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[Intervention Review]

Treatment for bleeding oesophageal varices in people with decompensated liver cirrhosis: a network meta-analysis

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ABSTRACT

Background

Approximately 40% to 95% of people with liver cirrhosis have oesophageal varices. About 15% to 20% of oesophageal varices bleed within about one to three years after diagnosis. Several different treatments are available, including, among others, endoscopic sclerotherapy, variceal band ligation, somatostatin analogues, vasopressin analogues, and balloon tamponade. However, there is uncertainty surrounding the individual and relative benefits and harms of these treatments.

Objectives

To compare the benefits and harms of different initial treatments for variceal bleeding from oesophageal varices in adults with decompensated liver cirrhosis, through a network meta-analysis; and to generate rankings of the different treatments for acute bleeding oesophageal varices, according to their benefits and harms.

Search methods

We searched CENTRAL, MEDLINE, Embase, Science Citation Index Expanded, World Health Organization International Clinical Trials Registry Platform, and trials registers until 17 December 2019, to identify randomised clinical trials (RCTs) in people with cirrhosis and acute bleeding from oesophageal varices.

Selection criteria

We included only RCTs (irrespective of language, blinding, or status) in adults with cirrhosis and acutely bleeding oesophageal varices. We excluded RCTs in which participants had bleeding only from gastric varices, those who failed previous treatment (refractory bleeding), those in whom initial haemostasis was achieved before inclusion into the trial, and those who had previously undergone liver transplantation.

Data collection and analysis

We performed a network meta-analysis with OpenBUGS software, using Bayesian methods, and calculated the differences in treatments using 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. We performed also the direct comparisons from RCTs using the same codes and the same technical details.

Main results

We included a total of 52 RCTs (4580 participants) in the review. Forty-eight trials (4042 participants) were included in one or more comparisons in the review. The trials that provided the information included people with cirrhosis due to varied aetiologies and those with and without a previous history of bleeding. We included outcomes assessed up to six weeks. All trials were at high risk of bias.

A total of 19 interventions were compared in the trials (sclerotherapy, somatostatin analogues, vasopressin analogues, sclerotherapy plus somatostatin analogues, variceal band ligation, balloon tamponade, somatostatin analogues plus variceal band ligation, nitrates plus vasopressin analogues, no active intervention, sclerotherapy plus variceal band ligation, balloon tamponade plus sclerotherapy, balloon tamponade plus somatostatin analogues, balloon tamponade plus vasopressin analogues, variceal band ligation plus vasopressin analogues, balloon tamponade plus nitrates plus vasopressin analogues, balloon tamponade plus variceal band ligation, portocaval shunt, sclerotherapy plus transjugular intrahepatic portosystemic shunt (TIPS), and sclerotherapy plus vasopressin analogues). We have reported the effect estimates for the primary and secondary outcomes when there was evidence of differences between the interventions against the reference treatment of sclerotherapy, but reported the other results of the primary and secondary outcomes versus the reference treatment of sclerotherapy without the effect estimates when there was no evidence of differences in order to provide a concise summary of the results.

Overall, 15.8% of the trial participants who received the reference treatment of sclerotherapy (chosen because this was the commonest treatment compared in the trials) died during the follow-up periods, which ranged from three days to six weeks. Based on moderate-certainty evidence, somatostatin analogues alone had higher mortality than sclerotherapy (OR 1.57, 95% CrI 1.04 to 2.41; network estimate; direct comparison: 4 trials; 353 participants) and vasopressin analogues alone had higher mortality than sclerotherapy (OR 1.70, 95% CrI 1.13 to 2.62; network estimate; direct comparison: 2 trials; 438 participants).

None of the trials reported health-related quality of life. Based on low-certainty evidence, a higher proportion of people receiving balloon tamponade plus sclerotherapy had more serious adverse events than those receiving only sclerotherapy (OR 4.23, 95% CrI 1.22 to 17.80; direct estimate; 1 RCT; 60 participants).

Based on moderate-certainty evidence, people receiving vasopressin analogues alone and those receiving variceal band ligation had fewer adverse events than those receiving only sclerotherapy (rate ratio 0.59, 95% CrI 0.35 to 0.96; network estimate; direct comparison: 1 RCT; 219 participants; and rate ratio 0.40, 95% CrI 0.21 to 0.74; network estimate; direct comparison: 1 RCT; 77 participants; respectively). Based on low-certainty evidence, the proportion of people who developed symptomatic rebleed was smaller in people who received sclerotherapy plus somatostatin analogues than those receiving only sclerotherapy (OR 0.21, 95% CrI 0.03 to 0.94; direct estimate; 1 RCT; 105 participants).

The evidence suggests considerable uncertainty about the effect of the interventions in the remaining comparisons where sclerotherapy was the control intervention.

Authors' conclusions

Based on moderate-certainty evidence, somatostatin analogues alone and vasopressin analogues alone (with supportive therapy) probably result in increased mortality, compared to endoscopic sclerotherapy. Based on moderate-certainty evidence, vasopressin analogues alone and band ligation alone probably result in fewer adverse events compared to endoscopic sclerotherapy. Based on low-certainty evidence, balloon tamponade plus sclerotherapy may result in large increases in serious adverse events compared to sclerotherapy. Based on low-certainty evidence, sclerotherapy plus somatostatin analogues may result in large decreases in symptomatic rebleed compared to sclerotherapy. In the remaining comparisons, the evidence indicates considerable uncertainty about the effects of the interventions, compared to sclerotherapy.

PLAIN LANGUAGE SUMMARY

Treatment for bleeding from enlarged veins in the oesophagus (food pipe) in people with advanced scarring of the liver

What is the aim of this Cochrane Review?

To find out the best available treatment for bleeding from oesophageal varices (enlarged veins in the oesophagus) in people with advanced scarring of the liver (liver cirrhosis, or late-stage scarring of the liver with complications). Bleeding from oesophageal varices in people with cirrhosis is a life-threatening event. Therefore, it is important to treat people when this happens, but the benefits and harms of different treatments available are currently unclear. The review authors collected and analysed all relevant randomised clinical trials (studies where participants are randomly assigned to one of two or more treatment groups) with the aim of finding out what the best treatment is. They found 52 randomised clinical trials. During analysis of data, the review authors used standard Cochrane methods, which allow the

comparison of only two treatments at a time. The 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
17 December 2019

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 bleeding oesophageal varices. Participants were given different treatments for bleeding oesophageal varices. The authors excluded studies in people who had bleeding from the stomach, failed treatment by another method before study entry, those in whom bleeding was controlled by another method before taking part in the study, and those who previously had liver transplantation. The average age of participants, when reported, ranged from 39 to 62 years. The treatments used in the trials included endoscopic sclerotherapy (injecting a scar-forming liquid into the enlarged veins (the scarring blocks the veins thereby shrinking the 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), somatostatin analogues (drugs that resemble gut hormones and narrow blood vessels), vasopressin analogues (drugs that resemble brain hormones and narrow blood vessels), and balloon tamponade (inserting a tube through the nose or mouth and inflating a balloon around the tube with the hope of pressing on the bleeding veins). The review authors wanted to gather and analyse data on death (percentage of participants who died within six weeks of receiving treatment), quality of life, serious adverse events and non-serious adverse events (i.e. serious and non-serious complications), recurrence of bleeding, and development of other complications of advanced liver disease.

What were the main results of the review?
The 52 trials included a small number of participants (4580 participants). Forty-eight trials with 4042 participants provided data for analyses. The follow-up of the trial participants ranged from less than one week to six weeks. The funding source for the research was unclear in 31 studies; commercial organisations funded 11 studies. There were no concerns regarding the source of funding for the remaining 10 studies. The review shows the following.

- None of the studies were conducted without flaws, and because of this, there is moderate to very high uncertainty in the findings.
- Approximately one in six people with cirrhosis and bleeding oesophageal varices who received the standard treatment of sclerotherapy died within six weeks.
- Somatostatin analogues alone and vasopressin analogues alone probably result in increased mortality, compared to sclerotherapy.
- Vasopressin analogues alone and band ligation alone probably result in fewer adverse events (complications), compared to sclerotherapy.
- Balloon tamponade plus sclerotherapy may result in large increase in serious adverse events compared to sclerotherapy.
- Sclerotherapy plus somatostatin analogues may result in large decrease in symptomatic rebleed compared to 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 randomised clinical trials are needed to find out the best treatment for people with cirrhosis and bleeding oesophageal varices.

Summary of findings 1. Treatment for bleeding oesophageal varices in people with decompensated liver cirrhosis (six commonest interventions)

Patient or population: people with liver cirrhosis and bleeding oesophageal varices
Settings: secondary or tertiary care
Intervention: various interventions
Comparison: sclerotherapy
Follow-up period: 3 days to 6 weeks

Outcomes/Interventions	Somatostatin analogues		Vasopressin analogues		Sclerotherapy plus somatostatin analogues		Variceal band ligation		Balloon tamponade	
Mortality										
Sclerotherapy 158 per 1000 (15.8%)	**OR 1.57** (1.04 to 2.41) **Network estimate**	**70 more per 1000** (6 more to 153 more)	**OR 1.70** (1.13 to 2.62) **Network estimate**	**84 more per 1000** (17 more to 172 more)	**OR 0.84** (0.56 to 1.26) **Network estimate**	**21 fewer per 1000** (63 fewer to 34 more)	**OR 0.90** (0.38 to 2.09) **Network estimate**	**13 fewer per 1000** (91 fewer to 124 more)	**OR 2.34** (0.96 to 5.92) **Network estimate**	**147 more per 1000** (6 fewer to 368 more)
	Moderate certainty [1]		**Moderate certainty** [1]		**Low certainty** [1,2]		**Low certainty** [1,2]		**Low certainty** [1,2]	
	Based on 353 participants (4 RCT)		Based on 438 participants (2 RCT)		Based on 693 participants (6 RCT)		Based on 183 participants (3 RCT)		Based on 43 participants (1 RCT)	
Health-related quality of life										
None of the trials reported this outcome.										
Serious adverse events (number of participants)										
Sclerotherapy 53 per 1000 (5.3%)	-		**OR 1.10** (0.01 to 227.47) **Network estimate**	**5 more per 1000** (52 fewer to 874 more)	-		-		**OR 0.13** (0.00 to 954.32) **Network estimate**	**46 fewer per 1000** (53 fewer to 929 more)
			Very low certainty [1,4,5]						**Very low certainty** [1,4,5]	
			Based on 219 participants (1 RCT)						No direct RCT	

Serious adverse events (number of events)										
Sclerotherapy 70 per 1000 (7 per 100 participants)	-		**Rate ratio 0.52** (0.13 to 1.70) **Network estimate**	**34 fewer per 1000** (61 fewer to 49 more)	-		-		-	
			Very low certainty [1,5]							
			Based on 219 participants (1 RCT)							
Any adverse events (number of participants)										
Sclerotherapy 281 per 1000 (28.1%)	**OR 0.39** (0.06 to 2.53) **Network estimate**	**148 fewer per 1000** (258 fewer to 216 more)	**OR 1.27** (0.19 to 9.01) **Network estimate**	**51 more per 1000** (211 fewer to 498 more)	**OR 1.55** (0.03 to 92.11) **Network estimate**	**96 more per 1000** (270 fewer to 692 more)	**OR 0.41** (0.01 to 16.22) **Network estimate**	**142 fewer per 1000** (277 fewer to 583 more)	**OR 1.48** (0.08 to 26.44) **Network estimate**	**85 more per 1000** (250 fewer to 631 more)
	Very low certainty [1,2,4]		**Very low certainty** [1,2,4]		**Very low certainty** [1,2,4]		**Very low certainty** [1,2,4]		**Very low certainty** [1,2,4]	
	Based on 166 participants (2 RCT)		Based on 438 participants (2 RCT)		No direct RCT		Based on 81 participants (1 RCT)		Based on 43 participants (1 RCT)	
Any adverse events (number of events)										
Sclerotherapy 386 per 1000 (38.6 per 100 participants)	-		**Rate ratio 0.59** (0.35 to 0.96) **Network estimate**	**159 fewer per 1000** (251 fewer to 16 fewer)	**Rate ratio 1.07** (0.69 to 1.68) **Network estimate**	**28 more per 1000** (121 fewer to 261 more)	**Rate ratio 0.40** (0.21 to 0.74) **Network estimate**	**230 fewer per 1000** (304 fewer to 102 fewer)	**Rate ratio 0.44** (0.13 to 1.47) **Network estimate**	**217 fewer per 1000** (336 fewer to 182 more)
			Moderate certainty [1]		**Low certainty** [1,2]		**Moderate certainty** [1]		**Low certainty** [1,2]	
			Based on 219 participants (1 RCT)		Based on 199 participants (1 RCT)		Based on 77 participants (1 RCT)		No direct RCT	
Symptomatic variceal rebleed										
Sclerotherapy 148 per 1000	**OR 1.48** (0.05 to 41.68)	**56 more per 1000**	-		-		-		-	

(14.8%)	**Network estimate**	(139 fewer to 731 more)								
	Very low certainty [1,5]									
	Based on 146 participants (2 RCT)									
Any variceal rebleed										
Sclerotherapy 188 per 1000 (18.8%)	**OR 1.22** (0.40 to 4.12) **Network estimate**	**33 more per 1000** (103 fewer to 300 more)	**OR 1.19** (0.49 to 3.31) **Network estimate**	**28 more per 1000** (86 fewer to 246 more)	**OR 0.38** (0.13 to 1.08) **Network estimate**	**107 fewer per 1000** (159 fewer to 12 more)	**OR 0.44** (0.10 to 1.89) **Network estimate**	**95 fewer per 1000** (166 fewer to 117 more)	**OR 5.98** (0.74 to 57.17) **Network estimate**	**393 more per 1000** (43 fewer to 742 more)
	Low certainty [1,2]		**Low certainty** [1,2]		**Low certainty** [1,2]		**Low certainty** [1,2]		**Very low certainty** [1,2,4]	
	Based on 96 participants (1 RCT)		Based on 438 participants (2 RCT)		Based on 209 participants (2 RCT)		Based on 102 participants (2 RCT)		No direct RCT	
Other decompensation events										
Sclerotherapy 40 per 1000 (4 per 100 participants)	-		-		**Rate ratio 1.04** (0.23 to 4.97) **Network estimate**	**1 more per 1000** (31 fewer to 157 more)	-		-	
					Very low certainty [1,5]					
					Based on 199 participants (1 RCT)					

*Ranking was not provided because of the considerable uncertainty in the ranking.
CrI: Credible interval; **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 inconsistency because there was evidence of statistical heterogeneity
[5]Downgraded two levels for imprecision because the sample size was small and the credible intervals were wide (included clinical benefit and harms)
[6]Empty boxes mean that there was no direct evidence or indirect evidence for the comparison.

Summary of findings 2. Treatment for bleeding oesophageal varices in people with decompensated liver cirrhosis (all interventions)

Patient or population: people with liver cirrhosis and bleeding oesophageal varices
Settings: secondary or tertiary care
Intervention: various interventions
Comparison: sclerotherapy
Follow-up period: 3 days to 6 weeks

Interventions	Relative effect (95% CrI)	Anticipated absolute effect* (95% CrI)			Certainty of evidence
		Sclerotherapy	Various interventions	Difference	
Mortality **Total studies: 45** **Total participants: 3781**					
Sclerotherapy	**Reference**				
Somatostatin analogues (4 RCT; 353 participants)	**OR 1.57** (1.04 to 2.41) **Network estimate**	**158 per 1000**	**228 per 1000** (163 to 311)	**70 more per 1000** (6 more to 153 more)	**Moderate certainty** [1]
Vasopressin analogues (2 RCT; 438 participants)	**OR 1.70** (1.13 to 2.62) **Network estimate**	**158 per 1000**	**242 per 1000** (175 to 330)	**84 more per 1000** (17 more to 172 more)	**Moderate certainty** [1]
Sclerotherapy plus somatostatin analogues (6 RCT; 693 participants)	**OR 0.84** (0.56 to 1.26) **Network estimate**	**158 per 1000**	**137 per 1000** (95 to 192)	**21 fewer per 1000** (63 fewer to 34 more)	**Low certainty** [1,2]
Variceal band ligation (3 RCT; 183 participants)	**OR 0.90** (0.38 to 2.09) **Network estimate**	**158 per 1000**	**145 per 1000** (67 to 282)	**13 fewer per 1000** (91 fewer to 124 more)	**Low certainty** [1,2]
Somatostatin analogues plus variceal band ligation	**OR 0.54** (0.24 to 1.20)	**158 per 1000**	**92 per 1000** (43 to 183)	**66 fewer per 1000** (115 fewer to 25 more)	**Low certainty** [1,2]

(No direct RCT)	**Network estimate**				
Balloon tamponade (1 RCT; 43 participants)	**OR 2.34** (0.96 to 5.92) **Network estimate**	**158 per 1000**	**305 per 1000** (152 to 526)	**147 more per 1000** (6 fewer to 368 more)	**Low certainty** [1,2]
Nitrates plus vasopressin analogues (No direct RCT)	**OR 1.49** (0.68 to 3.27) **Network estimate**	**158 per 1000**	**218 per 1000** (114 to 380)	**60 more per 1000** (44 fewer to 222 more)	**Low certainty** [1,2]
No active intervention (No direct RCT)	**OR 1.47** (0.63 to 3.46) **Network estimate**	**158 per 1000**	**217 per 1000** (106 to 394)	**59 more per 1000** (52 fewer to 236 more)	**Low certainty** [1,2]
Sclerotherapy plus variceal band ligation (No direct RCT)	**OR 0.68** (0.15 to 3.06) **Network estimate**	**158 per 1000**	**113 per 1000** (28 to 364)	**45 fewer per 1000** (130 fewer to 206 more)	**Low certainty** [1,2]
Balloon tamponade plus sclerotherapy (1 RCT; 60 participants)	**OR 2.37** (0.75 to 7.77) **Network estimate**	**158 per 1000**	**308 per 1000** (124 to 593)	**150 more per 1000** (34 fewer to 435 more)	**Low certainty** [1,2]
Balloon tamponade plus somatostatin analogues (No direct RCT)	**OR 1.73** (0.51 to 5.47) **Network estimate**	**158 per 1000**	**245 per 1000** (88 to 506)	**87 more per 1000** (70 fewer to 348 more)	**Low certainty** [1,2]
Balloon tamponade plus vasopressin analogues (No direct RCT)	**OR 1.70** (0.46 to 6.33) **Network estimate**	**158 per 1000**	**242 per 1000** (80 to 543)	**84 more per 1000** (78 fewer to 385 more)	**Low certainty** [1,2]
Variceal band ligation plus vasopressin analogues (No direct RCT)	**OR 0.45** (0.12 to 1.70) **Network estimate**	**158 per 1000**	**78 per 1000** (22 to 241)	**80 fewer per 1000** (136 fewer to 84 more)	**Low certainty** [1,2]
Balloon tamponade plus nitrates plus vasopressin analogues (No direct RCT)	**OR 1.88** (0.28 to 12.94) **Network estimate**	**158 per 1000**	**261 per 1000** (50 to 708)	**103 more per 1000** (108 fewer to 550 more)	**Low certainty** [1,2]
Balloon tamponade plus variceal band ligation (No direct RCT)	**OR 0.63** (0.11 to 3.61) **Network estimate**	**158 per 1000**	**106 per 1000** (20 to 403)	**52 fewer per 1000** (138 fewer to 246 more)	**Low certainty** [1,2]
Portocaval shunt (1 RCT; 64 participants)	**OR 1.13** (0.40 to 3.26) **Network estimate**	**158 per 1000**	**175 per 1000** (70 to 379)	**17 more per 1000** (88 fewer to 222 more)	**Low certainty** [1,2]

Sclerotherapy plus TIPS (1 RCT; 49 participants)	**OR 1.39** (0.31 to 6.67) **Network estimate**	**158 per 1000**	**207 per 1000** (55 to 556)	**49 more per 1000** (103 fewer to 398 more)	**Low certainty** [1,2]
Sclerotherapy plus vasopressin analogues (No direct RCT)	**OR 0.42** (0.07 to 2.29) **Network estimate**	**158 per 1000**	**72 per 1000** (12 to 301)	**85 fewer per 1000** (146 fewer to 143 more)	**Low certainty** [1,2]
Health-related quality of life					
None of the trials reported this information.					
Serious adverse events (number of participants) **Total studies: 5** **Total participants: 422**					
Sclerotherapy	**Reference**				
Vasopressin analogues (1 RCT; 219 participants)	**OR 1.10** (0.01 to 227.47) **Network estimate**	**53 per 1000**	**58 per 1000** (0 to 927)	**5 more per 1000** (52 fewer to 874 more)	**Very low certainty** [1,3,5]
Balloon tamponade (No direct RCT)	**OR 0.13** (0.00 to 954.32) **Network estimate**	**53 per 1000**	**7 per 1000** (0 to 981)	**46 fewer per 1000** (53 fewer to 929 more)	**Very low certainty** [1,3,5]
Nitrates plus vasopressin analogues (No direct RCT)	**OR 0.15** (0.00 to 95.87) **Network estimate**	**53 per 1000**	**8 per 1000** (0 to 842)	**45 fewer per 1000** (53 fewer to 789 more)	**Very low certainty** [1,3,5]
Balloon tamponade plus sclerotherapy (1 RCT; 60 participants)	**OR 4.23** (1.22 to 17.80) **Direct estimate**	**53 per 1000**	**190 per 1000** (63 to 497)	**137 more per 1000** (10 more to 444 more)	**Low certainty** [1,4]
Serious adverse events (number of events) **Total studies: 1** **Total participants: 219**					
Sclerotherapy	**Reference**				
Vasopressin analogues (1 RCT; 219 participants)	**Rate ratio 0.52** (0.13 to 1.70) **Network estimate**	**70 per 1000**	**36 per 1000** (9 to 119)	**34 fewer per 1000** (61 fewer to 49 more)	**Very low certainty** [1,5]
Any adverse events (number of participants)					

Total studies: 14 **Total participants: 1318**					
Sclerotherapy	**Reference**				
Somatostatin analogues (2 RCT; 166 participants)	**OR 0.39** (0.06 to 2.53) **Network estimate**	**281 per 1000**	**133 per 1000** (23 to 497)	**148 fewer per 1000** (258 fewer to 216 more)	**Very low certainty** 1,2,3
Vasopressin analogues (2 RCT; 438 participants)	**OR 1.27** (0.19 to 9.01) **Network estimate**	**281 per 1000**	**331 per 1000** (70 to 779)	**51 more per 1000** (211 fewer to 498 more)	**Very low certainty** 1,2,3
Sclerotherapy plus somatostatin analogues (No direct RCT)	**OR 1.55** (0.03 to 92.11) **Network estimate**	**281 per 1000**	**376 per 1000** (11 to 973)	**96 more per 1000** (270 fewer to 692 more)	**Very low certainty** 1,2,3
Variceal band ligation (1 RCT; 81 participants)	**OR 0.41** (0.01 to 16.22) **Network estimate**	**281 per 1000**	**138 per 1000** (4 to 864)	**142 fewer per 1000** (277 fewer to 583 more)	**Very low certainty** 1,2,3
Somatostatin analogues plus variceal band ligation (No direct RCT)	**OR 0.66** (0.00 to 136.87) **Network estimate**	**281 per 1000**	**204 per 1000** (1 to 982)	**77 fewer per 1000** (279 fewer to 701 more)	**Very low certainty** 1,2,3
Balloon tamponade (1 RCT; 43 participants)	**OR 1.48** (0.08 to 26.44) **Network estimate**	**281 per 1000**	**366 per 1000** (31 to 912)	**85 more per 1000** (250 fewer to 631 more)	**Very low certainty** 1,2,3
Nitrates plus vasopressin analogues (No direct RCT)	**OR 0.83** (0.03 to 22.49) **Network estimate**	**281 per 1000**	**246 per 1000** (13 to 898)	**35 fewer per 1000** (268 fewer to 617 more)	**Very low certainty** 1,2,3
Balloon tamponade plus somatostatin analogues (No direct RCT)	**OR 1.63** (0.04 to 67.69) **Network estimate**	**281 per 1000**	**389 per 1000** (15 to 964)	**108 more per 1000** (265 fewer to 683 more)	**Very low certainty** 1,2,3
Any adverse events (number of events) **Total studies: 9** **Total participants: 996**					
Sclerotherapy	**Reference**				
Vasopressin analogues (1 RCT; 219 participants)	**Rate ratio 0.59** (0.35 to 0.96)	**386 per 1000**	**227 per 1000** (135 to 370)	**159 fewer per 1000** (251 fewer to 16 fewer)	**Moderate certainty** [1]

	Network estimate				
Sclerotherapy plus somatostatin analogues (1 RCT; 199 participants)	**Rate ratio 1.07** (0.69 to 1.68) **Network estimate**	**386 per 1000**	**414 per 1000** (265 to 647)	**28 more per 1000** (121 fewer to 261 more)	**Low certainty** [1,2]
Variceal band ligation (1 RCT; 77 participants)	**Rate ratio 0.40** (0.21 to 0.74) **Network estimate**	**386 per 1000**	**156 per 1000** (82 to 284)	**230 fewer per 1000** (304 fewer to 102 fewer)	**Moderate certainty** [1]
Somatostatin analogues plus variceal band ligation (No direct RCT)	**Rate ratio 0.53** (0.28 to 0.98) **Network estimate**	**386 per 1000**	**205 per 1000** (109 to 380)	**181 fewer per 1000** (277 fewer to 6 fewer)	**Moderate certainty** [1]
Balloon tamponade (No direct RCT)	**Rate ratio 0.44** (0.13 to 1.47) **Network estimate**	**386 per 1000**	**169 per 1000** (50 to 568)	**217 fewer per 1000** (336 fewer to 182 more)	**Low certainty** [1,2]
Nitrates plus vasopressin analogues (No direct RCT)	**Rate ratio 0.44** (0.19 to 1.00) **Network estimate**	**386 per 1000**	**169 per 1000** (73 to 385)	**217 fewer per 1000** (313 fewer to 1 fewer)	**Moderate certainty** [1]
Sclerotherapy plus variceal band ligation (No direct RCT)	**Rate ratio 1.49** (0.14 to 46.06) **Network estimate**	**386 per 1000**	**575 per 1000** (56 to 17779)	**189 more per 1000** (330 fewer to 17393 more)	**Low certainty** [1,2]
Balloon tamponade plus vasopressin analogues (No direct RCT)	**Rate ratio 0.81** (0.14 to 4.97) **Network estimate**	**386 per 1000**	**311 per 1000** (54 to 1917)	**74 fewer per 1000** (332 fewer to 1531 more)	**Low certainty** [1,2]
Symptomatic variceal rebleed **Total studies: 4** **Total participants: 311**					
Sclerotherapy	**Reference**				
Somatostatin analogues (2 RCT; 146 participants)	**OR 1.48** (0.05 to 41.68) **Network estimate**	**148 per 1000**	**204 per 1000** (9 to 879)	**56 more per 1000** (139 fewer to 731 more)	**Very low certainty** [1,5]
Sclerotherapy plus somatostatin analogues (1 RCT; 105 participants)	**OR 0.21** (0.03 to 0.94) **Direct estimate**	**148 per 1000**	**34 per 1000** (4 to 141)	**114 fewer per 1000** (144 fewer to 7 fewer)	**Low certainty** [1,4]

