admissions until maximal follow-up) (Kanazawa 1991; Isaksson 1995; Cabrera 1996; Jalan 1997; Garcia-Villarreal 1999; García-Pagán 2009). The median control group mean was 29.9 days per participant. A total of seven treatments were compared in these trials.

Direct comparisons

There was no evidence of difference in any of the direct comparisons (i.e. there was no statistically significant difference in any of the comparisons) as shown in Table 4. There was no evidence of difference in the remaining comparison not connected to the network: beta-blockers plus nitrates plus variceal band ligation versus beta-blockers plus nitrates (mean difference (MD) 1.01 days (95% CrI -4.77 to 6.64)).

Network meta-analysis

One trial was not connected to the network because it had treatments unconnected to network (García-Pagán 2009). The network had five connected treatments. There were no triangular or quadrangular loops; therefore, inconsistency was not checked. The fixed-effect model was used because it had equivalent results and model fit as random-effects model.

In the network meta-analysis, beta-blockers plus sclerotherapy had shorter length of hospital stay than variceal band ligation: MD -20.19 days (95% CrI -36.57 to -3.92); no direct evidence.

There was no evidence of differences between the treatments in the remaining comparisons in the network meta-analysis. In the sensitivity analysis of excluding the two trials in which the standard deviation was imputed, there was no evidence of difference in any of the direct comparisons or network meta-analysis.

Work days lost

None of the trials reported work days lost.

Treatment costs

Two trials (103 participants) reported treatment costs (Isaksson 1995; Jalan 1997). A total of four treatments were compared in these

trials. One trial reported treatment costs in USD (Isaksson 1995). One trial reported treatment costs in pound sterling (Jalan 1997). 'Pound sterling' was converted to USD using Purchasing Power Parities and the conversion rates on 10 March 2020). None of the trials reported information to calculate the standard deviation.

The mean treatment costs reported in the trials were as follows.

- Portocaval shunt (USD 12049) versus sclerotherapy (USD 12027) (Isaksson 1995)
- TIPS (USD 9958) versus variceal band ligation (USD 11894) in the two trials (Jalan 1997).

Subgroup analysis

We did not perform any subgroup analysis. This is because none of the trials were at low risk of bias, there were no separate outcome 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.

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 plus nitrates versus beta-blockers:
  - main analysis: no evidence of difference between groups
  - worst-best analysis: no evidence of difference between groups
  - best-worst analysis: lower in sclerotherapy plus nitrates than beta-blockers
- Sclerotherapy plus nitrates versus variceal band ligation:
  - main analysis: lower in sclerotherapy plus nitrates than variceal band ligation
  - worst-best analysis: no evidence of difference between groups
  - best-worst analysis: lower in sclerotherapy plus nitrates than variceal band ligation
- No active intervention versus beta-blockers plus sclerotherapy:
  - main analysis: no evidence of difference between groups
  - worst-best analysis: higher in no active intervention than beta-blockers plus sclerotherapy
  - best-worst analysis: no evidence of difference between groups
- Sclerotherapy plus nitrates versus TIPS:
  - main analysis: no evidence of difference between groups
  - worst-best analysis: no evidence of difference between groups
  - best-worst analysis: lower in sclerotherapy plus nitrates than TIPS

Any variceal rebleed

- No active intervention versus sclerotherapy:
  - main analysis: higher in no active intervention than sclerotherapy
  - worst-best analysis: no evidence of difference between groups
  - best-worst analysis: higher in no active intervention than sclerotherapy

Therefore, these results should be interpreted with caution, as they are susceptible to attrition bias resulting from post-randomisation dropouts. There were no changes to interpretation of the results for the remaining analyses or outcomes. These outcomes and comparisons are therefore robust to post-randomisation dropouts.

Imputation of standard deviation

We did not perform any imputation of standard deviation.

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 the time, we performed the following analyses: baseline risk-adjusted network meta-analyses for mortality and any variceal rebleed, the two outcomes reported by most trials and the outcomes that determine whether an outcomes should be used. We also analysed a subset of trials published from 2000 year onwards because of the potential changes in baseline risk.

Since we could not explain the reason for the recommendations of the major gastroenterological associations in recommending combination of beta-blockers plus variceal band ligation over beta-blockers plus endoscopic sclerotherapy (for which there is moderate-certainty evidence that there is a decrease in 'any variceal bleed' by using a combination of beta-blockers plus sclerotherapy versus sclerotherapy alone or beta-blockers alone and low-certainty evidence that there is a decrease in 'any variceal rebleed' by using a combination of beta-blockers plus sclerotherapy versus variceal band ligation alone), we explored whether we could establish that there is no difference in effect when endoscopic sclerotherapy or variceal band ligation are added to beta-blockers. The answer for this question can be explored by a component network meta-analysis approach where it is possible to assess the contribution of adding a second treatment (in this case, endoscopic sclerotherapy or variceal band ligation) to an already existing treatment (in this case, beta-blockers) ('main effects') and assess the interaction between the additional treatment and the existing treatment ('interaction effects') (Welton 2009; Freeman 2018). However, this requires that there is at least one trial that compares beta-blockers plus variceal band ligation with either beta-blockers plus sclerotherapy or beta-blockers alone to be included in the network. In the absence of any such trials, we were unable to establish that there is no difference in effect when endoscopic sclerotherapy is replaced by variceal band ligation when used in combination with beta-blockers.

Baseline-risk adjusted analysis

We could not obtain convergence for the baseline-risk adjusted model for either mortality or any variceal rebleed.

Subset of trials published from the year 2000 onwards

Mortality

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

Any variceal bleed

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

DISCUSSION

Summary of main results

We performed a systematic review and network meta-analysis of the common treatments used for secondary prevention of oesophageal variceal bleeding in people with oesophageal varices due to liver cirrhosis. A total of 48 trials, including a total of 3526 participants, were included in this review. A total of 12 interventions were compared in these trials. A total of 46 trials including 3442 participants were included for one or more comparisons of this review (Westaby 1985a; Ampelas 1987; Bader 1987; Alexandrino 1988; Fleig 1988; Bonkovsky 1989; Jensen 1989; Parelon 1989; Sheen 1989; Bertoni 1990; Fornaciari 1990; Henderson 1990; Lundell 1990; Andreani 1991; Kanazawa 1991; Martin 1991; Rossi 1991; Dasarathy 1992; Dwivedi 1992; Ink 1992; Vinel 1992; Avgerinos 1993; Jiron 1993; Anonymous 1994; Bertoni 1994; Mckee 1994; Villanueva 1994; Isaksson 1995; Cabrera 1996; Urbistondo 1996; Avgerinos 1997; Baroncini 1997; Jalan 1997; Masliah 1997; Sanyal 1997; Sauer 1997; Cennamo 1998; Garcia-Villarreal 1999; Argonz 2000; Sauer 2002; Viazis 2002; Romero 2006; Ahmad 2009; García-Pagán 2009; Kong 2015; Kumar 2015).

Overall, 22.5% of the trial participants who received endoscopic sclerotherapy died during the follow-up period, ranging from two months to 61 months. Based on moderate-certainty evidence, sclerotherapy plus nitrates had lower mortality than sclerotherapy (HR 0.19; 95% CrI 0.02 to 0.86; direct comparison HR 0.18; 95% CrI 0.02 to 0.78; 1 trial; 76 participants), and sclerotherapy plus nitrates had lower mortality than variceal band ligation (HR 0.19; 95% CrI 0.02 to 0.97; no direct comparison), no active intervention (HR 0.15; 95% CrI 0.02 to 0.75; no direct comparison), and portocaval shunt (HR 0.15; 95% CrI 0.02 to 0.79; no direct comparison). However, this is driven by the results of one small trial at high risk of bias, which have not been reproduced because this was the only trial on the comparison. While there is guidance to downgrade evidence when there is heterogeneity between results (Guyatt 2011b), this assessment needs a minimum of two trials. There was no evidence of heterogeneity in the network meta-analysis. The results were robust to the exclusion of the loop which caused inconsistency. Therefore, the evidence was not downgraded for incongruence. While we followed the GRADE methodology and arrived at moderate-certainty evidence, we consider that there is considerable uncertainty to conclude about the effectiveness of sclerotherapy plus nitrates compared to sclerotherapy on mortality, driven by the effect estimates of a single small trial at high risk of bias.

None of the trials reported health-related quality of life. Based on low-certainty evidence, serious events (number of participants) were lower in variceal band ligation than in sclerotherapy (OR 0.19; 95% CrI 0.06 to 0.54; direct comparison; 1 trial; 100 participants) and more in beta-blockers plus sclerotherapy than in beta-blockers (OR 2.75; 95% CrI 1.18 to 6.82; direct comparison; 1 trial; 131 participants).

Based on low-certainty evidence, the adverse events (number of participants) were different across many comparisons; however, these differences are due to very small trials at high risk of bias showing large differences in some comparisons leading to many differences despite absence of direct evidence. Similarly, based on low-certainty evidence, the adverse events (number of events) were different across many comparisons; however, these differences are due to very small trials at high risk of bias showing large differences in some comparisons leading to many differences despite absence of direct evidence.

Based on low-certainty evidence, symptomatic variceal rebleed was lower in TIPS than in variceal band ligation (HR 0.12; 95% CrI 0.03 to 0.41; 1 trial; 58 participants).

Based on moderate-certainty evidence, any variceal rebleed was lower in sclerotherapy than in no active intervention (HR 0.62; 95% CrI 0.35 to 0.99; direct comparison HR 0.66; 95% CrI 0.11 to 3.13; 3 trials; 296 participants), beta-blockers plus sclerotherapy than sclerotherapy (HR 0.60; 95% CrI 0.37 to 0.95; direct comparison HR 0.50; 95% CrI 0.07 to 2.96; 4 trials; 231 participants), TIPS than sclerotherapy (HR 0.18; 95% CrI 0.08 to 0.38; direct comparison HR 0.22; 95% CrI 0.01 to 7.51; 2 trials; 109 participants), portocaval shunt than in sclerotherapy (HR 0.21; 95% CrI 0.05 to 0.77); no direct comparison), beta-blockers plus sclerotherapy than beta-blockers (HR 0.37; 95% CrI 0.21 to 0.62; direct comparison HR 0.36; 95% CrI 0.18 to 0.70; 1 trial; 131 participants), TIPS than beta-blockers (HR 0.11; 95% CrI 0.05 to 0.25; no direct comparison), portocaval shunt than beta-blockers (HR 0.13; 95% CrI 0.03 to 0.45; direct comparison HR 0.13; 95% CrI 0.03 to 0.37; 1 trial; 50 participants), TIPS than variceal band ligation (HR 0.11; 95% CrI 0.04 to 0.33; no direct comparison), TIPS than no active intervention (HR 0.11; 95% CrI 0.04 to 0.27; no direct comparison), beta-blockers plus sclerotherapy than variceal band ligation (0.37; 95% CrI 0.14 to 0.91; no direct comparison), TIPS versus beta-blockers plus sclerotherapy (HR 0.31; 95% CrI 0.14 to 0.65; direct comparison HR 0.20; 95% CrI 0.07 to 0.49; 1 trial; 83 participants), beta-blockers plus sclerotherapy than no active intervention (0.37; 95% CrI 0.17 to 0.70; no direct comparison), portocaval shunt than variceal band ligation (HR 0.13; 95% CrI 0.02 to 0.57; no direct comparison), portocaval shunt than no active intervention (HR 0.13; 95% CrI 0.03 to 0.50; no direct comparison), and portocaval shunt than beta-blockers plus nitrates (HR 0.10; 95% CrI 0.02 to 0.47; no direct comparison). Based on moderate-certainty evidence, any variceal rebleed was higher in beta-blockers plus nitrates than beta-blockers plus sclerotherapy (HR 3.54; 95% CrI 1.23 to 10.82; no direct comparison), beta-blockers plus nitrates than TIPS (HR 11.57; 95% CrI 3.43 to 41.93; no direct comparison), sclerotherapy plus variceal band ligation than TIPS (HR 9.98; 95% CrI 2.11 to 50.00; no direct comparison), and sclerotherapy plus variceal band ligation than portocaval shunt (HR 8.88; 95% CrI 1.37 to 63.43; no direct comparison).

Overall, the key information is that there is no evidence of difference in 'any' oesophageal variceal rebleed between variceal band ligation and sclerotherapy, nor was there any trial comparing 'any' variceal rebleed between beta-blockers plus variceal band

ligation versus sclerotherapy or variceal band ligation. The only trial in which there was a difference in mortality (sclerotherapy plus nitrates had lower mortality than sclerotherapy (HR 0.18; 95% CrI 0.02 to 0.78; 1 trial; 76 participants)) did not report 'any' oesophageal variceal rebleed (Bertoni 1994).

Based on very low-certainty evidence, other features of decompensation were lower in beta-blockers plus sclerotherapy than beta-blockers (rate ratio 0.18; 95% CrI 0.03 to 0.82; no direct comparison). Based on very low-certainty evidence, other features of decompensation were higher in beta-blockers than sclerotherapy (rate ratio 2.40; 95% CrI 1.35 to 4.55; direct comparison: rate ratio 2.37; 95% CrI 1.35 to 4.67; 1 trial; 65 participants), TIPS than sclerotherapy (rate ratio 2.27; 95% CrI 1.19 to 4.59; direct comparison: rate ratio 2.30; 95% CrI 1.20 to 4.65; 2 trials; 109 participants), and TIPS than beta-blockers plus sclerotherapy (rate ratio 5.01; 95% CrI 1.57 to 23.45; direct comparison rate ratio 4.79; 95% CrI 1.53 to 18.82; 1 trial; 83 participants). Hepatic encephalopathy events were the major other decompensation events in the TIPS group.

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

The weighted median mortality in the sclerotherapy was 22.5% up to about 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% is 2402 participants. The prevalence of oesophageal varices varies between 40% and 95% in people with cirrhosis (Chawla 2012; McCarty 2017). Approximately 15% to 20% of people with oesophageal varices bleed in about one to three years (Gluud 2012; Qi 2015; Roccarina 2020). Therefore, it is very much possible to power studies in this population based on mortality.

In terms of population, it is probably better to perform different trials in people with oesophageal variceal bleeding based on other features of decompensation: one trial in people with ascites but without history of hepatic encephalopathy, and another in those without ascites. This is because the interventions to be compared are likely to be different in these two groups of patients. In people with history of oesophageal variceal bleeding and ascites, but without a history of encephalopathy, TIPS can be considered the intervention. This is because TIPS may decrease rebleeding (as shown by the above summary) and may increase the resolution of ascites compared to paracentesis plus fluid replacement (Benmassaoud 2020), but may increase hepatic encephalopathy as shown by this review and supported by other studies (Saab 2006; Zhou 2019). The control group in such a trial should ideally be beta-blockers plus sclerotherapy on which plenty of trials have been conducted. But considering that it may be difficult to conduct such a trial, use of variceal band ligation as control group is probably also acceptable. The use of beta-blockers in ascites is controversial (Njei 2016). Therefore, probably the most acceptable control group is endoscopic treatment alone.

In people without ascites, the interventions to be compared can be beta-blockers plus sclerotherapy, variceal band ligation alone, and beta-blockers plus variceal band ligation as most of the evidence on the effectiveness of treatment in preventing rebleeding relates to beta-blockers plus sclerotherapy, while the variceal band ligation is associated with fewer adverse events with the potential to give equivalent results as sclerotherapy. TIPS is another option as an intervention in people without hepatic encephalopathy.

Among the ongoing trials that address the above comparisons, NCT00966082 compares variceal band ligation plus beta-blockers versus variceal band ligation with an estimated recruitment target of 180 participants; NCT02477384 compares TIPS versus variceal band ligation plus beta-blockers. The estimated recruitment target for this trial is 72 participants. These numbers seem too low. Therefore, further randomised clinical trials are necessary.

Future trials should assess the health-related quality of life as this is an outcome that is considered as important by patients.

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 with a previous 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 other causes of portal hypertension such as portal vein thrombosis or schistosomiasis. The review is also not applicable in people who undergo liver transplantation. We did not find any trials comparing liver transplantation with one of these treatments; therefore, the review does provide any information about comparison of any of these treatments with liver transplantation.

Quality of the evidence

The overall certainty of evidence varied between moderate, low, or very low. One of the main reasons for this was the unclear or high risk of bias in all the trials. 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 or TIPS are used as one of the interventions. However, 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 use of placebo (in pharmacological intervention trials) 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 numbers of events, none of the direct comparisons had adequate sample size. As a result, the credible intervals 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, 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 90% of trials reported mortality, only around 10% of trials reported serious adverse events adequately; only around 50% of trials reported variceal rebleed adequately; and only around 15% of trials described other decompensation events. These are outcomes which would 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 network meta-analysis according to NICE DSU (National Institute for Health and Care Excellence Decision Support Unit) guidance. In addition, we have 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 have excluded studies that compared variations in duration or dose in the different interventions. Hence, this review does not provide information on whether one variation is better than another.

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. There were sparse events for some interventions for adverse events resulting in very wide credible intervals. Therefore, direct comparisons are more reliable for these comparisons.

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 the most outcomes where we could assess this. Therefore, the concern about the transitivity assumption is 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 on harm. 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 attempted a post hoc analysis adjusting for baseline risk, which did not converge and performed an analysis including only trials published from 2000 onwards, which showed no evidence that any of the interventions was better than other interventions .

Agreements and disagreements with other studies or reviews

This is the first network meta-analysis on different secondary prevention interventions as first-line therapy in people with a previous history of oesophageal variceal bleeding. Our inclusion criteria are different from the other recent systematic reviews on secondary prevention treatments (Brand 2018; Dwinata 2019). In both systematic reviews, there was no restriction based on the previous site of variceal bleeding (Brand 2018; Dwinata 2019), while we restricted to previous history of oesophageal varices. In addition, the participants were refractory to endoscopic therapy in most trials (Brand 2018). Therefore, our conclusions differ from these reviews.

We found no evidence to support the recommendations of the major associations including AASLD (American Association for the Study of Liver Diseases), Baveno Consensus Workshop, BSG (British Society of Gastroenterology), EASL (European Association for the Study of the Liver) to use beta-blockers plus variceal band ligation for secondary prevention of bleeding from oesophageal varices (de Franchis 2015; Tripathi 2015; Garcia-Tsao 2017; EASL 2018). Moderate- or low-certainty evidence in our review suggested that serious adverse events (number of participants) was lower in variceal band ligation than sclerotherapy, but there is considerable uncertainty in the results of the effectiveness of these treatments compared to endoscopic sclerotherapy.