Balloon tamponade plus sclerotherapy (1 RCT; 60 participants)	**OR 2.53** (0.02 to 299.17) **Network estimate**	**148 per 1000**	**306 per 1000** (4 to 981)	**157 more per 1000** (144 fewer to 833 more)	**Very low certainty** 1,5
Any variceal rebleed **Total studies: 20** **Total participants: 1748**					
Sclerotherapy	**Reference**				
Somatostatin analogues (1 RCT; 96 participants)	**OR 1.22** (0.40 to 4.12) **Network estimate**	**188 per 1000**	**221 per 1000** (85 to 489)	**33 more per 1000** (103 fewer to 300 more)	**Low certainty** 1,2
Vasopressin analogues (2 RCT; 438 participants)	**OR 1.19** (0.49 to 3.31) **Network estimate**	**188 per 1000**	**216 per 1000** (103 to 435)	**28 more per 1000** (86 fewer to 246 more)	**Low certainty** 1,2
Sclerotherapy plus somatostatin analogues (2 RCT; 209 participants)	**OR 0.38** (0.13 to 1.08) **Network estimate**	**188 per 1000**	**81 per 1000** (29 to 200)	**107 fewer per 1000** (159 fewer to 12 more)	**Low certainty** 1,2
Variceal band ligation (2 RCT; 102 participants)	**OR 0.44** (0.10 to 1.89) **Network estimate**	**188 per 1000**	**93 per 1000** (22 to 305)	**95 fewer per 1000** (166 fewer to 117 more)	**Low certainty** 1,2
Somatostatin analogues plus variceal band ligation (No direct RCT)	**OR 0.21** (0.05 to 1.06) **Network estimate**	**188 per 1000**	**47 per 1000** (10 to 197)	**141 fewer per 1000** (178 fewer to 9 more)	**Low certainty** 1,2
Balloon tamponade (No direct RCT)	**OR 5.98** (0.74 to 57.17) **Network estimate**	**188 per 1000**	**581 per 1000** (146 to 930)	**393 more per 1000** (43 fewer to 742 more)	**Low certainty** 1,2
Sclerotherapy plus variceal band ligation (No direct RCT)	**OR 0.24** (0.01 to 4.15) **Network estimate**	**188 per 1000**	**54 per 1000** (3 to 491)	**135 fewer per 1000** (186 fewer to 302 more)	**Low certainty** 1,2
Balloon tamponade plus sclerotherapy (No direct RCT)	**OR 0.13** (0.01 to 1.19) **Network estimate**	**188 per 1000**	**30 per 1000** (3 to 217)	**159 fewer per 1000** (185 fewer to 29 more)	**Low certainty** 1,2
Balloon tamponade plus somatostatin analogues (No direct RCT)	**OR 1.56** (0.17 to 15.49) **Network estimate**	**188 per 1000**	**266 per 1000** (38 to 782)	**78 more per 1000** (150 fewer to 594 more)	**Low certainty** 1,2
Balloon tamponade plus vasopressin analogues	**OR 7.74** (0.66 to 104.17) **Network estimate**	**188 per 1000**	**642 per 1000** (133 to 960)	**454 more per 1000** (56 fewer to 772 more)	**Low certainty** 1,2

(No direct RCT)					
Variceal band ligation plus vasopressin analogues (No direct RCT)	**OR 0.23** (0.02 to 2.61) **Network estimate**	**188 per 1000**	**51 per 1000** (5 to 377)	**138 fewer per 1000** (184 fewer to 189 more)	**Low certainty** [1,2]
Balloon tamponade plus variceal band ligation (No direct RCT)	**OR 0.63** (0.02 to 37.34) **Network estimate**	**188 per 1000**	**128 per 1000** (5 to 897)	**60 fewer per 1000** (183 fewer to 708 more)	**Low certainty** [1,2]
Other decompensation events **Total studies: 2** **Total participants: 259**					
Sclerotherapy	**Reference**				
Sclerotherapy plus somatostatin analogues (1 RCT; 199 participants)	**Rate ratio 1.04** (0.23 to 4.97) **Network estimate**	**40 per 1000**	**41 per 1000** (9 to 197)	**1 more per 1000** (31 fewer to 157 more)	**Very low certainty** [1,5]
Balloon tamponade plus sclerotherapy (1 RCT; 60 participants)	**Rate ratio 0.95** (0.16 to 5.14) **Network estimate**	**40 per 1000**	**38 per 1000** (6 to 204)	**2 fewer per 1000** (34 fewer to 164 more)	**Very low certainty** [1,5]

*Ranking was not provided because of the considerable uncertainty in the ranking.
CrI: Credible interval; **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 inconsistency because there was evidence of statistical heterogeneity
[4]Downgraded one level for imprecision because the sample size was small
[5]Downgraded two levels for imprecision because the sample size was small and the credible intervals were wide (included clinical benefit and harms)

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 US, the prevalence of chronic liver disease varies between 0.3% and 2.1% (Scaglione 2015; Setiawan 2016); in the UK, the prevalence was 0.1% in one study (Fleming 2008). In 2010, liver cirrhosis was responsible for an estimated 2% of all global deaths, equivalent to one million deaths (Mokdad 2014). There is an increasing trend of cirrhosis-related deaths in some countries such as the UK, while there is a decreasing trend in other countries such as France (Mokdad 2014; Williams 2014). The major cause of complications and deaths in people with liver cirrhosis is 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), and they are a feature of clinically significant portal hypertension. The prevalence of oesophageal varices varies between 40% and 95% in people with cirrhosis (Chawla 2012; McCarty 2017). The annual incidence of oesophageal varices in people with cirrhosis varies from 3% to 22% (Cales 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 acknowledge this variability (Tripathi 2015; EASL 2018). These guidelines suggest that small varices tend to be narrow, flattening easily with air, during endoscopy; as compared to large varices which are usually broader and flatten with difficulty, or do not flatten at all (Tripathi 2015; EASL 2018). Other definitions for small oesophageal varices include less than 5 mm in size and less than 25% of oesophageal lumen (Abby Philips 2016). Other risk factors for bleeding from oesophageal varices include the pressure within the varices (hepatic venous pressure gradient at least 12 mmHg), increased tension on the variceal wall as indicated by red spots or red wale markings (longitudinal red streaks on the varices) on endoscopy, and severity of the liver disease (Beppu 1981; NIEC 1988; de Franchis 2015; Tripathi 2015). Approximately 15% to 20% of people with oesophageal varices bleed within about one to three years (Gluud 2012; Qi 2015; Plaz Torres 2021; Roccarina 2021). Short-term mortality of an episode of acute variceal bleeding is about 15% to 30% (Ioannou 2003; Gøtzsche 2008; D'Amico 2010; Rios 2015). Five-year mortality in people with variceal bleeding in Taiwan was more than 80% (Liu 2016). Mean in-hospital costs of treating acute episode of bleeding was EUR 13,500 in France in 2007 (Thabut 2007); mean six-month costs of treating people with variceal bleeding in USA 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 liver, pancreas, spleen, and intestines) (Gines 2009; Moore 2013), portal hypertension causes dilation of the collaterals between the portal venous system and systemic venous system (Sass 2009). One of the major locations of these collaterals is the lower end of the oesophagus and proximal part of the stomach. Therefore, portal hypertension leads to oesophageal varices (Sass 2009). According to Frank's modification of the Laplace law, the tension on the walls of blood vessels is dependent upon the diameter of the blood vessel and the pressure gradient across the walls (that is, the difference between pressure inside the varices and the oesophageal pressure) (Herman 2015). Portal hypertension leads to an increase in both the diameter of the blood vessels and in the pressure at which blood flows in the varices; therefore, the tension on the walls of the blood vessels increases. This results in 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

Treatments for acute oesophageal variceal bleeding can be broadly classified into four main categories: resuscitation and supportive interventions, pharmacological interventions, endoscopic interventions, and other interventions (de Franchis 2015; Tripathi 2015; Garcia-Tsao 2017; EASL 2018).

Resuscitation and supportive interventions

The initial management steps for a person experiencing acute variceal bleeding centre around resuscitation and stabilisation, usually in the intensive care setting (Ertel 2016). Decompensated liver disease complicates resuscitation because of the inability to tolerate volume shifts and susceptibility to dilutional coagulopathy (Ertel 2016). Therefore, there is some uncertainty regarding the optimum transfusion strategy approach and the target systolic blood pressure when administering intravenous fluids and blood products (Tripathi 2015). A restrictive transfusion strategy may be preferable to a liberal transfusion strategy (Villanueva 2013). Prophylactic broad-spectrum antibiotic therapy and prophylaxis for hepatic encephalopathy (for example, antibiotic and lactulose used concurrently) are also often used as supportive treatments to

prevent complications in the management of people with bleeding varices (de Franchis 2015; Tripathi 2015; Garcia-Tsao 2017; EASL 2018).

Pharmacological interventions

The two major classes of drugs that have been used in the control of acute variceal bleeding include vasoconstrictors such as vasopressin or terlipressin; and somatostatin or its analogue, octreotide (de Franchis 2015; Tripathi 2015; Garcia-Tsao 2017; EASL 2018). These are generally used in combination with endoscopic interventions (de Franchis 2015; Tripathi 2015; Garcia-Tsao 2017; EASL 2018).

Endoscopic interventions

The two main endoscopic treatments for variceal haemorrhage are variceal band ligation and sclerotherapy (de Franchis 2015; Tripathi 2015; Garcia-Tsao 2017; EASL 2018).

Other interventions

Early transjugular intrahepatic portosystemic shunt (TIPS) may be used for bleeding oesophageal varices at high risk of failure by pharmacological or endoscopic interventions (de Franchis 2015). Balloon tamponade and self-expanding oesophageal metal stents are generally reserved for refractory bleeding (bleeding not controlled by pharmacological or endoscopic interventions) (de Franchis 2015). Other treatments for refractory bleeding include surgical portosystemic shunts, surgical devascularisation procedures, and liver transplantation (Olson 2016).

How the intervention might work

Vasoactive medications act to decrease portal pressure by reducing portal blood flow (via splanchnic vasoconstriction) or reducing intrahepatic vascular resistance or both (Ioannou 2003; Tripathi 2015). The TIPS procedure and surgical portosystemic shunts are aimed at diverting blood flow from the portal system to the systemic circulation, thereby decreasing portal pressure and reducing oesophageal varices. Endoscopic interventions using variceal band ligation or sclerotherapy aim to achieve haemostasis by obliterating the varix and decreasing variceal wall tension (Ertel 2016). Balloon tamponade and removable oesophageal stenting methods apply direct pressure on the varices, and thus mechanically stop the haemorrhage (Olson 2016).

Why it is important to do this review

Acute variceal haemorrhage is a medical emergency and can be life-threatening. 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). Furthermore, in the context of end-stage liver disease, a variceal bleed can precipitate other features of decompensation such spontaneous bacterial peritonitis, hepatic encephalopathy, and renal impairment, all of which can result in significant morbidity or mortality for patients (Perri 2016). There are several different treatment approaches available for treating bleeding oesophageal varices with significant uncertainty about their individual and relative benefits and harms. Although there have been Cochrane Reviews focusing on the comparison of some of the treatments for bleeding oesophageal varices (Ioannou 2003; Khan 2006; Gøtzsche 2008; D'Amico 2010), there have been no previous network meta-analyses on the topic. Network meta-analysis allows for a combination of direct and indirect evidence and the ranking of different interventions for different outcomes (Salanti 2011; Salanti 2012). With this systematic review and network meta-analysis, we aim to provide the best level of evidence for the benefits and harms of different treatments for acute bleeding oesophageal varices due to liver cirrhosis. We have also presented results from direct comparisons whenever possible, in addition to performing the network meta-analysis.

OBJECTIVES

To compare the benefits and harms of different initial treatments for variceal bleeding from oesophageal varices in adults with decompensated liver cirrhosis through a network meta-analysis, and to generate rankings of the different treatments for acute bleeding oesophageal varices according to their benefits and harms. For ranking the interventions, we planned to consider the intervention ranks for the primary outcomes (mortality, health-related quality of life, and serious adverse events).

METHODS

Criteria for considering studies for this review

Types of studies

We considered only randomised clinical trials (RCTs) (including cross-over and cluster-RCTs) 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 treatment decisions should be driven by effects on mortality (when the mortality due to the condition is high), rather than by treatment-related adverse events.

Types of participants

We included RCTs in adults with acutely bleeding oesophageal varices due to decompensated liver cirrhosis.

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. We also excluded trials in which the participants had failed previous treatments (refractory bleeding varices) and those in whom initial haemostasis was achieved prior to randomisation. We also excluded trials in which the participants had previously undergone liver transplantation.

Types of interventions

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

- Vasopressin or analogues, i.e. terlipressin (systemic vasoconstrictors).
- Somatostatin or analogues, i.e. octreotide, vapreotide, lanreotide (splanchnic vasoconstrictors).
- Endoscopic variceal band ligation (obliterate varix mechanically).

- Endoscopic sclerotherapy (obliterate varix chemically by inducing inflammation, or by using a glue).
- Endoscopic spray treatment using haemostatic powder (tissue adhesive that promotes clotting).
- Balloon tamponade (mechanical haemostasis).
- Removable self-expanding oesophageal stents (mechanical haemostasis).
- TIPS procedure (decrease portal hypertension).
- Surgical shunt creation or devascularisation procedures (decrease portal hypertension).
- Surgical devascularisation procedures (decrease portal hypertension).
- Tranexamic acid (antifibrinolytic).
- No active intervention (no intervention, use of placebo, or only supportive treatment).

We considered 'sclerotherapy' as the reference intervention, as this was the commonest intervention used in the trials. Each of the above categories was considered as a 'treatment node'. We considered variations in endoscopic interventions or drugs within the same class, doses of drugs, frequency and duration of interventions as the same treatment node. We treated each different combination of the categories as different treatment nodes. All the above interventions were considered to be part of the 'decision set', i.e. all the above interventions were of direct interest.

While we identified some additional interventions that are not listed above, we did not include those interventions, as they are not currently used for initial treatment of bleeding oesophageal varices. We excluded supportive treatments and interventions aimed at people with failed initial treatment or at secondary prophylaxis.

We evaluated the plausibility of the network meta-analysis transitivity assumption by looking at the inclusion and exclusion criteria in the trials. The transitivity assumption means that participants included in the different trials with different treatments (in this case, for acute oesophageal variceal bleeding) can be considered to be a part of a multi-arm RCT 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. This necessitates that information on potential effect-modifiers such as previous history of oesophageal bleeding, interval from the onset of bleeding, presence or absence of other features of decompensation such as ascites, and the co-interventions (i.e. use of prophylactic antibiotics) are similar across comparisons.

Types of outcome measures

Primary outcomes

- Proportion of participants who died due to any cause (all-cause mortality)
- Health-related quality of life as defined in the included trials using a validated scale such as the European Quality of Life - 5 Dimentions (EQ-5D) or 36-Item Short Form Health Survey (SF-36) (EuroQol 2018; Optum 2018)
- Serious adverse events. 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. 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
- Proportion of participants with variceal rebleeding at six weeks (as defined by trial authors)
  * Symptomatic variceal bleeding (for example, shortness of breath, shock)
  * Any variceal bleeding
- Proportion of participants with other features of decompensation at six weeks

Exploratory outcomes

- Requirement for additional treatments to control the acute bleeding episode
- Blood transfusion requirements (whole blood or red cell concentrate - all episodes of bleeding within six weeks)
  * Proportion of participants requiring blood transfusion
  * Amount of blood transfused
- Length of hospital stay (all hospital admissions)
- Number of days of lost work (in people who work)
- Treatment costs (including the cost of the treatment and any resulting complications)

We assessed all the primary, secondary, and exploratory outcomes up to six weeks.

We chose outcomes based on their importance to patients. Our sources for this information were a survey related to research priorities for people with liver diseases (Gurusamy 2018); an online survey about the outcomes, promoted through Cochrane Consumer Network; and feedback from this project's patient and public representative.

We planned to rank the interventions based on their ranks for mortality, health-related quality of life, and serious adverse events.

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 each database's inception, until the search date of 17 December 2019. We searched for RCTs 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 at the US National Institutes of Health, and the World Health Organization International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/). The ICTRP indexes many other trials registries, including the International Standard Randomised Controlled Trial Number (ISRCTN) registry, and ClinicalTrials.gov. We also searched the European Medicines Agency (EMA) (www.ema.europa.eu/ema/) and the US Food and Drug Administration (FDA) (www.fda.gov) registries for RCTs. We provided the search strategies, along with the search date, in Appendix 1.

Searching other resources

To identify additional trials for inclusion, we searched the references of the identified trials, and the existing Cochrane Reviews on bleeding oesophageal varices.

Data collection and analysis

Selection of studies

Two review authors (KG and DR 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.

Data extraction and management

After translation of articles published in languages other than English, pairs of review authors (from among KG, DR, NW, LB, SA, TB, MC) independently extracted the types of data listed below into a prepiloted data extraction form, based on Microsoft Excel.

- 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 for count outcomes;
  - definition of outcomes or scale used, if appropriate.
- Data on potential effect modifiers:
  - participant characteristics, such as age, sex, previous history of bleeding oesophageal varices, presence of other features of decompensation such as ascites, the aetiology for cirrhosis, and the interval between diagnosis of variceal bleeding and treatment;
  - details of the intervention and control (including dose, frequency, and duration);
  - length of follow-up;
  - information related to risk of bias assessment (see Assessment of risk of bias in included studies).
- 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 all outcome data up to six weeks follow-up.

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* (Higgins 2011) to assess the risk of bias in included trials. 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 was only quasi-randomised. We excluded such quasi-randomised studies.

Allocation concealment

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

Blinding of participants and personnel

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

- High risk of bias: any of the following: no blinding or incomplete blinding, and the outcome was likely to be influenced by lack of blinding; or blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome was likely to be influenced by lack of blinding.

Blinded outcome assessment

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

Incomplete outcome data

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

Selective outcome reporting

- Low risk of bias: the trial reported the following predefined outcomes: all-cause mortality, adverse events, and variceal 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 trials 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. mortality, 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 with its 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 (the assumption in Poisson likelihood).

Relative ranking

We estimated the ranking probabilities for all interventions of being at each possible rank for each intervention for each outcome when NMA (network meta-analysis) was performed. When we performed NMA, 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 (Salanti 2011; Chaimani 2013).

Unit of analysis issues

The unit of analysis was the participant undergoing treatment for bleeding oesophageal varices according to the intervention group to which the participant is randomly assigned.

If we identified any cluster-RCTs, we planned to include cluster-RCTs, 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* (Higgins 2011).

Cross-over RCTs

If we identified any cross-over RCTs, 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-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 (CHBG 2021), whenever possible, for binary and time-to-event outcomes, where binomial likelihood was used. This was to assess the potential bias introduced by missing data.

For continuous outcomes, we imputed the standard deviation from P values, according to guidance in the *Cochrane Handbook* (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 (see Subgroup analysis and investigation of heterogeneity) in trial reports of different drug dosages, previous history of bleeding, interval between onset of bleeding and treatment, presence of other features of decompensation (for example, 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 for variceal bleeding). 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 zero, and by calculating the NMA-specific I^2 statistic (Jackson 2014), using Stata/SE 15.1. When possible, we explored substantial clinical, methodological, or statistical heterogeneity and addressed the heterogeneity in subgroup analysis (see 'Subgroup analysis and investigation of heterogeneity').

Assessment of transitivity across treatment comparisons

We assessed the transitivity assumption by comparing the distribution of the potential effect modifiers (clinical: previous history of bleeding, interval between onset of bleeding and treatment, presence of other features of decompensation (for example, ascites); methodological: risk of bias, year of randomisation, duration of follow-up) across the different pair-wise 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 due to higher risk of bias in older studies (Chaimani 2012). As 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 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

Methods for indirect and mixed comparisons

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 (see below). 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 software, according to guidance from 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, and log rate ratio for count 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, 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.

To assist with the assessment of convergence, we used a hierarchical Bayesian model, using three different sets of initial values to start the simulation-based parameter estimation. We employed codes provided by NICE DSU (Dias 2016). We used a normal distribution with large variance (10,000) for treatment effect priors (vague or flat priors) centred at no effect. For the random-effects model, we used a prior distributed uniformly (limits: 0 to 5) for the between-trial standard deviation parameter and assumed this variability would be the same across treatment comparisons (Dias 2016). We used a 'burn-in' of 30,000 simulations, checked for convergence (of effect estimates and between-study heterogeneity) visually (i.e. whether the values in different chains mixed very well by visualisation), and ran the models for another 10,000 simulations to obtain effect estimates. If we did not obtain convergence, we increased the number of simulations for the 'burn-in' and used the 'thin' and 'over relax' functions to decrease the autocorrelation. If we still did not obtain convergence, we used alternate initial values and priors, employing methods suggested by Van Valkenhoef 2012. We estimated the probability that each intervention ranked at each of the possible positions, based on estimated effect sizes and their corresponding uncertainty, using the NICE DSU codes (Dias 2016).

Assessment of inconsistency

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

Direct comparison

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

Subgroup analysis and investigation of heterogeneity

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

- Trials at low risk of bias compared to trials at high risk of bias.
- Based on previous history of bleeding oesophageal varices.
- Based on the presence of other features of decompensation (for example, ascites).
- Based on the aetiology for cirrhosis (for example, alcohol-related liver disease, viral liver diseases, autoimmune liver disease).
- Based on the severity of cirrhosis prior to the bleeding episode (for example, assessed by Child-Pugh score).
- Based on the interval between the variceal bleed and the start of treatment.
- Based on the cointerventions (for example, both groups receive prophylactic antibiotics to decrease the risk of subacute bacterial peritonitis in people with low-protein ascites).
- Based on the definition used by study authors for serious adverse events and any adverse events (ICH-GCP 1997 compared to other definitions).

As explained in the Results, we could not conduct any of the subgroup analyses.

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

Whenever possible, 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. We also performed a sensitivity analysis excluding the trials in which mean or standard deviation, or both, were imputed, and we used the median standard deviation in the trials to impute missing standard deviations.

Presentation of results

We followed the PRISMA-NMA statement while reporting (Hutton 2015). We presented the effect estimates with 95% CrI for each pairwise comparison calculated from the direct comparisons and 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 do so because of the sparse data. This could have led 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 than just listing the best treatment for the outcomes (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 'Zenodo' open source database of the European Organization for Nuclear Research: the link is available here.

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 the GRADE Working Group (Brignardello-Petersen 2018; Yepes-Nunez 2019). First, we calculated the direct and indirect effect estimates (when possible) and 95% CrI, using the node-splitting approach (Dias 2010). That is, we calculated 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 (if appropriate) 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 2011). We then presented the relative and absolute estimates of the meta-analysis with the best certainty of evidence (Yepes-Nunez 2019). For illustration of the absolute measures, we used weighted median (Edgeworth 1887), control group proportion, or mean. We also presented the 'Summary of findings' tables in a second format presenting all the outcomes for selected interventions (Yepes-Nunez 2019); we selected somatostatin analogues, vasopressin analogues, sclerotherapy plus somatostatin analogues, variceal band ligation, and balloon tamponade, the five interventions that were compared in the most trials and were most relevant clinically (Table 1).

Recommendations for future research

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

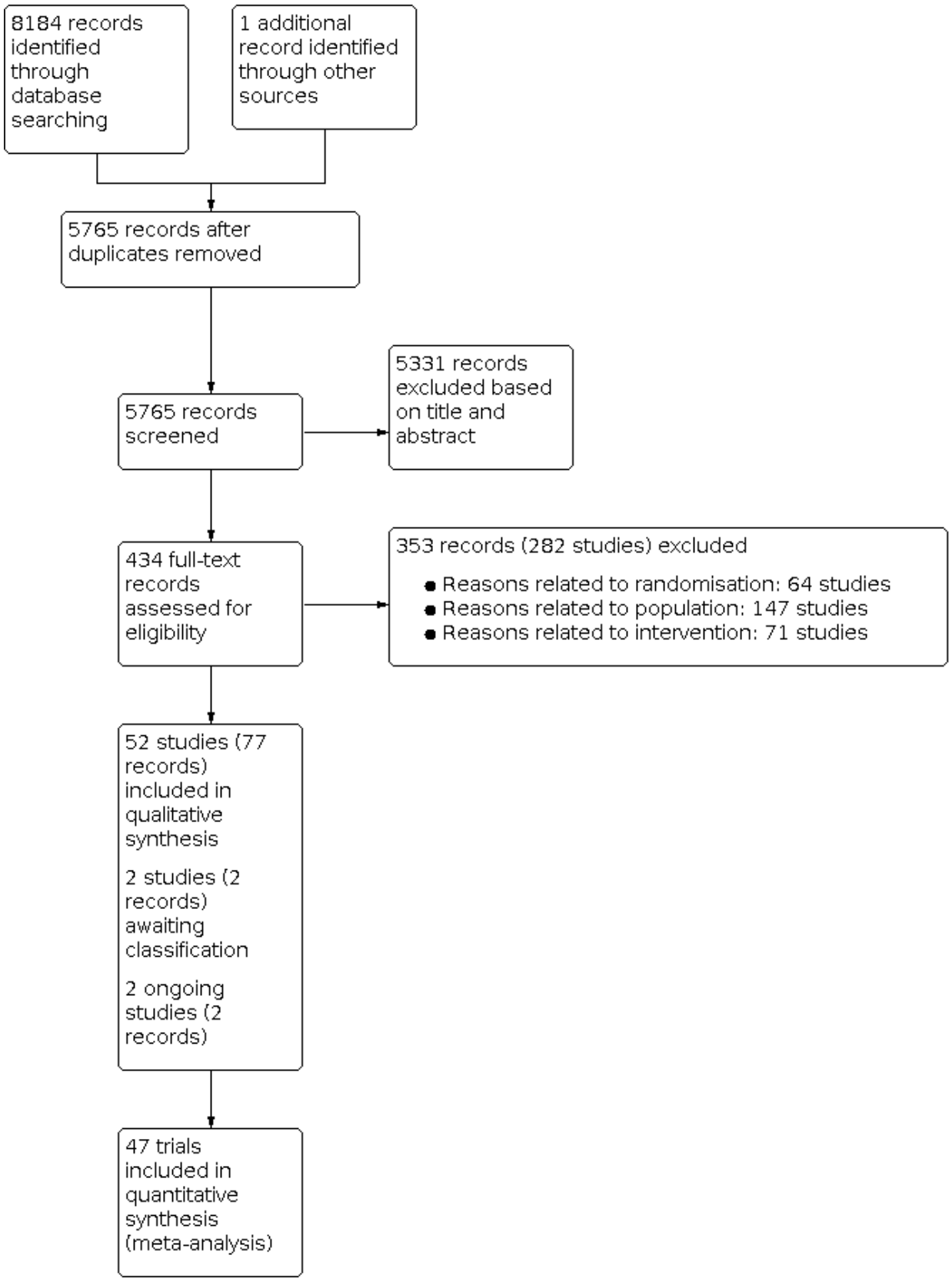
RESULTS

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 ICTRP (n = 110), FDA (n = 36), and EMA (n = 439). We identified one record by reference searching. After removing duplicate records, there were 5765 records. We excluded 5331 clearly irrelevant records through reading titles and abstracts. We retrieved a total of 434 full text records for further assessment in detail. We excluded 353 records (282 studies) for the reasons stated in the 'Characteristics of excluded studies'. Two records are awaiting classification and two references are records of ongoing trials. Thus, we included a total of 52 trials described in 77 records (Characteristics of included studies). The reference flow is shown in Figure 1.