To find out if variceal band ligation might have been considered to be equivalent to sclerotherapy despite the lack of power to rule out differences in effect between them, we performed a component network meta-analysis. Our attempt at component network meta-analysis also demonstrates that it is not possible to establish that there is no difference in effect when endoscopic sclerotherapy is replaced by variceal band ligation when used in combination with beta-blockers using currently available information. Therefore, the reasons for the differences between our systematic review and clinical practice guidelines can be speculative at best, and we have avoided such speculations.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence indicates considerable uncertainty about the effects of the interventions on mortality. Variceal band ligation might result in fewer serious adverse events than sclerotherapy. Transjugular intrahepatic portosystemic shunt (TIPS) might result in a large decrease in symptomatic rebleed than variceal band ligation. Sclerotherapy probably results in fewer 'any' variceal rebleeding than no active intervention. Beta-blockers plus sclerotherapy and TIPS probably result in fewer 'any' variceal rebleeding than sclerotherapy. Beta-blockers alone and TIPS may result in more other compensation events than sclerotherapy. The evidence indicates considerable uncertainty about the effect of the interventions in the remaining comparisons.

Implications for research

Further well-designed randomised clinical trials are necessary. Some aspects of the design of the randomised clinical trials are as follows.

Study design

Parallel, randomised clinical trial.

Participants
People with liver cirrhosis and history of bleeding from oesophageal varices.

Interventions/control

In those with ascites and no hepatic encephalopathy: TIPS versus sclerotherapy or variceal band ligation

In those without ascites: beta-blockers plus sclerotherapy, variceal band ligation alone, and beta-blockers plus variceal band ligation. TIPS can also be considered in those without hepatic encephalopathy.

Outcomes

Primary outcome: mortality.

Secondary outcomes: health-related quality of life, rebleeding, decompensation events, adverse events, transfusion requirements, and resource utilisation measures including length of hospital stay, costs.

Minimum length of follow-up: three years.

Sample size

For a simple two-arm parallel randomised clinical trial, the sample size required to detect or reject a relative risk reduction of 20% in the experimental group from the control group proportion of 22,5% mortality, with type I error of 5%, and type II error of 20%, 2402 participants are required.

Other aspects

Trials need to be conducted and reported according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement (Chan 2013) and CONSORT statement (Schulz 2010).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Ahmad 2009

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Pakistan Period of recruitment: 2003-2005 Number randomised: 160 Post-randomisation dropouts: 10 (6.3%) Revised sample size: 150 Reasons for post-randomisation dropouts: intolerance to drug (8), lost to follow-up (2) Average age (years): 52 Females: 49 (32.7%) Other features of decompensation: 30 (20.0%) Alcohol-related cirrhosis: 1 (0.7%) Viral-related cirrhosis: 149 (99.3%) Autoimmune disease-related cirrhosis: 0 (0.0%) Other causes for cirrhosis: 0 (0.0%) Other inclusion/exclusion criteria: Exclusion: previous endoscopic or drug therapy; any contraindication to either treatment; bleeding gastric varices or gastropathy; advanced hepatocellular carcinoma, acute on chronic liver disease or any other debilitating disease
Interventions	Group 1: beta-blockers plus nitrates plus variceal band ligation (n = 37) Further details: propranolol: 10 mg three times a day increased over one week (duration not stated) plus isosorbide mononitrate 10 mg twice daily increasing over one week to 20 mg (duration not stated) plus variceal band ligation (Saeed Sixshooter every 3 weeks until eradication) Group 2: beta-blockers plus nitrates (n = 35) Further details: propranolol: 10 mg three times a day increased over one week (duration not stated) plus isosorbide mononitrate 10 mg twice daily increasing over one week to 20 mg (duration not stated) Group 3: variceal band ligation (n = 39) Further details: variceal band ligation (Saeed Sixshooter every 3 weeks until eradication)

Ahmad 2009 *(Continued)*

	Group 4: beta-blockers (n = 39) Further details: propranolol: 10 mg three times daily increased over one week (duration not stated)
Outcomes	Outcomes reported: mortality at maximal follow-up, variceal rebleed at maximal follow-up (symptomatic recovery) (number of patients) Follow-up (months): 9
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned to one of the four treatment groups, using opaque, sealed envelopes, that contained a treatment assignment derived from computer-generated random numbers"
Allocation concealment (selection bias)	Low risk	Quote: "randomly assigned to one of the four treatment groups, using opaque, sealed envelopes, that contained a treatment assignment derived from computer-generated random numbers"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts which were related to the intervention and probably related to the outcome
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available and adverse events were not reported
Other bias	Low risk	Comment: no other bias noted

Alexandrino 1988

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Portugal Period of recruitment: not stated Number randomised: 65 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 65 Average age (years): 47 Females: 16 (24.6%) Other features of decompensation: not stated Alcohol-related cirrhosis: 52 (80.0%) Viral-related cirrhosis: not stated

Alexandrino 1988 *(Continued)*

	Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: 13 (20.0%) Other inclusion/exclusion criteria: not stated
Interventions	Group 1: beta-blockers (n = 34) Further details: propranolol: reduction of pulse rate by 25%, duration not stated but probably until the follow-up period (29 months) Group 2: sclerotherapy (n = 31) Further details: sclerotherapy: ethanolamine oleate every 3 weeks until obliteration
Outcomes	Outcomes reported: variceal rebleed at maximal follow-up (any) (number of patients), other features of decompensation at maximal follow-up Follow-up (months): 29
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was done by a list of random numbers allocated to sealed envelopes in two separate groups for Child's A and B patients:" Comment: further details how the random sequence was not provided
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomization was done by a list of random numbers allocated to sealed envelopes in two separate groups for Child's A and B patients:" Comment: further information was not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available and mortality and adverse events were not reported
Other bias	Low risk	Comment: no other bias noted

Ampelas 1987

Study characteristics

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

Ampelas 1987 *(Continued)*

	Number randomised: 50 Post-randomisation dropouts: not stated Revised sample size: 50 Average age (years): not stated Females: 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 for cirrhosis: not stated Other inclusion/exclusion criteria: Exclusion: age >80 years, contraindications to beta-blocker
Interventions	Group 1: portocaval shunt (n = 24) Further details: azygo-portal disconnection Group 2: beta-blockers (n = 26) Further details: propranolol: reduce heart rate by 25% (duration not reported)
Outcomes	Outcomes reported: mortality at maximal follow-up, variceal rebleed at maximal follow-up (any) (number of patients) Follow-up (months): 18
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias

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

Andreani 1991

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: France Period of recruitment: 1985-1988 Number randomised: 75 Post-randomisation dropouts: not stated Revised sample size: 75 Average age (years): not stated Females: 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 for cirrhosis: not stated Other inclusion/exclusion criteria: Exclusion: previous treatment of portal hypertension (not specified), contraindications to beta-blocker
Interventions	Group 1: beta-blockers (n = 35) Further details: propranolol: reduction of pulse rate by 25%, duration not stated but probably until the follow-up period (29 months) Group 2: sclerotherapy (n = 40) Further details: sclerotherapy: polidocanol (no further details)
Outcomes	Outcomes reported: mortality at maximal follow-up Follow-up (months): 12
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available and mortality and adverse events were not reported

Andreani 1991 *(Continued)*

Other bias	Low risk	Comment: no other bias noted

Anonymous 1994

Study characteristics

Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: 1985-1989 Number randomised: 204 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 204 Average age (years): not stated Females: 0 (0.0%) Other features of decompensation: not stated Alcohol-related cirrhosis: 204 (100.0%) Viral-related cirrhosis: 0 (0.0%) Autoimmune disease-related cirrhosis: 0 (0.0%) Other causes for cirrhosis: 0 (0.0%) Other inclusion/exclusion criteria: Exclusion: inability to give informed consent, contraindications to upper endoscopy, a positive test for Hepatitis B surface antigen in serum, a history of sclerotherapy or shunt surgery for varices, oesophageal or gastric malignancy, myocardial infarction within the past 6 months, need for p-adrenergic antagonist drug therapy, current bleeding from source other than oesophageal varices or a decision by the treating physician to exclude the patient
Interventions	Group 1: no active intervention (n = 107) Further details: placebo Group 2: sclerotherapy (n = 97) Further details: sclerotherapy: not stated; 0.5 to 2 mL, maximum of 20 mL per session
Outcomes	Outcomes reported: mortality at maximal follow-up, variceal rebleed at maximal follow-up (any) (number of patients) Follow-up (months): 12
Notes	Source of funding (quote): "Funded by the VA cooperative study branch (author responses)" Trial name/trial registry number: THE VETERANS AFFAIRS COOPERATIVE VARICEAL SCLEROTHERAPY GROUP Attempts were made to contact the authors in February 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was carried out using sealed envelopes prepared centrally " Comment: details on how the sequence generation was generated was not reported
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomization was carried out using sealed envelopes prepared centrally " Comment: further details were not available

Anonymous 1994 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Only the endoscopists were aware of patients' treatment assignment; all other caregivers, and the patients as well, remained blinded" Comment: the healthcare professionals providing the care to the participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Only the endoscopists were aware of patients' treatment assignment; all other caregivers, and the patients as well, remained blinded" Comment: the healthcare professionals who provided the care to the participants were outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available and adverse events were not reported
Other bias	Low risk	Comment: no other bias noted

Argonz 2000

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Argentina Period of recruitment: 1994-1997 Number randomised: 80 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 80 Average age (years): 53 Females: 18 (22.5%) Other features of decompensation: 28 (35.0%) Alcohol-related cirrhosis: 46 (57.5%) Viral-related cirrhosis: 20 (25.0%) Autoimmune disease-related cirrhosis: 11 (13.8%) Other causes for cirrhosis: 5 (6.3%) Other inclusion/exclusion criteria: Exclusion criteria were 1) portal vein thrombosis 2) fundal gastric varices 3) hepatocellular carcinoma or any other malignant tumour 4) more than one sclerotherapy or variceal band ligation procedure after control of acute variceal bleeding
Interventions	Group 1: sclerotherapy plus variceal band ligation (n = 39) Further details: sclerotherapy: 2% 1 mL polidocanol up to 10 mL plus variceal band ligation (bard interventional products) up to 10 bands 1 to 2 weeks until eradication of varices Group 2: variceal band ligation (n = 41) Further details: variceal band ligation (bard interventional products) up to 10 bands 1 to 2 weeks until eradication of varices
Outcomes	Outcomes reported: mortality at maximal follow-up, any adverse events (number of people), variceal rebleed at maximal follow-up (symptomatic recovery) (number of patients) Follow-up (months): 12

Argonz 2000 *(Continued)*

Notes	Source of funding (quote): "Supported in part by a grant from Fundacion Argentina para el Estudio de la Enfermedades del Higado (FUNDHIG)" Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020 Individual patients had multiple cirrhosis aetiologies

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The assignment was determined by means of a table of random numbers"
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was carried out utilizing consecutively numbered, sealed opaque envelopes containing the treatment assignment"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all participants were included in the analysis
Selective reporting (reporting bias)	Low risk	Comment: no prepublished protocol was available, but the authors reported mortality, adverse events, and variceal rebleeding
Other bias	Low risk	Comment: no other bias noted

Avgerinos 1993

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Greece Period of recruitment: 1986-1989 Number randomised: 85 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 85 Average age (years): 58 Females: 24 (28.2%) Other features of decompensation: not stated Alcohol-related cirrhosis: 22 (25.9%) Viral-related cirrhosis: 43 (50.6%) Autoimmune disease-related cirrhosis: 5 (5.9%) Other causes for cirrhosis: 15 (17.6%) Other inclusion/exclusion criteria: Inclusion: 1) initial control of haemorrhage 2) no history of previous variceal bleeding 3) absence of hepatocellular carcinoma 4) no contraindication to propanolol such as airway obstruction, left ventricu-

Avgerinos 1993 *(Continued)*

	lar failure or diabetes mellitus (type I) 5) no history of previous treatment for portal hypertension 6) absence of severe liver disease defined by the presence of coma, intractable ascites, or severe hyperbilirubinaemia (>85 mmol/L)
Interventions	Group 1: beta-blockers plus sclerotherapy (n = 45) Further details: propranolol to decrease the heart rate by 25% plus sclerotherapy: 5% ethanolamine oleate, maximum 20 mL per session at weekly intervals, until varices became too small to inject Group 2: sclerotherapy (n = 40) Further details: sclerotherapy: 5% ethanolamine oleate, maximum 20 mL per session at weekly intervals, until varices became too small to inject
Outcomes	Outcomes reported: mortality at maximal follow-up, any adverse events (number of events), variceal rebleed at maximal follow-up (any) (number of patients), variceal rebleed at maximal follow-up (any) (number of rebleeds) Follow-up (months): 23.9
Notes	Source of funding (quote): "This work was supported by a grant from the Faculty of Medicine, University of Athens" Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "All endoscopies and sclerotherapies were performed by a group of three experienced endoscopists who did not know which patients had received propranolol" Comment: it was not clear if these were the outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: no prepublished protocol was available, but the authors reported mortality, adverse events, and variceal rebleeding
Other bias	Low risk	Comment: no other bias noted

Avgerinos 1997

Study characteristics

Methods	Randomised clinical trial

Avgerinos 1997 *(Continued)*

Participants	Country: Greece Period of recruitment: 1992-1993 Number randomised: 77 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 77 Average age (years): 55 Females: 14 (18.2%) Other features of decompensation: 38 (49.4%) Alcohol-related cirrhosis: 35 (45.5%) Viral-related cirrhosis: 31 (40.3%) Autoimmune disease-related cirrhosis: 1 (1.3%) Other causes for cirrhosis: 10 (13.0%) Other inclusion/exclusion criteria: Inclusion: a) control of the acute bleeding episode from oesophageal varices by endoscopic injection sclerotherapy b) no history of previous endoscopic or surgical treatment for varices c) absence of hepatocellular carcinoma
Interventions	Group 1: variceal band ligation (n = 37) Further details: variceal band ligation (Bard intervention products, Tewkesbury, Massachusetts, USA) 2 to 9 bands (average interval between sessions: 8.8 days) Group 2: sclerotherapy (n = 40) Further details: sclerotherapy (5% ethanolamine oleate) (average interval between sessions: 7.6 days)
Outcomes	Outcomes reported: mortality at maximal follow-up, any adverse events (number of people), any adverse events (number of events), variceal rebleed at maximal follow-up (any) (number of rebleeds) Follow-up (months): 15.2
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated randomization sequence"
Allocation concealment (selection bias)	Unclear risk	Quote: "The investigators managing the patients were not aware of the treatment a patient would be assigned before randomization took place" Comment: further details were not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: no prepublished protocol was available, but the authors reported mortality, adverse events, and variceal rebleeding

Avgerinos 1997 *(Continued)*

Other bias	Low risk	Comment: no other bias noted

Bader 1987

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: France Period of recruitment: 1984-1986 Number randomised: 37 Post-randomisation dropouts: 2 (5.4%) Revised sample size: 35 Reasons for post-randomisation dropouts: not stated Average age (years): 55 Females: 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 for cirrhosis: not stated Other inclusion/exclusion criteria: Exclusion: liver cancer, contraindications to beta-blockers, repeated haemorrhage
Interventions	Group 1: beta-blockers (n = 17) Further details: propranolol 40 to 160 mg (average 80 mg)/day (duration not stated) Group 2: sclerotherapy (n = 18) Further details: sclerotherapy: 2% Polidocanol (no further details)
Outcomes	Outcomes reported: mortality at maximal follow-up Follow-up (months): 14
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias

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

Bader 1987 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: one patient in each group were excluded because of non-compliance or complications related to treatment. it is not clear whether this would have affected the effect estimate
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available, and adverse events and oesophageal variceal rebleed were not reported
Other bias	Low risk	Comment: no other bias noted

Baroncini 1996

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: 1995-1996 Number randomised: 14 Post-randomisation dropouts: not stated Revised sample size: 14 Average age (years): 60 Females: 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 for cirrhosis: not stated Other inclusion/exclusion criteria: Exclusion: other disease likely to reduce survival and hepatocellular carcinoma
Interventions	Group 1: sclerotherapy plus variceal band ligation (n = not stated) Further details: sclerotherapy (1% polidocanol maximum 20 mL per session) plus variceal band ligation (no further details) every 15 days until eradication of varices Group 2: variceal band ligation (n = not stated) Further details: variceal band ligation (no further details) every 15 days until eradication of varices Additional details: number of participants in each group was not reported
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

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

Baroncini 1996 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available, and none of the outcomes of interest for this review were reported
Other bias	Low risk	Comment: no other bias noted

Baroncini 1997

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: 1993-1995 Number randomised: 111 Post-randomisation dropouts: not stated Revised sample size: 111 Average age (years): 62 Females: 36 (32.4%) Other features of decompensation: 24 (21.6%) Alcohol-related cirrhosis: 15 (13.5%) Viral-related cirrhosis: 93 (83.8%) Autoimmune disease-related cirrhosis: 2 (1.8%) Other causes for cirrhosis: 1 (0.9%) Other inclusion/exclusion criteria: Exclusion: bleeding from gastric varices, hepatocellular carcinoma or severe diseases likely to reduce survival
Interventions	Group 1: variceal band ligation (n = 57) Further details: variceal band ligation (Bard Interventional Products), repeated every 1 to 2 weeks until eradication Group 2: sclerotherapy (n = 54) Further details: sclerotherapy: 1% polidocanol 5 mL to 9 mL, repeated every 1 to 2 weeks until eradication
Outcomes	Outcomes reported: mortality at maximal follow-up, any adverse events (number of events), liver transplantation at maximal follow-up, variceal rebleed at maximal follow-up (symptomatic recovery) (number of patients) Follow-up (months): 16.9
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Baroncini 1997 *(Continued)*

Risk of bias

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

Bertoni 1990

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: not stated Number randomised: 28 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 28 Average age (years): 59 Females: 10 (35.7%) Other features of decompensation: not stated Alcohol-related cirrhosis: 16 (57.1%) Viral-related cirrhosis: 4 (14.3%) Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: 8 (28.6%) Other inclusion/exclusion criteria: Exclusion: insulin dependent diabetes, asthma, severe cardiac disease, persistent bleeding, age >75
Interventions	Group 1: beta-blockers plus sclerotherapy (n = 14) Further details: nadolol to reduce heart rate by 25% Group 2: sclerotherapy (n = 14) Further details: sclerotherapy: 1% polidocanol at weekly intervals until eradication
Outcomes	Outcomes reported: mortality at maximal follow-up

Bertoni 1990 *(Continued)*

	Follow-up (months): 2
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available, and adverse events and oesophageal variceal rebleed were not reported
Other bias	Low risk	Comment: no other bias noted