Figure 1. Study flow diagram
Date of last search 17 December 2019



Included studies

We included 52 trials (Clanet 1978; Paquet 1985; Gimson 1986; Tsai 1986; Cello 1987; Colin 1987; Lee 1988; Freeman 1989; Burroughs 1990; Fort 1990a; Hsia 1990; McKee 1990; Saari 1990; Avgerinos 1991; Huang 1992; Hwang 1992; Lo 1992; Laine 1993; Pauwels 1994; Planas 1994; VA Coop. Variceal Sclerotherapy Group 1994; Besson 1995; Freitas 1995; Lo 1995; Laine 1996; Signorelli 1996; Cello 1997; Cipolletta 1997; Ramon 1997; Jensen 1998; Lee 1999a; Villanueva 1999; Armonis 2000; Bildozola 2000; Chon 2000; Escorsell 2000; Farooqi 2000; Freitas 2000; Yousuf 2000; Chelarescu 2001; Hafta 2001; Patsanas 2002; Shah 2005; Chen 2006; Cho 2006; Villanueva 2006; Morales 2007; NCT00534677; Abid 2009; Liu 2009; Asad 2014; Kumar 2015). A total of 4580 participants were randomised to different interventions. The number of participants per trial ranged from 25 to 324. A total of 4042 participants from 48 trials were included in one or more comparisons (Clanet 1978; Paquet 1985; Gimson 1986; Tsai 1986; Cello 1987; Colin 1987; Lee 1988; Freeman 1989; Burroughs 1990; Fort 1990a; Hsia 1990; McKee 1990; Avgerinos 1991; Huang 1992; Hwang 1992; Lo 1992; Laine 1993; Pauwels 1994; Planas 1994; Besson 1995; Freitas 1995; Lo 1995; Laine 1996; Signorelli 1996; Cello 1997; Cipolletta 1997; Ramon 1997; Jensen 1998; Lee 1999a; Armonis 2000; Bildozola 2000; Chon 2000; Escorsell 2000; Farooqi 2000; Freitas 2000; Yousuf 2000; Chelarescu 2001; Hafta 2001; Patsanas 2002; Shah 2005; Chen 2006; Cho 2006; Villanueva 2006; Morales 2007; Abid 2009; Liu 2009; Asad 2014; Kumar 2015). We did not identify any cluster-RCTs or crossover RCTs that addressed the objectives of the review.

The characteristics of included trials, ordered by pairwise comparisons, are listed in Table 1.

Participants

The mean or median age of participants in the trials ranged from 39 to 62 years in the trials that reported this information (Gimson 1986; Tsai 1986; Cello 1987; Colin 1987; Lee 1988; Freeman 1989; Burroughs 1990; Fort 1990a; Hsia 1990; Saari 1990; Avgerinos 1991; Huang 1992; Hwang 1992; Lo 1992; Laine 1993; Planas 1994; Besson 1995; Freitas 1995; Lo 1995; Laine 1996; Cello 1997; Cipolletta 1997; Villanueva 1999; Bildozola 2000; Chon 2000; Escorsell 2000; Farooqi 2000; Freitas 2000; Yousuf 2000; Hafta 2001; Patsanas 2002; Shah 2005; Chen 2006; Cho 2006; Villanueva 2006; Morales 2007; Abid 2009; Liu 2009; Kumar 2015). The proportion of females ranged from 0.0% to 50.0% in the trials that reported this information (Paquet 1985; Gimson 1986; Tsai 1986; Cello 1987; Colin 1987; Lee 1988; Burroughs 1990; Hsia 1990; Saari 1990; Avgerinos 1991; Huang 1992; Hwang 1992; Lo 1992; Laine 1993; Planas 1994; VA Coop. Variceal Sclerotherapy Group 1994; Besson 1995; Freitas 1995; Lo 1995; Laine 1996; Cello 1997; Cipolletta 1997; Villanueva 1999; Bildozola 2000; Chon 2000; Escorsell 2000; Farooqi 2000; Freitas 2000; Yousuf 2000; Hafta 2001; Patsanas 2002; Shah 2005; Chen 2006; Cho 2006; Villanueva 2006; Morales 2007; Abid 2009; Liu 2009; Kumar 2015). Follow-up was not reported in one trial (NCT00534677). The follow-up period in the remaining trials ranged from one day to six weeks.

In the 13 trials that reported these data, the proportion of participants who had other features of decompensation ranged from 11.4% to 65.6% (Cello 1987; Burroughs 1990; Planas 1994; Besson 1995; Lo 1995; Cello 1997; Villanueva 1999; Bildozola 2000; Shah 2005; Chen 2006; Cho 2006; Villanueva 2006; Kumar 2015). Thirty-five trials reported the proportion of participants who had alcohol-related cirrhosis: in two trials, none of the participants had alcohol-related cirrhosis (Farooqi 2000; Yousuf 2000); in one trial, all the participants had alcohol-related cirrhosis (VA Coop. Variceal Sclerotherapy Group 1994); and in the remaining 30 trials, the proportion of participants who had alcohol-related cirrhosis ranged from 3.8% to 94.2% (Paquet 1985; Gimson 1986; Cello 1987; Colin 1987; Freeman 1989; Burroughs 1990; Fort 1990a; Saari 1990; Avgerinos 1991; Huang 1992; Hwang 1992; Lo 1992; Laine 1993; Planas 1994; Besson 1995; Freitas 1995; Lo 1995; Laine 1996; Cello 1997; Villanueva 1999; Bildozola 2000; Chon 2000; Escorsell 2000; Freitas 2000; Hafta 2001; Patsanas 2002; Shah 2005; Chen 2006; Cho 2006; Villanueva 2006; Morales 2007; Kumar 2015). Twenty-three trials reported the proportion of participants who had viral-related cirrhosis: in one trial, none of the participants had viral-related cirrhosis (VA Coop. Variceal Sclerotherapy Group 1994); in two trials, all the participants had viral-related cirrhosis (Farooqi 2000; Yousuf 2000); and in the remaining 20 trials, the proportion of participants who had viral-related cirrhosis ranged from 6.5% to 96.2% (Paquet 1985; Gimson 1986; Tsai 1986; Lee 1988; Freeman 1989; Hsia 1990; Avgerinos 1991; Huang 1992; Hwang 1992; Lo 1992; Laine 1993; Lo 1995; Hafta 2001; Patsanas 2002; Shah 2005; Chen 2006; Cho 2006; Morales 2007; Abid 2009; Kumar 2015). Sixteen trials reported the proportion of participants who had autoimmune disease-related cirrhosis: in eight trials, none of the participants had autoimmune disease-related cirrhosis (VA Coop. Variceal Sclerotherapy Group 1994; Farooqi 2000; Yousuf 2000; Hafta 2001; Shah 2005; Cho 2006; Morales 2007; Kumar 2015); and in the remaining eight trials, the proportion of participants who had autoimmune disease-related cirrhosis ranged from 1.7% to 26.7% (Gimson 1986; Freeman 1989; Burroughs 1990; Avgerinos 1991; Lo 1992; Laine 1993; Lo 1995; Patsanas 2002). Twenty-two trials reported the proportion of participants who had other causes of cirrhosis: in six trials, none of the participants had other causes of cirrhosis (VA Coop. Variceal Sclerotherapy Group 1994; Farooqi 2000; Yousuf 2000; Hafta 2001; Shah 2005; Cho 2006); and in the remaining 16 trials, the proportion of participants who had other causes of cirrhosis ranged from 5.8% to 45.7% (Paquet 1985; Gimson 1986; Freeman 1989; Burroughs 1990; Fort 1990a; Hsia 1990; Avgerinos 1991; Hwang 1992; Lo 1992; Laine 1993; Lo 1995; Patsanas 2002; Chen 2006; Morales 2007; Abid 2009; Kumar 2015).

Interventions

A total of 19 interventions were compared in the included trials (sclerotherapy, somatostatin analogues, vasopressin analogues, sclerotherapy plus somatostatin analogues, variceal band ligation, balloon tamponade, somatostatin analogues plus variceal band ligation, nitrates plus vasopressin analogues, no active intervention, sclerotherapy plus variceal band ligation, balloon tamponade plus sclerotherapy, balloon tamponade plus somatostatin analogues, balloon tamponade plus vasopressin analogues, variceal band ligation plus vasopressin analogues, balloon tamponade plus nitrates plus vasopressin analogues, balloon tamponade plus variceal band ligation, portocaval shunt, sclerotherapy plus tips, sclerotherapy plus vasopressin analogues). Forty-eight trials reported one or more outcomes for this review (Clanet 1978; Paquet 1985; Gimson 1986; Tsai 1986; Cello 1987; Colin 1987; Lee 1988; Freeman 1989; Burroughs 1990; Fort 1990a; Hsia 1990; McKee 1990; Avgerinos 1991; Huang 1992; Hwang 1992; Lo 1992; Laine 1993; Pauwels 1994; Planas 1994; Besson 1995; Freitas 1995; Lo 1995; Laine 1996; Signorelli 1996; Cello 1997; Cipolletta 1997; Ramon 1997; Lee 1999a; Villanueva 1999;

Armonis 2000; Bildozola 2000; Chon 2000; Escorsell 2000; Farooqi 2000; Freitas 2000; Yousuf 2000; Chelarescu 2001; Hafta 2001; Patsanas 2002; Shah 2005; Chen 2006; Cho 2006; Villanueva 2006; Morales 2007; Abid 2009; Liu 2009; Asad 2014; Kumar 2015). In 50 trials, two interventions were compared (Clanet 1978; Paquet 1985; Gimson 1986; Tsai 1986; Cello 1987; Colin 1987; Lee 1988; Freeman 1989; Burroughs 1990; Fort 1990a; Hsia 1990; McKee 1990; Saari 1990; Huang 1992; Hwang 1992; Lo 1992; Laine 1993; Planas 1994; VA Coop. Variceal Sclerotherapy Group 1994; Besson 1995; Freitas 1995; Lo 1995; Laine 1996; Signorelli 1996; Cello 1997; Cipolletta 1997; Ramon 1997; Jensen 1998; Lee 1999a; Villanueva 1999; Armonis 2000; Bildozola 2000; Chon 2000; Escorsell 2000; Farooqi 2000; Freitas 2000; Yousuf 2000; Chelarescu 2001; Hafta 2001; Patsanas 2002; Shah 2005; Chen 2006; Cho 2006; Villanueva 2006; Morales 2007; NCT00534677; Abid 2009; Liu 2009; Asad 2014; Kumar 2015). In the remaining two trials, three interventions were compared (Avgerinos 1991; Pauwels 1994).

The important characteristics, potential effect modifiers, and follow-up periods in each trial are reported in Table 1. Overall, there do not seem to be any systematic differences between the comparisons.

Funding

The source of funding for 11 trials was industrial organisations who would benefit from the results of the trial (Freeman 1989; Burroughs 1990; McKee 1990; Hwang 1992; VA Coop. Variceal Sclerotherapy Group 1994; Besson 1995; Freitas 1995; Jensen 1998; Bildozola 2000; Escorsell 2000; Freitas 2000); 10 trials were funded by neutral organisations who have no vested interests in the results of the trial (Tsai 1986; Avgerinos 1991; Lo 1992; Laine 1993; Lo 1995; Laine 1996; Villanueva 2006; Morales 2007; Abid 2009; Kumar 2015); the source of funding for the remaining 31 trials was unclear (Clanet 1978; Paquet 1985; Gimson 1986; Cello 1987; Colin 1987; Lee 1988; Fort 1990a; Hsia 1990; Saari 1990; Huang 1992; Pauwels 1994; Planas 1994; Signorelli 1996; Cello 1997; Cipolletta 1997; Ramon 1997; Lee 1999a; Villanueva 1999; Armonis 2000; Chon 2000; Farooqi 2000; Yousuf 2000; Chelarescu 2001; Hafta 2001; Patsanas 2002; Shah 2005; Chen 2006; Cho 2006; NCT00534677; Liu 2009; Asad 2014).

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: 64 studies (Orloff 1962; Brunswig 1973; Berardi 1974; Orloff 1974; Paquet 1983; Adson 1984; Soderlund 1985; Conn 1986; Prindiville 1986; Terblanche 1986; Conn 1987; Rabeneck 1989; Teres 1989; Fort 1990b; Gilbert 1991; Lo 1991; Silvain 1991; Garden 1992; Kochman 1992; Altman 1993; Conn 1993; Sarin 1993; Thiel 1993; Bernard 1994; Korula 1994; Mezick 1994; Westaby 1994; Mino 1995; Tricerri 1995; Zoller 1995; Soderlund 1996; Nevens 1997; Am. Soc. Gastro. Endo. 1998; Burroughs 1998; Dobrucali 1998; Gong 1998; Lee 1998; Xu 1998; Combier 1999; Lee 1999b; Ling 2000; Moloney 2000; Wong 2001; Taniai 2002; Gronbaek 2003; Okano 2003a; Okano 2003b; Lo 2004; Yoshida 2004; NCT00331188; Zhang 2006; Cheng 2009; Krag 2009; Afdhal 2010; NCT01335516; Xu 2012; Zhou 2013; NCT02311608; Orloff 2014; Orloff 2015; Abd-Elsalam 2018; Chen 2018; Johnston 2019; NCT03583996)
- Reasons related to population: 147 studies (Conn 1975; Biggs 1976; Hecketsweiler 1978; Terblanche 1979; Mallory 1980; Ihre 1981; Reynolds 1981; Smith-Laing 1981; Anonymous 1996; Barsoum 1982; Fogel 1982; Otte 1983; Westaby 1983; Yassin 1983; Kravetz 1984; Pinto Correia 1984; Jenkins 1985; Korula 1985; Flati 1986; Kusumobroto 1986; Teres 1987; El-Zayadi 1988; Moreto 1988; Prioton 1988; Cardona 1989; O'Connor 1989; Valenzuela 1989; Westaby 1989; Spina 1990; Terés 1990; El-Newihi 1991; Armengol 1992; Shields 1992; Stiegmann 1992; Walker 1992; Gimson 1993; Jensen 1993; Ramage 1993; Rikkers 1993; Silvain 1993; Sung 1993; Xu 1993; Blanc 1994; D'Amico 1994; Kusumobroto 1994; Lo 1994; Pedretti 1994; Gotzsche 1995; Hou 1995; Levacher 1995; Sayed 1995; Sung 1995; Chen 1996a; Djurdjevic 1996; Feu 1996; Li 1996; Lin 1996; Mostafa 1996; Nakase 1996; Rosemurgy 1996; Shiha 1996; Avgerinos 1997; Balatsos 1997; Durdevic 1997; El-Khavat 1997; Fakhry 1997; Garcia-Compean 1997; Iso 1997; Saeed 1997; El-Zayadi 1998; Merli 1998; Shafqat 1998; Shin 1998; Siqueira 1998; Sung 1998; Zhao 1998; Al Traif 1999; Djurdjevic 1999; Gralnek 1999; Salem 1999; Bruha 2000; Junquera 2000; Ludwig 2000; Morales 2000; Ramires 2000; Shigemitsu 2000; Sivri 2000; Zhang 2000; Zuberi 2000; Cales 2001; Chen 2001; Cheng 2001; Hou 2001; Kullavanijaya 2001; Nakamura 2001; Villanueva 2001; Bobadilla-Diaz 2002; Shaikh 2002; Zhang 2002; Zhou 2002; Lee 2003; Souza 2003; Yol 2003; Bosch 2004; Chatterjee 2004; Cheema 2004; Monescillo 2004; Piqueras 2004; Dowidar 2005; Villanueva 2005; Zhu 2005; Henderson 2006; Santambrogio 2006; Seo 2006; Bhuiyan 2007; Huang 2007; Vlachogiannakos 2007; NCT01131962; Zargar 2008; Zhang 2008; NCT00966355; Orloff 2009; El Amin 2010; Gong 2010; NCT01103154; Luz 2011; NCT01426087; Priyadarshi 2011; eudract2012-000236-26; Orloff 2012; eudract2012-002489-11; Sun 2013; Ximing 2013; Sahu 2014; Seo 2014; eudract2014-002300-24; Geng 2015; NCT02377141; CTRI/2016/11/007483; Zuckerman 2016; Mansour 2017; ChiCTR1800015012; Dong 2018; Lin 2018; Dunne 2019; Ibrahim 2019; Yan 2019)
- Reasons related to intervention: 71 studies (Bockel 1981; Cello 1982; EVASP Study Group 1978; Freeman 1982; Burroughs 1983; Hecker 1983; Copenhagen Esophag. Varices Sclero. Proj. 1984; Fleischer 1985; Huizinga 1985; Larson 1986; Walker 1986; Bagarani 1987; Bonniere 1987; Loperfido 1987; Hosking 1988; Marbet 1988; Akriviadis 1989; Bosch 1989; Burroughs 1989; Jensen 1989; Alexandrino 1990; Chiu 1990; Soderlund 1990; Gupta 1991; Jaramillo 1991; Arcidiacono 1992; Moller 1992; de Franchis 1993; Blaise 1994; Orloff 1994; Becker 1995; Jenkins 1997; Li 1997; Lo 1997; Liu 1998; Yang 1998; Mishin 1999; Cheng 2000; NCT00161915; Company 2001; Yang 2001; Company 2002; Silva 2004; Kim 2005; NCT00369694; NCT00371943; Ma 2007; NCT00563602; Bambha 2008; De 2008; eudract2007-002237-37; Hu 2008; NCT00863837; eudract2009-016500-24; Garcia-Pagan 2010; NCT01242280; ACTRN12611000049976; Adarsh 2011; Altraif 2011; Ljubicic 2011; Lo 2011; Azam 2012; NCT01851564; Huang 2013; Peng 2013; NCT02361593; Escorsell 2016; Gupta 2016; ChiCTR1800020347; ChiCTR1900021217; Elsebaey 2019)

Risk of bias in included studies

The risk of bias is summarised in Figure 2, Figure 3, and in Table 2. All 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, for all outcomes.

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

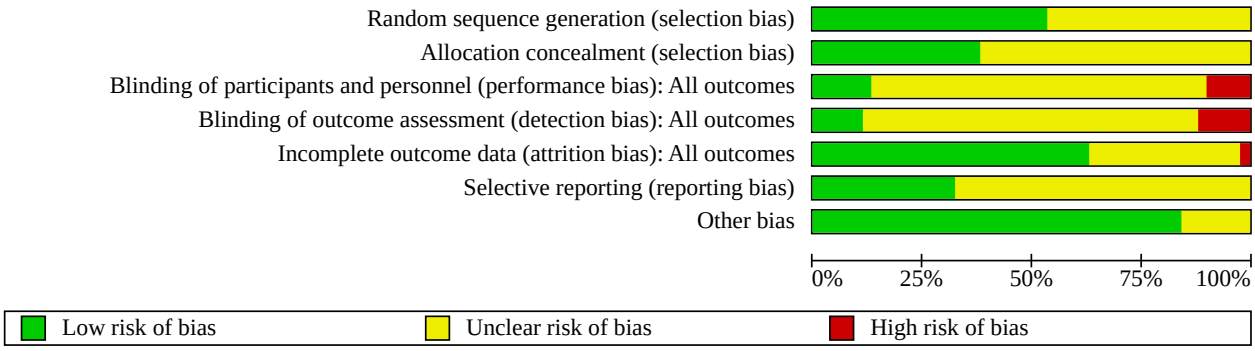


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

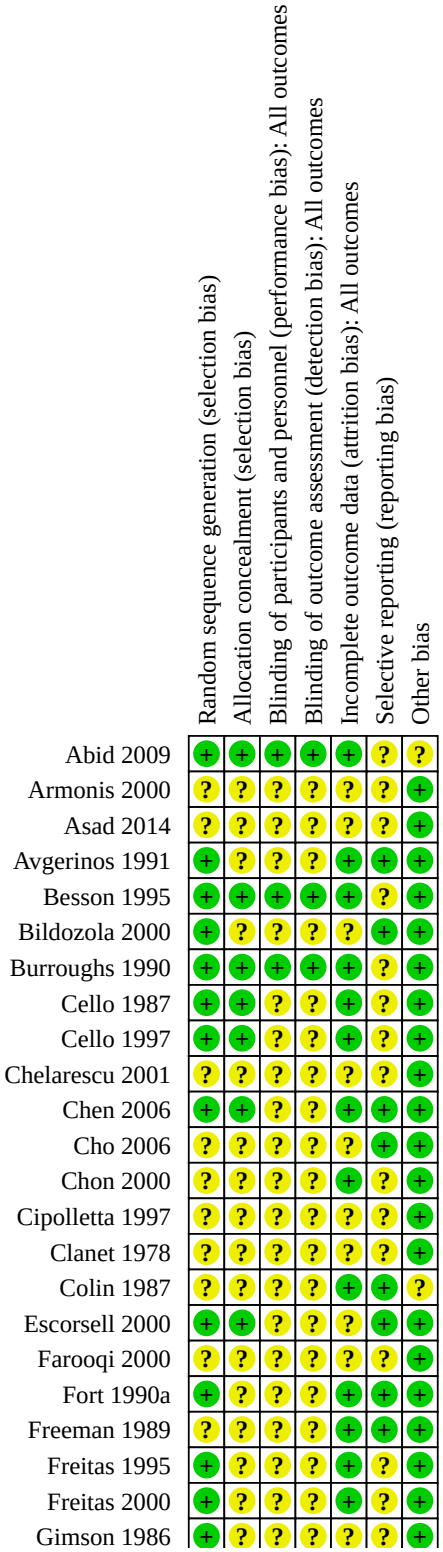
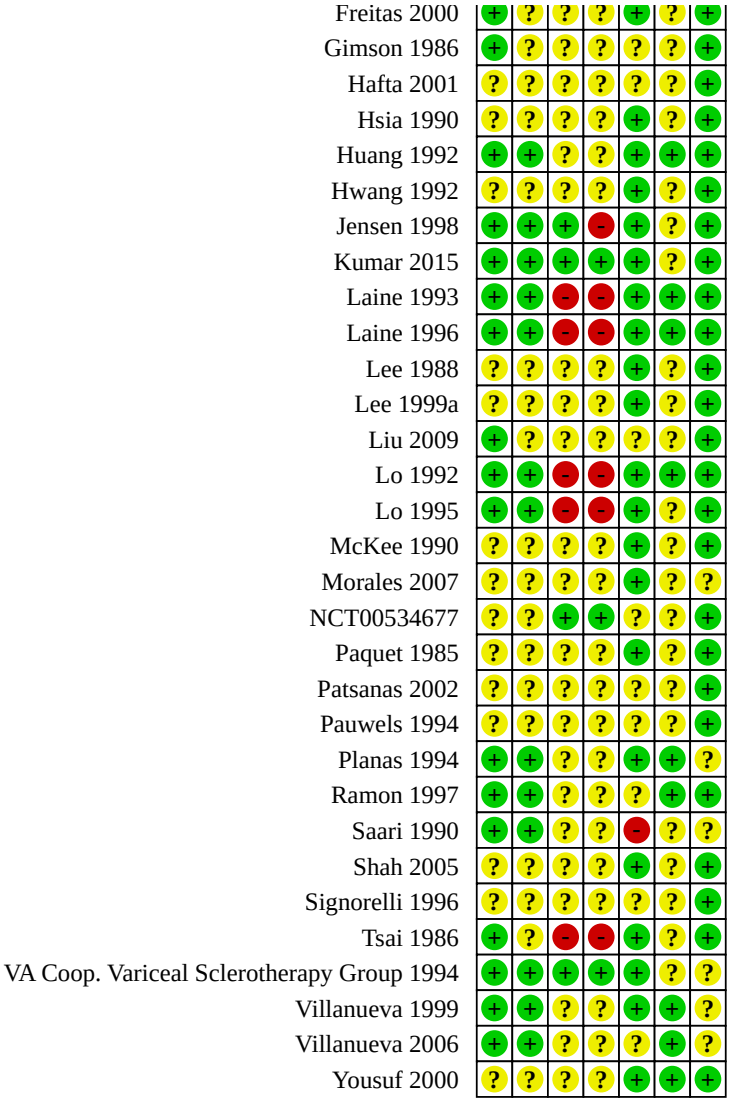


Figure 3. (Continued)



Allocation

Twenty-eight trials were at low risk of selection bias due to problems with sequence generation (Gimson 1986; Tsai 1986; Cello 1987; Burroughs 1990; Fort 1990a; Saari 1990; Avgerinos 1991; Huang 1992; Lo 1992; Laine 1993; Planas 1994; VA Coop. Variceal Sclerotherapy Group 1994; Besson 1995; Freitas 1995; Lo 1995; Laine 1996; Cello 1997; Ramon 1997; Jensen 1998; Villanueva 1999; Bildozola 2000; Escorsell 2000; Freitas 2000; Chen 2006; Villanueva 2006; Abid 2009; Liu 2009; Kumar 2015). The remaining 24 trials, which did not provide sufficient information, were at unclear risk of sequence generation bias (Clanet 1978; Paquet 1985; Colin 1987; Lee 1988; Freeman 1989; Hsia 1990; McKee 1990; Hwang 1992; Pauwels 1994; Signorelli 1996; Cipolletta 1997; Lee 1999a; Armonis 2000; Chon 2000; Farooqi 2000; Yousuf 2000; Chelarescu 2001; Hafta 2001; Patsanas 2002; Shah 2005; Cho 2006; Morales 2007; NCT00534677; Asad 2014).

Twenty trials were at low risk of selection bias due to problems with allocation concealment (Cello 1987; Burroughs 1990; Saari 1990; Huang 1992; Lo 1992; Laine 1993; Planas 1994; VA Coop. Variceal Sclerotherapy Group 1994; Besson 1995; Lo 1995; Laine 1996; Cello 1997; Ramon 1997; Jensen 1998; Villanueva 1999; Escorsell 2000; Chen 2006; Villanueva 2006; Abid 2009; Kumar 2015). The remaining 32 trials, which did not provide sufficient information, were at unclear risk of allocation concealment bias (Clanet 1978; Paquet 1985; Gimson 1986; Tsai 1986; Colin 1987; Lee 1988; Freeman 1989; Fort 1990a; Hsia 1990; McKee 1990; Avgerinos 1991; Hwang 1992; Pauwels 1994; Freitas 1995; Signorelli 1996; Cipolletta 1997; Lee 1999a; Armonis 2000; Bildozola 2000; Chon 2000; Farooqi 2000; Freitas 2000; Yousuf 2000; Chelarescu 2001; Hafta 2001; Patsanas 2002; Shah 2005; Cho 2006; Morales 2007; NCT00534677; Liu 2009; Asad 2014).

Blinding

Seven trials were at low risk of performance bias as patients and healthcare providers were blinded (Burroughs 1990; VA Coop. Variceal Sclerotherapy Group 1994; Besson 1995; Jensen 1998; Abid 2009; Kumar 2015; NCT00534677). Forty trials, which did not

provide sufficient information, were at unclear risk of performance bias (Clanet 1978; Paquet 1985; Gimson 1986; Cello 1987; Colin 1987; Lee 1988; Freeman 1989; Fort 1990a; Hsia 1990; McKee 1990; Saari 1990; Avgerinos 1991; Huang 1992; Hwang 1992; Pauwels 1994; Planas 1994; Freitas 1995; Signorelli 1996; Cello 1997; Cipolletta 1997; Ramon 1997; Lee 1999a; Villanueva 1999; Armonis 2000; Bildozola 2000; Chon 2000; Escorsell 2000; Farooqi 2000; Freitas 2000; Yousuf 2000; Chelarescu 2001; Hafta 2001; Patsanas 2002; Shah 2005; Chen 2006; Cho 2006; Villanueva 2006; Morales 2007; Liu 2009; Asad 2014). The remaining five trials were at high risk of performance bias, as the participants or healthcare providers were not blinded (Tsai 1986; Lo 1992; Laine 1993; Lo 1995; Laine 1996).

Six trials were at low risk of detection bias, as outcome assessors were blinded (Burroughs 1990; VA Coop. Variceal Sclerotherapy Group 1994; Besson 1995; NCT00534677; Abid 2009; Kumar 2015). Forty trials, which did not provide sufficient information, were at unclear risk of detection bias (Clanet 1978; Paquet 1985; Gimson 1986; Cello 1987; Colin 1987; Lee 1988; Freeman 1989; Fort 1990a; Hsia 1990; McKee 1990; Saari 1990; Avgerinos 1991; Huang 1992; Hwang 1992; Pauwels 1994; Planas 1994; Freitas 1995; Signorelli 1996; Cello 1997; Cipolletta 1997; Ramon 1997; Lee 1999a; Villanueva 1999; Armonis 2000; Bildozola 2000; Chon 2000; Escorsell 2000; Farooqi 2000; Freitas 2000; Yousuf 2000; Chelarescu 2001; Hafta 2001; Patsanas 2002; Shah 2005; Chen 2006; Cho 2006; Villanueva 2006; Morales 2007; Liu 2009; Asad 2014). The remaining six trials were at high risk of detection bias, as outcome assessors were not blinded (Tsai 1986; Lo 1992; Laine 1993; Lo 1995; Laine 1996; Jensen 1998).

Incomplete outcome data

Thirty-three trials were at low risk of attrition bias, as there were no post-randomisation dropouts, or an intention-to-treat analysis was used (Paquet 1985; Tsai 1986; Cello 1987; Colin 1987; Lee 1988; Freeman 1989; Burroughs 1990; Fort 1990a; Hsia 1990; McKee 1990; Avgerinos 1991; Huang 1992; Hwang 1992; Lo 1992; Laine 1993; Planas 1994; VA Coop. Variceal Sclerotherapy Group 1994; Besson 1995; Freitas 1995; Lo 1995; Laine 1996; Cello 1997; Jensen 1998; Lee 1999a; Villanueva 1999; Chon 2000; Freitas 2000; Yousuf 2000; Shah 2005; Chen 2006; Morales 2007; Abid 2009; Kumar 2015). Eighteen trials were at unclear risk of attrition bias, because it was not clear whether there were post-randomisation dropouts, or whether the post-randomisation dropouts were related to the outcomes (if there were post-randomisation dropouts) (Clanet 1978; Gimson 1986; Pauwels 1994; Signorelli 1996; Cipolletta 1997; Ramon 1997; Armonis 2000; Bildozola 2000; Escorsell 2000; Farooqi 2000; Chelarescu 2001; Hafta 2001; Patsanas 2002; Cho 2006; Villanueva 2006; NCT00534677; Liu 2009; Asad 2014). The one remaining trial was at high risk of attrition bias, as the post-randomisation dropouts were probably related to the outcomes (Saari 1990).

Selective reporting

Seventeen trials were at low risk of selective outcome reporting bias, as the important clinical outcomes expected to be reported in such trials were reported, even though a protocol published prior to recruitment was not available (Colin 1987; Freeman 1989; Fort 1990a; Avgerinos 1991; Huang 1992; Lo 1992; Laine 1993; Planas 1994; Laine 1996; Ramon 1997; Villanueva 1999; Bildozola 2000; Escorsell 2000; Yousuf 2000; Chen 2006; Cho 2006; Villanueva 2006). The remaining 35 trials were at unclear risk of selective outcome reporting bias, as a protocol published prior to recruitment was not available (Clanet 1978; Paquet 1985; Gimson 1986; Tsai 1986; Cello 1987; Lee 1988; Burroughs 1990; Hsia 1990; McKee 1990; Saari 1990; Hwang 1992; Pauwels 1994; VA Coop. Variceal Sclerotherapy Group 1994; Besson 1995; Freitas 1995; Lo 1995; Signorelli 1996; Cello 1997; Cipolletta 1997; Jensen 1998; Lee 1999a; Armonis 2000; Chon 2000; Farooqi 2000; Freitas 2000; Chelarescu 2001; Hafta 2001; Patsanas 2002; Shah 2005; Morales 2007; NCT00534677; Abid 2009; Liu 2009; Asad 2014; Kumar 2015).

Other potential sources of bias

Forty-four trials were at low risk of other bias (Clanet 1978; Paquet 1985; Gimson 1986; Tsai 1986; Cello 1987; Lee 1988; Freeman 1989; Burroughs 1990; Fort 1990a; Hsia 1990; McKee 1990; Avgerinos 1991; Huang 1992; Hwang 1992; Lo 1992; Laine 1993; Pauwels 1994; Besson 1995; Freitas 1995; Lo 1995; Laine 1996; Signorelli 1996; Cello 1997; Cipolletta 1997; Ramon 1997; Jensen 1998; Lee 1999a; Armonis 2000; Bildozola 2000; Chon 2000; Escorsell 2000; Farooqi 2000; Freitas 2000; Yousuf 2000; Chelarescu 2001; Hafta 2001; Patsanas 2002; Shah 2005; Chen 2006; Cho 2006; NCT00534677; Liu 2009; Asad 2014; Kumar 2015). The remaining eight trials were at unclear risk of other bias (Colin 1987; Saari 1990; VA Coop. Variceal Sclerotherapy Group 1994; Planas 1994; Villanueva 1999; Villanueva 2006; Morales 2007; Abid 2009). In four trials, there were baseline differences in important prognostic factors (Saari 1990; VA Coop. Variceal Sclerotherapy Group 1994; Morales 2007; Abid 2009). In one trial, number of episodes rather than number of participants were used as the unit of analysis in the paper, while we based the outcomes on the number of participants rather than number of episodes (Colin 1987); in three trials, participants were enrolled in a subsequent randomised controlled trial of different treatments if they were alive: this was done in both groups. However, it was not clear whether this was balanced in the two groups (Planas 1994; Villanueva 1999; Villanueva 2006).

Effects of interventions

See: **Summary of findings 1** Treatment for bleeding oesophageal varices in people with decompensated liver cirrhosis (six commonest interventions); **Summary of findings 2** Treatment for bleeding oesophageal varices in people with decompensated liver cirrhosis (all interventions)

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

Figure 4. Network plots: A high resolution version of this image can be found 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 BT = Balloon tamponade
NoActiveIntervention = No active intervention
PC_shunt = Portocaval shunt
Sclero = Sclerotherapy
Somato = Somatostatin analogues
TIPS = Transjugular intrahepatic portosystemic shunt
Vaso = Vasopressin analogues

VBL = Variceal band ligation

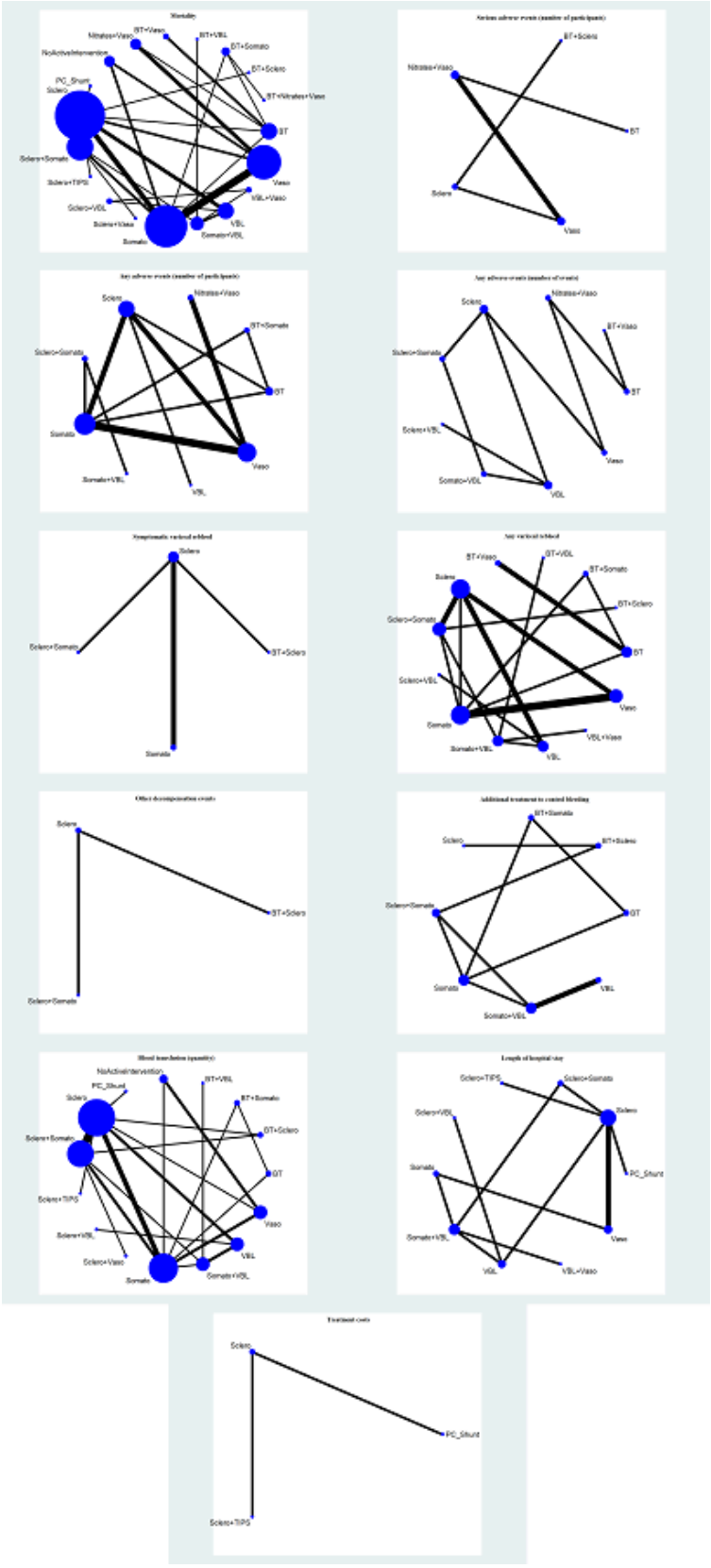
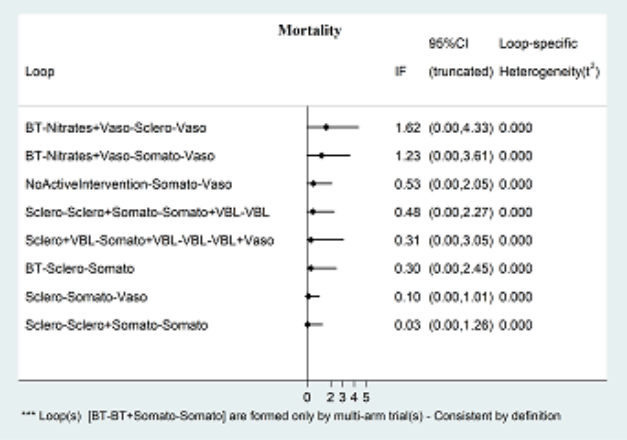
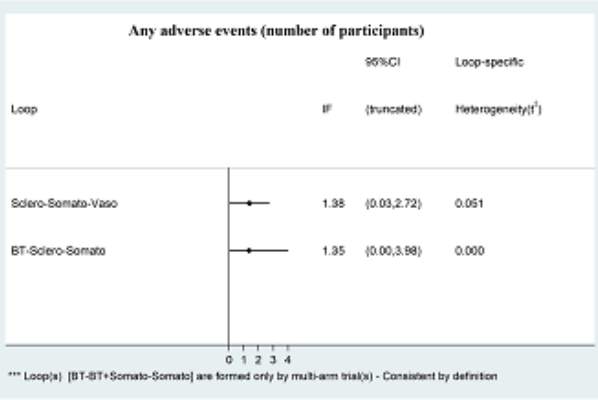
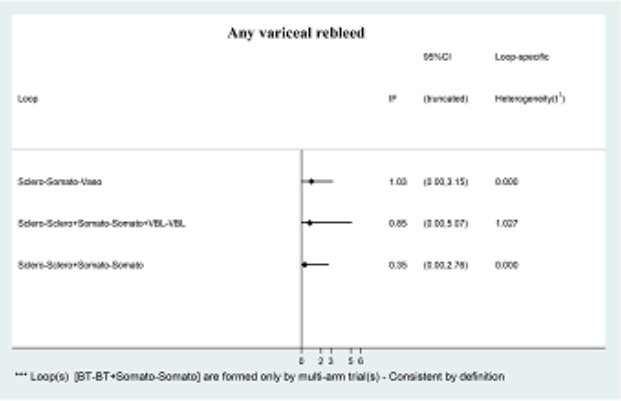
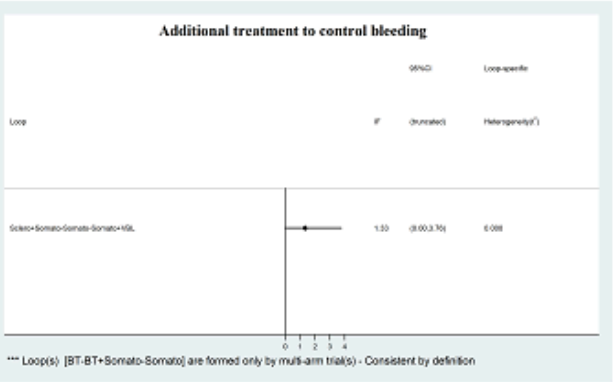


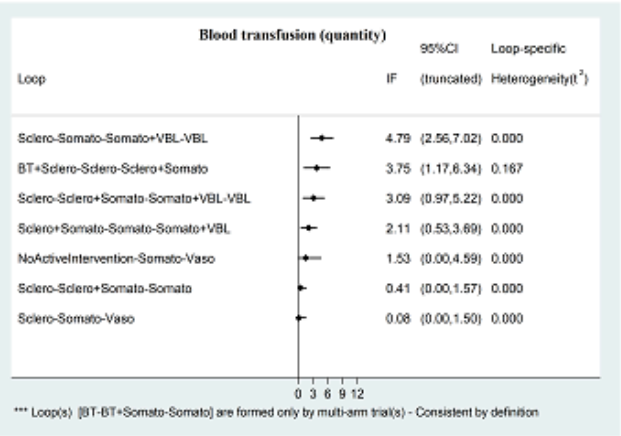
Figure 5. Inconsistency factor plots showing the inconsistency factors for the outcomes with direct and indirect evidence available for one or more comparisons. There was no evidence of inconsistency except for blood transfusion (amount) and length of hospital stay (where the confidence intervals of the inconsistency factor do not overlap 0). A higher resolution image of this picture is available here. Abbreviations BT = Balloon tamponade
PC_shunt = Portocaval shunt
Sclero = Sclerotherapy
Somato = Somatostatin analogues
TIPS = Transjugular intrahepatic portosystemic shunt
Vaso = Vasopressin analogues
VBL = Variceal band ligation











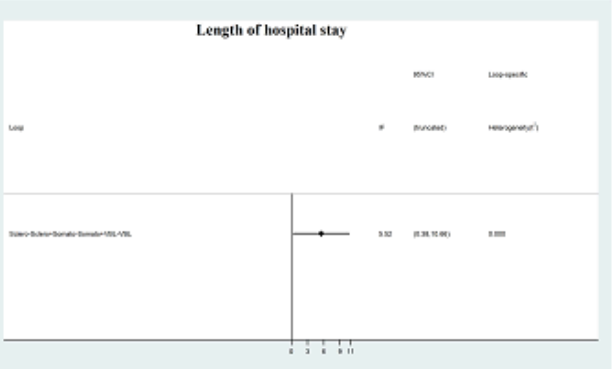
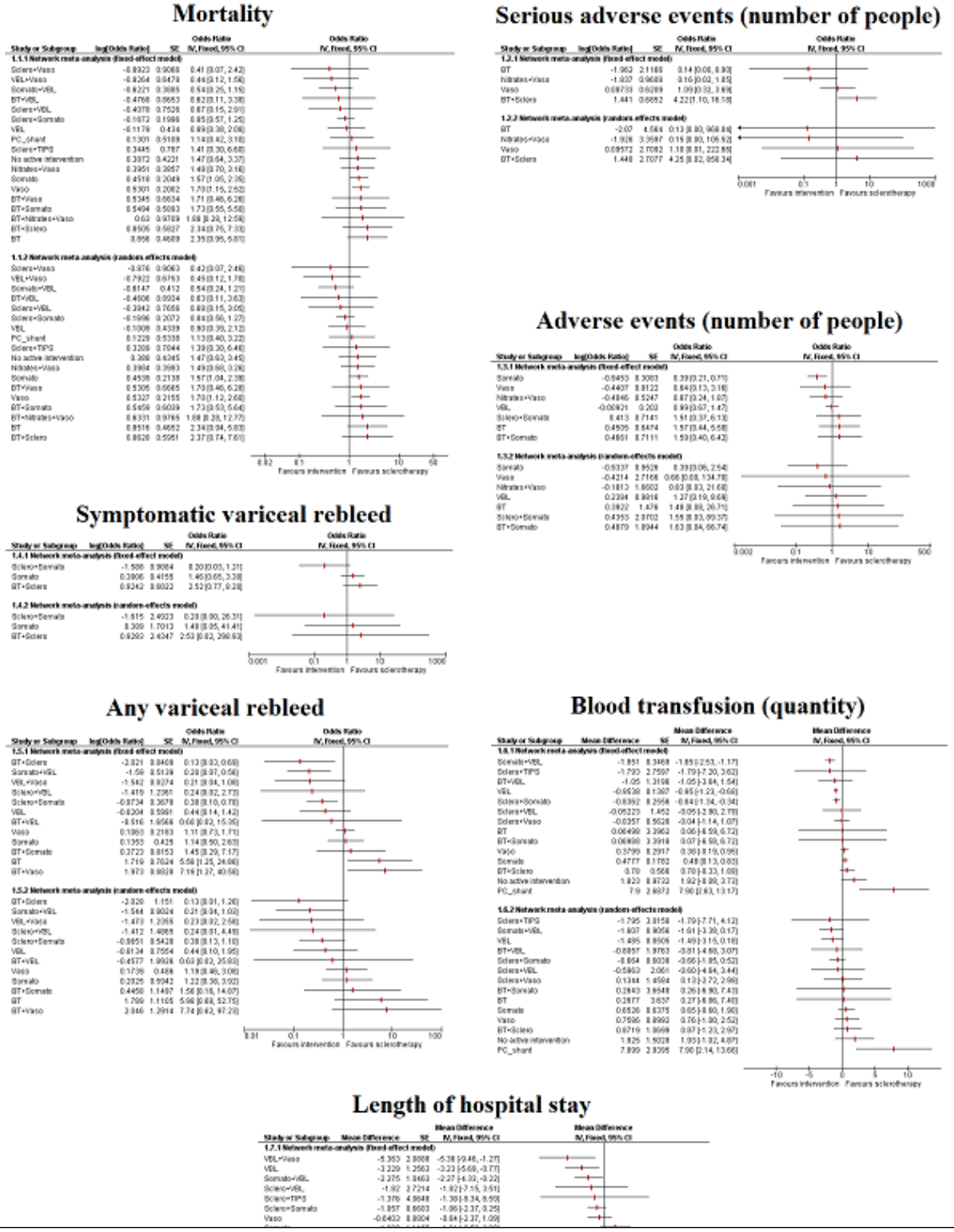


Figure 6. Forest plots showing the outcomes for which the random-effects model were different from the fixed-effect model. The more conservative random-effects model was used. A higher resolution image of this picture is available here. This is a temporary link and will be replaced with upload at zenodo.org once the review is finalised.
Abbreviations BT = Balloon tamponade
PC_shunt = Portocaval shunt
Sclero = Sclerotherapy
Som = Somatostatin analogues
TIPS = Transjugular intrahepatic portosystemic shunt
Vas = Vasopressin analogues
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 plots, as we considered that presenting this information would be unhelpful and potentially misleading, and would ignore the differences in systematic errors in the trials.

The GRADE 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 was fewer than 300 events; hence, we downgraded for imprecision by one level. For network meta-analysis, for outcomes other than mortality, any adverse events (number of participants), any adverse events (number of events), and any variceal rebleed, the number of events was 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 serious adverse events (number of participants), and any adverse events (number of participants). As there was no evidence of inconsistency for any of the outcomes, we did not downgrade for incongruence or indirectness of evidence.

Mortality

Forty-seven trials (3922 participants) reported mortality (Clanet 1978; Paquet 1985; Gimson 1986; Tsai 1986; Cello 1987; Colin 1987; Lee 1988; Freeman 1989; Burroughs 1990; Fort 1990a; Hsia 1990; McKee 1990; Avgerinos 1991; Huang 1992; Hwang 1992; Lo 1992; Laine 1993; Pauwels 1994; Planas 1994; Besson 1995; Freitas 1995; Laine 1996; Signorelli 1996; Cello 1997; Cipolletta 1997; Ramon 1997; Lee 1999a; Villanueva 1999; Armonis 2000; Bildozola 2000; Chon 2000; Escorsell 2000; Farooqi 2000; Freitas 2000; Yousuf 2000; Chelarescu 2001; Hafta 2001; Patsanas 2002; Shah 2005; Chen 2006; Cho 2006; Villanueva 2006; Morales 2007; Abid 2009; Liu 2009; Asad 2014; Kumar 2015). A total of 19 treatments were compared in these trials. There were 706 deaths in total (18.4%). The weighted median control group proportion dying was 15.8%. 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 intervention groups (McKee 1990; Liu 2009).

Direct comparisons

There was no evidence of differences between the treatments in the direct comparisons (i.e. there were no direct comparisons that were statistically significant) (very low-certainty evidence), as shown in Table 4.

Network meta-analysis

All treatments were connected. There was no evidence of inconsistency according to model fit, inconsistency factor, and the 'between-design' variance. The random-effects model was used because it was more conservative, even though the model fit was similar to that of the fixed-effect model. The 'between-study variance' was 0.01 (95% CrI 0.00 to 0.12).

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

- Sclerotherapy plus somatostatin analogues compared to somatostatin analogues: OR 0.54 (95% CrI 0.31 to 0.92); direct comparison: OR 0.20 (95% CrI 0.00 to 12.76); 2 trials; 130 participants; moderate-certainty evidence
- Somatostatin analogues plus variceal band ligation compared to somatostatin analogues: OR 0.35 (95% CrI 0.14 to 0.82); no direct comparison; moderate-certainty evidence
- Sclerotherapy plus somatostatin analogues compared to vasopressin analogues: OR 0.49 (95% CrI 0.28 to 0.86); no direct comparison; moderate-certainty evidence
- Somatostatin analogues plus variceal band ligation compared to vasopressin analogues: OR 0.32 (95% CrI 0.13 to 0.77); no direct comparison; moderate-certainty evidence
- Variceal band ligation plus vasopressin analogues compared to balloon tamponade: OR 0.19 (95% CrI 0.04 to 0.97); no direct comparison; moderate-certainty evidence

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

- Somatostatin analogues compared to sclerotherapy: OR 1.57 (95% CrI 1.04 to 2.41); direct comparison: OR 1.59 (95% CrI 0.52 to 4.94); 4 trials; 353 participants; moderate-certainty evidence
- Vasopressin analogues compared to sclerotherapy: OR 1.70 (95% CrI 1.13 to 2.62); direct comparison: OR 1.64 (95% CrI 0.08 to 31.34); 2 trials; 438 participants; moderate-certainty evidence
- Balloon tamponade compared to sclerotherapy plus somatostatin analogues: OR 2.77 (95% CrI 1.05 to 7.53); no direct comparison; moderate-certainty evidence
- Balloon tamponade compared to somatostatin analogues plus variceal band ligation: OR 4.30 (95% CrI 1.32 to 15.00); no direct comparison; no direct comparison; moderate-certainty evidence
- Balloon tamponade plus sclerotherapy compared to somatostatin analogues plus variceal band ligation: OR 4.38 (95% CrI 1.08 to 18.30); 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 or very low-certainty evidence), as shown in Table 4.

Health-related quality of life

None of the trials reported health-related quality of life (very low-certainty evidence).

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', to consider them as serious adverse events.