Bertoni 1994

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: 1990-1992 Number randomised: 76 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 76 Average age (years): 62 Females: 23 (30.3%) Other features of decompensation: not stated Alcohol-related cirrhosis: 20 (26.3%) Viral-related cirrhosis: 32 (42.1%) Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: 24 (31.6%) Other inclusion/exclusion criteria: Exclusion: prolonged severe encephalopathy, advanced intra or extrahepatic tumour, resumption of beta-blocker therapy, previous sclerotherapy, intractable ascites, imminent liver transplantation

Bertoni 1994 *(Continued)*

Interventions	Group 1: sclerotherapy plus nitrates (n = 37) Further details: sclerotherapy: continuation of the sclerotherapy performed as emergency or elective procedure, until eradication of varices plus isosorbide mononitrate 50 mg/day until eradication of varices Group 2: sclerotherapy (n = 39) Further details: sclerotherapy: continuation of the sclerotherapy performed as emergency or elective procedure, until eradication of varices plus placebo
Outcomes	Outcomes reported: mortality at maximal follow-up, variceal rebleed at maximal follow-up (any) (number of rebleeds) Follow-up (months): 2
Notes	Source of funding (quote): "We are grateful to 'Chiesi Farmaceutici (Parma, Italy) for supplying the trial capsules" Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised in a double-blind fashion by means of a table of random numbers"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients were randomised in a double-blind fashion by means of a table of random numbers" Comment: blinding was achieved by the use of a placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Patients were randomised in a double-blind fashion by means of a table of random numbers" Comment: blinding was achieved by the use of a placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available and adverse events were not reported
Other bias	Low risk	Comment: no other bias noted

Bonkovsky 1989

Study characteristics

Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: not stated Number randomised: 20 Post-randomisation dropouts: not stated

Bonkovsky 1989 *(Continued)*

	Revised sample size: 20 Average age (years): not stated Females: 1 (5.0%) Other features of decompensation: not stated Alcohol-related cirrhosis: 13 (65.0%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: not stated Other inclusion/exclusion criteria: Exclusion: severe encephalopathy, diabetes mellitus, asthma, cardiac disease, renal insufficiency
Interventions	Group 1: no active intervention (n = 10) Further details: placebo Group 2: beta-blockers (n = 10) Further details: atenolol 50 mg to 100 mg to decrease heart rate by 25%; duration not stated
Outcomes	Outcomes reported: mortality at maximal follow-up, variceal rebleed at maximal follow-up (any) (number of patients) Follow-up (months): 12
Notes	Source of funding (quote): "Supported by ICI/Stuart Pharmaceuticals" Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "…were assigned randomly (by random number-opaque envelope technique) to receive atenolol and matching placebo" Comment: the details of sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Quote: "…were assigned randomly (by random number-opaque envelope technique) to receive atenolol and matching placebo" comment: not clear if the envelopes were sealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Patients did not know which treatment they were receiving" Comment: not clear whether healthcare providers were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available and adverse events were not reported
Other bias	Low risk	Comment: no other bias noted

Cabrera 1996

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Spain Period of recruitment: 1991-1994 Number randomised: 63 Post-randomisation dropouts: 2 (3.2%) Revised sample size: 61 Reasons for post-randomisation dropouts: not stated Average age (years): 56 Females: 20 (32.8%) Other features of decompensation: 21 (34.4%) Alcohol-related cirrhosis: 43 (70.5%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: not stated Other inclusion/exclusion criteria: Exclusion: 1. Hepatocellular carcinoma 2. Non-variceal bleeding 3. Chronic encephalopathy 4. Neoplastic disease 5. Portal vein thrombosis 6. End-stage liver disease
Interventions	Group 1: TIPS (n = 32) Further details: TIPS: a 10-mm diameter Wallstent endoprosthesis Group 2: sclerotherapy (n = 31) Further details: sclerotherapy: 1% polidocanol 10 mL to 30 mL per session, weekly for the first month and at 1 to 3 month intervals until obliteration of varices
Outcomes	Outcomes reported: mortality at maximal follow-up, any adverse events (number of events), variceal rebleed at maximal follow-up (any) (number of patients), other features of decompensation at maximal follow-up, length of hospital stay (days) (all admissions until maximal follow-up), length of hospital stay (days) (all admissions until maximal follow-up) (sensitivity analysis) Follow-up (months): 15
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed 3 days after the variceal bleeding was controlled using computer generated random numbers"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available

Cabrera 1996 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: no prepublished protocol was available, but the authors reported mortality, adverse events, and variceal rebleeding
Other bias	Low risk	Comment: no other bias noted

Cennamo 1998

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: 1996-1998 Number randomised: 34 Post-randomisation dropouts: not stated Revised sample size: 34 Average age (years): not stated Females: 7 (20.6%) Other features of decompensation: not stated Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: not stated Other inclusion/exclusion criteria: not stated
Interventions	Group 1: variceal band ligation plus sclerotherapy (n = 16) Further details: variceal band ligation (no further details) plus sclerotherapy: 1% polidocanol up to 20 mL until eradication Group 2: variceal band ligation (n = 18) Further details: variceal band ligation (no further details)
Outcomes	Outcomes reported: other features of decompensation at maximal follow-up Follow-up (months): 12.6
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

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

Cennamo 1998 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available, and mortality, adverse events, and oesophageal variceal rebleed were not reported
Other bias	Low risk	Comment: no other bias noted

Dasarathy 1992

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: India Period of recruitment: 1986-1990 Number randomised: 104 Post-randomisation dropouts: 13 (12.5%) Revised sample size: 91 Reasons for post-randomisation dropouts: adverse events related to propranolol, refusal to follow study protocol Average age (years): 45 Females: 15 (16.5%) Other features of decompensation: not stated Alcohol-related cirrhosis: 25 (27.5%) Viral-related cirrhosis: 23 (25.3%) Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: 43 (47.3%) Other inclusion/exclusion criteria: Exclusion: 1) Child class A patients 2) Endoscopic diagnosis of small oesophageal varices and of varices without signs of high risk of bleeding 3) Presence of any other potential bleeding site 4) Contraindication to the use of beta-blocking agents and previous treatment with beta-blockers, endoscopic sclerotherapy or surgery for portal hypertension
Interventions	Group 1: beta-blockers (n = 46) Further details: propranolol to achieve a reduction in heart rate of 25% Group 2: sclerotherapy (n = 45) Further details: sclerotherapy: 1% polidocanol at 10-day intervals until obliteration
Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), variceal rebleed at maximal follow-up (any) (number of patients), variceal rebleed at maximal follow-up (symptomatic recovery) (number of rebleeds)

Dasarathy 1992 *(Continued)*

	Follow-up (months): 12
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts, that are likely to be related to the intervention and the outcome
Selective reporting (reporting bias)	Low risk	Comment: no prepublished protocol was available, but the authors reported mortality, adverse events, and variceal rebleeding
Other bias	Low risk	Comment: no other bias noted

Dwivedi 1992

Study characteristics

Methods	Randomised clinical trial
Participants	Country: India Period of recruitment: 1986-1987 Number randomised: 32 Post-randomisation dropouts: 2 (6.3%) Revised sample size: 30 Reasons for post-randomisation dropouts: Complications of beta-blockers Average age (years): 40 Females: 7 (23.3%) Other features of decompensation: 13 (43.3%) Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: not stated Other inclusion/exclusion criteria: Inclusion: liver cirrhosis

Dwivedi 1992 *(Continued)*

	Exclusion: contraindications to use of beta-blockers
Interventions	Group 1: beta-blockers (n = 14) Further details: propranolol to decrease the heart rate by 25% Group 2: sclerotherapy (n = 16) Further details: sclerotherapy: sclerosant not stated, repeated at 3-week intervals until obliteration
Outcomes	Outcomes reported: mortality at maximal follow-up, variceal rebleed at maximal follow-up (any) (number of patients), variceal rebleed at maximal follow-up (any) (number of rebleeds) Follow-up (months): 7.5
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "random number tables"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts related to the intervention and outcomes
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available and adverse events were not reported
Other bias	Low risk	Comment: no other bias noted

Esquivel Lopez 1984

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Mexico Period of recruitment: not stated Number randomised: 19 Post-randomisation dropouts: not stated Revised sample size: 19 Average age (years): 48 Females: 2 (10.5%)

Esquivel Lopez 1984 *(Continued)*

	Other features of decompensation: not stated Alcohol-related cirrhosis: 17 (89.5%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: not stated Other inclusion/exclusion criteria: Inclusion: liver cirrhosis and variceal bleeding Exclusion: heart failure, diabetes and lung disease
Interventions	Group 1: no active intervention (n = 8) Further details: no treatment Group 2: beta-blockers (n = 11) Further details: propranolol to maintain heart rate at 25% below normal rate
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias

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

Fleig 1988

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Germany Period of recruitment: 1983-not stated

Fleig 1988 *(Continued)*

	Number randomised: 115 Post-randomisation dropouts: 10 (8.7%) Revised sample size: 105 Reasons for post-randomisation dropouts: not stated, but an interim reported exclusion of 8 patients for immediate rebleeding and protocol violations Average age (years): not stated Females: 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 for cirrhosis: not stated Other inclusion/exclusion criteria: Inclusion: liver cirrhosis Exclusion: noncirrhotic portal hypertension, contraindications to the use of beta-blocking agents, previous sclerotherapy or emergency sclerotherapy in the treatment of the index bleed, severe ascites, disorientation due to severe portal-systemic encephalopathy [grade 3 and more], patients not willing to be subject to randomisation
Interventions	Group 1: beta-blockers (n = 50) Further details: propranolol to reduce the resting heart rate by about 25% Group 2: sclerotherapy (n = 55) Further details: sclerotherapy: 1% polidocanol approximately 40 mL per session 3 to 4 day intervals until they reduced to grade 1 varices
Outcomes	Outcomes reported: mortality at maximal follow-up, variceal rebleed at maximal follow-up (any) (number of patients), variceal rebleed at maximal follow-up (any) (number of rebleeds) Follow-up (months): 25
Notes	Source of funding (quote): "K. Rainer was supported by a grant from the ICI-Rhein Pharma, Plankstadt, Federal Republic of Germany" Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Quote: "randomly allocated by sealed envelopes to treatment with either sclerotherapy or propranolol" Comment: further details were not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were no post-randomisation dropouts

Fleig 1988 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available, but the authors reported mortality, adverse events, and variceal rebleeding
Other bias	Low risk	Comment: no other bias noted

Fornaciari 1990

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: not stated Number randomised: 28 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 28 Average age (years): not stated Females: 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 for cirrhosis: not stated Other inclusion/exclusion criteria: Exclusion: contraindication to beta-blocker
Interventions	Group 1: beta-blockers plus sclerotherapy (n = 14) Further details: nadolol to reduce heart rate by 25% plus sclerotherapy: no further details Group 2: sclerotherapy (n = 14) Further details: sclerotherapy: no further details
Outcomes	Outcomes reported: mortality at maximal follow-up Follow-up (months): 3
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias

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

Fornaciari 1990 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available, and adverse events and oesophageal variceal rebleed were not reported
Other bias	Low risk	Comment: no other bias noted

García-Pagán 2009

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Spain Period of recruitment: 2003-2005 Number randomised: 160 Post-randomisation dropouts: 2 (1.3%) Revised sample size: 158 Reasons for post-randomisation dropouts: prehepatic portal hypertension, portal vein thrombosis Average age (years): 57 Females: 40 (25.3%) Other features of decompensation: 54 (34.2%) Alcohol-related cirrhosis: 100 (63.3%) Viral-related cirrhosis: 62 (39.2%) Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: 15 (9.5%) Other inclusion/exclusion criteria: Inclusion: 1) successful treatment of the index bleed with vasoactive drugs (terlipressin or somatostatin), antibiotics and endoscopic treatment 2) age between 18 and 75 years 3) no previous randomisation in the study and 4) provided signed, informed, written consent to participate in the study Exclusion: 1) failure to fulfil entry criteria 2) pregnancy 3) known hepatocellular carcinoma 4) chronic renal failure 5) Child–Pugh score >13 or a concomitant disease with reduced life expectancy 6) contraindications to beta-blocker or isosorbide mononitrate 7) previous treatment to prevent rebleeding with a portosystemic shunt or with combined pharmacological therapy with beta-blocker plus isosorbide mononitrate 8) treatment with EBL in the 3 months before the index bled 9) bleeding from isolated gastric or ectopic varices and 10) portal vein thrombosis
Interventions	Group 1: beta-blockers plus nitrates plus variceal band ligation (n = 80) Further details: nadolol maximum tolerated dose (i.e. systolic blood pressure >=95 mmHg and resting heart rate >50 beats/min plus isosorbide nitrate 10 mg to 40 mg (maximum tolerated dose: same criteria as for nadolol) plus variceal band ligation (multiband devices), repeated every 10 to 14 days until variceal eradication Group 2: beta-blockers plus nitrates (n = 78) Further details: nadolol maximum tolerated dose (i.e. systolic blood pressure >=95 mm Hg and resting heart rate >50 beats/min plus isosorbide nitrate 10 mg to 40 mg (maximum tolerated dose: same criteria as for nadolol)
Outcomes	Outcomes reported: mortality at maximal follow-up, any adverse events (number of people), any adverse events (number of events), liver transplantation at maximal follow-up, length of hospital stay (days) (all admissions until maximal follow-up), length of hospital stay (days) (all admissions until maximal follow-up) (sensitivity analysis) Follow-up (months): 15

García-Pagán 2009 *(Continued)*

Notes	Source of funding (quote): "Nadolol was kindly supplied by Sanofi Winthrop (Barcelona, Spain). Isosorbide mononitrate was kindly provided by Lacer (Barcelona, Spain)." Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation sequence was generated by computer in blocks of 8 and the code was kept at the coordinating centre in sealed, consecutively numbered, opaque envelopes"
Allocation concealment (selection bias)	Low risk	Quote: "The randomisation sequence was generated by computer in blocks of 8 and the code was kept at the coordinating centre in sealed, consecutively numbered, opaque envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were two post-randomisation dropouts, however, they are unrelated to the treatment
Selective reporting (reporting bias)	Low risk	Comment: no prepublished protocol was available, but the authors reported mortality, adverse events, and variceal rebleeding
Other bias	Low risk	Comment: no other bias noted

Garcia-Villarreal 1999

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Spain Period of recruitment: 1993-1997 Number randomised: 46 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 46 Average age (years): 56 Females: 9 (19.6%) Other features of decompensation: 21 (45.7%) Alcohol-related cirrhosis: 33 (71.7%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: not stated Other inclusion/exclusion criteria:

Garcia-Villarreal 1999 *(Continued)*

	Inclusion: 1) endoscopically proven oesophageal variceal bleeding 2) diagnosis of cirrhosis based on clinical history and laboratory, ultrasonography, and/or liver biopsy findings 3) age between 18 and 75 years and 4) informed consent from the patient or his/her next of kin when encephalopathy was present Exclusion: 1) history of chronic encephalopathy 2) portal vein thrombosis 3) hepatocellular carcinoma 4) end-stage liver disease defined by the presence of more than one of the following parameters: prothrombin index, 35%, bilirubin 5 mg/dL, and plasma creatinine 3 mg/dL and 5) follow-up not possible
Interventions	Group 1: TIPS (n = 22) Further details: TIPS, performed under local anaesthesia (no further details) Group 2: sclerotherapy (n = 24) Further details: sclerotherapy: 5% ethanolamide oleate, 12 to 20 mL per session repeated every 7 to 10 days until variceal obliteration
Outcomes	Outcomes reported: mortality at maximal follow-up, variceal rebleed at maximal follow-up (any) (number of patients), other features of decompensation at maximal follow-up, length of hospital stay (days) (all admissions until maximal follow-up), length of hospital stay (days) (all admissions until maximal follow-up) (sensitivity analysis) Follow-up (months): 20.6
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed using computer-generated random numbers"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available and adverse events were not reported
Other bias	Low risk	Comment: no other bias noted

Henderson 1990

Study characteristics

Henderson 1990 *(Continued)*

Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: 1981-1985 Number randomised: 72 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 72 Average age (years): not stated Females: not stated Other features of decompensation: 8 (11.1%) Alcohol-related cirrhosis: 43 (59.7%) Viral-related cirrhosis: 13 (18.1%) Autoimmune disease-related cirrhosis: 5 (6.9%) Other causes for cirrhosis: 11 (15.3%) Other inclusion/exclusion criteria: Inclusion: oesophageal bleeding secondary to liver cirrhosis, suitability for either distal spleno-renal shunt or sclerotherapy, no previous sclerotherapy Exclusion: non-cirrhotic portal hypertension related bleeding
Interventions	Group 1: portocaval shunt (n = 35) Further details: distal splenorenal shunt Group 2: sclerotherapy (n = 37) Further details: sclerotherapy: 1.5% to 2% sodium morrhuate and 0.75% to 1% sodium tetradecyl sulphate monthly intervals until obliteration
Outcomes	Outcomes reported: mortality at maximal follow-up, variceal rebleed at maximal follow-up (symptomatic recovery) (number of patients) Follow-up (months): 61
Notes	Source of funding (quote): "Supported by Public Health Service Research Grant AM 15736 and General Clinical Research Center Public Health Service Grant 5M01RR00039" Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020 Individual patients had multiple cirrhosis aetiologies

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomization was by closed envelope with a recurring block size of four" Comment: further details were not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available

Henderson 1990 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available and adverse events were not reported
Other bias	Low risk	Comment: no other bias noted

Ink 1992

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: France Period of recruitment: 1986-1989 Number randomised: 131 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 131 Average age (years): 53 Females: 30 (22.9%) Other features of decompensation: 41 (31.3%) Alcohol-related cirrhosis: 126 (96.2%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: not stated Other inclusion/exclusion criteria: Inclusion: a) recent episode of bleeding from oesophageal varices that was confirmed by emergency endoscopy (endoscopic stigmata of recent variceal bleeding or oesophageal varices with no other pathological condition present to explain major upper gastrointestinal trace bleeding) b) bleeding that had stopped for at least 24 hours without any sclerotherapy session c) a Child-Pugh score greater than 6 and d) oral acceptance to participate from the patient or from the next of kin if the patient was too ill to consent Exclusion: a) previous treatment with propranolol or sclerotherapy for portal hypertension b) contraindication to the use of propranolol because of asthma, cardiac insufficiency or use of insulin or sulfamides indicating diabetes mellitus, disturbance of atrioventricular conduction or Raynaud's syndrome c) contraindication to sclerotherapy because of severe encephalopathy, previous oesophageal surgery, hiatal hernia longer than 4 cm or oesophageal stenosis d) existence of hepatocellular carcinoma or serious illness reducing life expectancy (for example, ongoing cancer, hepatic coma or prothrombin time less than 20%) or e) unfeasibility of regular surveillance (for reasons of distance or apparent indiscipline)
Interventions	Group 1: beta-blockers plus sclerotherapy (n = 65) Further details: propranolol titrated to reduce the resting pulse rate by 25% (duration not stated; likely to be until follow-up period) plus sclerotherapy 1% polidocanol 40 mL to 60 mL initially weekly and then monthly to eradicate varices Group 2: beta-blockers (n = 66) Further details: propranolol titrated to reduce the resting pulse rate by 25% (duration not stated; likely to be until follow-up period)
Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), variceal rebleed at maximal follow-up (any) (number of patients) Follow-up (months): 24
Notes	Source of funding: not stated