Serious adverse events (number of participants)

Thirteen trials (1163 participants) reported serious adverse events (number of participants) (Gimson 1986; Tsai 1986; Freeman 1989; Fort 1990a; Lo 1992; Planas 1994; Freitas 1995; Ramon 1997; Villanueva 1999; Bildozola 2000; Freitas 2000; Cho 2006; Villanueva 2006). A total of 10 treatments were compared in these trials. There were 79 events in total (6.8%). The weighted median control group proportion was 5.3%.

Four trials were not connected to the network because they had zero events in both intervention groups (Freeman 1989; Freitas 1995; Freitas 2000; Cho 2006). The comparisons in these trials were vasopressin analogues versus no active intervention (Freeman 1989), somatostatin analogues versus sclerotherapy (Freitas 1995), sclerotherapy plus somatostatin analogues versus sclerotherapy (Freitas 2000), and variceal band ligation plus vasopressin analogues versus variceal band ligation plus somatostatin analogues (Cho 2006). Two trials were not connected to the network because they had treatments unconnected to the network (once the trials with zero events in both groups were excluded) (Villanueva 1999; Villanueva 2006). The comparisons in these trials were sclerotherapy plus somatostatin analogues versus somatostatin analogues alone (Villanueva 1999), and somatostatin analogues plus variceal band ligation versus sclerotherapy plus somatostatin analogues (Villanueva 2006). 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 intervention groups (Planas 1994; Bildozola 2000). The comparison included in these trials was somatostatin analogues versus sclerotherapy (Planas 1994; Bildozola 2000).

Direct comparisons

Somatostatin analogues plus variceal band ligation had lower serious adverse events (number of participants) compared with sclerotherapy plus somatostatin analogues: OR 0.28 (95% CrI 0.07 to 0.87); 1 trial; 179 participants; low-certainty evidence.

In the direct comparisons, the first intervention had higher serious adverse events (number of participants) compared with the second intervention in the following comparisons.

- Balloon tamponade plus sclerotherapy versus sclerotherapy: OR 4.23 (95% CrI 1.22 to 17.80); 1 trial; 60 participants; low-certainty evidence
- Sclerotherapy plus somatostatin analogues versus somatostatin analogues: OR 11.0 (95% CrI 1.58 to 330.3); 1 trial; 100 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), as shown in Table 4.

Network meta-analysis

The network had five connected treatments. There were no triangular or quadrangular loops; therefore, inconsistency was not checked. The random-effects model was used because it was more conservative, even though the model fit was similar to the fixed-effect model. The 'between-study variance' was 2.50 (95% CrI 0.01 to 22.49).

In the network meta-analysis, there was no evidence of differences in any of the comparisons (low-certainty evidence) as shown in Table 4.

Serious adverse events (number of events)

Three trials (523 participants) reported serious adverse events (number of events) (Escorsell 2000; Chen 2006; Villanueva 2006). A total of five treatments were compared in these trials. There were 34 events in total (0.1 events per participant). The median control event rate was 0.07 per participant. There were no connecting treatments in the trials. Therefore, only direct comparisons were performed.
Somatostatin analogues plus variceal band ligation had lower serious adverse events (number of events) than sclerotherapy plus somatostatin analogues: rate ratio 0.31 (95% CrI 0.08 to 0.92); 1 trial; 179 participants; low-certainty evidence.

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

- Vasopressin analogues versus sclerotherapy: rate ratio 0.52 (95% CrI 0.13 to 1.70); 1 trial; 219 participants; very low-certainty evidence
- Somatostatin analogues plus variceal band ligation versus variceal band ligation: rate ratio 2.13 (95% CrI 0.39 to 17.53); 1 trial; 125 participants; very low-certainty evidence.

Any adverse events

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

Any adverse events (number of participants)

Fourteen trials (1318 participants) reported any adverse events (number of participants) (Paquet 1985; Tsai 1986; Lee 1988; Hsia 1990; Avgerinos 1991; Huang 1992; Hwang 1992; Planas 1994; Cipolletta 1997; Ramon 1997; Villanueva 1999; Escorsell 2000; Yousuf 2000; Villanueva 2006). A total of nine treatments were compared in these trials. There were 315 events in total (23.9%). The weighted median control group proportion was 28.1%.

Direct comparison

Somatostatin analogues plus variceal band ligation had lower adverse events (number of participants) than sclerotherapy plus somatostatin analogues: OR 0.42 (95% CrI 0.19 to 0.88); 1 trial; 179 participants; low-certainty evidence.

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

- Vasopressin analogues versus somatostatin analogues: OR 4.56 (95% CrI 2.06 to 10.84); 3 trials; 135 participants; low-certainty evidence
- Sclerotherapy plus somatostatin analogues versus somatostatin analogues: OR 3.86 (95% CrI 1.20 to 15.44); 1 trial; 100 participants; low-certainty evidence
- Balloon tamponade versus somatostatin analogues: OR 5.12 (95% CrI 1.31 to 26.63); 1 trial; 61 participants; low-certainty evidence

- Balloon tamponade plus somatostatin analogues versus somatostatin analogues: OR 4.85 (95% CrI 1.27 to 24.85); 1 trial; 62 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) as shown in Table 4.

Network meta-analysis

All the trials were connected to the network. There was no evidence of inconsistency according to model fit, inconsistency factor, and the 'between-design' variance. The random-effects model was used because it was more conservative and had better model fit. The 'between-study variance' was 1.99 (95% CrI 0.39 to 10.20).

In the network meta-analysis, there was no evidence of differences in any of the comparisons (very low-certainty evidence), as shown in Table 4.

Any adverse events (number of events)

Ten trials (1116 participants) reported any adverse events (number of events) (Gimson 1986; Colin 1987; Burroughs 1990; Fort 1990a; Laine 1993; Besson 1995; Laine 1996; Escorsell 2000; Chen 2006; Villanueva 2006). A total of 11 treatments were compared in these trials. There were 379 events in total (0.3 events per participant). The weighted median control event rate was 0.386 per participants. One trial was not connected to the network because it had treatments unconnected to the network (somatostatin analogues versus no active intervention) (Burroughs 1990).

Direct comparisons

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

- Vasopressin analogues versus sclerotherapy: rate ratio 0.58 (95% CrI 0.35 to 0.96); 1 trial; 219 participants; low-certainty evidence
- Variceal band ligation versus sclerotherapy: rate ratio 0.40 (95% CrI 0.17 to 0.87); 1 trial; 77 participants; low-certainty evidence
- Somatostatin analogues plus variceal band ligation versus sclerotherapy plus somatostatin analogues: rate ratio 0.48 (95% CrI 0.25 to 0.92); 1 trial; 179 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), as shown in Table 4.

There was no evidence of differences in remaining comparison not connected to the network: somatostatin analogues versus no active intervention: rate ratio 0.90 (95% CrI 0.51 to 1.59); 1 trial; 120 participants; very low-certainty evidence.

Network meta-analysis

The network had nine connected treatments. Only one trial was included in each of the comparisons; therefore, only the fixed-effect model is applicable.

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

- Vasopressin analogues compared to or with sclerotherapy: rate ratio 0.59 (95% CrI 0.35 to 0.96); direct comparison: rate ratio 0.58 (95% CrI 0.35 to 0.96); 1 trial; 219 participants; moderate-certainty evidence
- Variceal band ligation compared to or with sclerotherapy: rate ratio 0.40 (95% CrI 0.21 to 0.74); direct comparison: rate ratio 0.40 (95% CrI 0.17 to 0.87); 1 trial; 77 participants; moderate-certainty evidence
- Somatostatin analogues plus variceal band ligation compared to or with sclerotherapy: rate ratio 0.53 (95% CrI 0.28 to 0.98); no direct comparison; moderate-certainty evidence
- Nitrates plus vasopressin analogues compared to or with sclerotherapy: rate ratio 0.44 (95% CrI 0.19 to 1.00); no direct comparison; moderate-certainty evidence
- Variceal band ligation compared to or with sclerotherapy plus somatostatin analogues: rate ratio 0.38 (95% CrI 0.20 to 0.70); no direct comparison; moderate-certainty evidence
- Somatostatin analogues plus variceal band ligation compared to or with sclerotherapy plus somatostatin analogues: rate ratio 0.52 (95% CrI 0.28 to 0.95); direct comparison: rate ratio 0.48 (95% CrI 0.24 to 0.92); 1 trial; 179 participants; moderate-certainty evidence

There was no evidence of differences between the treatments in the remaining comparisons in the network meta-analysis (low- or very low-certainty evidence), as shown in Table 4.

Variceal rebleed

Symptomatic variceal rebleed

Seven trials (485 participants) reported symptomatic variceal rebleed (Freeman 1989; Fort 1990a; Lo 1992; Planas 1994; Bildozola 2000; Shah 2005; Liu 2009). The symptoms were haematemesis, melaena, or requiring blood transfusion related to variceal rebleed. A total of nine treatments were compared in these trials. There were 77 events in total (15.9%). The weighted median control group proportion was 14.8%.

Two trials were not connected to the network because they had treatments unconnected to the network (Freeman 1989; Fort 1990a). The comparisons in these trials were vasopressin analogues versus no active intervention (Freeman 1989) and nitrates plus vasopressin analogues versus balloon tamponade (Fort 1990a). One trial was not connected to the network because it was the only trial for the comparison (variceal band ligation plus somatostatin analogues versus somatostatin analogues) and had zero events in one of the intervention groups (Liu 2009).

Direct comparisons

Sclerotherapy plus somatostatin analogues had lower symptomatic variceal rebleed (number of patients) than sclerotherapy: OR 0.21 (95% CrI 0.03 to 0.94); 1 trial; 105 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), as shown in Table 4. There was no evidence of

differences in the remaining comparisons not connected to the network.

- Vasopressin analogues versus no active intervention: OR 0.24 (95% CrI 0.01 to 2.63); 1 trial; 31 participants; very low-certainty evidence
- Nitrates plus vasopressin analogues versus balloon tamponade: OR 2.92 (95% CrI 0.61 to 16.31); 1 trial; 42 participants; very low-certainty evidence

Network meta-analysis

The network had four connected treatments. There were no triangular or quadrangular loops; therefore, inconsistency was not checked. The random-effects model was used because it was more conservative, even though the model fit was similar to that of the fixed-effect model. The 'between-study variance' was 1.30 (95% CrI 0.00 to 21.65).

In the network meta-analysis, there was no evidence of differences in any of the comparisons (very low-certainty evidence), as shown in Table 4.

Any variceal rebleed

Twenty trials (1762 participants) reported any variceal rebleed (Clanet 1978; Colin 1987; McKee 1990; Avgerinos 1991; Huang 1992; Laine 1993; Pauwels 1994; Laine 1996; Ramon 1997; Lee 1999a; Villanueva 1999; Armonis 2000; Chon 2000; Escorsell 2000; Farooqi 2000; Yousuf 2000; Chen 2006; Cho 2006; Villanueva 2006; Morales 2007). A total of 14 treatments were compared in these trials. There were 316 events in total (17.9%). The weighted median control group proportion was 18.8%. All the trials were connected to the network. However, one treatment in a three-armed trial was not included in the analysis as this trial was the only trial which included the treatment and there were no events in this arm of the trial (no active intervention) (Pauwels 1994).

Direct comparisons

Balloon tamponade plus somatostatin analogues had lower any variceal rebleed than balloon tamponade: OR 0.26 (95% CrI 0.08 to 0.81); 1 trial; 61 participants. Balloon tamponade had higher any variceal rebleed than somatostatin analogues: OR 4.83 (95% CrI 1.48 to 18.23); 1 trial; 61 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) as shown in Table 4.

Network meta-analysis

There was no evidence of inconsistency according to model fit, inconsistency factor, and the 'between-design' variance. The random-effects model was used because it was more conservative, even though the model fit was similar to the fixed-effect model. The 'between-study variance' was 0.23 (95% CrI 0.00 to 2.14).

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

- Balloon tamponade plus sclerotherapy compared to balloon tamponade: OR 0.02 (95% CrI 0.00 to 0.40); no direct comparison; moderate-certainty evidence
- Variceal band ligation plus vasopressin analogues compared to balloon tamponade: OR 0.04 (95% CrI 0.00 to 0.84); no direct comparison; moderate-certainty evidence
- Variceal band ligation plus vasopressin analogues compared to balloon tamponade plus vasopressin analogues: OR 0.03 (95% CrI 0.00 to 0.84); no direct comparison; moderate-certainty evidence.

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

- Balloon tamponade compared to sclerotherapy plus somatostatin analogues: OR 15.75 (95% CrI 1.76 to 167.00); no direct comparison; moderate-certainty evidence
- Balloon tamponade plus vasopressin analogues compared to sclerotherapy plus somatostatin analogues: OR 20.45 (95% CrI 1.62 to 300.97); no direct comparison; moderate-certainty evidence
- Balloon tamponade compared to variceal band ligation: OR 13.63 (95% CrI 1.10 to 194.03); no direct comparison; moderate-certainty evidence
- Balloon tamponade plus vasopressin analogues compared to variceal band ligation: OR 17.60 (95% CrI 1.05 to 338.66); no direct comparison; moderate-certainty evidence
- Balloon tamponade compared to somatostatin analogues plus variceal band ligation: OR 28.05 (95% CrI 2.25 to 393.86); no direct comparison; moderate-certainty evidence
- Balloon tamponade plus vasopressin analogues compared to somatostatin analogues plus variceal band ligation: OR 36.23 (95% CrI 2.15 to 671.83); no direct comparison; moderate-certainty evidence
- Balloon tamponade plus vasopressin analogues compared to balloon tamponade plus sclerotherapy: OR 59.32 (95% CrI 2.47 to 1707.87); 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 or very certainty evidence) as shown in Table 4.

Other decompensation events

Two trials (259 participants) reported other decompensation events (Lo 1992; Besson 1995). In Besson 1995, the other decompensation events were severe hepatic encephalopathy, and in Lo 1992, this included hepatic failure and ascites with spontaneous bacterial peritonitis. A total of three treatments were compared in these trials. There were 14 events in total (5.4 events per participant). The weighted median control event rate was 4 per participant.

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) (very low-certainty evidence).

Network meta-analysis

Both trials were connected to the network. There were no triangular or quadrangular loops; therefore, inconsistency was not checked. Only one trial was included in each of the comparisons; therefore, only the fixed-effect model is applicable. In the network meta-analysis, there was no evidence of differences in any of the comparisons (very low-certainty evidence), as shown in Table 4.

Exploratory outcomes

Additional treatment to control variceal bleeding

Eleven trials (956 participants) reported additional treatment to control variceal bleeding (Gimson 1986; Freeman 1989; McKee 1990; Avgerinos 1991; Lo 1992; Villanueva 1999; Shah 2005; Chen 2006; Villanueva 2006; Liu 2009; Kumar 2015). The additional treatments included balloon tamponade or endoscopic or pharmacological treatments other than the intervention. A total of 11 treatments were compared in these trials. There were 101 events in total (10.6%). The weighted median control event rate was 3.7%.

Two trials were not connected to the network because they had treatments unconnected to the network (Gimson 1986; Freeman 1989). The comparisons included in these trials were: nitrates plus vasopressin analogues versus vasopressin analogues (Gimson 1986), and vasopressin analogues versus no active intervention (Freeman 1989). One trial was not connected to the network because it was the only trial for the comparison (sclerotherapy plus somatostatin analogues versus sclerotherapy), and had zero events in one of the intervention groups (Shah 2005).

Direct comparisons

The first intervention had fewer additional treatment to control variceal bleeding than second intervention in the following comparisons.

- Sclerotherapy plus somatostatin analogues versus somatostatin analogues: OR 0.21 (95% CrI 0.04 to 0.75); 1 trial; 100 participants
- Balloon tamponade plus sclerotherapy versus sclerotherapy plus somatostatin analogues: OR 0.09 (95% CrI 0.00 to 0.73); 1 trial; 40 participants

Balloon tamponade had higher additional treatment effect to control variceal bleeding than somatostatin analogues: OR 8.26 (95% CrI 1.02 to 278.66); 1 trial; 61 participants

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. There was no evidence of differences in the remaining comparisons, not connected to the network:

- Nitrates plus vasopressin analogues versus vasopressin analogues: OR 0.73 (95% CrI 0.18 to 2.83); 1 trial; 62 participants
- Vasopressin analogues versus no active intervention: OR 0.38 (95% CrI 0.08 to 1.64); 1 trial; 31 participants
- Somatostatin analogues plus variceal band ligation versus variceal band ligation: OR 2.82 (95% CrI 0.05 to 244.94); 2 trials; 186 participants

Network meta-analysis

The network had eight connected treatments. There was no evidence of inconsistency according to model fit, inconsistency factor, but there was inconsistency according to the 'between-design' variance: 3.57 (95% CrI 0.01 to 22.97). The random-effects model was used because it was more conservative, even though the model fit was similar to the fixed-effect model. The 'between-study variance' was 2.19 (95% CrI 0.01 to 21.07).

In the network meta-analysis, there was no evidence of differences in any of the comparisons, as shown in Table 4.

Blood transfusion (red blood cells (RBC) or whole blood)

Blood transfusion proportion

One trial (34 participants) reported blood transfusion (proportion) (Hafta 2001). A total of two treatments were compared in this trial. There were 24 events in total (70.6%). There was no evidence of difference (i.e. there was no statistically significant difference) between sclerotherapy plus vasopressin analogues and sclerotherapy plus somatostatin analogues: OR 0.55 (95% CrI 0.11 to 2.55); 1 trial; 34 participants.

Blood transfusion quantity

Twenty-eight trials (2643 participants) reported blood transfusion (quantity) (Cello 1987; Freeman 1989; McKee 1990; Avgerinos 1991; Lo 1992; Laine 1993; Pauwels 1994; Planas 1994; Besson 1995; Freitas 1995; Lo 1995; Laine 1996; Signorelli 1996; Cello 1997; Lee 1999a; Villanueva 1999; Bildozola 2000; Escorsell 2000; Freitas 2000; Hafta 2001; Patsanas 2002; Shah 2005; Chen 2006; Villanueva 2006; Morales 2007; Abid 2009; Liu 2009; Kumar 2015). A total of 15 treatments were compared in these trials. The weighted median control group mean was 2.9 units of blood per participant.

Direct comparisons

The first intervention had lower blood transfusion (quantity) than the second intervention in the following direct comparisons.

- Somatostatin analogues plus variceal band ligation versus somatostatin analogues: MD -4.00 units (95% CrI -5.14 to -2.85); 1 trial; 101 participants
- Somatostatin analogues plus variceal band ligation versus sclerotherapy plus somatostatin analogues: MD -0.80 units (95% CrI -1.51 to -0.09); 1 trial; 179 participants

The first intervention had higher blood transfusion (quantity) than the second intervention in the following direct comparisons.

- Balloon tamponade plus sclerotherapy versus sclerotherapy: MD 2.50 units (95% CrI 0.95 to 4.02); 1 trial; 60 participants
- Portocaval shunt versus sclerotherapy: MD 7.89 units (95% CrI 2.62 to 13.14); 1 trial; 64 participants

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

Network meta-analysis

All the trials were connected to the network. There was evidence of inconsistency according to the inconsistency factor and the 'between-design' variance (1.78, 95% CrI 0.04 to 10.28), but not by model fit. The inconsistent loops included comparisons of

primary interest for this review, such as sclerotherapy and variceal band ligation. Therefore, no analysis excluding these loops was performed. There is thus uncertainty in the validity of the NMA results: direct comparisons are more reliable. Therefore, we have provided the results of the network meta-analysis only in Table 4, but we do not describe it in a narrative analysis. The random-effects model was used because it was more conservative and had better model fit. The 'between-study variance' was 1.18 (95% CrI 0.24 to 4.07). The sensitivity analysis excluding trials in which standard deviation was imputed did not alter the evidence of inconsistency.

Length of hospital stay (days)

Twelve trials (1295 participants) reported length of hospital stay (Cello 1987; Laine 1993; Laine 1996; Cello 1997; Ramon 1997; Chon 2000; Escorsell 2000; Shah 2005; Chen 2006; Cho 2006; Villanueva 2006; Liu 2009). A total of 10 treatments were compared in these trials. The weighted median control group mean was 18 days per participant.

Direct comparisons

Somatostatin analogues plus variceal band ligation had lower length of hospital stay than somatostatin analogues: MD -4.00 days (95% CrI -5.05 to -2.95); 1 trial; 101 participants. There was no evidence of differences between the treatments in the remaining direct comparisons (i.e. the remaining direct comparisons were not statistically significant) as shown in Table 4.

Network meta-analysis

All the trials were connected to the network. There was no evidence of inconsistency as shown by model fit, but there was evidence of inconsistency by inconsistency factor and design-by-treatment variance (between-design variance: 4.24 (95% CrI 0.01 to 22.72)). As the inconsistency loop involved somatostatin analogues, sclerotherapy, and vasopressin analogues (some of the important treatments being evaluated in this review), we did not perform an analysis excluding these treatments. Therefore, there is uncertainty about the the NMA results, and direct comparisons may be more reliable. The random-effects model was used because it was more conservative, even though the model fit was similar to the fixed-effect model. The 'between-study variance' was 2.73 (95% CrI 0.01 to 21.02).

In the network meta-analysis, there was no evidence of differences in any of the comparisons, as shown in Table 4.

Work days lost (days)

None of the trials reported work days lost.

Treatment costs

Four trials (538 participants) reported treatment costs (Cello 1987; Cello 1997; Abid 2009; Liu 2009). A total of six treatments were compared in these trials. Three trials reported treatment costs in USD (Cello 1987; Cello 1997; Abid 2009). One trial reported treatment costs in China CNY ('Yuan') (Liu 2009). We converted CNY to USD using Purchasing Power Parities and the conversion rates on 10 March 2020. The weighted median group mean costs were USD 23,077. Two trials were not connected to the network because they had treatments unconnected to the network (Abid 2009; Liu 2009). The comparisons in these two trials were vasopressin analogues versus somatostatin analogues (Abid 2009) and variceal band ligation plus somatostatin analogues versus somatostatin analogues (Liu 2009).

Direct comparisons

Somatostatin analogues plus variceal band ligation had higher treatment costs than somatostatin analogues: MD USD 627.50 (95% CrI USD 499.50 to USD 755.00). 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. There was no evidence of differences in the remaining comparison, not connected to the network: vasopressin analogues versus somatostatin analogues: MD USD -1.12 (95% CrI USD -196.20 to USD 197.80).

Network meta-analysis

The network had three connected treatments. There were no triangular or quadrangular loops; therefore, inconsistency was not checked. Only one trial was included in each of the comparisons; therefore, only the fixed-effect model is applicable.

In the network meta-analysis, there was no evidence of differences in any of the comparisons, as shown in Table 4.

Subgroup analysis

We did not perform any of the planned subgroup analyses, for several reasons. None of the trials were at low risk of bias; separate data based on clinical features such as previous history of bleeding oesophageal varices, other features of decompensation, aetiology for cirrhosis, and the severity of cirrhosis prior to the bleeding episode were sparse; the treatment was started as soon as possible, because of the nature of the participants; 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

- Somatostatin analogues versus sclerotherapy:
  - Main analysis: higher in somatostatin analogues than sclerotherapy
  - Worst-best analysis: no evidence of difference between groups
  - Best-worst analysis: higher in somatostatin analogues than sclerotherapy
- Balloon tamponade versus sclerotherapy:
  - Main analysis: no evidence of difference between groups
  - Worst-best analysis: no evidence of difference between groups
  - Best-worst analysis: higher in balloon tamponade than sclerotherapy

- Variceal band ligation plus vasopressin analogues versus vasopressin analogues:
  * Main analysis: no evidence of difference between groups
  * Worst-best analysis: no evidence of difference between groups
  * Best-worst analysis: lower in variceal band ligation plus vasopressin analogues than vasopressin analogues

Any variceal bleed

There were many changes in interpretation. The complete list of changes is available in Appendix 2.

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

- Treatment costs: standard deviation was imputed in one trial (Cello 1987). Excluding this trial did not alter the interpretation of the trials.
- Blood transfusion (quantity): Standard deviation was imputed in eight trials (Freeman 1989; Avgerinos 1991; Besson 1995; Freitas 1995; Freitas 2000; Patsanas 2002; Morales 2007; Kumar 2015). Excluding them resulted in changes in the interpretation of several direct comparisons and the network meta-analysis. Therefore, these analyses should be interpreted with caution.

Assessment of reporting biases

Since there was no meaningful way in which to rank these trials (i.e. there was no specific change in the risk of bias in the trials, 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 variceal band ligation over endoscopic sclerotherapy, we explored whether adding endoscopic sclerotherapy or variceal band ligation to somatostatin analogues or vasopressin analogues made any difference to mortality or variceal rebleeding. We used 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, somatostatin analogues or vasopressin analogues) ('main effects') and assess the interaction between the additional treatment and the existing treatment ('interaction effects') (Welton 2009; Freeman 2018).

Baseline-risk adjusted analysis

The differences between the results of the standard model and the baseline risk adjusted model are available in Appendix 3. None of the differences resulted in any alterations in conclusions.

Mortality

The model fit was similar to that of the model that did not include the baseline risk (deviance information criteria (DIC): 460.0 in baseline-risk adjusted model versus 456.6 in standard model).

Any variceal bleed

The model fit was similar to that of the model that did not include the baseline risk (DIC: 212 in baseline-risk adjusted model versus 211.2 in standard model).

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.

Component network meta-analysis

Mortality

Somatostatin analogues as the first treatment

A total of four trials including 371 participants could be included for this analysis (Avgerinos 1991; Villanueva 1999; Patsanas 2002; Villanueva 2006). We could obtain convergence only for the 'main effects' model (i.e. the interaction between sclerotherapy or variceal band ligation with somatostatin analogues could not be taken into account). The fixed-effect model and random-effects model had similar model fit and gave similar results; therefore, we used the fixed-effect model. There was no evidence of any differences in mortality between somatostatin analogues alone and adding a second treatment such as sclerotherapy or variceal band ligation to somatostatin analogues.

Vasopressin analogues as the first treatment

We were unable to form a network that included sclerotherapy and variceal band ligation as the second treatment when we used vasopressin analogues as the first treatment (baseline treatment).

Any variceal bleed

Somatostatin analogues as the first treatment

A total of three trials including 341 participants could be included for this analysis (Avgerinos 1991; Villanueva 1999; Villanueva 2006). We could obtain convergence only for the 'main effects' model (i.e. the interaction between sclerotherapy or variceal band ligation with somatostatin analogues could not be taken into account). Since only one trial was included in each comparison, only the fixed-effect model is applicable. There was no evidence of any differences in mortality between somatostatin analogues alone and adding sclerotherapy or variceal band ligation to somatostatin analogues.

Vasopressin analogues as the first treatment

We were unable to form a network that included sclerotherapy and variceal band ligation as the second treatment when we used vasopressin analogues as the first treatment (baseline treatment).

DISCUSSION

Summary of main results

We performed a systematic review and network meta-analysis of the common treatments used for treating people with bleeding oesophageal varices secondary to liver cirrhosis. A total of 52 trials, including a total of 4580 participants, were included in this review. A total of 19 interventions were compared in these trials. A total of 48 trials including 4042 participants were included for one or more outcomes of this review (Clanet 1978; Paquet 1985; Gimson 1986; Tsai 1986; Cello 1987; Colin 1987; Lee 1988; Freeman 1989; Burroughs 1990; Fort 1990a; Hsia 1990; McKee 1990; Avgerinos 1991; Huang 1992; Hwang 1992; Lo 1992; Laine 1993; Pauwels 1994; Planas 1994; Besson 1995; Freitas 1995; Lo 1995; Laine 1996; Signorelli 1996; Cello 1997; Cipolletta 1997; Ramon 1997; Lee 1999a; Villanueva 1999; Armonis 2000; Bildozola 2000; Chon 2000; Escorsell 2000; Farooqi 2000; Freitas 2000; Yousuf 2000; Chelarescu 2001; Hafta 2001; Patsanas 2002; Shah 2005; Chen 2006; Cho 2006; Villanueva 2006; Morales 2007; Abid 2009; Liu 2009; Asad 2014; Kumar 2015).

Overall, 15.8% of the trial participants who received the control treatment of sclerotherapy died during the follow-up period ranging from three days to six weeks. Based on moderate-certainty evidence, somatostatin analogues alone had higher mortality than sclerotherapy (OR 1.57, 95% CrI 1.04 to 2.41; network estimate; direct comparison: 4 trials; 353 participants), vasopressin analogues alone had higher mortality than sclerotherapy (OR 1.70, 95% CrI 1.13 to 2.62; network estimate; direct comparison: 2 trials; 438 participants, and a combination of endoscopic treatment with somatostatin analogues or vasopressin analogues seem to be associated with lower mortality than the somatostatin analogues or vasopressin analogues alone in the network meta-analysis.

None of the trials reported health-related quality of life. Based on low-certainty evidence, the proportion of serious adverse events was higher with balloon tamponade plus sclerotherapy than sclerotherapy (OR 4.23, 95% CrI 1.22 to 17.80; direct estimate; 1 trial; 60 participants) and with sclerotherapy plus somatostatin analogues versus somatostatin analogues: (OR 11.00, 95% CrI 1.58 to 330.30; 1 trial); and the proportion and number of serious adverse events was lower in people receiving variceal band ligation plus somatostatin analogues than sclerotherapy plus somatostatin analogues (proportion: OR 0.28, 95% CrI 0.07 to 0.87; 1 trial; 179 participants; number: rate ratio 0.31, 95% CrI 0.08 to 0.92).

Based on moderate-certainty evidence, people receiving vasopressin analogues alone and those receiving variceal band ligation had fewer adverse events than sclerotherapy (rate ratio 0.59, 95% CrI 0.35 to 0.96; network estimate; direct comparison: 1 trial; 219 participants and rate ratio 0.40, 95% CrI 0.21 to 0.74; network estimate; direct comparison: 1 trial; 77 participants respectively). Based on low-certainty evidence, the proportion and number of any adverse events was lower in people variceal band ligation plus somatostatin analogues than sclerotherapy plus somatostatin analogues (proportion: OR 0.42, 95% CrI 0.19 to 0.88; 1 trial; 179 participants; number: rate ratio 0.48, 95% CrI 0.25 to 0.92). Based on low-certainty evidence, proportion of people who developed symptomatic rebleed was less in people who received sclerotherapy plus somatostatin analogues than sclerotherapy (OR 0.21, 95% CrI 0.03 to 0.94; direct estimate; 1 trial; 105 participants). Based on moderate-certainty evidence, the proportion of people who developed any variceal rebleed was more with balloon tamponade-based treatments than variceal band ligation or sclerotherapy.

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

In the comparisons not involving sclerotherapy, there was moderate, low, or very low certainty in evidence in the other comparisons. Broadly, combinations involving endoscopic interventions (sclerotherapy and/or variceal band ligation) had lower mortality than somatostatin analogues only, vasopressin analogues only, or balloon tamponade. A greater proportion of people receiving balloon tamponade alone or in combination with other interventions appeared to develop any adverse events and higher rebleeding those who did not receive balloon tamponade.

The weighted median mortality in the sclerotherapy was 15.8% up to six weeks. 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 2694 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; Plaz Torres 2021; Roccarina 2021). Therefore, it is very much possible to power studies in this population based on mortality.

Probably, the most important questions to be answered in this group of people are which of the endoscopic treatments is better, and what is the added value of somatostatin or vasopressin analogue to endoscopic therapy; as somatostatin analogues or vasopressin analogues are routinely recommended by major liver associations and variceal band ligation is the preferred endoscopic treatment (de Franchis 2015; Tripathi 2015; Garcia-Tsao 2017; EASL 2018). Of the ongoing trials, one trial compares somatostatin analogues plus variceal band ligation versus variceal band ligation alone in people with acute bleeding from oesophageal varices. This trial includes only 270 participants and uses rebleeding at three days as the primary outcome (CTRI/2018/03/012860). Therefore, this trial is unlikely to answer the most important questions. Another trial compares endoscopic sclerotherapy versus endoscopic variceal band ligation versus a combination of endoscopic sclerotherapy and endoscopic variceal band ligation. This trial includes only 90 participants in total, and only a proportion of the participants will be eligible for the review. The trial does not measure any of the outcomes of interest for this review.

Therefore, new trials are needed. However, the acceptability of such trials to participants and clinicians should be assessed before performing the definitive study, as all the major guidelines recommend variceal band ligation as the preferred endoscopic treatment and use of vasopressors with variceal band ligation. However, we disagree with these recommendations (Agreements and disagreements with other studies or reviews).

Any future RCTs should also consider health-related quality of life as one of the important outcomes.

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. Therefore, the results of the review are applicable in people with liver cirrhosis resulting from varied aetiologies, and having bleeding oesophageal varices. There also did not appear to be restrictions based on previous history of variceal bleeding. Therefore, the findings of this review are likely applicable for people having the first episode of bleeding and those who have had previous episodes of bleeding.

The findings of this review are applicable only for adults with cirrhosis in whom the source of bleeding is identified as oesophageal varices. They are not applicable to children, to people (of any age group) with gastric varices, to people (of any age group) with other causes of upper gastrointestinal bleeding, to people with oesophageal bleeding due to other causes of portal hypertension (such as portal vein thrombosis or schistosomiasis), nor to people (of any age group) with failed initial treatment of oesophageal varices, nor to those who responded successfully to the initial treatment.

It should also be noted that the trial participants received supportive care, such as fluid resuscitation and blood transfusion, as part of their care. Therefore, of course, such supportive care should also be provided.

Finally, endoscopic treatments in the trials were delivered by endoscopists. Therefore, the findings of this review are applicable only in centres with endoscopic expertise.

Quality of the evidence

The overall certainty (quality) of evidence varied between moderate to 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 are used as one of the interventions. However, it is possible to obtain low risk of performance bias by outlining the criteria clearly for additional treatments, blood transfusions, or hospital discharge. Outcome assessor blinding can be achieved for all comparisons by use of placebo or a second team to assess the outcomes. If that is not possible, using clear highly reproducible criteria for outcome definitions can decrease detection bias. In this review, the conclusions are not robust to different scenarios of imputation of missing data, leading to potential attrition bias. This can be avoided by performing an intention-to-treat analysis.

Another major reason for the decreased certainty of evidence was imprecision. While some network meta-analyses had sufficient number of events, none of the direct comparisons had adequate sample size. As a result, the credible intervals overlapped clinically significant benefits and clinically significant harms for most comparisons. Therefore, future trials should be adequately powered with sample sizes as described above. Some of the network meta-analyses such as serious adverse events had large uncertainty, mainly because many trials did not report this outcome.

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 evidence of heterogeneity in outcomes such as serious adverse events (proportion), any adverse events (number of participants), blood transfusion (quantity), and length of hospital stay. There was also clinical heterogeneity in the decompensation events reported by the trial authors and possibly differences in the way the trial authors reported adverse events (as the definitions of adverse events were not reported).

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 30% of trials reported serious adverse events adequately; only around 40% of trials reported variceal rebleed adequately; and less than 10% 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 guidance (Dias 2012a; Dias 2012b; Dias 2014; Dias 2016). In addition, we have analysed outcomes using the fixed-effect model and the 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. 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 such similarities and differences. Therefore, the concern about the transitivity assumption was low. However, this cannot be ruled out.

We included only RCTs, 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 future RCTs are powered on mortality, a systematic review on adverse events from observational studies will likely be unnecessary.

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

Agreements and disagreements with other studies or reviews

This is the first network meta-analysis of all the major interventions for initial management of oesophageal varices. One network meta-analysis compared the different pharmacologic interventions (somatostatin analogues and vasopressin analogues) in addition to endoscopic treatment for treating bleeding oesophageal varices and found that these were effective (Zou 2019). However, the authors used a five-day control of bleeding and rebleeding at five days as a measure of effectiveness in arriving at their conclusions. They did not find any evidence of difference in mortality and did not use other important outcomes such as variceal bleeding within six weeks, blood transfusions, requirement for additional treatments, or length of hospital stay to assess effectiveness of treatment (Zou 2019). Another systematic review evaluating the role of terlipressin in acute variceal bleeding (include any gastric or oesophageal variceal bleeding) recommended routine terlipressin for treatment of oesophageal varices, despite finding no evidence that adding terlipressin resulted in lower mortality or rebleeding (Zhou 2018),

AUTHORS' CONCLUSIONS

Implications for practice

Based on moderate-certainty evidence, somatostatin analogues alone and vasopressin analogues alone (with supportive therapy) probably result in increased mortality compared to endoscopic sclerotherapy. Based on moderate-certainty evidence, vasopressin analogues alone and band ligation alone probably result in fewer adverse events compared to endoscopic sclerotherapy. Based on low-certainty evidence, balloon tamponade plus sclerotherapy may result in large increase in serious adverse events compared to sclerotherapy. Based on low-certainty evidence, sclerotherapy plus somatostatin analogues may result in large decrease symptomatic rebleed compared to sclerotherapy. The evidence indicates considerable uncertainty about the effect of the interventions compared to sclerotherapy in the remaining comparisons.

Implications for research

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

Study design: parallel, randomised clinical trial

Participants: people with liver cirrhosis and acute bleeding oesophageal varices

Interventions/control: variceal banding plus vasoactive drugs (terlipressin or octreotide) versus endoscopic sclerotherapy plus vasoactive drugs (terlipressin or octreotide) versus endoscopic sclerotherapy alone.

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: six weeks

Sample size:

For a simple, two-arm, parallel randomised clinical trial, a sample size of 3834 participants is required to detect or reject a relative risk reduction of 20% in the experimental group from the control group proportion of 15.8% mortality, with type I error of 5%, and type II error of 20%.

Other aspects:

Trials need to be conducted and reported according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement (Chan 2013) and CONSORT statement (Schulz 2010). Trials ought to be registered before randomisation of the first participant.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Abid 2009

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Pakistan Period of recruitment: 2003-2005 Number randomised: 324 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 324 Average age (years): 53 Females: 94 (29.0%) Other features of decompensation: not stated Alcohol-related cirrhosis: not stated Viral-related cirrhosis: 253 (78.1%) Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: 45 (13.9%) Prophylactic antibiotics for variceal bleeding: 324 (100.0%) Other inclusion/exclusion criteria: Inclusion: 1. Patients with cirrhosis who presented to the emergency room 2. Endoscopic confirmed esophageal bleeding Exclusion:

Abid 2009 *(Continued)*

1. Nonvariceal bleed on endoscopy
2. Gastric variceal / portal hypertensive gastropathy related bleed at endoscopy.
3. Endoscopy after 24 hours because of any reason.
4. Sclerotherapy for oesophageal variceal bleeding were excluded as sclerotherapy was used as rescue treatment exclusively when ligation was not possible in this study
5. Patients with established hepatorenal syndrome
6. Patients with a history of myocardial ischaemia (myocardial infarction or unstable angina) in past 6 months or electrocardiographic changes at presentation suggestive of cardiac ischaemia (ST segment depression or elevation in contiguous leads)

Interventions	Group 1: vasopressin analogues (n = 163) Further details: terlipressin 2 mg (10 ml) by IV bolus followed by 1 mg (5 ml) IV every 6 hours along with a placebo bolus of 100 ml and then infusion by infusion pump at the rate of 50 ml/h for 72 hours (0.45 % dextrose saline as placebo for octreotide) Group 2: somatostatin analogues (n = 161) Further details: octreotide: 100 ml bolus of 100 mcg IV octreotide prepared as 1 mcg octreotide in 1 ml of 0.45 % dextrose saline and a placebo 10 ml IV bolus (0.45% dextrose saline as placebo for terlipressin)
Outcomes	Outcomes reported: mortality, treatment costs, blood transfusion (RBC or whole blood) (quantity) Follow-up (months): 0.17
Notes	Source of funding (quote): "Institutional support and research fund from Department of Medicine" 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 allocation of drug assignment was carried out by pharmacist using computer generated simple random sequence at the central pharmacy of the hospital"
Allocation concealment (selection bias)	Low risk	Quote: "the allocation of drug assignment was carried out by pharmacist using computer generated simple random sequence at the central pharmacy of the hospital"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients, attending physicians, and care providers were blinded to the study medications" Comment: placebo was used to achieve this
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Patients, attending physicians, and care providers were blinded to the study medications" Comment: placebo was used to achieve this; the outcome assessors were the physicians
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 adequately
Other bias	Unclear risk	Comment: there were different proportion of people with active variceal bleed at endoscopy

Armonis 2000

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Greece Period of recruitment: not stated Number randomised: 25 Post-randomisation dropouts: not stated Revised sample size: 25 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 of cirrhosis: not stated Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: patients with cirrhosis and variceal bleeding
Interventions	Group 1: variceal band ligation (n = 13) Further details: variceal band ligation (no further details) repeated every 7 to 10 days Group 2: sclerotherapy (n = 12) Further details: sclerotherapy (no further details) repeated every 7 to 10 days
Outcomes	Outcomes reported: mortality, variceal rebleed (any) (number of patients) Follow-up (months): 1.5
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)	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 adequately

Armonis 2000 *(Continued)*

Other bias	Low risk	Comment: no other bias noted

Asad 2014

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Pakistan Period of recruitment: Not stated Number randomised: 80 Post-randomisation dropouts: not stated Revised sample size: 80 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 of cirrhosis: not stated Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Inclusion: cirrhotic patients
Interventions	Group 1: variceal band ligation plus vasopressin analogues (n = 40) Further details: no further details available Group 2: sclerotherapy plus variceal band ligation (n = 40) Further details: no further details available
Outcomes	Outcomes reported: mortality Follow-up (months): 1
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

Asad 2014 *(Continued)*

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 adequately
Other bias	Low risk	Comment: no other bias noted

Avgerinos 1991

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Greece Period of recruitment: not stated Number randomised: 92 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 92 Average age (years): 62 Females: 30 (32.6%) Other features of decompensation: not stated Alcohol-related cirrhosis: 28 (30.4%) Viral-related cirrhosis: 39 (42.4%) Autoimmune disease-related cirrhosis: 3 (3.3%) Other causes of cirrhosis: 22 (23.9%) Prophylactic antibiotics for variceal bleeding: 92 (100.0%) Other inclusion/exclusion criteria: patients were included in the study only if active variceal bleeding was present at the time of emergency endoscopy (carried out within 6 hours after admission). Active variceal bleeding was defined as either a spurting or oozing varix or an adherent clot on a varix at endoscopy. Note from Table 3 that patients with oesophageal and gastric variceal bleeding included as outlined by the reported source of bleeding
Interventions	Group 1: balloon tamponade plus somatostatin analogues (n = 31) Further details: balloon tamponade (Sengstaken-Blakemore tube) gastric balloon for 48 hours plus oesophageal balloon for 24 hours plus somatostatin analogues 250 mg/hr for 24 hours Group 2: balloon tamponade (n = 30) Further details: balloon tamponade (Sengstaken-Blakemore tube) gastric balloon for 48 hours plus oesophageal balloon for 24 hours Group 3: somatostatin analogues (n = 31) Further details: somatostatin 250 mg/hr for 24 hours
Outcomes	Outcomes reported: mortality, any adverse events (number of participants), additional treatment to control variceal bleeding, variceal rebleed (any) (number of patients), blood transfusion (RBC or whole blood) (quantity) Follow-up (months): 0.25
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**

Avgerinos 1991 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "After endoscopy patients were randomized (using 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	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 pre-published protocol was available, but the authors reported mortality, adverse events, and rebleeding adequately
Other bias	Low risk	Comment: no other bias noted

Besson 1995

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: France Period of recruitment: 1992-1994 Number randomised: 199 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 199 Average age (years): 56 Females: 47 (23.6%) Other features of decompensation: 45 (22.6%) Alcohol-related cirrhosis: 182 (91.5%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Exclusion - Severe liver failure (defined as a hepatorenal syndrome or end-stage cirrhosis) - Hepatocellular carcinoma - 80 years old or older
Interventions	Group 1: sclerotherapy plus somatostatin analogues (n = 98) Further details: sclerotherapy: 2% polidocanol up to 20 ml plus octreotide 25 mcg per hour for 5 days Group 2: sclerotherapy (n = 101) Further details: sclerotherapy: 2% polidocanol up to 20 ml plus placebo
Outcomes	Outcomes reported: mortality, any adverse events (number of events), other features of decompensation, blood transfusion (RBC or whole blood) (quantity)

Besson 1995 *(Continued)*

	Follow-up (months): 0.5
Notes	Source of funding (quote): "….and Sandoz Pharmaceuticals for providing the study medications" 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: "Each hospital had a consecutively numbered series of sealed boxes corresponding to the assigned treatment…The code assigning patients to their treatment groups was kept by the statistician in charge of the analysis " Comment: although the details on sequence generation was not reported, the method of allocation concealment used makes it highly likely that the sequence was random
Allocation concealment (selection bias)	Low risk	Quote: "Each hospital had a consecutively numbered series of sealed boxes corresponding to the assigned treatment…The code assigning patients to their treatment groups was kept by the statistician in charge of the analysis "
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Each box contained six identical ampoules of octreotide or placebo, so that neither the physicians nor the patients were aware of the treatment"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Each box contained six identical ampoules of octreotide or placebo, so that neither the physicians nor the patients were aware of the treatment" Comment: the outcome assessors were the physicians
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 bleeding from oesophageal varices were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Bildozola 2000

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Argentina Period of recruitment: 1994-1997 Number randomised: 84 Post-randomisation dropouts: 8 (9.5%) Revised sample size: 76 Reasons for post-randomisation dropouts: portal vein thrombosis (5); protocol violation (2); and no cirrhotic liver (1) Average age (years): 53 Females: 16 (21.1%) Other features of decompensation: 22 (28.9%) Alcohol-related cirrhosis: 55 (72.4%)

Bildozola 2000 *(Continued)*

	Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Prophylactic antibiotics for variceal bleeding: 76 (100.0%) Other inclusion/exclusion criteria: Exclusion - pregnancy
Interventions	Group 1: somatostatin analogues (n = 39) Further details: octreotide intravenous bolus injection of 100 mcg, a continuous infusion of 50 mcg/h was administered during 48 hours, followed by 100 mcg/8h by the subcutaneous route during the following 72 hours Group 2: sclerotherapy (n = 37) Further details: sclerotherapy: 2% polidocanol, maximum 25 ml
Outcomes	Outcomes reported: mortality, serious adverse events (number of participants), variceal rebleed (symptomatic recovery) (number of patients), blood transfusion (RBC or whole blood) (quantity) Follow-up (months): 0.1
Notes	Source of funding (quote): "Octreotide (Sandostatin) was provided by Novartis, Buenos Aires, Argentina" 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 immediately after the diagnostic endoscopy, using a table of random numbers, to receive octreotide or sclerotherapy"
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: there were post-randomisation dropouts, but these were unlikely to be related to the treatment groups, but one cannot be absolutely sure about this
Selective reporting (reporting bias)	Low risk	Comment: no prepublished protocol was available, but the authors reported the mortality, adverse events, and rebleeding adequately
Other bias	Low risk	Comment: no other bias noted

Burroughs 1990

Study characteristics

Burroughs 1990 *(Continued)*

Methods	Randomised clinical trial
Participants	Country: England Period of recruitment: 1985-1987 Number randomised: 133 Post-randomisation dropouts: 13 (9.8%) Revised sample size: 120 Reasons for post-randomisation dropouts: non-variceal bleeding Average age (years): 54 Females: 46 (38.3%) Other features of decompensation: 16 (13.3%) Alcohol-related cirrhosis: 62 (51.7%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: 32 (26.7%) Other causes of cirrhosis: 26 (21.7%) Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Inclusion criteria: age >16 yrs (although note that lower age range of randomised patients was 18 yrs)
Interventions	Group 1: no active intervention (n = 59) Further details: placebo Group 2: somatostatin analogues (n = 61) Further details: somatostatin 250 mcg bolus followed by 250 mcg/hour for 5 days
Outcomes	Outcomes reported: mortality, any adverse events (number of events) Follow-up (months): 1
Notes	Source of funding (quote): "The authors would like to thank Serono Laboratories Ltd. for the supply of coded drugs" 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: "For each group there was a consecutively numbered series of opaque sealed envelopes containing the allocated treatment derived from a table of random numbers"
Allocation concealment (selection bias)	Low risk	Quote: "For each group there was a consecutively numbered series of opaque sealed envelopes containing the allocated treatment derived from a table of random numbers"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Placebo and somatostatin … were packaged in identical ampoules, so that both physicians and patients were blinded to the treatment given"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Placebo and somatostatin … were packaged in identical ampoules, so that both physicians and patients were blinded to the treatment given" Comment: the outcome assessors were the physicians
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were post-randomisation dropouts, however, these are unrelated to the interventions

Burroughs 1990 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available and bleeding from oesophageal varices were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Cello 1987

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: 1980-1984 Number randomised: 64 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 64 Average age (years): 44 Females: 9 (14.1%) Other features of decompensation: 42 (65.6%) Alcohol-related cirrhosis: 59 (92.2%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Inclusion: - Child Class C cirrhosis - Substantial oesophageal variceal bleeding, requiring at least six units of packed red cells or whole blood before random assignment
Interventions	Group 1: portocaval shunt (n = 32) Further details: end-to-side or side-to-side portocaval shunts Group 2: sclerotherapy (n = 32) Further details: sclerotherapy: 2 to 3 ml per injection of 5% sodium morrhuate (5 to 10 injections per session), and repeat injection, initially at 3 day intervals and then monthly intervals until eradication of varices
Outcomes	Outcomes reported: mortality, length of hospital stay (days), treatment costs, blood transfusion (RBC or whole blood) (quantity) Follow-up (months): 1
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: "After obtaining informed consent, we used a serially numbered, sealed, opaque envelopes for random assignment of patients to either endoscopic sclerotherapy or urgent portocaval shunt" Comment: although the details on sequence generation was not reported, the method of allocation concealment used makes it highly likely that the sequence was random

Cello 1987 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "After obtaining informed consent, we used a serially numbered, sealed, opaque envelopes for random assignment of patients to either endoscopic sclerotherapy or urgent portocaval shunt"
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 bleeding from oesophageal varices were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Cello 1997

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: 1991-1995 Number randomised: 49 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 49 Average age (years): 48 Females: 13 (26.5%) Other features of decompensation: 14 (28.6%) Alcohol-related cirrhosis: 33 (67.3%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Inclusion: patients admitted with massive or submassive acute gastrointestinal tract haemorrhage from large (>1 cm across) distal esophageal varices Exclusion: - >75 yrs old - Stage IV hepatic encephalopathy - Cancer other than skin cancer - Acquired immunodeficiency syndrome (AIDS) - Sepsis, pneumonia, peritonitis, clinical evidence of alcoholic hepatitis - Po2 less than 70 mmHg or an arterial pH of 7.20 or less on room air, a serum creatinine level of 221 µmol/L or more, a prothrombin time at least 5 seconds longer than control (despite the use of fresh frozen plasma), a platelet count less than 50 X 109/L, a serum bilirubin concentration of 7 mg/dL or more - Thrombosis of the portal vein, thrombosis of the hepatic veins, or thrombosis of the inferior vena cava

Cello 1997 *(Continued)*

Interventions	Group 1: sclerotherapy plus TIPS (n = 24) Further details: sclerotherapy: ethanolamine oleate up to 30 ml plus TIPS: performed within 48 hours (Ring TIPS set, Cook, Inc., Bloomington, Indiana) Group 2: sclerotherapy (n = 25) Further details: sclerotherapy: ethanolamine oleate up to 30 ml, repeated weekly, duration not stated
Outcomes	Outcomes reported: mortality, length of hospital stay (days), treatment costs, blood transfusion (RBC or whole blood) (quantity) Follow-up (months): 1
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: "serially numbered, sealed, opaque envelopes to randomly assign patients either to repeated sclerotherapy or to TIPS" Comment: although the details on sequence generation was not reported, the method of allocation concealment used makes it highly likely that the sequence was random
Allocation concealment (selection bias)	Low risk	Quote: "serially numbered, sealed, opaque envelopes to randomly assign patients either to repeated sclerotherapy or to TIPS"
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 adequately
Other bias	Low risk	Comment: no other bias noted

Chelarescu 2001

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Romania Period of recruitment: not stated Number randomised: 59 Post-randomisation dropouts: not stated Revised sample size: 59

Chelarescu 2001 *(Continued)*

	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 of cirrhosis: not stated Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Inclusion: cirrhotic patients with endoscopy-proved oesophageal bleeding
Interventions	Group 1: balloon tamponade plus nitrates plus vasopressin analogues (n = 32) Further details: balloon tamponade for 4 hours (no further details) plus transdermal nitroglycerin 10 mg/12 hours for first 24 hours plus terlipressin 2 mg IV initially and 1 mg every 4 hours for 24 hours Group 2: balloon tamponade plus somatostatin analogues (n = 27) Further details: balloon tamponade for 4 hours (no further details) plus somatostatin 0.05 mg initially and 0.05 mg/h IV infusion in next 48 hours
Outcomes	Outcomes reported: mortality Follow-up (months): 0.06
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	Quote: "double-blind" Comment: no further details of how this was achieved was reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: no further details of how this was achieved was reported
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 bleeding from oesophageal varices were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Chen 2006