Ink 1992 *(Continued)*

	Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Quote: "the patients in each center were randomly assigned to their treatment groups by sealed opaque envelopes" Comment: further details of whether they were consecutively numbered were not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: no prepublished protocol was available, but the authors reported mortality, adverse events, and variceal rebleeding
Other bias	Low risk	Comment: no other bias noted

Isaksson 1995

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Sweden Period of recruitment: 1982-1989 Number randomised: 45 Post-randomisation dropouts: not stated Revised sample size: 45 Average age (years): 52 Females: 12 (26.7%) Other features of decompensation: 19 (42.2%) Alcohol-related cirrhosis: 33 (73.3%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: not stated Other inclusion/exclusion criteria: Inclusion: 1) age between 20 to 75 years at randomisation 2) the bleeding source should be oesophageal varices verified endoscopically 3) presence of portal hypertension and 4) the diagnosis of liver cirrhosis should be verified on histological examination

Isaksson 1995 *(Continued)*

Interventions	Group 1: portocaval shunt (n = 24) Further details: mesocaval shunt Group 2: sclerotherapy (n = 21) Further details: 1% ethoxysclerol up to 30 mL twice a week initially and monthly until varices were eradicated
Outcomes	Outcomes reported: any adverse events (number of events), length of hospital stay (days) (all admissions until maximal follow-up), treatment costs Follow-up (months): 65.2
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Quote: "The randomization was done within the Child's groups and by using closed envelopes" Comment: further details were not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available, and mortality and oesophageal variceal rebleed were not reported
Other bias	Low risk	Comment: no other bias noted

Jalan 1997

Study characteristics

Methods	Randomised clinical trial
Participants	Country: UK Period of recruitment: 1993-1995 Number randomised: 58 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 58 Average age (years): 58

Jalan 1997 *(Continued)*

	Females: 21 (36.2%) Other features of decompensation: 16 (27.6%) Alcohol-related cirrhosis: 47 (81.0%) Viral-related cirrhosis: 4 (6.9%) Autoimmune disease-related cirrhosis: 5 (8.6%) Other causes for cirrhosis: 2 (3.4%) Other inclusion/exclusion criteria: Inclusion: liver cirrhosis, age 18-75 years, first episode of oesophageal varices haemorrhage Exclusion: bleeding from other varices, previous endoscopic treatment for variceal bleeding, hepatorenal failure, hepatic or extra-hepatic malignancy, portal vein thrombosis, failure to give consent
Interventions	Group 1: TIPS (n = 31) Further details: TIPS using 1 or 2 12 mm expandable metal stents Group 2: variceal band ligation (n = 27) Further details: variceal band ligation, single band; repeated weekly until eradication
Outcomes	Outcomes reported: mortality at maximal follow-up, any adverse events (number of people), variceal rebleed at maximal follow-up (symptomatic recovery) (number of patients), other features of decompensation at maximal follow-up, variceal rebleed at maximal follow-up (symptomatic recovery) (number of rebleeds), length of hospital stay (days) (all admissions until maximal follow-up), treatment costs, length of hospital stay (days) (all admissions until maximal follow-up) (sensitivity analysis) Follow-up (months): 16.2
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Treatment assignment was achieved using the closed-envelope method" Comment: further details were not available
Allocation concealment (selection bias)	Unclear risk	Quote: "Treatment assignment was achieved using the closed-envelope method" Comment: further details were not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: no prepublished protocol was available, but the authors reported mortality, adverse events, and variceal rebleeding
Other bias	Low risk	Comment: no other bias noted

Jensen 1989

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Denmark Period of recruitment: 1985-1987 Number randomised: 31 Post-randomisation dropouts: not stated Revised sample size: 31 Average age (years): 47 Females: 4 (12.9%) Other features of decompensation: not stated Alcohol-related cirrhosis: 26 (83.9%) Viral-related cirrhosis: 2 (6.5%) Autoimmune disease-related cirrhosis: 1 (9.7%) Other causes for cirrhosis: 2 (6.5%) Other inclusion/exclusion criteria: Inclusion: liver cirrhosis, 1st variceal bleeding (no previous bleeding) Exclusion: contraindications to use of beta-blockers
Interventions	Group 1: beta-blockers plus sclerotherapy (n = 15) Further details: propranolol 160 mg slow release for 6 months plus sclerotherapy (sclerosant not stated) at monthly intervals to obliterate varices Group 2: sclerotherapy (n = 16) Further details: sclerotherapy (sclerosant not stated) at monthly intervals to obliterate varices plus placebo for 6 months
Outcomes	Outcomes reported: mortality at maximal follow-up, any adverse events (number of people), variceal rebleed at maximal follow-up (any) (number of patients), other features of decompensation at maximal follow-up, variceal rebleed at maximal follow-up (any) (number of rebleeds) Follow-up (months): 9
Notes	Source of funding (quote): "The Inderal was provided by ICI, Pharmaceutical Division, UK" Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The patients were randomized in a double-blind manner by a computer-generated randomization schedule"
Allocation concealment (selection bias)	Low risk	Quote: "The patients were randomized in a double-blind manner by a computer-generated randomization schedule" Comment: although the precise method of allocation concealment was not reported, the allocation was probably concealed using a placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The patients were randomized in a double-blind manner by a computer-generated randomization schedule" Comment: blinding was achieved by the use of a placebo
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The patients were randomized in a double-blind manner by a computer-generated randomization schedule"

Jensen 1989 *(Continued)*

All outcomes		Comment: blinding was achieved by the use of a placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	Low risk	Comment: no prepublished protocol was available, but the authors reported mortality, adverse events, and variceal rebleeding
Other bias	Low risk	Comment: no other bias noted

Jiron 1993

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Chile Period of recruitment: 1983-1986 Number randomised: 57 Post-randomisation dropouts: not stated Revised sample size: 57 Average age (years): 54 Females: 23 (40.4%) Other features of decompensation: not stated Alcohol-related cirrhosis: 41 (71.9%) Viral-related cirrhosis: 1 (1.8%) Autoimmune disease-related cirrhosis: 1 (1.8%) Other causes for cirrhosis: 14 (24.6%) Other inclusion/exclusion criteria: Inclusion: liver cirrhosis, variceal bleeding happened within 1 week and no more than 15 days, oesophageal varices grade >1, absence of contraindications to the use of beta-blockers
Interventions	Group 1: no active intervention (n = 28) Further details: placebo Group 2: beta-blockers (n = 29) Further details: propranolol in increasing doses from 40 mg/ day until 25% decrease in baseline heart rate was reached (duration not reported)
Outcomes	Outcomes reported: mortality at maximal follow-up Follow-up (months): 48
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

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

Jiron 1993 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available, and adverse events and oesophageal variceal rebleed were not reported
Other bias	Low risk	Comment: no other bias noted

Kanazawa 1991

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Japan Period of recruitment: 1985-1990 Number randomised: 43 Post-randomisation dropouts: 4 (9.3%) Revised sample size: 39 Reasons for post-randomisation dropouts: lost to follow-up Average age (years): 52 Females: 8 (18.6%) Other features of decompensation: not stated Alcohol-related cirrhosis: 20 (46.5%) Viral-related cirrhosis: 20 (46.5%) Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: not stated Other inclusion/exclusion criteria: Inclusion: patients with vomiting blood as the chief complaint, presence of oesophageal varices in which haemostasis is obtained on endoscopy, liver biopsy diagnosed cirrhosis Exclusion: liver cancer on ultrasound, CT or angiography
Interventions	Group 1: beta-blockers plus sclerotherapy (n = 20) Further details: propranolol started at 30 mg titrated to reduce the heart rate by 25% plus sclerotherapy: ethanolamine oleate, repeated weekly to reduce it to F1 Group 2: sclerotherapy (n = 23) Further details: sclerotherapy: ethanolamine oleate, repeated weekly to reduce it to F1
Outcomes	Outcomes reported: mortality at maximal follow-up, any adverse events (number of people), any adverse events (number of events), length of hospital stay (days) (all admissions until maximal follow-up) Follow-up (months): 26.7
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Kanazawa 1991 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Quote: "The subjects were divided into two groups by the envelope method" Comment: further details were not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts; it was not clear whether these were related to the intervention and outcomes
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available and oesophageal variceal rebleed was not reported
Other bias	Low risk	Comment: no other bias noted

Kong 2015

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: China Period of recruitment: 2008-2012 Number randomised: 38 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 38 Average age (years): 53 Females: 15 (39.5%) Other features of decompensation: not stated Alcohol-related cirrhosis: 3 (7.9%) Viral-related cirrhosis: 20 (52.6%) Autoimmune disease-related cirrhosis: 4 (10.5%) Other causes for cirrhosis: 8 (21.1%) Other inclusion/exclusion criteria: Inclusion: liver cirrhosis, high variceal pressure, previous variceal bleeding Exclusion: portal vein thrombosis, treatment with beta-blockers, previous endoscopic treatment of varices (ligation or sclerotherapy), multifocal hepatocellular carcinoma, severe clotting defects, hepatic encephalopathy grade Ⅲ and Ⅳ, previous surgical portosystemic shunts or TIPS were also excluded from the study
Interventions	Group 1: variceal band ligation (n = 20)

Kong 2015 *(Continued)*

	Further details: variceal band ligation, super 7 multiple band ligator, every 2 to 3 weeks until all oesophageal varices were obliterated or were significantly reduced to small residual varices (F1) Group 2: sclerotherapy (n = 18) Further details: sclerotherapy: 1% lauromacrogol, every 1 to 2 weeks until all oesophageal varices were obliterated or were significantly reduced to small residual varices (F1)
Outcomes	Outcomes reported: mortality at maximal follow-up, any adverse events (number of people), variceal rebleed at maximal follow-up (any) (number of patients) Follow-up (months): 16
Notes	Source of funding (quote): "Educational and Health Department of Anhui Province, No. KJ2010A158, No. KJ2012Z189 and No. 2010B018; and National Natural Science Foundation of China, No. 81271736" Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "consecutively numbered envelopes that contained the treatment assignments, which were generated by a system using computer allocated random digit numbers"
Allocation concealment (selection bias)	Unclear risk	Quote: "consecutively numbered envelopes that contained the treatment assignments, which were generated by a system using computer allocated random digit numbers" Comment: not clear whether the envelopes were sealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: no prepublished protocol was available, but the authors reported mortality, adverse events, and variceal rebleeding
Other bias	Low risk	Comment: no other bias noted

Kumar 2015

Study characteristics

Methods	Randomised clinical trial
Participants	Country: India Period of recruitment: not stated Number randomised: 142 Post-randomisation dropouts: not stated

Kumar 2015 *(Continued)*

	Revised sample size: 142 Average age (years): 44 Females: not stated Other features of decompensation: not stated Alcohol-related cirrhosis: 84 (59.2%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: not stated Other inclusion/exclusion criteria: not stated
Interventions	Group 1: beta-blockers plus nitrates (n = 39) Further details: propranolol plus isosorbide-5-mononitrate (no further details) Group 2: variceal band ligation (n = 56) Further details: variceal band ligation (no further details) Group 3: beta-blockers (n = 47) Further details: carvedilol (no further details)
Outcomes	Outcomes reported: mortality at maximal follow-up, any adverse events (number of people), variceal rebleed at maximal follow-up (any) (number of patients) Follow-up (months): 16.4
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias

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

Lundell 1990

Study characteristics

Lundell 1990 *(Continued)*

Methods	Randomised clinical trial
Participants	Country: Sweden Period of recruitment: not stated Number randomised: 41 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 41 Average age (years): 57 Females: 19 (46.3%) Other features of decompensation: not stated Alcohol-related cirrhosis: 26 (63.4%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: not stated Other inclusion/exclusion criteria: Inclusion: patients admitted with bleeding from oesophageal varices Exclusion: patients who had previously received sclerotherapy
Interventions	Group 1: beta-blockers plus sclerotherapy (n = 19) Further details: sclerotherapy: 1% aethoxysclerol at monthly intervals until obliteration plus propranolol to decrease heart rate by 25% Group 2: sclerotherapy (n = 22) Further details: sclerotherapy: 1% aethoxysclerol at monthly intervals until obliteration
Outcomes	Outcomes reported: mortality at maximal follow-up, variceal rebleed at maximal follow-up (any) (number of patients) Follow-up (months): 7.9
Notes	Source of funding (quote): "This study was supported by grants from the Swedish Research Council (Project 17 X-760)" Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias

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

Lundell 1990 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available and adverse events were not reported
Other bias	Low risk	Comment: no other bias noted

Martin 1991

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: France Period of recruitment: 1984-1986 Number randomised: 76 Post-randomisation drop outs: not stated Revised sample size: 76 Average age (years): 53 Females: 12 (15.8%) Other features of decompensation: not stated Alcohol-related cirrhosis: 74 (97.4%) Viral-related cirrhosis: 0 (0.0%) Autoimmune disease-related cirrhosis: 0 (0.0%) Other causes for cirrhosis: 2 (2.6%) Other inclusion/exclusion criteria: Exclusion: 1) previous treatment with propranolol or sclerotherapy 2) age >75 years 3) contraindications to beta-blockers 4) hepatocellular carcinoma
Interventions	Group 1: beta-blockers (n = 34) Further details: propranolol dose resulting in a reduction in heart rate by at least 25% at rest and stable with effort Group 2: sclerotherapy (n = 42) Further details: sclerotherapy 3% polidocanol mixed with radio-opaque material, repeated every 3 weeks until obliteration of varices
Outcomes	Outcomes reported: mortality at maximal follow-up, any adverse events (number of events), variceal rebleed at maximal follow-up (any) (number of patients) Follow-up (months): 35.6
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Quote: "The patients were randomized into 2 groups by random drawing with sealed envelopes" Comment: further details were not available

Martin 1991 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	Low risk	Comment: no prepublished protocol was available, but the authors reported mortality, adverse events, and variceal rebleeding
Other bias	Low risk	Comment: no other bias noted

Masliah 1997

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: France Period of recruitment: 1991-1996 Number randomised: 95 Post-randomisation dropouts: not stated Revised sample size: 95 Average age (years): not stated Females: 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 for cirrhosis: not stated Other inclusion/exclusion criteria: not stated
Interventions	Group 1: beta-blockers plus nitrates (n = 46) Further details: propranolol plus isosorbide mononitrate (no further details) Group 2: beta-blockers (n = 49) Further details: propranolol alone, no further details
Outcomes	Outcomes reported: any adverse events (number of people) Follow-up (months): 29
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

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

Masliah 1997 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available, and mortality and oesophageal variceal rebleed were not reported
Other bias	Low risk	Comment: no other bias noted

Mckee 1994

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Scotland Period of recruitment: 1986-1989 Number randomised: 40 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 40 Average age (years): 59 Females: 17 (42.5%) Other features of decompensation: not stated Alcohol-related cirrhosis: 27 (67.5%) Viral-related cirrhosis: 5 (12.5%) Autoimmune disease-related cirrhosis: 4 (10.0%) Other causes for cirrhosis: 4 (10.0%) Other inclusion/exclusion criteria: Inclusion: patients who were referred for the first time to the hospital with suspected variceal bleeding Exclusion: age <65, Child's grade A or B
Interventions	Group 1: sclerotherapy (n = 22) Further details: no further details Group 2: no active intervention (n = 18) Further details: no treatment (on demand sclerotherapy, when they developed bleeding)
Outcomes	Outcomes reported: mortality at maximal follow-up, any adverse events (number of people), variceal rebleed at maximal follow-up (any) (number of patients) Follow-up (months): 24
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Mckee 1994 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Quote: "Sealed, numbered envelopes" Comment: further details such as opaqueness or consecutive numbers were not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: no prepublished protocol was available, but the authors reported mortality, adverse events, and variceal rebleeding
Other bias	Low risk	Comment: no other bias noted

Parelon 1989

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: France Period of recruitment: 1982-1985 Number randomised: 55 Post-randomisation dropouts: 5 (9.1%) Revised sample size: 50 Reasons for post-randomisation dropouts: died before procedure or titration could be achieved Average age (years): 56 Females: 9 (18.0%) Other features of decompensation: not stated Alcohol-related cirrhosis: 33 (66.0%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: not stated Other inclusion/exclusion criteria: Exclusion: 1) age >80 years 2) severe visceral illness (cardiac, respiratory or renal failure) 3) contraindications to surgical intervention and/or limited life expectancy 4) contraindication to beta-blockers
Interventions	Group 1: portocaval shunt (n = 24) Further details: porto-azygos anastomosis Group 2: beta-blockers (n = 26)

Parelon 1989 *(Continued)*

	Further details: propranolol to reduce the heart rate by 25%
Outcomes	Outcomes reported: mortality at maximal follow-up Follow-up (months): 39
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias

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

Romero 2006

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Argentina Period of recruitment: 1998-2002 Number randomised: 109 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 109 Average age (years): 52 Females: 37 (33.9%) Other features of decompensation: 40 (36.7%) Alcohol-related cirrhosis: 67 (61.5%) Viral-related cirrhosis: 28 (25.7%) Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: 27 (24.8%) Other inclusion/exclusion criteria:

Romero 2006 *(Continued)*

	Inclusion criteria: 1) cirrhosis 2) the index variceal bleeding episode, demonstrated by emergency endoscopy, in the prior 3 months without any other evidence of bleeding within this time 3) informed consent signed by the patient Exclusion criteria: 1) portal vein thrombosis 2) fundal gastric varices 3) any malignant tumour 4) more than one endoscopic treatment after the control of acute variceal bleeding 5) creatinine > or =1.6 mg/dL 6) contraindications to receive beta-blockers 7) bacterial infection and/or encephalopathy 8) inability to attend follow-up visits
Interventions	Group 1: sclerotherapy plus variceal band ligation (n = 52) Further details: variceal band ligation using single band device initially and for later patients using a multiband ligator every two weeks until obliteration of varices plus sclerotherapy, one or two sessions at the end of ligation sessions for any residual varices Group 2: beta-blockers plus nitrates (n = 57) Further details: nadolol dosage to achieve a 25% decrease in resting heart rate or until 55 bpm plus isosorbide mono nitrate starting with 10 mg twice daily, which was increased to 40 mg twice daily unless hypotension (systolic <90 mmHg) or severe headache occurred
Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), any adverse events (number of events), variceal rebleed at maximal follow-up (any) (number of patients), variceal rebleed at maximal follow-up (any) (number of rebleeds) Follow-up (months): 11.7
Notes	Source of funding (quote): "This study was supported in part by a grant from Fundacion Argentina para el Estudio de las Enfermedades del Higado (FUNDHIG)" Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020 Individual patients had multiple cirrhosis aetiologies

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a table of random numbers"
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was carried out utilizing consecutively numbered, opaque, sealed envelopes containing the treatment assignment"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: no prepublished protocol was available, but the authors reported mortality, adverse events, and variceal rebleeding
Other bias	Low risk	Comment: no other bias noted

Rossi 1991

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: France Period of recruitment: 1983-1987 Number randomised: 79 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 79 Average age (years): 54 Females: 19 (24.1%) Other features of decompensation: 46 (58.2%) Alcohol-related cirrhosis: 79 (100.0%) Viral-related cirrhosis: 0 (0.0%) Autoimmune disease-related cirrhosis: 0 (0.0%) Other causes for cirrhosis: 0 (0.0%) Other inclusion/exclusion criteria: Inclusion criteria: 1) cirrhosis confirmed histologically or suggested by biochemical and clinical data 2) age <75 years 3) bleeding from oesophageal varices Exclusion criteria: 1) hepatic carcinoma 2) life expectancy <1 year (i.e. Child Pugh Score >13) 3) another cause of upper gastrointestinal bleeding, gastric or duodenal ulcer, gastric varices or severe congestive gastropathy 4) contraindication to beta-blockers 5) previous course of sclerotherapy or any treatment known to alter portal haemodynamics 6) if the patient had required a transfusion of more than 6 units of blood within the first 24 hours 7) patients expected to have a low level of compliance or refused to participate
Interventions	Group 1: sclerotherapy (n = 26) Further details: sclerotherapy 1% polidocanol, a total of 30 to 45 mL was injected, and repeated every 5 to 7 days until obliteration of varices Group 2: beta-blockers (n = 27) Further details: propranolol titrated until a 20% to 25% reduction in resting heart rate was achieved up to a maximum of 160 mg/day Group 3: no active intervention (n = 26) Further details: no treatment
Outcomes	Outcomes reported: mortality at maximal follow-up, variceal rebleed at maximal follow-up (any) (number of patients) Follow-up (months): 19
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Low risk	Quote: "eligible patients were randomly assigned to treatment using a consecutively numbered series of sealed individual opaque envelopes"

Rossi 1991 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Patients were not blinded since the two treatment procedures were different, and therefore, the control group was not given placebo. Consequently, physicians were also not blinded"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The person assessing the outcome did not belong to the center where the trial took place and did not know which treatment had been given"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available and adverse events were not reported
Other bias	Low risk	Comment: no other bias noted

Sanyal 1997

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: 1991-1994 Number randomised: 80 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 80 Average age (years): 50 Females: 26 (32.5%) Other features of decompensation: 16 (20.0%) Alcohol-related cirrhosis: 33 (41.3%) Viral-related cirrhosis: 36 (45.0%) Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: 11 (13.8%) Other inclusion/exclusion criteria: Inclusion: active bleeding stopped for at least 72 hours Exclusion: portal vein thrombosis, evident hepatoma on ultrasound, end-stage cancer or systemic diseases with life expectancy under 1 yr, pregnancy, history of non-compliance to treatment, failure to obtain consent
Interventions	Group 1: TIPS (n = 41) Further details: TIPS: wallstent; the stents were dilated with an 8-mm balloon catheter Group 2: sclerotherapy (n = 39) Further details: sclerotherapy 5% ethanolamine oleate 10 to 30 mL per session, initially at weekly intervals for 1st month and then every 1 to 3 months until obliteration
Outcomes	Outcomes reported: mortality at maximal follow-up, liver transplantation at maximal follow-up Follow-up (months): 32
Notes	Source of funding (quote): "In part by an award from the National Institutes of Health to the Clinical Research Center at the Medical College of Virginia (RR-00065) and an award from the American College of Gastroenterology" Trial name/trial registry number: not stated

Sanyal 1997 *(Continued)*

Attempts were made to contact the authors in February 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated randomization code"
Allocation concealment (selection bias)	Unclear risk	Quote: "sealed opaque envelope" Comments: Further details were not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Patients were not blinded (author replies)"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Investigators were also not blinded (author replies)"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available, and adverse events and oesophageal variceal rebleed were not reported
Other bias	Low risk	Comment: no other bias noted

Sauer 1997

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Germany Period of recruitment: 1992-1995 Number randomised: 83 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 83 Average age (years): 56 Females: 35 (42.2%) Other features of decompensation: 21 (25.3%) Alcohol-related cirrhosis: 51 (61.4%) Viral-related cirrhosis: 23 (27.7%) Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: 9 (10.8%) Other inclusion/exclusion criteria: Exclusion: gastric varices, previous endoscopic or surgical treatment of varices, neoplastic disease or severe co-morbid condition with expected survival less than 6 months, septicaemia, portal vein thrombosis, uncontrolled bleeding, contraindication to propanolol
Interventions	Group 1: TIPS (n = 42) Further details: TIPS stents were dilated to 8 mm to 12 mm

Sauer 1997 *(Continued)*

	Group 2: beta-blockers plus sclerotherapy (n = 41) Further details: propranolol at oral doses which reduced the resting heart rate by approximately 25% plus sclerotherapy 5% ethanolamine oleate 10 to 30 mL per session, initially at weekly intervals for 1st month and then every 1 to 3 months until obliteration
Outcomes	Outcomes reported: mortality at maximal follow-up, any adverse events (number of events), liver transplantation at maximal follow-up, variceal rebleed at maximal follow-up (any) (number of patients), other features of decompensation at maximal follow-up, variceal rebleed at maximal follow-up (any) (number of rebleeds) Follow-up (months): 18
Notes	Source of funding (quote): "The study was funded exclusively by institutional resources (author replies)" Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "using computer-generated random numbers by an independent person not involved in the treatment of patients"
Allocation concealment (selection bias)	Low risk	Quote: "using computer-generated random numbers by an independent person not involved in the treatment of patients"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "None of the participants (patients, healthcare professionals or assessors) were blinded (author replies)"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "None of the participants (patients, healthcare professionals or assessors) were blinded (author replies)"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: no prepublished protocol was available, but the authors reported mortality, adverse events, and variceal rebleeding
Other bias	Low risk	Comment: no other bias noted

Sauer 2002

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Germany Period of recruitment: 1995-1999 Number randomised: 85 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 85 Average age (years): 54 Females: 35 (41.2%)

Sauer 2002 *(Continued)*

	Other features of decompensation: 34 (40.0%) Alcohol-related cirrhosis: 53 (62.4%) Viral-related cirrhosis: 21 (24.7%) Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: 11 (12.9%) Other inclusion/exclusion criteria: Exclusion: gastric varices, previous endoscopic or surgical treatment of varices, neoplastic disease or severe co-morbid condition with expected survival less than 6 months, encephalopathy grade 3 or 4, septicaemia, portal vein thrombosis, uncontrolled bleeding, contraindication to propanolol
Interventions	Group 1: beta-blockers plus variceal band ligation (n = 42) Further details: propranolol at oral doses which reduced the resting heart rate by approximately 25% plus variceal band ligation, was performed initially at intervals of 1-2 weeks until the varices disappeared Group 2: TIPS (n = 43) Further details: TIPS stents were dilated to 8-12 mm
Outcomes	Outcomes reported: mortality at maximal follow-up, any adverse events (number of events) Follow-up (months): 46.8
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was carried out as early as possible, using computer-generated random numbers, by an independent person not involved in the treatment of the patients"
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was carried out as early as possible, using computer-generated random numbers, by an independent person not involved in the treatment of the patients"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available and oesophageal variceal rebleed was not reported
Other bias	Low risk	Comment: no other bias noted

Sheen 1989

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: China Period of recruitment: 1983-1985 Number randomised: 36 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 36 Average age (years): 44 Females: 5 (13.9%) Other features of decompensation: 0 (0.0%) Alcohol-related cirrhosis: 16 (44.4%) Viral-related cirrhosis: 16 (44.4%) Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: 8 (22.2%) Other inclusion/exclusion criteria: Exclusion: previous treatment with endoscopic sclerotherapy, heart or lung disease, hepatocellular carcinoma, refusal to participate
Interventions	Group 1: no active intervention (n = 18) Further details: no treatment Group 2: beta-blockers (n = 18) Further details: propranolol in increasing dosages until the heart rate was reduced by approximately 25%
Outcomes	Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), any adverse events (number of people), variceal rebleed at maximal follow-up (symptomatic recovery) (number of patients), other features of decompensation at maximal follow-up Follow-up (months): 12.5
Notes	Source of funding (quote): "This work was supported in part by a grant from the Prosperous Foundation, Taipei" Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Quote: "simple randomization by sealed envelope were carried out" Comment: further details were not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias)	Low risk	Comment: there were no post-randomisation dropouts

Sheen 1989 *(Continued)*
All outcomes

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

Urbistondo 1996

Study characteristics

Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: 1989-1994 Number randomised: 43 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 43 Average age (years): 47 Females: 5 (11.6%) Other features of decompensation: not stated Alcohol-related cirrhosis: 43 (100.0%) Viral-related cirrhosis: 0 (0.0%) Autoimmune disease-related cirrhosis: 0 (0.0%) Other causes for cirrhosis: 0 (0.0%) Other inclusion/exclusion criteria: Exclusion criteria: other etiologies of liver disease besides alcohol
Interventions	Group 1: beta-blockers (n = 15) Further details: propranolol titrated to obtain 25% reduction in heart rate from baseline or less than 60 beats per minute Group 2: sclerotherapy (n = 13) Further details: sclerotherapy: 1.5% sodium tetradecyl sulphate 12 mL to 16 mL per session, twice a week initially and then once a week until obliteration Group 3: portocaval shunt (n = 15) Further details: distal splenorenal shunt
Outcomes	Outcomes reported: mortality at maximal follow-up, variceal rebleed at maximal follow-up (symptomatic recovery) (number of patients) Follow-up (months): 23.2
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

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	Comment: this information was not available

Urbistondo 1996 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available and adverse events were not reported
Other bias	Low risk	Comment: no other bias noted

Viazis 2002

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Greece Period of recruitment: 1995-1998 Number randomised: 73 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 73 Average age (years): 63 Females: 32 (43.8%) Other features of decompensation: not stated Alcohol-related cirrhosis: 28 (38.4%) Viral-related cirrhosis: 32 (43.8%) Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: 13 (17.8%) Other inclusion/exclusion criteria: Inclusion: patients admitted to hospital, age >18, established cirrhosis, bleeding of varices controlled by one session of endoscopic variceal sclerotherapy plus or minus somatostatin, variceal rebleeding requiring endoscopic treatment with 42 days after admission, informed consent Exclusion: variceal rebleeding requiring endoscopic treatment within 42 days after admission, history of previous chronic endoscopic or surgical treatment for varices and portal hypertension
Interventions	Group 1: variceal band ligation (n = 36) Further details: variceal band ligation using multiband ligator repeated at 7- to 10-day intervals until variceal eradication was achieved Group 2: sclerotherapy (n = 37) Further details: sclerotherapy using up to 20 mL of ethanolamine repeated at 7- to 10-day intervals until variceal eradication was achieved
Outcomes	Outcomes reported: mortality at maximal follow-up, variceal rebleed at maximal follow-up (any) (number of patients) Follow-up (months): 1.8
Notes	Source of funding (quote): "Dr Nikos Viazis was supported by a grant from the Hellenic Society of Gastroenterology"

Viazis 2002 *(Continued)*

	Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Quote: "After randomization according to a sealed envelope technique" Comment: further details were not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Oesophageal manometry and pH monitoring were performed by a physician who was not aware of the type of endoscopic treatment the patients had received" Comment: not clear if patients and other healthcare professionals involved in treatment were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Oesophageal manometry and pH monitoring were performed by a physician who was not aware of the type of endoscopic treatment the patients had received" Comment: not clear if patients and other healthcare professionals involved in assessment of clinical outcomes were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available and adverse events were not reported
Other bias	Low risk	Comment: no other bias noted

Villanueva 1994

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Spain Period of recruitment: 1989-1991 Number randomised: 40 Post-randomisation dropouts: not stated Revised sample size: 40 Average age (years): 57 Females: 17 (42.5%) Other features of decompensation: not stated Alcohol-related cirrhosis: 20 (50.0%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: not stated Other inclusion/exclusion criteria:

Villanueva 1994 *(Continued)*

	Exclusion: age <16 or >75, non cirrhotic portal hypertension, hepatocellular carcinoma, portal vein thrombosis, Child Pugh class C, life expectancy under 1 year, contraindication to beta-blockers, already taking beta-blocker, bleeding from gastric varices or other sources of bleeding
Interventions	Group 1: beta-blockers plus sclerotherapy (n = 22) Further details: nadolol dose titrated until a 25% reduction in baseline heart rate was achieved, without decreasing below 55 beats per minute plus sclerotherapy 10 to 20 mL of 5% ethanolamine in each session, initially twice weekly and later at monthly intervals Group 2: sclerotherapy (n = 18) Further details: sclerotherapy 10 to 20 mL of 5% ethanolamine in each session, initially twice weekly and later at monthly intervals
Outcomes	Outcomes reported: mortality at maximal follow-up, any adverse events (number of people), liver transplantation at maximal follow-up Follow-up (months): 26
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Quote: "The randomization was carried out through the system of sealed envelopes, which were opened just before the beginning of the elective treatment" Comment: not clear whether the sealed envelopes were opaque
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available and oesophageal variceal rebleed was not reported
Other bias	Low risk	Comment: no other bias noted

Vinel 1992

Study characteristics

Methods	Randomised clinical trial

Vinel 1992 *(Continued)*

Participants	Country: France Period of recruitment: not stated Number randomised: 75 Post-randomisation dropouts: 1 (1.3%) Revised sample size: 74 Reasons for post-randomisation dropouts: not stated Average age (years): 56 Females: 16 (21.6%) Other features of decompensation: 17 (23.0%) Alcohol-related cirrhosis: 66 (89.2%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: not stated Other inclusion/exclusion criteria: Exclusion: Previous treatment with propanolol, sclerotherapy, shunt or deconnection surgery, hepatocellular carcinoma or contraindication to beta-blockers
Interventions	Group 1: beta-blockers plus sclerotherapy (n = 39) Further details: propranolol adjusted to decrease resting heart rate by 25% plus sclerotherapy using 1% polidocanol repeated every week initially and then every 2 weeks until obliteration Group 2: sclerotherapy (n = 35) Further details: sclerotherapy using 1% polidocanol repeated every week initially and then every 2 weeks until obliteration
Outcomes	Outcomes reported: mortality at maximal follow-up, variceal rebleed at maximal follow-up (any) (number of patients), variceal rebleed at maximal follow-up (any) (number of rebleeds) Follow-up (months): 3.2
Notes	Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Quote: "randomized into two groups using sealed opaque envelopes" Comment: further details such as whether they were consecutively numbered were not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: one participant was excluded: there reason for exclusion was not stated; therefore, it is not possible to determine whether the dropout was related to the intervention or outcome

Vinel 1992 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available and adverse events were not reported
Other bias	Low risk	Comment: no other bias noted

Westaby 1985a

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: UK Period of recruitment: 1977-1981 Number randomised: 116 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 116 Average age (years): 53 Females: 52 (44.8%) Other features of decompensation: not stated Alcohol-related cirrhosis: 63 (54.3%) Viral-related cirrhosis: 10 (8.6%) Autoimmune disease-related cirrhosis: 25 (21.6%) Other causes for cirrhosis: 18 (15.5%) Other inclusion/exclusion criteria: Exclusion: rapid deterioration, previous surgery for varices, HBV, or physician refused patient enter study
Interventions	Group 1: no active intervention (n = 60) Further details: no treatment Group 2: sclerotherapy (n = 56) Further details: sclerotherapy: sclerosant not stated, repeated every 3 weeks until variceal obliteration
Outcomes	Outcomes reported: mortality at maximal follow-up, liver transplantation at maximal follow-up Follow-up (months): 37
Notes	Source of funding (quote): "Through King's College Hospital " Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available
Allocation concealment (selection bias)	Unclear risk	Quote: "sealed envelope" Comment: further details were not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "not possible for endoscopists to be blinded (author replies)"

Westaby 1985a *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "not blinded (author replies)"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available, and adverse events and oesophageal variceal rebleed were not reported
Other bias	Low risk	Comment: no other bias noted

CT: computerised tomography; **EBL:** endoscopic band ligation; **HBV:** hepatitis B virus; **TIPS:** transjugular intrahepatic portosystemic shunt.