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Taiwan, Republic of China Period of recruitment: 2000 - 2004 Number randomised: 125 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 125 Average age (years): 53 Females: 30 (24.0%) Other features of decompensation: 34 (27.2%) Alcohol-related cirrhosis: 53 (42.4%) Viral-related cirrhosis: 59 (47.2%) Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: 13 (10.4%) Prophylactic antibiotics for variceal bleeding: 125 (100.0%) Other inclusion/exclusion criteria: Inclusion: - Hospital arrival within 12 hours after onset of the symptoms - Age between 20 and 75 years Exclusion: - Child-Pugh score greater than 12 points - Hepatorenal syndrome or uremia - Comatose status - Hepatocellular carcinoma or other malignancy - Portal vein thrombosis - Previous surgical or transjugular intrahepatic portosystemic stent shunt
Interventions	Group 1: somatostatin analogues plus variceal band ligation (n = 63) Further details: no further details Group 2: variceal band ligation (n = 62) Further details: somatostatin 250 mcg bolus followed by 250 mcg/h for 48 hours followed by variceal band ligation 4 to 8 rubber bands
Outcomes	Outcomes reported: mortality, serious adverse events (number of events), any adverse events (number of events), additional treatment to control variceal bleeding, variceal rebleed (any) (number of patients), length of hospital stay (days), blood transfusion (RBC or whole blood) (quantity) Follow-up (months): 1.5
Notes	Source of funding (quote): "This study was supported, in part, by a grant from Kaohsiung Veterans General Hospital Research Program (VGHKS 92-18)" 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 random numbers"
Allocation concealment (selection bias)	Low risk	Quote: "A statistician created sequentially numbered opaque and sealed envelopes containing a digit (1 for the emergency EVL group and 2 for the SMT group) derived from computer-generated random numbers. The investigators opened the envelopes and assigned the patients to the designated groups"

Chen 2006 *(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)	Low risk	Comment: no prepublished protocol was available, but the authors reported the mortality, adverse events, and rebleeding adequately
Other bias	Low risk	Comment: no other bias noted

Cho 2006

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: South Korea Period of recruitment: 2005 Number randomised: 88 Post-randomisation dropouts: not stated Revised sample size: 88 Average age (years): 55 Females: 14 (15.9%) Other features of decompensation: 10 (11.4%) Alcohol-related cirrhosis: 34 (38.6%) Viral-related cirrhosis: 54 (61.4%) Autoimmune disease-related cirrhosis: 0 (0.0%) Other causes of cirrhosis: 0 (0.0%) Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Exclusion: 1. Previous portal vein shunt surgery or procedures 2. Patients in who ligation failed or endoscopy was stopped because of unstable vital signs during endoscopy 3. Malignant tumours other than hepatocellular carcinoma, or those with severe chronic disease 4. Patients who were given vasoactive drug medication prior to emergency endoscopy due to past history of variceal bleeding
Interventions	Group 1: variceal band ligation plus vasopressin analogues (n = 43) Further details: variceal band ligation (no further details) plus terlipressin 2 mg IV and then 1 mg every 4 hours for 3 days Group 2: somatostatin analogues plus variceal band ligation (n = 45) Further details: variceal band ligation (no further details) and octreotide 25 mcg/h for 5 days
Outcomes	Outcomes reported: mortality, serious adverse events (number of participants), variceal rebleed (any) (number of patients), length of hospital stay (days)

Cho 2006 *(Continued)*

	Follow-up (months): 1.5
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)	Unclear risk	Quote: "Patient selection was randomly selected by the internal gastroenterologist and emergency department on-call doctor according to a fixed random number" Comment: it was not clear how the random number was generated
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: authors state that they excluded patients without 42 day follow-up, but do not mention how many they excluded and it was not possible to assess whether it could be related to intervention and outcome
Selective reporting (reporting bias)	Low risk	Comment: no prepublished protocol was available, but the authors reported the mortality, adverse events, and rebleeding adequately
Other bias	Low risk	Comment: no other bias noted

Chon 2000

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Korea Period of recruitment: 1997-1998 Number randomised: 28 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 28 Average age (years): 51 Females: 2 (7.1%) Other features of decompensation: not stated Alcohol-related cirrhosis: 15 (53.6%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria:

Chon 2000 *(Continued)*

	Inclusion: - Patients aged 18-70 years - Requiring more than 500 ml transfusion Exclusion: - History of gastric surgery - Patients with cancer, heart failure, renal failure, severe systemic diseases such as diabetes - Patients with coagulation disorder by cause other than liver disease - Pregnant women
Interventions	Group 1: vasopressin analogues (n = 13) Further details: vasopressin 0.2 IU/hr for 48 hours Group 2: somatostatin analogues (n = 15) Further details: somatostatin 250 mcg bolus followed by 250 mcg/hr for 48 hours
Outcomes	Outcomes reported: mortality, variceal rebleed (any) (number of patients), length of hospital stay (days) Follow-up (months): 0.5
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)	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 bleeding from oesophageal varices were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Cipolletta 1997

Study characteristics	
Methods	Randomised clinical trial

Cipolletta 1997 *(Continued)*

Participants	Country: Italy Period of recruitment: 1994-1996 Number randomised: 81 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 81 Average age (years): 55 Females: 35 (43.2%) Other features of decompensation: not stated Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Inclusion: cirrhotic patients with bleeding oesophageal varices or with signs of recent bleeding
Interventions	Group 1: variceal band ligation (n = 41) Further details: variceal band ligation: Stiegmann technique with single ligatures, at regular intervals of 5 to 30 days according to patient needs until disappearance of varices Group 2: sclerotherapy (n = 40) Further details: sclerotherapy: 1% polidocanol 20 to 25 ml per session, at regular intervals of 5 to 30 days according to patient needs until disappearance of varices
Outcomes	Outcomes reported: mortality, any adverse events (number of participants) Follow-up (months): 0.5
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)	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 bleeding from oesophageal varices were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Clanet 1978

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: France Period of recruitment: not stated Number randomised: 44 Post-randomisation dropouts: not stated Revised sample size: 44 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 of cirrhosis: not stated Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: not stated
Interventions	Group 1: balloon tamponade plus vasopressin analogues (n = 26) Further details: balloon tamponade with Linton-Nicholas tube, balloon inflated with 600 ml and traction applied with 1 kg (duration not stated) plus vasopressin intravenous or intraarterial 0.4 units/min (duration not reported) Group 2: balloon tamponade (n = 18) Further details: balloon tamponade with Linton-Nicholas tube, balloon inflated with 600 ml and traction applied with 1 kg (duration not stated)
Outcomes	Outcomes reported: mortality, variceal rebleed (any) (number of patients) Follow-up (months): 0.5
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)	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

Clanet 1978 *(Continued)*

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

Colin 1987

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: France Period of recruitment: 1984-1986 Number randomised: 52 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 52 Average age (years): 51 Females: 17 (32.7%) Other features of decompensation: not stated Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Exclusion criteria: hepatocarcinoma, previous portacaval anastomosis, contraindications to vasopressin such as coronary artery disease, arrhythmias, malignant hypertension and chronic respiratory failure
Interventions	Group 1: balloon tamponade plus vasopressin analogues (n = 26) Further details: Sengstaken-Blakemore tube removed 24 hours after bleeding stopped plus glypressin 2 mg bolus every 6 hours for first 48 hours and then 1 mg bolus every 6 hours for next 48 hours Group 2: balloon tamponade (n = 26) Further details: Sengstaken-Blakemore tube removed 24 hours after bleeding stopped Additional details: there were three groups in this trial. All the three groups received Sengstaken-Blakemore tube, but the oesophageal balloon was not inflated in Glypressin (G) group. Therefore, the three groups became G plus SB (oesophageal balloon not inflated), SB alone (oesophageal balloon inflated), G plus SB (oesophageal balloon inflated). Balloon tamponade involves inflating the oesophageal balloon; insertion of a tube without balloon tamponade is not an intervention of interest for this review. Therefore, only SB alone (oesophageal balloon inflated), G plus SB (oesophageal balloon inflated) groups were included for this review
Outcomes	Outcomes reported: mortality, any adverse events (number of events), variceal rebleed (any) (number of patients) Follow-up (months): 0.2
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**

Colin 1987 *(Continued)*

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)	Low risk	Comment: no prepublished protocol was available, but the authors reported the mortality, adverse events, and rebleeding adequately
Other bias	Unclear risk	Comment: the number of episodes rather than the number of patients were used as the unit of analysis in the paper; we based the outcomes on the number of participants rather than number of episodes

Escorsell 2000

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Spain Period of recruitment: 1994-1996 Number randomised: 221 Post-randomisation dropouts: 2 (0.9%) Revised sample size: 219 Reasons for post-randomisation dropouts: major protocol violations Average age (years): 55 Females: 61 (27.9%) Other features of decompensation: not stated Alcohol-related cirrhosis: 88 (40.2%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Inclusion: clinical evidence of bleeding (hematemesis and/or melena) during the previous 24 hours; endoscopically proven haemorrhage from esophageal varices as shown by the finding on emergency endoscopy, performed within 6 hours of admission, of active bleeding from a varix, stigmata of recent haemorrhage, or fresh blood in the stomach and esophageal varices as the only potential source of bleeding; age between 18 and 70 years; no previous randomization in this study; no previous use of vasopressin and/or terlipressin and/or endoscopic injection sclerotherapy to control the bleeding episode; signed informed consent to participate in the study

Escorsell 2000 *(Continued)*

	Exclusion criteria: bleeding from fundal varices; concomitant gastrointestinal bleeding from sources other than esophageal varices; previous (5-day period) sclerotherapy or variceal banding ligation; earlier TIPS to treat previous episodes of variceal haemorrhage; a history of severe cardiovascular disease, including acute myocardial infarction, atrioventricular block, heart failure, chronic peripheral ischaemia, and arterial hypertension (defined by a systolic blood pressure of 180 mmHg and/or a diastolic blood pressure 100 mmHg); a known hypersensitivity to terlipressin or sclerosing agents; known hepatocellular carcinoma; pregnancy; chronic renal failure; ongoing treatment for bronchial asthma; and body weight <50 kg
Interventions	Group 1: vasopressin analogues (n = 105) Further details: terlipressin 2 mg IV every 4 hours until control of bleeding (24-hour bleeding-free period) for first 48 hours, followed by 1 mg/4 hours for 5 days Group 2: sclerotherapy (n = 114) Further details: sclerotherapy: 5% ethanolamine or 1% polidocanol, one session only
Outcomes	Outcomes reported: mortality, serious adverse events (number of events), any adverse events (number of participants), any adverse events (number of events), variceal rebleed (any) (number of patients), length of hospital stay (days), blood transfusion (RBC or whole blood) (quantity) Follow-up (months): 1.5
Notes	Source of funding (quote): "Supported in part by grants from the Fondo de Investigaciones Sanitarias (FIS 97/1309) and by Ferring AB (Malmo, Sweden)" 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: "Separate blocked lists of randomization were generated by computer for each participating centre by Ferring AB"
Allocation concealment (selection bias)	Low risk	Quote: "The assigned treatments were kept, by each investigator, in sealed, consecutively numbered, opaque envelopes until randomization"
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 is not clear whether they could be related to the intervention and outcomes
Selective reporting (reporting bias)	Low risk	Comment: no prepublished protocol was available, but the authors reported the mortality, adverse events, and rebleeding adequately
Other bias	Low risk	Comment: no other bias noted

Farooqi 2000

Study characteristics

Farooqi 2000 *(Continued)*

Methods	Randomised clinical trial
Participants	Country: Pakistan Period of recruitment: 1994-1998 Number randomised: 141 Post-randomisation dropouts: not stated Revised sample size: 141 Average age (years): 39 Females: 62 (44.0%) Other features of decompensation: not stated Alcohol-related cirrhosis: 0 (0.0%) Viral-related cirrhosis: 141 (100.0%) Autoimmune disease-related cirrhosis: 0 (0.0%) Other causes of cirrhosis: 0 (0.0%) Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Inclusion: cirrhotic patients with an upper gastrointestinal bleed of less than 24 hours duration; clinically significant bleeding; endoscopically confirmed acute variceal bleeding Exclusion: bleeding other than oesophageal varices; bleeding of more than 24 hours duration; vasoactive drug or injection sclerotherapy given in the previous 7 days
Interventions	Group 1: sclerotherapy plus somatostatin analogues (n = 72) Further details: sclerotherapy: ethanolamine oleate (no further details) plus octreotide 50 mcg IV for 48 hours Group 2: sclerotherapy (n = 69) Further details: sclerotherapy: ethanolamine oleate (no further details)
Outcomes	Outcomes reported: mortality, variceal rebleed (any) (number of patients) Follow-up (months): 0.5
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)	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

Farooqi 2000 *(Continued)*

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

Fort 1990a

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: France Period of recruitment: 1987-1989 Number randomised: 42 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 42 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 of cirrhosis: not stated Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Exclusion: bleeding from gastric varices, Sengstaken–Blakemore tube already in situ, severe cirrhosis and liver failure, coronary heart disease
Interventions	Group 1: nitrates plus vasopressin analogues (n = 20) Further details: nitroglycerin 0.4 sublingually every 20 minutes for 4 hours plus terlipressin 2 mg IV bolus and then 1 mg given every 6 hours as bolus for 30 hours Group 2: balloon tamponade (n = 22) Further details: Sengstaken-Blakemore tube, gastric balloon inflated with 120 to 160 ml of air and oesophageal balloon with 40 ml air and left inflated for 24 hours and then the tube was removed 12 to 24 hours after deflation
Outcomes	Outcomes reported: mortality, serious adverse events (number of participants), any adverse events (number of events), variceal rebleed (symptomatic recovery) (number of patients) Follow-up (months): 0.25
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: "The subjects were randomized by a table of random numbers"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available

Fort 1990a *(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)	Low risk	Comment: no prepublished protocol was available, but the authors reported the mortality, adverse events, and rebleeding adequately
Other bias	Low risk	Comment: no other bias noted

Freeman 1989

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: England Period of recruitment: not stated Number randomised: 31 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 31 Average age (years): 53 Females: not stated Other features of decompensation: not stated Alcohol-related cirrhosis: 24 (77.4%) Viral-related cirrhosis: 2 (6.5%) Autoimmune disease-related cirrhosis: 3 (9.7%) Other causes of cirrhosis: 2 (6.5%) Prophylactic antibiotics for variceal bleeding: 31 (100.0%) Other inclusion/exclusion criteria: Inclusion: patients actively bleeding from esophageal varices, other sources of haemorrhage having been endoscopically excluded
Interventions	Group 1: no active intervention (n = 16) Further details: placebo Group 2: vasopressin analogues (n = 15) Further details: terlipressin 2 mg every 4 hours until the bleeding stops
Outcomes	Outcomes reported: mortality, serious adverse events (number of participants), additional treatment to control variceal bleeding, variceal rebleed (symptomatic recovery) (number of patients), blood transfusion (RBC or whole blood) (quantity) Follow-up (months): 0.25
Notes	Source of funding (quote): "We thank Ferring Pharmaceuticals for provision of glypressin and placebo ampoules" Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020

Freeman 1989 *(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: a placebo was used, but it was not clear whether blinding was achieved
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: a placebo was used, but it was not clear whether blinding was achieved
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 the mortality, adverse events, and rebleeding adequately
Other bias	Low risk	Comment: no other bias noted

Freitas 1995

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Portugal Period of recruitment: 1989-1994 Number randomised: 111 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 111 Average age (years): 55 Females: 35 (31.5%) Other features of decompensation: not stated Alcohol-related cirrhosis: 104 (93.7%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Inclusion: endoscopically proved bleeding esophageal varices
Interventions	Group 1: somatostatin analogues (n = 58) Further details: octreotide IV 25 mcg/hr for 48 hours Group 2: sclerotherapy (n = 53) Further details: sclerotherapy: absolute alcohol 0.5 to 1 ml for each varix

Freitas 1995 *(Continued)*

Outcomes	Outcomes reported: mortality, serious adverse events (number of participants), blood transfusion (RBC or whole blood) (quantity) Follow-up (months): 1
Notes	Source of funding (quote): "We thank Produtos Sandoz, Lda. for the offer of Octreotide (Sandostatin®) to perform this research work" 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 digit table"
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 adequately
Other bias	Low risk	Comment: no other bias noted

Freitas 2000

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Portugal Period of recruitment: 1989-1994 Number randomised: 86 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 86 Average age (years): 56 Females: 21 (24.4%) Other features of decompensation: not stated Alcohol-related cirrhosis: 81 (94.2%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Prophylactic antibiotics for variceal bleeding: not stated

Freitas 2000 *(Continued)*

	Other inclusion/exclusion criteria: Inclusion: patients admitted for upper GI bleeding resulting from esophageal variceal rupture
Interventions	Group 1: sclerotherapy plus somatostatin analogues (n = 44) Further details: sclerotherapy: absolute alcohol 0.5 to 1 ml for each varix plus octreotide IV 25 mcg/hr for 48 hours Group 2: sclerotherapy (n = 42) Further details: sclerotherapy: absolute alcohol 0.5 to 1 ml for each varix
Outcomes	Outcomes reported: mortality, serious adverse events (number of participants), blood transfusion (RBC or whole blood) (quantity) Follow-up (months): 1
Notes	Source of funding (quote): "We thank Produtos Sandoz, Lda. for the offer of Octreotide (Sandostatin®) to perform this research work" 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 digit table"
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 bleeding from oesophageal varices were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Gimson 1986

Study characteristics

Methods	Randomised clinical trial
Participants	Country: United Kingdom Period of recruitment: 1982-1984 Number randomised: 62 Post-randomisation dropouts: not stated

Gimson 1986 *(Continued)*

	Revised sample size: 62 Average age (years): 52 Females: 20 (32.3%) Other features of decompensation: not stated Alcohol-related cirrhosis: 30 (48.4%) Viral-related cirrhosis: 4 (6.5%) Autoimmune disease-related cirrhosis: 14 (22.6%) Other causes of cirrhosis: 14 (22.6%) Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Inclusion: signs of continuing haemorrhage (hematemesis and fresh melena) Exclusion: site of bleeding other than varices at endoscopy
Interventions	Group 1: nitrates plus vasopressin analogues (n = 32) Further details: nitroglycerin 40 mcg per minute up to 400 mcg per minute, as long as the systolic blood pressure was >100 mmHg; total duration = 12 hours plus vasopressin 20 units bolus and then 0.4 units per min for 12 hours Group 2: vasopressin analogues (n = 30) Further details: vasopressin 20 units bolus and then 0.4 units per min for 12 hours
Outcomes	Outcomes reported: mortality, serious adverse events (number of participants), any adverse events (number of events), additional treatment to control variceal bleeding Follow-up (months): 0.5
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: "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	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: the participant flow was not clear
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available and bleeding from oesophageal varices were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Hafta 2001

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Turkey Period of recruitment: 1999-2000 Number randomised: 34 Post-randomisation dropouts: not stated Revised sample size: 34 Average age (years): 57 Females: 14 (41.2%) Other features of decompensation: not stated Alcohol-related cirrhosis: 3 (8.8%) Viral-related cirrhosis: 31 (91.2%) Autoimmune disease-related cirrhosis: 0 (0.0%) Other causes of cirrhosis: 0 (0.0%) Prophylactic antibiotics for variceal bleeding: 34 (100.0%) Other inclusion/exclusion criteria: Exclusion: chronic renal disease, bleeding from gastric ulcer or fundal varices, severe heart disease (e.g. acute myocardial infarction, atrio-ventricular block, heart failure), chronic peripheric ischaemia, arterial hypertension (systolic >170 mmHg and/or diastolic >100 mmHg), those receiving treatment for bronchial asthma; patients over 70 or under 18 years old, under 45 kg in weight, without histopathologic diagnosis, history of previous variceal bleeding
Interventions	Group 1: sclerotherapy plus vasopressin analogues (n = 17) Further details: sclerotherapy: 1% polidocanol about 20 ml plus terlipressin 2 mg bolus followed by 2 mg every 4 hours for 72 hours Group 2: sclerotherapy plus somatostatin analogues (n = 17) Further details: sclerotherapy: 1% polidocanol about 20 ml plus somatostatin 250 mg bolus followed by 250 mg/hr for 72 hours
Outcomes	Outcomes reported: mortality, blood transfusion (RBC or whole blood) (proportion), blood transfusion (RBC or whole blood) (quantity) Follow-up (months): 0.1
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

Hafta 2001 *(Continued)*
All outcomes

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 adequately
Other bias	Low risk	Comment: no other bias noted

Hsia 1990

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Taiwan, Republic of China Period of recruitment: not stated Number randomised: 46 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 46 Average age (years): 62 Females: 4 (8.7%) Other features of decompensation: not stated Alcohol-related cirrhosis: not stated Viral-related cirrhosis: 30 (65.2%) Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: 21 (45.7%) Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Exclusion: history of coronary artery disease, arrhythmia, previous portacaval anastomosis, malignant hypertension, poorly controlled diabetes mellitus (fasting blood sugar >200 mg/dl), congenital haemorrhagic diathesis, cerebral vascular accident, pregnancy or chronic respiratory failure
Interventions	Group 1: vasopressin analogues (n = 24) Further details: vasopressin 0.4 units/min for 24 hours Group 2: somatostatin analogues (n = 22) Further details: somatostatin 250 mcg bolus followed by 250 mcg/hr for 24 hours
Outcomes	Outcomes reported: mortality, any adverse events (number of participants) Follow-up (months): 1.5
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)	Unclear risk	Comment: this information was not available

Hsia 1990 *(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	Low risk	Comment: there were no post-randomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available and bleeding from oesophageal varices were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Huang 1992

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Taiwan, Republic of China Period of recruitment: 1991 Number randomised: 41 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 41 Average age (years): 49 Females: 8 (19.5%) Other features of decompensation: not stated Alcohol-related cirrhosis: 14 (34.1%) Viral-related cirrhosis: 20 (48.8%) Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Exclusion: past history of ischaemic heart disease, arrhythmia, severe hypertension (diastolic blood pressure >115 mmHg); previous porto-caval or Warren shunt' previous sclerotherapy for variceal bleeding; pregnancy, chronic obstructive respiratory disease, cerebral vascular stroke, taking vasoactive drug(s), poorly controlled diabetes mellitus with a fasting sugar >300 mg, renal insufficiency
Interventions	Group 1: vasopressin analogues (n = 21) Further details: vasopressin 0.4 units/min for 24 hours Group 2: somatostatin analogues (n = 20) Further details: somatostatin 100 mcg bolus followed by 25 mcg/hr for 24 hours
Outcomes	Outcomes reported: mortality, any adverse events (number of participants), variceal rebleed (any) (number of patients) Follow-up (months): 0.25
Notes	Source of funding: not stated

Huang 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)	Low risk	Comment: although the details were not available, the method of allocation concealment suggests that randomisation was probably done
Allocation concealment (selection bias)	Low risk	Quote: "by sealed envelopes" Comment: although, detailed specification is not available, it was probably randomised
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 the mortality, adverse events, and rebleeding adequately
Other bias	Low risk	Comment: no other bias noted

Hwang 1992

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Taiwan, Republic of China Period of recruitment: 1990-1991 Number randomised: 48 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 48 Average age (years): 61 Females: 3 (6.3%) Other features of decompensation: not stated Alcohol-related cirrhosis: 8 (16.7%) Viral-related cirrhosis: 26 (54.2%) Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: 14 (29.2%) Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Exclusion: coronary artery disease, arrhythmias, previous portacaval anastomosis, malignancy hypertension, congenital haemorrhagic diathesis, cerebral vascular accident, pregnancy, chronic respiratory failure

Hwang 1992 *(Continued)*

Interventions	Group 1: vasopressin analogues (n = 24) Further details: vasopressin 0.4 units/min for 24 hours Group 2: somatostatin analogues (n = 24) Further details: octreotide 100 mcg bolus followed by 25 mcg/hr for 24 hours
Outcomes	Outcomes reported: mortality, any adverse events (number of participants) Follow-up (months): 1.5
Notes	Source of funding (quote): "Sandostatin, generously supplied by Sandoz Pharmaceutical Ltd. Taiwan Branch" 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 bleeding from oesophageal varices were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Jensen 1998

Study characteristics

Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: not stated Number randomised: 57 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 57 Average age (years): not stated Females: not stated Other features of decompensation: not stated Alcohol-related cirrhosis: not stated

Jensen 1998 *(Continued)*

	Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Inclusion: patients with cirrhosis and documented severe esophageal variceal haemorrhage
Interventions	Group 1: sclerotherapy plus variceal band ligation (n = 29) Further details: sclerotherapy plus variceal band ligation (no further details) repeated after a week and then monthly until obliteration Group 2: sclerotherapy (n = 28) Further details: sclerotherapy (no further details) repeated after a week and then monthly until obliteration
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding (quote): "Supported in part by NIH ROI DK 33273 and Microvasive-Boston Scientific Corp" Trial name/trial registry number: Not stated Attempts were made to contact the authors in February 2020. Authors provided additional information on risk of bias in March 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Computer generated" (author replies)
Allocation concealment (selection bias)	Low risk	Quote: "The randomization cards were sealed in opaque envelops, place in a study notebook, & only opened during the emergency endoscopy by the investigator-endoscopist when both clinical & endoscopic entry criteria were met & the patient lacked exclusion criteria" (author replies)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both the patient and their healthcare providers (primary, ICU, hepatologists, radiologists, liver surgeons, & others) were blinded during the study" (author replies)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "outcome assessors were not blinded" (author replies)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "No patient was excluded after randomization" (author replies)
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available and none of the outcomes of interest for this review were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Kumar 2015

Study characteristics

Kumar 2015 *(Continued)*

Methods	Randomised clinical trial
Participants	Country: India Period of recruitment: 2005-2009 Number randomised: 61 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 61 Average age (years): 44 Females: 13 (21.3%) Other features of decompensation: 10 (16.4%) Alcohol-related cirrhosis: 22 (36.1%) Viral-related cirrhosis: 20 (32.8%) Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: 19 (31.1%) Prophylactic antibiotics for variceal bleeding: 61 (100.0%) Other inclusion/exclusion criteria: Inclusion: patients with acute variceal bleeding from esophageal varices within 24 hours before admission Exclusion: non-cirrhotic cause of portal hypertension, age <12 or >75, hepatic encephalopathy grade 3 or 4, renal failure with serum creatinine >2 mg/dL, any evidence of bleeding from additional source, patient already on vasoactive drugs like somatostatin or terlipressin during current episode of bleeding, patients already received endoscopic variceal ligation or sclerotherapy elsewhere, patients with history of surgery for portal hypertension or TIPS, concomitant severe cardio-pulmonary disease, concomitant malignancy, hepatic venous pressure gradient measurement not possible within 24 hours, patients refusing to participate in the study
Interventions	Group 1: somatostatin analogues plus variceal band ligation (n = 31) Further details: somatostatin 250 mcg/hr, with an initial bolus of 250 mcg for five days plus variceal band ligation (multiband ligator) Group 2: variceal band ligation (n = 30) Further details: variceal band ligation (multiband ligator) plus placebo
Outcomes	Outcomes reported: mortality, additional treatment to control variceal bleeding, blood transfusion (RBC or whole blood) (quantity) Follow-up (months): 0.25
Notes	Source of funding (quote): "The study was done with institutional support, and it did not require any external funding." Trial name/trial registry number: NCT01267669 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 randomization was done by the statistician using computer generated random numbers"
Allocation concealment (selection bias)	Low risk	Quote: "The randomization sequence remained with the statistician, and the sequence remained concealed from the investigators"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the investigators as well as the patients were blinded to the treatment allotted" Comment: a placebo was used to achieve this
Blinding of outcome assessment (detection bias)	Low risk	Quote: "the investigators as well as the patients were blinded to the treatment allotted"