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

Study	Reason for exclusion
Abd Elmoety 2015	Not clear if the studies included non-cirrhotic participants or gastric variceal bleeding
Abraldes 2016	Not a comparison of interest for this review
Acharya 1993	Not a population of interest for this review
Adson 1984	Not a RCT
Agarwal 2015	Not a comparison of interest for this review
Agarwala 2011	Not a comparison of interest for this review
Akriviadis 1989	Not a comparison of interest for this review
Albillos 1996	Not a population of interest for this review
Al Traif 1999	Not a population of interest for this review
Am. Soc. Gastro. Endo. 1998	Not a RCT
Baik 2005	Not a comparison of interest for this review
Balatsos 1997	Not a population of interest for this review
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
Bellis 2003	Not a population of interest for this review
Benner 1996	Not a RCT
Berardi 1974	Not a RCT

Study	Reason for exclusion
Berner 1994	Not a population of interest for this review
Bhargava 1992	Not a population of interest for this review
Bhargava 1997	Not a population of interest for this review
Bhuiyan 2007	Not a population of interest for this review
Bobadilla-Diaz 2002	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
Bonilha 2010	Not a population of interest for this review
Bories 1987	Not a comparison of interest for this review
Bosch 2013	Not a RCT
Braga 1991	Not a population of interest for this review
Brensing 2002	Not a RCT
Burroughs 1983	Not clear if the studies included non-cirrhotic participants or gastric variceal bleeding
Buuren 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
Chen 2013	Not clear if the studies included non-cirrhotic participants or gastric variceal bleeding
Chen 2016	Not clear if the studies included non-cirrhotic participants or gastric variceal bleeding
Chen 2018	Not a RCT
Chen 2019	Not clear if the studies included non-cirrhotic participants or gastric variceal bleeding
Cheng 2001	Not a population of interest for this review
ChiCTR08000228	Not a population of interest for this review
ChiCTR11000192	Not a comparison of interest for this review
ChiCTR11001577	Not a population of interest for this review
ChiCTR12002148	Not clear if the studies included non-cirrhotic participants or gastric variceal bleeding
ChiCTR15007655	Not a comparison of interest for this review
ChiCTR1800018070	Not a comparison of interest for this review
ChiCTR1800020322	Not a population of interest for this review

Study	Reason for exclusion
ChiCTR1900021212	Not a population of interest for this review
Cipolletta 2002	Not a comparison of interest for this review
Cirera 1995	Not a population of interest for this review
Colombo 1989	Not a population of interest for this review
Conn 1986	Not a RCT
Conn 1987	Not a RCT
Conn 1993	Not a RCT
Copaci 2012	Not a population of interest for this review
Costa 2016	Not clear if the studies included non-cirrhotic participants or gastric variceal bleeding
D'Amico 1998	Not a population of interest for this review
D'Amico 2008	Not a RCT
De 2002	Not a population of interest for this review
De 2003	Not a population of interest for this review
Dehesa 1994	Not a comparison of interest for this review
de la Pena 1999	Not a population of interest for this review
de la Pena 2005	Not a population of interest for this review
Djurdjevic 1999	Not a population of interest for this review
Dollet 1988	Not clear if the studies included non-cirrhotic participants or gastric variceal bleeding
Domagk 2000	Not a population of interest for this review (Not clear if participants had active bleeding)
Dong 2018	Not a population of interest for this review
Dunk 1988	Not a population of interest for this review
Dunne 2019	Not a population of interest for this review
Durdevic 1997	Not a population of interest for this review
Dwivedi 1995	Not a RCT
Eleftheriadis 1998	Not a comparison of interest for this review
El-Saadany 2007	Not a comparison of interest for this review
Elsayed 1996	Not a population of interest for this review
El-Tourabi 1994	Not clear if the studies included non-cirrhotic participants or gastric variceal bleeding

Study	Reason for exclusion
Escorsell 1996	Not a population of interest for this review
Escorsell 1997	Not a population of interest for this review
Escorsell 1997a	Not a population of interest for this review
Escorsell 1998	Not a comparison of interest for this review
Escorsell 2001	Not a population of interest for this review
Escorsell 2002	Not a population of interest for this review
Estevens 1996	Not a population of interest for this review
EUCTR2005-003557-27	Not a comparison of interest for this review
EUCTR2006-006393-14	Not a population of interest for this review
EUCTR2012-002489-11	Not a population of interest for this review
EUCTR2014-002018-21	Not a population of interest for this review
Evrard 2003	Not a population of interest for this review
Evrard 2008	Not a RCT
Fakhry 1997	Not clear if the studies included non-cirrhotic participants or gastric variceal bleeding
Farag 2005	Not clear if the studies included non-cirrhotic participants or gastric variceal bleeding
Fernandez 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
Fiaccadori 1993	Not a comparison of interest for this review
Fort 1990	Not a RCT
Garcia-Pagan 1991	Not a population of interest for this review
Garcia-Pagan 1996	Not a population of interest for this review
Garden 1990	Not clear if the studies included non-cirrhotic participants or gastric variceal bleeding
Garg 1999	Not a population of interest for this review
Gatta 1987	Not a population of interest for this review
Geng 2015	Not a population of interest for this review
George 2013	Not a population of interest for this review

Study	Reason for exclusion
Gilbert 1991	Not a RCT
Goff 1986	Not a comparison of interest for this review
Gong 1998	Not a RCT
Gong 2010	Not a population of interest for this review
Gonzalez-Abraldes 2001	Not a comparison of interest for this review
Gonzalez-Suarez 2006	Not a RCT
Gotoh 1999	Not a population of interest for this review
Gournay 2000	Not a population of interest for this review
Gralnek 1999	Not a population of interest for this review
Graupera 2011	Not a population of interest for this review
Groszmann 2002	Not a RCT
Gulberg 2002	Additional treatments neither equal nor randomised between groups
Hanno 2016	Not a population of interest for this review
Harki 2016a	Not a population of interest for this review
Harras 2010	Not a population of interest for this review
Hashizume 1993	Not a population of interest for this review
Helmy 2015	Not a population of interest for this review
Holster 2016	Not a population of interest for this review
Hua 2007	Not a RCT
Huang 2017	Not a comparison of interest for this review
Iso 1997	Not a population of interest for this review
ISRCTN14174793	Not a population of interest for this review
ISRCTN77521636	Not a population 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 1971	Not clear if the studies included non-cirrhotic participants or gastric variceal bleeding
Jeng 1989	Not a population of interest for this review
Jenkins 1997	Not clear if the studies included non-cirrhotic participants or gastric variceal bleeding

Study	Reason for exclusion
Jiang 2001	Not a comparison of interest for this review
Johansson 1988	Not a population of interest for this review
Kalambokis 2005	Not a population of interest for this review
Kamal 2017	Not a comparison of interest for this review
Kanazawa 1988	Not a population of interest for this review
Khaitiyar 2000	Not a RCT
Kim 1997	Additional treatments neither equal nor randomised between groups
Kitano 1989	Not a population of interest for this review
Kitano 1992	Not a population of interest for this review
Kleber 1987	Not a RCT
Kleber 1991	Not a population of interest for this review
Korula 1985	Not a population of interest for this review
Krige 1996	Not a comparison of interest for this review
Kumar 2009	Not a population of interest for this review
Kuran 2006	Not a RCT
Kuwayama 2005	Not a population of interest for this review
Lacet 2016	Not a population of interest for this review
Lebrec 1981	Not a population of interest for this review
Lee 2001	Not a population of interest for this review
Li 1995	Not a population of interest for this review
Li 2000	Not a comparison of interest for this review
Li 2000a	Not a comparison of interest for this review
Li 2016	Not a population of interest for this review
Liao 2015	Not a population of interest for this review
Lin 1996	Not clear if the studies included non-cirrhotic participants or gastric variceal bleeding
Lin 2002	Not a population of interest for this review
Lin 2005	Not a population of interest for this review
Lin 2006	Not clear if the studies included non-cirrhotic participants or gastric variceal bleeding

Study	Reason for exclusion
Liu 1998	Not a comparison of interest for this review
Liu 2004	Not a population of interest for this review
Lo 1993	Not a population of interest for this review
Lo 1998	Not a population of interest for this review
Lo 2000	Not a comparison of interest for this review
Lo 2002	Not a population of interest for this review
Lo 2008	Not a population of interest for this review
Lo 2009a	Not a population of interest for this review
Lo 2009b	Not a comparison of interest for this review
Lo 2012	Not a population of interest for this review
Lu 2004	Not a comparison of interest for this review
Luo 2011	Not a population of interest for this review
Luo 2015	Not a population of interest for this review
Lv 2018	Not a population of interest for this review
Magnano 1994	Not a comparison of interest for this review
Maldonado 2002	Not a RCT
Marrero 2002	Not a RCT
Masci 1999	Not clear if the studies included non-cirrhotic participants or gastric variceal bleeding
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
Merli 1998	Not a population of interest for this review
Mikkelsen 1974	Not a comparison of interest for this review
Ministro 1995	Not clear if the studies included non-cirrhotic participants or gastric variceal bleeding
Mino 1995	Not a RCT
Mo 2014	Not a population of interest for this review

Study	Reason for exclusion
Monici 2010	Not a comparison of interest for this review
Morales 2007	Not a population of interest for this review
Moreto 1994	Not a population of interest for this review
Nakamura 1998	Not a comparison of interest for this review
Nakamura 2001	Not a population of interest for this review
Nakase 1996	Not a population of interest for this review
Narahara 2001	Not clear if the studies included non-cirrhotic participants or gastric variceal bleeding
NCT00006161	Not a population of interest for this review
NCT00570973	Not a population of interest (only those who failed initial treatment were included)
NCT00799851	Not a population of interest for this review
NCT01103154	Not a population of interest for this review
NCT01640964	Not a population of interest for this review
NCT02119884	Not clear if the studies included non-cirrhotic participants or gastric variceal bleeding
NCT02508623	Not a population of interest for this review
NCT02646202	Not a population of interest for this review
NCT02740166	Not a comparison of interest for this review
NCT03583996	Not a RCT
NCT03687216	Not clear if the studies included non-cirrhotic participants or gastric variceal bleeding
NCT03783065	Not clear if the studies included non-cirrhotic participants or gastric variceal bleeding
Nevens 1996a	Not a population of interest for this review
Nevens 1996b	Not a population of interest for this review
Nishikawa 1999	Not a population of interest for this review
Nos 1995	Not an intervention of interest for this review
O'Connor 1989	Not a population of interest for this review
Ohmoto 2006	Not a population of interest for this review
Okano 2003a	Not a RCT
Okano 2003b	Not a RCT
Orloff 1962	Not a RCT

Study	Reason for exclusion
Orloff 1974	Not a RCT
Orloff 2014	Not a RCT
Otte 1983	Not a population of interest for this review
Palazzi 1989	Not a comparison of interest for this review
Pang 1997	Not a population of interest for this review
Paquet 1983	Not a RCT
Patch 2002	Not a population of interest for this review
Pena 1999	Not a population of interest for this review
Pena 2005	Not a population of interest for this review
Pereira 1997	Not a RCT
Pfisterer 2018	Not a RCT
Piai 1987	Not a RCT
Planas 1991	Not a population of interest for this review
Pomier-Layrargues 2001	Not clear if the studies included non-cirrhotic participants or gastric variceal bleeding
Pontes 1995	Not a population of interest for this review
Pozzi 2005	Not a population of interest for this review
Primignani 1994	Not a population of interest for this review
Primignani 1995	Not a population of interest for this review
Prioton 1988	Not a population of interest for this review
Priyadarshi 2011	Not clear if the studies included non-cirrhotic participants or gastric variceal bleeding
Qi 2007	Not a population of interest for this review
Queuniet 1987	Not a population of interest for this review
Rawat 2015	Not a comparison of interest for this review
Resnick 1969	Not a population of interest for this review
Resnick 1974	Not a population of interest for this review
Reynolds 1981	Not a population of interest for this review
Rhodes 1986	Not a comparison of interest for this review
Rikkers 1978	Not a population of interest for this review

Study	Reason for exclusion
Rikkers 1993	Not a population of interest for this review
Romero 2000	Not a population of interest for this review
Rosemurgy 1996	Not a population of interest for this review
Rossle 1997	Not a population of interest for this review
Russo 2000	Not a RCT
Saeed 1997	Not a population of interest for this review
Santambrogio 1990	Not a population of interest for this review
Santambrogio 2006	Additional treatments neither equal nor randomised between groups
Santos 2011	Not a population of interest for this review
Saraya 1993	Not clear if the studies included non-cirrhotic participants or gastric variceal bleeding
Sarin 1995	Not a comparison of interest for this review
Sarin 1997	Not a population of interest for this review
Sarin 2005	Not a population of interest for this review
Sauerbruch 2015	Not a comparison 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
Serwah 2002	Not clear if the studies included non-cirrhotic participants or gastric variceal bleeding
Shah 2001	Not a RCT
Sheikh 1998	Not a RCT
Shigemitsu 2000	Not a population of interest for this review
Shin 1998	Not a population of interest for this review
Silva 2004	Not a population of interest for this review
Siqueira 1998	Not clear if the studies included non-cirrhotic participants or gastric variceal bleeding
Smith 2013	Not clear if the studies included non-cirrhotic participants or gastric variceal bleeding
Sohn 2013	Not a population of interest for this review
Sotto 1989	Not a population of interest for this review

Study	Reason for exclusion
Spina 1990	Not a population of interest for this review
Srinivasan 1997	Not a RCT
Stanley 2014	Not clear if the studies included non-cirrhotic participants or gastric variceal bleeding
Sugano 1997	Not a population of interest for this review
Sugano 2001	Not a population of interest for this review
Sun 2013	Not a population of interest for this review
Sung 1998	Not a RCT
Svoboda 1992	Not a RCT
Taniai 2002	Not a RCT
Taranto 1990	Not a population of interest for this review
Taupignon 1989	Not a population of interest for this review
Terabayashi 1987	Not a comparison of interest for this review
Terblanche 1979	Not a population of interest for this review
Terblanche 1983	Not a population of interest for this review
Terblanche 1988	Not a RCT
Teres 1987	Not a population of interest for this review
Teres 1993	Not a population of interest for this review
Testa 1991	Not a population of interest for this review
Thiel 1993	Not a RCT
Tommasini 1989	Not a population of interest for this review
Triger 1992	Not a comparison of interest for this review
Tripathi 2004	Not a population of interest for this review
Umehara 1999	Not a population of interest for this review
Van Buuren 2000	Not clear if the studies included non-cirrhotic participants or gastric variceal bleeding
Van Buuren 2008	Not a population of interest for this review
Van Stiegmann 1993	Not a RCT
Vickers 1994	Not a population of interest for this review
Villanueva 1996	Not a population of interest for this review

Study	Reason for exclusion
Villanueva 2001	Not a population of interest for this review
Villanueva 2002	Not a RCT
Villanueva 2009	Not a comparison of interest for this review
Villanueva 2017	Not a comparison of interest for this review
Villeneuve 1986	Not a population of interest for this review
Vorobioff 2002	Not a population of interest for this review
Vorobioff 2007	Not a population of interest for this review
Wang 2012	Not a population of interest for this review
Westaby 1984	Not a population of interest for this review
Westaby 1985b	Not clear if the studies included non-cirrhotic participants or gastric variceal bleeding
Westaby 1986	Not a population of interest for this review
Westaby 1989	Not clear if the studies included non-cirrhotic participants or gastric variceal bleeding
Wiest 2002	Not a RCT
Witzel 1982	Not a population of interest for this review
Yoshida 2004	Not a RCT
Young 1993	Not a population of interest for this review
Zargar 2008	Not a population of interest for this review
Zhang 2008	Not a population of interest for this review
Zhao 1998	Not a population of interest for this review
Zhao 2013	Not a population of interest for this review
Zhou 2013	Not a RCT
Zhu 2004	Not a comparison of interest for this review
Zironi 1996	Not a population of interest for this review
Zuckerman 2016	Not a population of interest for this review

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

Jirón 1992

Methods	Not stated

Jirón 1992 *(Continued)*

Participants	Not stated
Interventions	Group 1: sclerotherapy Further details: not stated Group 2: beta-blocker Further details: propranolol
Outcomes	Not stated
Notes	Not available

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

ChiCTR-IIR-16007964

Study name	Sequential therapy with oesophageal varice ligation and sclerotherapy compared with ligation alone on the obliteration and recurrence of oesophageal varices in patients with decompensated cirrhosis-A randomized double-blinded controlled study
Methods	Randomised clinical trial
Participants	Inclusion/exclusion criteria Inclusion: 1) Consecutive patients with decompensated cirrhosis and oesophageal varices, with the age between 18-65 years old; 2) patients underwent endoscopic varices ligation therapy within 1 year, with current diameter of oesophageal varices<=0.6 cm; 3) all the enrolled patients signed informed consent Exclusion: 1) With liver cancer (>stage B in Barcelona Clinic Liver Cancer staging classification) or other malignancy; 2) with gastric varices or other ectopic varices; 3) with severe illness in heart, brain, lung or kidney, such as stroke, uremia, acute coronary syndrome, respiratory failure or type I hepatorenal syndrome; 4) no tolerance to endoscopy; 5) transjugular intrahepatic portosystemic stent shunt or surgery before entry; 6) total bilirubin >170 umol/L or Child-Pugh score >13; 7 without cirrhosis; 8 use of sclerotherapy or cyanoacrylate 1 year before entry
Interventions	Group 1: endoscopic variceal ligation Further details: undergoing regular ligation therapy until the obliteration of varice Group 2: sclerotherapy plus endoscopic variceal ligation Further details: undergoing regular sclerotherapy with diameter of varices≤0.6cm after ligation until the obliteration of varices
Outcomes	Planned outcomes: Primary: • Time to oesophageal variceal recurrence Secondary: • re-bleeding rate after 6 weeks and 1 year of index endoscopic therapy • mortality after 6 weeks and 1 year of index endoscopic therapy • time to oesophageal variceal obliteration

ChiCTR-IIR-16007964 *(Continued)*

	• number of endoscopic therapy sessions until the obliteration of varices
Starting date	From 1 March 2016
Contact information	Anjiang Wang waj1103b@163.com 17 Yongwai Main Street, West Nanjing Road, Donghu District, Nancang, Jiangxi, China
Notes	

NCT00966082

Study name	EBL versus EBL and propranolol for the prevention of variceal rebleeding in pts with previous variceal treatment
Methods	Randomised clinical trial
Participants	Inclusion/exclusion criteria Inclusion: • Liver cirrhosis • Age between 18 and 70 years • Successful control of oesophageal variceal bleeding within 6 weeks before enrolment Exclusion: • Gastric variceal bleeding • Patients with systolic blood pressure <100 mmHg or basal heart rate <60/minute • Portal vein thrombosis • Prominent hepatic encephalopathy • Coexisting untreated malignancy • Severe cerebrovascular or cardiovascular disease, renal failure • No previous history of endoscopic, radiologic, or surgical treatment for varices or ascites • Contraindication to beta-blocker • Pregnancy • Refusal to give consent to participate in the trial
Interventions	Group 1: endoscopic variceal ligation Further details: perform endoscopic band ligation until eradication of oesophageal varices, and then follow-up endoscopy with 3-6 months interval Group 2: endoscopic variceal ligation plus betablocker Further details: perform endoscopic band ligation until eradication of oesophageal varices, and then follow-up endoscopy with 3-6 months interval, with propranolol
Outcomes	Primary: Rebleeding from oesophageal varices (Time Frame: 2 years) Secondary: Upper gastrointestinal bleeding; significant oesophageal variceal bleeding; mortality; adverse events (Time Frame: 2 years)
Starting date	First posted 26 August 2009
Contact information	Soon Ho Um umsh@korea.ac.kr

NCT00966082 *(Continued)*	
	Yeon Seok Seo drseo@korea.ac.kr
Notes	

NCT02477384	
Study name	8mm-TIPS versus endoscopic variceal ligation (EVL) plus propranolol for prevention of variceal re-bleeding
Methods	Randomised clinical trial
Participants	Inclusion/exclusion criteria Inclusion: 1. Cirrhosis 2. Patients who had bled from oesophageal varices (≥5 days and ≤28 days) 3. Child-Pugh B or Child-Pugh C≤13 Exclusion: 1. Presence of gastric varices 2. Non-cirrhotic portal hypertension 3. Portal vein thrombosis 4. The history of hepatic encephalopathy 5. Total bilirubin ≥51.3 umol/L 6. Previous treatment of TIPS or surgery 7. Proven malignancy including hepatocellular carcinoma 8. Contraindications to TIPS, EVL or propranolol 9. End-stage renal disease under renal replacement therapy; 10.Cardiorespiratory failure 11.Pregnancy or patients not giving informed consent for endoscopic procedures
Interventions	Group 1: 8mm-TIPS Further details: patients in this group would underwent TIPS placement with 8mm-diameter ePTFE-covered stents Group 2: endoscopic variceal ligation plus betablocker Further details: patients in this group would underwent sequential endoscopic variceal ligation and propranolol treatment
Outcomes	Primary: • Variceal rebleeding rate (Time Frame: 3 years) Secondary: • Hepatic encephalopathy rate (Time Frame: 3 years) • Number of participants with improving or worsening hepatic function (Time Frame: 3 years) • TIPS dysfunction rate (Time Frame: 3 years) • The incidence of complications (Time Frame: 3 years) • Number of participants with improving or worsening quality of life (Time Frame: 3 years) • Mortality rate (Time Frame: 3 years)
Starting date	First posted 22 June 2015

NCT02477384 *(Continued)*

Contact information	Xuefeng Luo West China Hospital Chengdu, Sichuan, China, 610041
Notes	

NCT03094234

Study name	8mm-TIPS versus endoscopic variceal ligation (EVL) plus propranolol for prevention of variceal re-bleeding in patients with Child A cirrhosis
Methods	Randomised clinical trial
Participants	Inclusion/exclusion criteria Inclusion: cirrhosis patients who had bled from oesophageal varices (≥5 days and ≤28 days) Child-Pugh A Exclusion: presence of gastric varices, non-cirrhotic portal hypertension, portal vein thrombosis, history of hepatic encephalopathy, total bilirubin ≥51.3 umol/L, previous treatment of TIPS or surgery, proven malignancy including hepatocellular carcinoma, contraindications to TIPS, EVL or propranolol, end-stage renal disease under renal replacement therapy, cardiorespiratory failure, pregnancy or patients not giving informed consent for endoscopic procedure
Interventions	Group 1: 8 mm-TIPS Further details: patients in this group would underwent TIPS placement with 8 mm-diameter ePTFE-covered stents Group 2: endoscopic variceal ligation plus beta-blocker Further details: patients in this group would underwent sequential endoscopic variceal ligation and propranolol treatment
Outcomes	Primary: • Variceal rebleeding rate (Time Frame: 3 years) Secondary: • Hepatic encephalopathy rate (Time Frame: 3 years) • TIPS dysfunction rate (Time Frame: 3 years) • The incidence of complications (Time Frame: 3 years) • Mortality rate (Time Frame: 3 years)
Starting date	First posted 29 March 2017
Contact information	xuefeng luo luo_xuefeng@yeah.net
Notes	

NCT04074473

Study name	Impact of nonselective beta-blocker on acute kidney injury in cirrhotic patients with oesophageal varices
Methods	Randomised clinical trial
Participants	Inclusion/exclusion criteria

NCT04074473 *(Continued)*

	Inclusion: Age of 20 to 85 years Cirrhotic patients with oesophageal varices regardless of bleeding event or not will be enrolled in this study. Exclusion: Terminal stage hepatocellular carcinoma/other malignancy/stroke or active sepsis/chronic kidney disease stage 4 under renal replacement therapy/contraindications to non-selective beta-blockers/a 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 (NYHA Fc III/IV)/bronchial asthma or chronic obstructive pulmonary disease/second or third degree atrioventricular block/severe hypotension/refusal to participate
Interventions	Group 1: betablocker Further details: propranolol 10 mg twice daily initially and titrate dosage every week to achieve 25% drop of heart rate (keep heart rate> 55 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 (DC inderal after EV eradication) Further details: patients randomised to banding ligation group discontinue propranolol after eradication of oesophageal varices
Outcomes	Outcomes planned Primary: 1. Acute kidney injury (Time Frame: 3 years) 2. Heparenal syndrome (Time Frame: 3 years) 3. Overall survival (Time Frame: 3 years) Secondary: 1. EV bleeding/rebleeding (Time Frame: 3 years) 2. Infection rate (Time Frame: 3 years)
Starting date	Actual study start date 5 November 2015
Contact information	Ming-Chih Hou mchou@vghtpe.gov.tw Han-Chieh Lin hclin@vghtpe.gov.tw
Notes	

EBL: endoscopic band ligation; **ePTFE:** expanded polytetrafluoroethylene; **EVL:** endoscopic variceal ligation; **HBV:** hepatitis B virus; **NYHA:** New York Heart Association; **pts:** patients;**TIPS:** transjugular intrahepatic portosystemic shunt.

ADDITIONAL TABLES

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

Study name	Intervention 1 (number of participants) versus Intervention 2 (number of participants)	Included participants with other features of decompensation	Etiology of cirrhosis	Interval between variceal bleeding and treatment > 1 year	Period of recruitment	Follow-up in months	Overall risk of bias
Alexandrino 1988	Beta-blockers (34) versus Sclerotherapy (31)	Not stated	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Not stated Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: Participants with other-causes for cirrhosis and without other-causes for cirrhosis	No	Not stated	29	High
Andreani 1991	Beta-blockers (35) versus Sclerotherapy (40)	Not stated	Alcohol-related cirrhosis: Not stated Viral-related cirrhosis: Not stated Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: Not stated	No	1985 - 1988	12	High
Bader 1987	Beta-blockers (17) versus Sclerotherapy (18)	Not stated	Alcohol-related cirrhosis: Not stated Viral-related cirrhosis: Participants with viral-related cirrhosis and without viral-related cirrhosis Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: Not stated	No	1984-1986	14	High
Dasarathy 1992	Beta-blockers (46) versus Sclerotherapy (45)	Not stated	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Participants with viral-related cirrhosis and without viral-related cirrhosis Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: Participants with other-causes for cirrhosis and without other-causes for cirrhosis	Not stated	1996 - 1990	12	High

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

Dwivedi 1992	Beta-blockers (14) versus Sclerotherapy (16)	Yes (encephalopathy)	Alcohol-related cirrhosis: Not stated Viral-related cirrhosis: Not stated Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: Not stated	Not stated	1986 - 1987	7.5	High
Fleig 1988	Beta-blockers (50) versus Sclerotherapy (55)	Not stated	Alcohol-related cirrhosis: Not stated Viral-related cirrhosis: Not stated Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: Not stated	Not stated	1983 - Not stated	25	High
Martin 1991	Beta-blockers (34) versus Sclerotherapy (42)	Not stated	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: No participants had viral-related cirrhosis Autoimmune disease-related cirrhosis: No participants had autoimmune disease-related cirrhosis Other-causes for cirrhosis: Participants with other-causes for cirrhosis and without other-causes for cirrhosis	No	1984 - 1986	35.6	High
Rossi 1991	Beta-blockers (27) versus Sclerotherapy (26)	Yes (ascites)	Alcohol-related cirrhosis: All participants had alcohol-related cirrhosis Viral-related cirrhosis: No participants had viral-related cirrhosis Autoimmune disease-related cirrhosis: No participants had autoimmune disease-related cirrhosis Other-causes for cirrhosis: No participants had other-causes for cirrhosis	Not stated	1983 - 1987	19	High
Urbistondo 1996	Beta-blockers (15) versus Sclerotherapy (13)	Not stated	Alcohol-related cirrhosis: All participants had alcohol-related cirrhosis Viral-related cirrhosis: No participants had viral-related cirrhosis Autoimmune disease-related cirrhosis: No participants had autoimmune disease-related cirrhosis Other-causes for cirrhosis: No participants had other-causes for cirrhosis	No	1989 - 1994	23.2	High

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

Avgerinos 1997	Variceal band ligation (37) versus Sclerotherapy (40)	Yes (ascites)	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Participants with viral-related cirrhosis and without viral-related cirrhosis Autoimmune disease-related cirrhosis: Participants with autoimmune disease-related cirrhosis and without autoimmune disease-related cirrhosis Other-causes for cirrhosis: Participants with other-causes for cirrhosis and without other-causes for cirrhosis	No	1992 - 1993	15.2	High
Baroncini 1997	Variceal band ligation (57) versus Sclerotherapy (54)	Yes (encephalopathy)	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Participants with viral-related cirrhosis and without viral-related cirrhosis Autoimmune disease-related cirrhosis: Participants with autoimmune disease-related cirrhosis and without autoimmune disease-related cirrhosis Other-causes for cirrhosis: Participants with other-causes for cirrhosis and without other-causes for cirrhosis	Not stated	1993 - 1995	16.9	High
Kong 2015	Variceal band ligation (20) versus Sclerotherapy (18)	Not stated	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Participants with viral-related cirrhosis and without viral-related cirrhosis Autoimmune disease-related cirrhosis: Participants with autoimmune disease-related cirrhosis and without autoimmune disease-related cirrhosis Other-causes for cirrhosis: Participants with other-causes for cirrhosis and without other-causes for cirrhosis	Not stated	2008 - 2012	16	High
Viazis 2002	Variceal band ligation (36) versus	Not stated	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Not stated	1995 - 1998	1.8	High

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

	Sclerotherapy (37)		Viral-related cirrhosis: Participants with viral-related cirrhosis and without viral-related cirrhosis Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: Participants with other-causes for cirrhosis and without other-causes for cirrhosis				
Ahmad 2009	Variceal band ligation (39) versus Beta-blockers (39)	Yes (encephalopathy)	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Participants with viral-related cirrhosis and without viral-related cirrhosis Autoimmune disease-related cirrhosis: No participants had autoimmune disease-related cirrhosis Other-causes for cirrhosis: No participants had other-causes for cirrhosis	No	2003 - 2005	9	High
Kumar 2015	Variceal band ligation (56) versus Beta-blockers (47)	Not stated	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Not stated Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: Not stated	Not stated	Not stated	16.4	High
Avgerinos 1993	Beta-blockers plus Sclerotherapy (45) versus Sclerotherapy (40)	Not stated	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Participants with viral-related cirrhosis and without viral-related cirrhosis Autoimmune disease-related cirrhosis: Participants with autoimmune disease-related cirrhosis and without autoimmune disease-related cirrhosis Other-causes for cirrhosis: Participants with other-causes for cirrhosis and without other-causes for cirrhosis	No	1986 - 1989	23.9	High

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

Bertoni 1990	Beta-blockers plus Sclerotherapy (14) versus Sclerotherapy (14)	Not stated	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Participants with viral-related cirrhosis and without viral-related cirrhosis Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: Participants with other-causes for cirrhosis and without other-causes for cirrhosis	Not stated	Not stated	2	High
Fornaciari 1990	Beta-blockers plus Sclerotherapy (14) versus Sclerotherapy (14)	Not stated	Alcohol-related cirrhosis: Not stated Viral-related cirrhosis: Not stated Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: Not stated	Not stated	Not stated	3	High
Jensen 1989	Beta-blockers plus Sclerotherapy (15) versus Sclerotherapy (16)	Not stated	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Participants with viral-related cirrhosis and without viral-related cirrhosis Autoimmune disease-related cirrhosis: Participants with autoimmune disease-related cirrhosis and without autoimmune disease-related cirrhosis Other-causes for cirrhosis: Participants with other-causes for cirrhosis and without other-causes for cirrhosis	Not stated	1985 - 1987	9	High
Kanazawa 1991	Beta-blockers plus Sclerotherapy (20) versus Sclerotherapy (23)	Not stated	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Participants with viral-related cirrhosis and without viral-related cirrhosis Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: Not stated	Not stated	1985 - 1990	26.7	High
Lundell 1990	Beta-blockers plus Sclerotherapy (19) versus	Not stated	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Not stated	Not stated	7.9	High

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

	Sclerotherapy (22)		Viral-related cirrhosis: Not stated Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: Not stated				
Villanueva 1994	Beta-blockers plus Sclerotherapy (22) versus Sclerotherapy (18)	Not stated	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Not stated Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: Not stated	Not stated	1989 - 1991	26	High
Vinel 1992	Beta-blockers plus Sclerotherapy (39) versus Sclerotherapy (35)	Yes (encephalopathy)	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Not stated Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: Not stated	Not stated	Not stated	3.2	High
Ink 1992	Beta-blockers plus Sclerotherapy (65) versus Beta-blockers (66)	Yes (encephalopathy)	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Not stated Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: Not stated	No	1986 - 1989	24	High
Anonymous 1994	No active intervention (107) versus Sclerotherapy (97)	Yes (not stated)	Alcohol-related cirrhosis: All participants had alcohol-related cirrhosis Viral-related cirrhosis: No participants had viral-related cirrhosis Autoimmune disease-related cirrhosis: No participants had autoimmune disease-related cirrhosis Other-causes for cirrhosis: No participants had other-causes for cirrhosis	No	1985 - 1989	12	High
Mckee 1994	No active intervention (18) versus Sclerotherapy (22)	Not stated	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Participants with viral-related cirrhosis and without viral-related cirrhosis	Not stated	1986 - 1989	24	High

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

			Autoimmune disease-related cirrhosis: Participants with autoimmune disease-related cirrhosis and without autoimmune disease-related cirrhosis Other-causes for cirrhosis: Participants with other-causes for cirrhosis and without other-causes for cirrhosis				
Rossi 1991	No active intervention (26) versus Sclerotherapy (26)	Yes (ascites)	Alcohol-related cirrhosis: All participants had alcohol-related cirrhosis Viral-related cirrhosis: No participants had viral-related cirrhosis Autoimmune disease-related cirrhosis: No participants had autoimmune disease-related cirrhosis Other-causes for cirrhosis: No participants had other-causes for cirrhosis	Not stated	1983 - 1987	19	High
Westaby 1985a	No active intervention (60) versus Sclerotherapy (56)	Not stated	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Participants with viral-related cirrhosis and without viral-related cirrhosis Autoimmune disease-related cirrhosis: Participants with autoimmune disease-related cirrhosis and without autoimmune disease-related cirrhosis Other-causes for cirrhosis: Participants with other-causes for cirrhosis and without other-causes for cirrhosis	Not stated	1977 - 1981	37	High
Bonkovsky 1989	No active intervention (10) versus Beta-blockers (10)	Not stated	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Not stated Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: Not stated	Not stated	Not stated	12	High
Esquivel Lopez 1984	No active intervention (8) versus Beta-blockers (11)	Not stated	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Not stated	Not stated	Not stated	12	High

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

			Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: Not stated				
Jiron 1993	No active intervention (28) versus Beta-blockers (29)	Not stated	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Participants with viral-related cirrhosis and without viral-related cirrhosis Autoimmune disease-related cirrhosis: Participants with autoimmune disease-related cirrhosis and without autoimmune disease-related cirrhosis Other-causes for cirrhosis: Participants with other-causes for cirrhosis and without other-causes for cirrhosis	No	1983 - 1986	48	High
Rossi 1991	No active intervention (26) versus Beta-blockers (27)	Yes (ascites)	Alcohol-related cirrhosis: All participants had alcohol-related cirrhosis Viral-related cirrhosis: No participants had viral-related cirrhosis Autoimmune disease-related cirrhosis: No participants had autoimmune disease-related cirrhosis Other-causes for cirrhosis: No participants had other-causes for cirrhosis	Not stated	1983 - 1987	19	High
Sheen 1989	No active intervention (18) versus Beta-blockers (18)	Yes (encephalopathy)	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Participants with viral-related cirrhosis and without viral-related cirrhosis Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: Participants with other-causes for cirrhosis and without other-causes for cirrhosis	No	1983 - 1985	12.5	High
Cabrera 1996	TIPS (32) versus Sclerotherapy (31)	Yes (ascites)	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Not stated	No	1991 - 1994	15	High

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

			Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: not stated				
Garcia-Villarreal 1999	TIPS (22) versus Sclerotherapy (24)	Yes (ascites)	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Not stated Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: Not stated	No	1993 - 1997	20.6	High
Sanyal 1997	TIPS (41) versus Sclerotherapy (39)	Yes (encephalopathy)	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Participants with viral-related cirrhosis and without viral-related cirrhosis Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: Participants with other-causes for cirrhosis and without other-causes for cirrhosis	No	1991-1994	32	High
Jalan 1997	TIPS (31) versus Variceal band ligation (27)	Yes (encephalopathy)	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Participants with viral-related cirrhosis and without viral-related cirrhosis Autoimmune disease-related cirrhosis: Participants with autoimmune disease-related cirrhosis and without autoimmune disease-related cirrhosis Other-causes for cirrhosis: Participants with other-causes for cirrhosis and without other-causes for cirrhosis	No	1993 - 1995	16.2	High
Sauer 1997	TIPS (42) versus Beta-blockers plus Sclerotherapy (41)	Yes (ascites)	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Participants with viral-related cirrhosis and without viral-related cirrhosis	No	1992-1995	18	High

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

			Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: Participants with other-causes for cirrhosis and without other-causes for cirrhosis				
Ahmad 2009	Beta-blockers plus Nitrates (35) versus Beta-blockers (39)	Yes (encephalopathy)	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Participants with viral-related cirrhosis and without viral-related cirrhosis Autoimmune disease-related cirrhosis: No participants had autoimmune disease-related cirrhosis Other-causes for cirrhosis: No participants had other-causes for cirrhosis	No	2003 - 2005	9	High
Kumar 2015	Beta-blockers plus Nitrates (39) versus Beta-blockers (47)	Not stated	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Not stated Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: Not stated	Not stated	Not stated	16.4	High
Masliah 1997	Beta-blockers plus Nitrates (46) versus Beta-blockers (49)	Not stated	Alcohol-related cirrhosis: Not stated Viral-related cirrhosis: Not stated Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: Not stated	Not stated	1991 - 1996	29	High
Ahmad 2009	Beta-blockers plus Nitrates (35) versus Variceal band ligation (39)	Yes (encephalopathy)	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Participants with viral-related cirrhosis and without viral-related cirrhosis Autoimmune disease-related cirrhosis: No participants had autoimmune disease-related cirrhosis Other-causes for cirrhosis: No participants had other-causes for cirrhosis	No	2003 - 2005	9	High

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

Kumar 2015	Beta-blockers plus Nitrates (39) versus Variceal band ligation (56)	Not stated	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Not stated Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: Not stated	Not stated	Not stated	16.4	High
Henderson 1990	Portocaval shunt (35) versus Sclerotherapy (37)	Yes (encephalopathy)	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Participants with viral-related cirrhosis and without viral-related cirrhosis Autoimmune disease-related cirrhosis: Participants with autoimmune disease-related cirrhosis and without autoimmune disease-related cirrhosis Other-causes for cirrhosis: Participants with other-causes for cirrhosis and without other-causes for cirrhosis	Not stated	1981 - 1985	61	High
Isaksson 1995	Portocaval shunt (24) versus Sclerotherapy (21)	Yes (encephalopathy)	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Not stated Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: Not stated	Not stated	1982 - 1989	65.2	High
Urbistondo 1996	Portocaval shunt (15) versus Sclerotherapy (13)	Not stated	Alcohol-related cirrhosis: All participants had alcohol-related cirrhosis Viral-related cirrhosis: No participants had viral-related cirrhosis Autoimmune disease-related cirrhosis: No participants had autoimmune disease-related cirrhosis Other-causes for cirrhosis: No participants had other-causes for cirrhosis	No	1989 - 1994	23.2	High
Ampelas 1987	Portocaval shunt (24) versus Beta-blockers (26)	Not stated	Alcohol-related cirrhosis: Not stated Viral-related cirrhosis: Not stated Autoimmune disease-related cirrhosis: Not stated	No	Not stated	18	High

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

			Other-causes for cirrhosis: Not stated				
Parelon 1989	Portocaval shunt (24) versus Beta-blockers (26)	Not stated	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Not stated Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: Not stated	Not stated	1982 - 1985	39	High
Urbistondo 1996	Portocaval shunt (15) versus Beta-blockers (15)	Not stated	Alcohol-related cirrhosis: All participants had alcohol-related cirrhosis Viral-related cirrhosis: No participants had viral-related cirrhosis Autoimmune disease-related cirrhosis: No participants had autoimmune disease-related cirrhosis Other-causes for cirrhosis: No participants had other-causes for cirrhosis	No	1989 - 1994	23.2	High
Argonz 2000	Sclerotherapy plus Variceal band ligation (39) versus Variceal band ligation (41)	Yes (ascites)	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Participants with viral-related cirrhosis and without viral-related cirrhosis Autoimmune disease-related cirrhosis: Participants with autoimmune disease-related cirrhosis and without autoimmune disease-related cirrhosis Other-causes for cirrhosis: Participants with other-causes for cirrhosis and without other-causes for cirrhosis	Not stated	1994 - 1997	12	High
Baroncini 1996	Sclerotherapy plus Variceal band ligation () versus Variceal band ligation ()	Not stated	Alcohol-related cirrhosis: Not stated Viral-related cirrhosis: Not stated Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: Not stated	Not stated	1995 - 1996	4	High
Cennamo 1998	Sclerotherapy plus Variceal band ligation (16) versus	Not stated	Alcohol-related cirrhosis: Not stated Viral-related cirrhosis: Not stated Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: Not stated	Not stated	1996 - 1998	12.6	High

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

	Variceal band ligation (18)						
Romero 2006	Sclerotherapy plus Variceal band ligation (52) versus Beta-blockers plus Nitrates (57)	Yes (ascites)	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Participants with viral-related cirrhosis and without viral-related cirrhosis Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: Participants with other-causes for cirrhosis and without other-causes for cirrhosis	Not stated	1998 - 2002	11.7	High
Ahmad 2009	Beta-blockers plus Nitrates plus Variceal band ligation (37) versus Beta-blockers (39)	Yes (encephalopathy)	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Participants with viral-related cirrhosis and without viral-related cirrhosis Autoimmune disease-related cirrhosis: No participants had autoimmune disease-related cirrhosis Other-causes for cirrhosis: No participants had other-causes for cirrhosis	No	2003 - 2005	9	High
Ahmad 2009	Beta-blockers plus Nitrates plus Variceal band ligation (37) versus Variceal band ligation (39)	Yes (encephalopathy)	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Participants with viral-related cirrhosis and without viral-related cirrhosis Autoimmune disease-related cirrhosis: No participants had autoimmune disease-related cirrhosis Other-causes for cirrhosis: No participants had other-causes for cirrhosis	No	2003 - 2005	9	High
Ahmad 2009	Beta-blockers plus Nitrates plus Variceal band ligation (37) versus Be-	Yes (encephalopathy)	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Participants with viral-related cirrhosis and without viral-related cirrhosis	No	2003 - 2005	9	High

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

	ta-blockers plus Nitrates (35)		Autoimmune disease-related cirrhosis: No participants had autoimmune disease-related cirrhosis Other-causes for cirrhosis: No participants had other-causes for cirrhosis				
García-Pagán 2009	Beta-blockers plus Nitrates plus Variceal band ligation (80) versus Beta-blockers plus Nitrates (78)	Yes (ascites)	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Participants with viral-related cirrhosis and without viral-related cirrhosis Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: Participants with other-causes for cirrhosis and without other-causes for cirrhosis	No	2003 - 2005	15	High
Sauer 2002	Beta-blockers plus Variceal band ligation (42) versus TIPS (43)	Yes (ascites)	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Participants with viral-related cirrhosis and without viral-related cirrhosis Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: Participants with other-causes for cirrhosis and without other-causes for cirrhosis	No	1995 - 1999	46.8	High
Bertoni 1994	Sclerotherapy plus Nitrates (37) versus Sclerotherapy (39)	Not stated	Alcohol-related cirrhosis: Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis Viral-related cirrhosis: Participants with viral-related cirrhosis and without viral-related cirrhosis Autoimmune disease-related cirrhosis: Not stated Other-causes for cirrhosis: Participants with other-causes for cirrhosis and without other-causes for cirrhosis	No	1990 - 1992	2	High

Table 2. Risk of bias (ordered by comparisons)

Study name	Intervention 1 (number of participants) versus Intervention 2 (number of participants)	Sequence generation	Allocation concealment	Blinding of patients and healthcare providers	Blinding of outcome assessors	Missing outcome bias	Selective outcome reporting	Other bias	Overall risk of bias
Alexandrino 1988	Beta-blockers (34) versus Sclerotherapy (31)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	High
Andreani 1991	Beta-blockers (35) versus Sclerotherapy (40)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
Bader 1987	Beta-blockers (17) versus Sclerotherapy (18)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
Dasarathy 1992	Beta-blockers (46) versus Sclerotherapy (45)	Unclear	Unclear	Unclear	Unclear	High	Low	Low	High
Dwivedi 1992	Beta-blockers (14) versus Sclerotherapy (16)	Low	Unclear	Unclear	Unclear	High	Unclear	Low	High
Fleig 1988	Beta-blockers (50) versus Sclerotherapy (55)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
Martin 1991	Beta-blockers (34) versus Sclerotherapy (42)	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	High
Rossi 1991	Beta-blockers (27) versus Sclerotherapy (26)	Unclear	Low	High	Low	Low	Unclear	Low	High
Urbistondo 1996	Beta-blockers (15) versus Sclerotherapy (13)	Low	Unclear	Unclear	Unclear	Low	Unclear	Low	High
Avgerinos 1997	Variceal band ligation (37) versus Sclerotherapy (40)	Low	Unclear	Unclear	Unclear	Low	Low	Low	High
Baroncini 1997	Variceal band ligation (57) versus Sclerotherapy (54)	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	High
Kong 2015	Variceal band ligation (20) versus Sclerotherapy (18)	Low	Unclear	Unclear	Unclear	Low	Low	Low	High
Viazis 2002	Variceal band ligation (36) versus Sclerotherapy (37)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	High

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

Ahmad 2009	Variceal band ligation (39) versus Beta-blockers (39)	Low	Low	Unclear	Unclear	High	Unclear	Low	High
Kumar 2015	Variceal band ligation (56) versus Beta-blockers (47)	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	High
Avgerinos 1993	Beta-blockers plus Sclerotherapy (45) versus Sclerotherapy (40)	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	High
Bertoni 1990	Beta-blockers plus Sclerotherapy (14) versus Sclerotherapy (14)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	High
Fornaciari 1990	Beta-blockers plus Sclerotherapy (14) versus Sclerotherapy (14)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	High
Jensen 1989	Beta-blockers plus Sclerotherapy (15) versus Sclerotherapy (16)	Low	Low	Low	Low	Unclear	Low	Low	High
Kanazawa 1991	Beta-blockers plus Sclerotherapy (20) versus Sclerotherapy (23)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
Lundell 1990	Beta-blockers plus Sclerotherapy (19) versus Sclerotherapy (22)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	High	High
Villanueva 1994	Beta-blockers plus Sclerotherapy (22) versus Sclerotherapy (18)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
Vinel 1992	Beta-blockers plus Sclerotherapy (39) versus Sclerotherapy (35)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
Ink 1992	Beta-blockers plus Sclerotherapy (65) versus Beta-blockers (66)	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	High
Anonymous 1994	No active intervention (107) versus Sclerotherapy (97)	Unclear	Unclear	Low	Low	Low	Unclear	Low	High
Mckee 1994	No active intervention (18) versus Sclerotherapy (22)	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	High
Rossi 1991	No active intervention (26) versus Sclerotherapy (26)	Unclear	Low	High	Low	Low	Unclear	Low	High

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

Westaby 1985a	No active intervention (60) versus Sclerotherapy (56)	Unclear	Unclear	High	High	Low	Unclear	Low	High
Bonkovsky 1989	No active intervention (10) versus Beta-blockers (10)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
Esquivel Lopez 1984	No active intervention (8) versus Beta-blockers (11)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
Jiron 1993	No active intervention (28) versus Beta-blockers (29)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
Rossi 1991	No active intervention (26) versus Beta-blockers (27)	Unclear	Low	High	Low	Low	Unclear	Low	High
Sheen 1989	No active intervention (18) versus Beta-blockers (18)	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	High
Cabrera 1996	TIPS (32) versus Sclerotherapy (31)	Low	Unclear	Unclear	Unclear	Low	Low	Low	High
Garcia-Villarreal 1999	TIPS (22) versus Sclerotherapy (24)	Low	Unclear	Unclear	Unclear	Low	Unclear	Low	High
Sanyal 1997	TIPS (41) versus Sclerotherapy (39)	Low	Unclear	High	High	Low	Unclear	Low	High
Jalan 1997	TIPS (31) versus Variceal band ligation (27)	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	High
Sauer 1997	TIPS (42) versus Beta-blockers plus Sclerotherapy (41)	Low	Low	High	High	Low	Low	Low	High
Ahmad 2009	Beta-blockers plus Nitrates (35) versus Beta-blockers (39)	Low	Low	Unclear	Unclear	High	Unclear	Low	High
Kumar 2015	Beta-blockers plus Nitrates (39) versus Beta-blockers (47)	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	High
Masliah 1997	Beta-blockers plus Nitrates (46) versus Beta-blockers (49)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
Ahmad 2009	Beta-blockers plus Nitrates (35) versus Variceal band ligation (39)	Low	Low	Unclear	Unclear	High	Unclear	Low	High

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

Kumar 2015	Beta-blockers plus Nitrates (39) versus Variceal band ligation (56)	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	High
Henderson 1990	Portocaval shunt (35) versus Sclerotherapy (37)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	High
Isaksson 1995	Portocaval shunt (24) versus Sclerotherapy (21)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
Urbistondo 1996	Portocaval shunt (15) versus Sclerotherapy (13)	Low	Unclear	Unclear	Unclear	Low	Unclear	Low	High
Ampelas 1987	Portocaval shunt (24) versus Beta-blockers (26)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
Parelon 1989	Portocaval shunt (24) versus Beta-blockers (26)	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low	High
Urbistondo 1996	Portocaval shunt (15) versus Beta-blockers (15)	Low	Unclear	Unclear	Unclear	Low	Unclear	Low	High
Argonz 2000	Sclerotherapy plus Variceal band ligation (39) versus Variceal band ligation (41)	Low	Low	Unclear	Unclear	Low	Low	High	High
Baroncini 1996	Sclerotherapy plus Variceal band ligation () versus Variceal band ligation ()	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
Cennamo 1998	Sclerotherapy plus Variceal band ligation (16) versus Variceal band ligation (18)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
Romero 2006	Sclerotherapy plus Variceal band ligation (52) versus Beta-blockers plus Nitrates (57)	Low	Low	Unclear	Unclear	Low	Low	Low	High
Ahmad 2009	Beta-blockers plus Nitrates plus Variceal band ligation (37) versus Beta-blockers (39)	Low	Low	Unclear	Unclear	High	Unclear	Low	High
Ahmad 2009	Beta-blockers plus Nitrates plus Variceal band ligation (37) versus Variceal band ligation (39)	Low	Low	Unclear	Unclear	High	Unclear	Low	High
Ahmad 2009	Beta-blockers plus Nitrates plus Variceal band ligation (37) versus Beta-blockers plus Nitrates (35)	Low	Low	Unclear	Unclear	High	Unclear	Low	High

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

García-Pagán 2009	Beta-blockers plus Nitrates plus Variceal band ligation (80) versus Beta-blockers plus Nitrates (78)	Low	Low	Unclear	Unclear	Low	Low	Low	High
Sauer 2002	Beta-blockers plus Variceal band ligation (42) versus TIPS (43)	Low	Low	Unclear	Unclear	Low	Unclear	Low	High
Bertoni 1994	Sclerotherapy plus Nitrates (37) versus Sclerotherapy (39)	Low	Unclear	Low	Low	Low	Unclear	Low	High

Table 3. Network meta-analysis model fit

Mortality	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	402	390.4	391
DIC	454.3	451.9	459.3
pD	52.38	61.45	68.36
Serious adverse events (number of people)	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	29.49	381.7	381.8
DIC	35.52	440.9	447.6
pD	6.026	59.2	65.82
Any adverse events (number of people)	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	101.1	102	101.1
DIC	120.1	122	118.2
pD	18.97	20.04	17.14
Any adverse events (number of events)	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	112.2	112.1	94.85
DIC	125.1	125.1	110.7
pD	12.96	12.93	15.87
Liver transplantation	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	27.01	152	150.5
DIC	33.49	175.7	176.3
pD	6.486	23.75	25.78
Symptomatic variceal rebleed	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	82.88	74.73	74.66
DIC	97.66	91.41	91.34
pD	14.77	16.69	16.68
Any variceal rebleed	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	222.9	216.3	216.7

Table 3. Network meta-analysis model fit *(Continued)*

DIC	252.7	251.9	256.5
pD	29.8	35.63	39.82
Other features of decompensation	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	55.92	55.9	-
DIC	66.58	66.53	-
pD	10.66	10.63	-

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

Table 4. Effect estimates

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The table provides the effect estimates 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, say A versus B, look at the cell that occupies the row corresponding to intervention A and the column corresponding to intervention B for the effect estimate that is obtained directly. If that cell is empty (indicated by a '-'), look at 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 exactly the opposite; look at the cell that occupies the column corresponding to intervention A and the row corresponding to intervention B for the direct effect estimate. If that cell is empty, look at 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. Green colour indicates that the intervention A is better than B and red colour indicates that the intervention A is worse than B.
Additional information
The credible intervals for adverse events (number of participants) is extremely wide for some comparisons. This is because of the major differences in the proportion of participants with adverse events between the interventions in some direct comparisons, which might increase even further (depending upon the data) when indirect evidence is calculated.
Because of the confusion that arose when we reported the 'no active intervention' (which is not the current standard clinical practice) as intervention versus another more common intervention used in clinical practice, we have inverted the intervention and control for comparisons involving no active intervention. This would result in differences between the effect estimates in this table and text.

APPENDICES

Appendix 1. Search strategies

Database	Time span	Search strategy
Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	Issue 12, 2019	#1 MeSH descriptor: [Esophageal and Gastric Varices] explode all trees #2 *esophageal varic* #3 #1 or #2
MEDLINE Ovid	January 1947 to December 2019	1. exp "Esophageal and Gastric Varices"/

(Continued)

		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	January 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)	January 1945 to December 2019	#1 TS= (*esophageal varic*) #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

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WHAT'S NEW

Date	Event	Description
6 September 2022	Amended	An error about the reason for exclusion of the study Sauerbruch 2015 was corrected.

HISTORY

Protocol first published: Issue 9, 2018
Review first published: Issue 3, 2021

CONTRIBUTIONS OF AUTHORS

Protocol

Conceiving the protocol: KG
Designing the protocol: KG
Coordinating 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, DF
Writing the review: KG, LB
Providing advice on the review: SF, AJS, NC, EJM, MC, CSP, BRD, ET
Securing funding for the review: KG
All authors gave their final approval of the current review version to be published.

DECLARATIONS OF INTEREST

None known for any of the authors.

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

1. Title change. The protocol had the following title: "Secondary prevention of bleeding in people with previous oesophageal variceal bleeding due to decompensated liver cirrhosis: a network meta-analysis"
2. We clarified that we are evaluating the initial treatments rather than treatment of refractory bleeding after secondary prevention interventions.
3. We have added information about the definitions of treatment nodes and the ‘decision set’ to improve clarity.
4. We used the 'sclerotherapy' (endoscopic sclerotherapy) as the reference group (changed from 'non cardioselective beta-blockers'), as sclerotherapy was the commonest intervention compared in the trials.
5. We removed the sentence 'We excluded such quasi-randomised studies.' from the two bias risk domains on randomisation, as we write in Types of studies that we would not include non-randomised studies.
6. We have replaced 'For profit' bias domain has been replaced with an Other bias domain. This was based on the guidance from CHBG.
7. 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.
8. We used the latest guidance from the GRADE Working group (Yepes-Nunez 2019) rather than the previous guidance (Puhan 2014) for presenting the 'Summary of findings' table.
9. 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.
10. 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 rebleeding were reported, as we anticipated these outcomes to be routinely measured in clinical trials of this nature.
11. 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.
12. 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 have highlighted this clearly within the text of the review along with the reasons for not presenting them.
13. We performed additional analyses following peer reviewer comments. The rationale for the additional analyses and impact on results are provided in the main text.

NOTES

The methods section of this protocol is 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).

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic beta-2 Receptor Antagonists [therapeutic use]; Bias; Esophageal and Gastric Varices [*complications] [mortality]; Gastrointestinal Hemorrhage [etiology] [mortality] [*prevention & control]; Ligation [adverse effects] [methods]; Liver Cirrhosis [*complications]; Liver Transplantation [statistics & numerical data]; *Network Meta-Analysis; Nitrates [therapeutic use]; *Portasystemic Shunt, Transjugular Intrahepatic [statistics & numerical data]; Randomized Controlled Trials as Topic; Sclerotherapy [adverse effects] [mortality]; Secondary Prevention [*methods]

MeSH check words

Adult; Humans; Middle Aged