Kumar 2015 *(Continued)*

All outcomes		Comment: a placebo was used to achieve this
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 bleeding from oesophageal varices were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Laine 1993

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: 1990-1992 Number randomised: 77 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 77 Average age (years): 46 Females: 19 (24.7%) Other features of decompensation: not stated Alcohol-related cirrhosis: 61 (79.2%) Viral-related cirrhosis: 8 (10.4%) Autoimmune disease-related cirrhosis: 3 (3.9%) Other causes of cirrhosis: 5 (6.5%) Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Inclusion: Patients with chronic liver disease who had not received sclerotherapy in the past 6 months were eligible if they had 1) witnessed hematemesis, bloody nasogastric aspirate, melena, or hematochezia; 2) systolic blood pressure <90 mmHg, heart rate >110/min, or orthostatic change in blood pressure of >20 mmHg or in heart rate of >20/min; transfusion of 2 units of blood; or a decrease in hematocrit level of 0.06 within 12 hours; and 3) endoscopy within 24 hours of admission showing active variceal bleeding or grade 2 to 4 esophageal varices (grading scale of Korula and colleagues) without any other lesion in the upper gastrointestinal tract Exclusion: gastric varices or findings of severe portal hypertensive gastropathy were present, if they were unable or unwilling to sign an informed consent, if they had hepatocellular carcinoma or other malignancy, or if they were homeless
Interventions	Group 1: variceal band ligation (n = 38) Further details: variceal band ligation using endoscopic ligation device repeated weekly until variceal obliteration Group 2: sclerotherapy (n = 39) Further details: sclerotherapy 3% sodium tetradecyl sulfate repeated weekly until variceal obliteration
Outcomes	Outcomes reported: mortality, any adverse events (number of events), variceal rebleed (any) (number of patients), length of hospital stay (days), blood transfusion (RBC or whole blood) (quantity) Follow-up (months): 0.3
Notes	Source of funding (quote): "no funding (author replies)" Trial name/trial registry number: not stated

Laine 1993 *(Continued)*

Attempts were made to contact the authors in February 2020. Authors provided additional information to assess the risk of bias in March 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)	Low risk	Quote: "Allocation was concealed (opaque covering over assignment removed after decision to randomize patient) (author replies)"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Allocation was concealed (opaque covering over assignment removed after decision to randomize patient) (author replies)"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Allocation was concealed (opaque covering over assignment removed after decision to randomize patient) (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 the mortality, adverse events, and rebleeding adequately
Other bias	Low risk	Comment: no other bias noted

Laine 1996

Study characteristics

Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: 1993-1995 Number randomised: 41 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 41 Average age (years): 47 Females: 11 (26.8%) Other features of decompensation: not stated Alcohol-related cirrhosis: 31 (75.6%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Inclusion: patients with chronic liver disease were eligible if they had 1) witnessed hematemesis, bloody nasogastric aspirate, melena, or hematochezia; 2) systolic blood pressure <90 mmHg, heart rate >110/min, or orthostatic changes in blood pressure of >20 mmHg or in heart rate of >20/min; transfusion of 2 U of blood; or a decrease in hematocrit of 6% within 12 hours; and 3) endoscopy within 24 hours of admission showing active variceal bleeding or grade 2–4 esophageal varices (grading scale of

Laine 1996 *(Continued)*

	Korula et al.) without other potential bleeding lesions in the upper gastrointestinal tract (patients with gastric varices were therefore not eligible) Exclusion: if they had received endoscopic therapy for varices in the past 6 months, if they had hepatocellular carcinoma or other malignancy, if they were unable or unwilling to sign the informed consent, or if they were homeless.
Interventions	Group 1: sclerotherapy plus variceal band ligation (n = 21) Further details: sclerotherapy 1 mL 1.5% tetradecyl injected just above each band plus variceal band ligation using endoscopic ligation device repeated weekly until variceal obliteration Group 2: variceal band ligation (n = 20) Further details: variceal band ligation using endoscopic ligation device repeated weekly until variceal obliteration repeated weekly until variceal obliteration
Outcomes	Outcomes reported: mortality, any adverse events (number of events), variceal rebleed (any) (number of patients), length of hospital stay (days), blood transfusion (RBC or whole blood) (quantity) Follow-up (months): 0.3
Notes	Source of funding (quote): "no funding (author replies)" Trial name/trial registry number: not stated Attempts were made to contact the authors in February 2020. Authors provided additional information to assess the risk of bias in March 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated randomization"
Allocation concealment (selection bias)	Low risk	Quote: "Allocation was concealed (opaque covering over assignment removed after decision to randomize patient) (author replies)"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Allocation was concealed (opaque covering over assignment removed after decision to randomize patient) (author replies)"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Allocation was concealed (opaque covering over assignment removed after decision to randomize patient) (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 the mortality, adverse events, and rebleeding adequately
Other bias	Low risk	Comment: no other bias noted

Lee 1988

Study characteristics

Methods	Randomised clinical trial

Lee 1988 *(Continued)*

Participants	Country: Taiwan, Republic of China Period of recruitment: 1987-1988 Number randomised: 45 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 45 Average age (years): 58 Females: 2 (4.4%) Other features of decompensation: not stated Alcohol-related cirrhosis: not stated Viral-related cirrhosis: 31 (68.9%) Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Exclusion: patients known to have coronary artery disease, arrhythmias, previous portacaval anastomosis, malignant hypertension, cerebral vascular accident, chronic respiratory failure
Interventions	Group 1: nitrates plus vasopressin analogues (n = 24) Further details: nitroglycerin 0.6 mg sublingually every 6 hours plus vasopressin IV 0.66 units per minute for 24 hours Group 2: vasopressin analogues (n = 21) Further details: glypressin 2 mg bolus and then 1 mg 6 hourly for 24 hours
Outcomes	Outcomes reported: mortality, any adverse events (number of participants) Follow-up (months): 1.5
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)	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 bleeding from oesophageal varices were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Lee 1999a

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Korea Period of recruitment: Not stated Number randomised: 38 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 38 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 of cirrhosis: not stated Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Inclusion: patients with bleeding esophageal varices
Interventions	Group 1: balloon tamponade plus variceal band ligation (n = 18) Further details: Sengstaken-Blakemore tube until endoscopic variceal ligation (no further details) Group 2: somatostatin analogues plus variceal band ligation (n = 20) Further details: somatostatin 250 mcg bolus followed by 250 mcg/hour for 5 days
Outcomes	Outcomes reported: mortality, variceal rebleed (any) (number of patients), blood transfusion (RBC or whole blood) (quantity) Follow-up (months): 0.25
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

Lee 1999a *(Continued)*

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

Liu 2009

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: China Period of recruitment: 2003-2008 Number randomised: 101 Post-randomisation dropouts: not stated Revised sample size: 101 Average age (years): 41 Females: 19 (18.8%) Other features of decompensation: not stated Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Inclusion: a history of cirrhosis with no hepatocellular carcinoma or other malignancy diseases; endoscopy examination confirmed bleeding from oesophageal varices; no other potential site of bleeding was identified; age from 20 to 70 years; hospitalised within 12 hours after the onset of symptoms; no use of vasoactive medicine or endoscopic therapy before referral to our hospital; patients agreed to participate in the investigation Exclusion: patients with moribund conditions which could not tolerate endoscopy examination of therapy procedure; refused to sign the operation consent; previous endoscopic therapy had been performed within 3 months; patients with gastric fundus varices; Child-Pugh score higher than 12 or with hepatic coma
Interventions	Group 1: somatostatin analogues plus variceal band ligation (n = 51) Further details: octreotide 25 mcg/h plus variceal band ligation (multiband ligator), until haemostasis Group 2: somatostatin analogues (n = 50) Further details: octreotide 25 mcg/h until haemostasis
Outcomes	Outcomes reported: mortality, additional treatment to control variceal bleeding, variceal rebleed (symptomatic recovery) (number of patients), length of hospital stay (days), treatment costs, blood transfusion (RBC or whole blood) (quantity) Follow-up (months): 0.3
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**

Liu 2009 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "The random number was generated from the Microsoft Excel"
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 adequately
Other bias	Low risk	Comment: no other bias noted

Lo 1992

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Taiwan, Republic of China Period of recruitment: 1988-1990 Number randomised: 60 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 60 Average age (years): 59 Females: 9 (15.0%) Other features of decompensation: not stated Alcohol-related cirrhosis: 9 (15.0%) Viral-related cirrhosis: 41 (68.3%) Autoimmune disease-related cirrhosis: 3 (5.0%) Other causes of cirrhosis: 7 (11.7%) Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Inclusion: fresh blood seen in oesophagus with red colour signs on varices and no other potential site of bleeding Exclusion: Associated with hepatocellular carcinoma; associated with peptic ulcers; bleeding from fundal varices; stopped bleeding on endoscopic examination
Interventions	Group 1: balloon tamponade plus sclerotherapy (n = 31) Further details: Sengstaken-Blakemore tube for 12 to 24 hours followed by sclerotherapy: 1.5% sodium tetradecyl sulfate up to 25 ml per session Group 2: sclerotherapy (n = 29) Further details: sclerotherapy: 1.5% sodium tetradecyl sulfate up to 25 ml per session

Lo 1992 *(Continued)*

Outcomes	Outcomes reported: mortality, serious adverse events (number of participants), additional treatment to control variceal bleeding, variceal rebleed (symptomatic recovery) (number of patients), other features of decompensation, blood transfusion (RBC or whole blood) (quantity) Follow-up (months): 0.6
Notes	Source of funding (quote): "The study was not funded" 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: "by a system of random numbers"
Allocation concealment (selection bias)	Low risk	Quote: "allocation was based on a random number in a sealed envelope (author replies)"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "study was not blinded (author replies)"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "study was not 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 the mortality, adverse events, and rebleeding adequately
Other bias	Low risk	Comment: no other bias noted

Lo 1995

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Taiwan, Republic of China Period of recruitment: 1992-1993 Number randomised: 120 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 120 Average age (years): 56 Females: 23 (19.2%) Other features of decompensation: 71 (59.2%) Alcohol-related cirrhosis: 27 (22.5%) Viral-related cirrhosis: 84 (70.0%) Autoimmune disease-related cirrhosis: 2 (1.7%) Other causes of cirrhosis: 7 (5.8%) Prophylactic antibiotics for variceal bleeding: not stated

Lo 1995 *(Continued)*

	Other inclusion/exclusion criteria: Exclusion: association with hepatocellular carcinoma or other malignancies; severity of encephalopathy greater than stage II; hepatorenal syndrome with serum creatinine >4 mg/dL and oliguria; gastric varices found on enrolment; history of shunt operation or injection sclerotherapy; reluctance to receive the assigned treatment
Interventions	Group 1: variceal band ligation (n = 61) Further details: variceal band ligation using Bard Interventional Products repeated until obliteration every 2 to 3 weeks Group 2: sclerotherapy (n = 59) Further details: sclerotherapy: 1.5% sodium tetradecyl sulfate up to 25 ml per session repeated until obliteration every 2 to 3 weeks
Outcomes	Outcomes reported: blood transfusion (RBC or whole blood) (quantity) Follow-up (months): 3
Notes	Source of funding (quote): "The study was funded by National Science Council, Taiwan." 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 allocated according to a table of random numbers"
Allocation concealment (selection bias)	Low risk	Quote: "allocation was based on a random number in a sealed envelope (author replies)"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "study was not blinded (author replies)"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "study was 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 mortality, adverse events, and bleeding from oesophageal varices were not reported adequately
Other bias	Low risk	Comment: no other bias noted

McKee 1990

Study characteristics

Methods	Randomised clinical trial
Participants	Country: UK Period of recruitment: 1986-1988

McKee 1990 *(Continued)*

	Number randomised: 40 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 40 Average age (years): 54 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 of cirrhosis: not stated Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Inclusion: endoscopically proven active bleeding from oesophageal varices
Interventions	Group 1: balloon tamponade plus sclerotherapy (n = 20) Further details: Sengstaken-Blakemore tube (Minnesota modification) for 48 hours, no details on sclerotherapy Group 2: sclerotherapy plus somatostatin analogues (n = 20) Further details: octreotide IV 25 mcg/hr for 48 hours, no details on sclerotherapy
Outcomes	Outcomes reported: mortality, additional treatment to control variceal bleeding, variceal rebleed (any) (number of patients), blood transfusion (RBC or whole blood) (quantity) Follow-up (months): 0.2
Notes	Source of funding (quote): "We are grateful to Sandoz for supplying SMS 201-995 for this study " 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 were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Morales 2007

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Brazil Period of recruitment: 2001-2004 Number randomised: 70 Post-randomisation dropouts: 2 (2.9%) Revised sample size: 68 Reasons for post-randomisation dropouts: hepatocellular carcinoma Average age (years): 52 Females: 23 (33.8%) Other features of decompensation: not stated Alcohol-related cirrhosis: 33 (48.5%) Viral-related cirrhosis: 50 (73.5%) Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: 7 (10.3%) Prophylactic antibiotics for variceal bleeding: 68 (100.0%) Other inclusion/exclusion criteria: Inclusion: active variceal bleeding at endoscopy (spurting or oozing from oesophageal or cardinal varices) or non bleeding varices with stigmata of recent bleeding or evidence of blood in the upper gastrointestinal tract with no other potential source of haemorrhage Exclusion: advanced hepatocellular carcinoma not considered for liver transplantation, other malignancies, failure to control haemorrhagic shock resulting in death before randomisation, bleeding from sources other than oesophageal varices, patients who received vasoactive drugs in the last week before admission
Interventions	Group 1: sclerotherapy plus somatostatin analogues (n = 40) Further details: sclerotherapy: 5% ethanolamine oleate maximum of 20 ml plus octreotide 50 mcg/h for first 24 hours and then 24 mcg/h for next 24 hours Group 2: sclerotherapy (n = 28) Further details: sclerotherapy: 5% ethanolamine oleate maximum of 20 ml plus placebo
Outcomes	Outcomes reported: mortality, variceal rebleed (any) (number of patients), blood transfusion (RBC or whole blood) (quantity) Follow-up (months): 0.25
Notes	Source of funding (quote): "This work was supported in part by grants of Brazilian Ministry of Education (CAPES Foundation) and the Ministry of Science and Technology (CNPq)" 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: "Sealed opaque envelopes" Comment: Further information was not available

Morales 2007 *(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 post-randomisation dropouts, but it is probably not related to the outcomes
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available
Other bias	Unclear risk	Comment: there were more Child-Pugh class C patients in sclerotherapy plus somatostatin analogue group than sclerotherapy alone group

NCT00534677

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Pakistan Period of recruitment: 2004-2005 Number randomised: 320 Post-randomisation dropouts: not stated Revised sample size: 320 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 of cirrhosis: not stated Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Inclusion: all cirrhotic patients with upper gastrointestinal bleed secondary to esophageal varices of 18 years or more age Exclusion: ulcerative oesophagitis, Mallory Weiss tear, bleeding gastric or duodenal ulcers, bleeding from gastric varices or portal hypertensive gastropathy, upper gastrointestinal bleed as a result of thrombocytopenia or bleeding diathesis
Interventions	Group 1: vasopressin analogues (n = not stated) Further details: terlipressin 2 mg stat & then 1 mg four times daily (duration not stated) Group 2: somatostatin analogues (n = not stated) Further details: octreotide 50 mcg/hr infusion (duration not stated)
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding: not stated Trial name/trial registry number: NCT00534677 Attempts were made to contact the authors in February 2020

NCT00534677 *(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	Low risk	Quote: "Masking: Triple (Participant, Care Provider, Investigator)"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Masking: Triple (Participant, Care Provider, Investigator)"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	Unclear risk	Comment: a prepublished protocol was not available and none of the outcomes of interest for this review were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Paquet 1985

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: (West) Germany Period of recruitment: 1980-1981 Number randomised: 43 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 43 Average age (years): not stated Females: 13 (30.2%) Other features of decompensation: not stated Alcohol-related cirrhosis: 30 (69.8%) Viral-related cirrhosis: 8 (18.6%) Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: 5 (11.6%) Prophylactic antibiotics for variceal bleeding: 43 (100.0%) Other inclusion/exclusion criteria: Inclusion: patients proved to be actively bleeding from esophageal varices by emergency endoscopy
Interventions	Group 1: balloon tamponade (n = 22) Further details: Sengstaken-Blakemore tube 12 to 24 hours Group 2: sclerotherapy (n = 21) Further details: sclerotherapy 0.5% to 1.0 polidocanol 30 to 50 ml

Paquet 1985 *(Continued)*

Outcomes	Outcomes reported: mortality, any adverse events (number of participants) Follow-up (months): 1
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 and bleeding from oesophageal varices were not reported adequately
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available
Other bias	Low risk	Comment: no other bias noted

Patsanas 2002

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Greece Period of recruitment: not stated Number randomised: 30 Post-randomisation dropouts: not stated Revised sample size: 30 Average age (years): 51 Females: 9 (30.0%) Other features of decompensation: not stated Alcohol-related cirrhosis: 13 (43.3%) Viral-related cirrhosis: 10 (33.3%) Autoimmune disease-related cirrhosis: 2 (6.7%) Other causes of cirrhosis: 5 (16.7%) Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria:

Patsanas 2002 *(Continued)*

	Inclusion: liver cirrhosis documented by needle biopsy on previous admissions; presence of oesophageal varices confirmed by endoscopy Exclusion: other causes of bleeding except from oesophageal varices; undergoing endoscopic variceal sclerotherapy in the week prior to entry; hepatic encephalopathy or severity of liver dysfunction which prevented endoscopy; administration of vasoactive drugs during the last 48 hours; previous surgical treatment of variceal bleeding
Interventions	Group 1: sclerotherapy plus somatostatin analogues (n = 15) Further details: no further details Group 2: somatostatin analogues (n = 15) Further details: sclerotherapy 5% ethanolamine plus octreotide 50 mcg/h for 5 days
Outcomes	Outcomes reported: mortality, blood transfusion (RBC or whole blood) (quantity) Follow-up (months): 1.5
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)	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 and bleeding from oesophageal varices were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Pauwels 1994

Study characteristics

Methods	Randomised clinical trial
Participants	Country: France Period of recruitment: 1986-1988 Number randomised: 60

Pauwels 1994 *(Continued)*

	Post-randomisation dropouts: 11 (18.3%) Revised sample size: 49 Reasons for post-randomisation dropouts: other causes of bleeding 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 of cirrhosis: not stated Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: not stated
Interventions	Group 1: somatostatin analogues (n = 18) Further details: terlipressin IV 2 mg every 6 hours until bleeding stopped Group 2: no active intervention (n = 14) Further details: somatostatin 250 mcg bolus followed by 250 mcg/hr until 4 hours after bleeding stopped Group 3: vasopressin analogues (n = 17) Further details: no further details
Outcomes	Outcomes reported: mortality, variceal rebleed (any) (number of patients), blood transfusion (RBC or whole blood) (quantity) Follow-up (months): 1
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: there were post-randomisation dropouts. it was not clear whether the dropouts could be related to the intervention or the outcome
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available and adverse events were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Planas 1994

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Spain Period of recruitment: 1990-1993 Number randomised: 70 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 70 Average age (years): 57 Females: 20 (28.6%) Other features of decompensation: 11 (15.7%) Alcohol-related cirrhosis: 50 (71.4%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Prophylactic antibiotics for variceal bleeding: 70 (100.0%) Other inclusion/exclusion criteria: Inclusion: patients with bleeding esophageal varices Exclusion: age over 75, hepatocellular carcinoma, bleeding from gastric varices
Interventions	Group 1: somatostatin analogues (n = 35) Further details: somatostatin 250 mcg bolus and then 250 mcg/hr for 48 hours Group 2: sclerotherapy (n = 35) Further details: sclerotherapy: 1% polidocanol about 48 ml
Outcomes	Outcomes reported: mortality, serious adverse events (number of participants), any adverse events (number of participants), variceal rebleed (symptomatic recovery) (number of patients), blood transfusion (RBC or whole blood) (quantity) Follow-up (months): 1.5
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: "using sealed envelopes labelled according to a computer-generated random number series"
Allocation concealment (selection bias)	Low risk	Quote: "using sealed envelopes labelled according to a computer-generated random number series"
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

Planas 1994 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Comment: no prepublished protocol was available, but the authors reported the mortality, adverse events, and rebleeding adequately
Other bias	Unclear risk	Comment: patients were enrolled in a subsequent trial of medical versus surgical treatment if they were alive at 1 week: this was done in both groups. however, it was not clear whether this was balanced in the two groups

Ramon 1997

Study characteristics

Methods	Randomised clinical trial
Participants	Country: France, Spain Period of recruitment: not stated Number randomised: 219 Post-randomisation dropouts: not stated Revised sample size: 219 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 of cirrhosis: not stated Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Inclusion: cirrhotic patients admitted for haemorrhage from ruptured oesophageal varices
Interventions	Group 1: vasopressin analogues (n = 105) Further details: terlipressin 2 mg IV every 4 hours until bleeding stops for 24 hours and then 1 mg/4 h for 5 days Group 2: sclerotherapy (n = 114) Further details: sclerotherapy (no further details)
Outcomes	Outcomes reported: mortality, serious adverse events (number of participants), any adverse events (number of participants), variceal rebleed (any) (number of patients), length of hospital stay (days) Follow-up (months): 1.5
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: "were divided into two groups by drawing lots"
Allocation concealment (selection bias)	Low risk	Quote: "were divided into two groups by drawing lots"

Ramon 1997 *(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 the mortality, adverse events, and rebleeding adequately
Other bias	Low risk	Comment: no other bias noted

Saari 1990

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Finland Period of recruitment: 1985-1988 Number randomised: 73 Post-randomisation dropouts: 19 (26.0%) Revised sample size: 54 Reasons for post-randomisation dropouts: wrong diagnosis, additional treatments during treatment Average age (years): 52 Females: 27 (50.0%) Other features of decompensation: not stated Alcohol-related cirrhosis: 35 (64.8%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Inclusion: active bleeding from the varices, signs of recent bleeding or varices without signs of recent bleeding but no other potential source for bleeding Exclusion: any explanation for the haemorrhage other than the oesophageal varices
Interventions	Group 1: vasopressin analogues (n = 22) Further details: vasopressin 0.6 IU bolus followed by 0.4 IU/min Group 2: somatostatin analogues (n = 32) Further details: somatostatin 250 mcg bolus followed by 4.3 mcg/min for 72 hours
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

Saari 1990 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation was done immediately, when any of the inclusive criteria were met, by opening a sealed numbered envelope which included a code of the drug to be used. The envelopes were used in numerical order, and the numbering was done by an independent office" Comment: although the details on sequence generation was not reported, the method of allocation concealment used makes it highly likely that the sequence was random
Allocation concealment (selection bias)	Low risk	Quote: "The randomisation was done immediately, when any of the inclusive criteria were met, by opening a sealed numbered envelope which included a code of the drug to be used. The envelopes were used in numerical order, and the numbering was done by an independent office"
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 were clearly related to the intervention (the dropouts were not balanced) and the outcome (patients were excluded because of continued bleeding). this is considered so biased that outcome data were not extracted as this will not provide a reasonable estimate of the effects that were relevant for this review
Selective reporting (reporting bias)	Unclear risk	Comment: no prepublished protocol was available and none of the outcomes of interest for this review were not reported adequately
Other bias	Unclear risk	Comment: there were more Child-Pugh class C patients in somatostatin analogue group than vasopressin analogues group

Shah 2005

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Pakistan Period of recruitment: 1997-1998 Number randomised: 105 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 105 Average age (years): 50 Females: 37 (35.2%) Other features of decompensation: 33 (31.4%) Alcohol-related cirrhosis: 4 (3.8%) Viral-related cirrhosis: 101 (96.2%) Autoimmune disease-related cirrhosis: 0 (0.0%) Other causes of cirrhosis: 0 (0.0%)

Shah 2005 *(Continued)*

	Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Inclusion: a history of hematemesis or melena (or both) within 24 hours prior to admission; cirrhosis of the liver had either been diagnosed previously or on current admission on the basis of clinical signs of chronic liver disease such as ascites, palmar erythema, spider angiomas, splenomegaly and biochemical evidence of derangement of liver function, abdominal ultrasound and/or liver biopsy where possible; active esophageal variceal bleeding (spurt or ooze from a varix seen at endoscopy); non-bleeding esophageal varices with signs of recent bleed in the upper gastrointestinal tract like presence of blood, red marks on varices and no other source of upper gastrointestinal bleed were also enrolled Exclusion: previous sclerotherapy within the last eight days; evidence of severe liver failure i.e. prothrombin time greater than 10 seconds prolong, serum albumin less than 1.5 grams per dl, serum bilirubin greater than 5 mg and/or significant impairment of renal function i.e. serum creatinine greater than 4 mg; age above 85 years and non-cirrhotic portal hypertension
Interventions	Group 1: sclerotherapy plus somatostatin analogues (n = 51) Further details: sclerotherapy 5% injection ethanolamine oleate up to 20 ml plus octreotide 50 mcg/h for 48 hours Group 2: sclerotherapy (n = 54) Further details: sclerotherapy 5% injection ethanolamine oleate up to 20 ml plus placebo
Outcomes	Outcomes reported: mortality, additional treatment to control variceal bleeding, variceal rebleed (symptomatic recovery) (number of patients), length of hospital stay (days), blood transfusion (RBC or whole blood) (quantity) Follow-up (months): 0.2
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: "A sealed envelope containing the treatment option was opened and treatment given accordingly" 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 adverse events were not reported adequately

Shah 2005 *(Continued)*

Other bias	Low risk	Comment: no other bias noted

Signorelli 1996

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: Not stated Number randomised: 94 Post-randomisation drop-outs: not stated Revised sample size: 94 Average age (years): not stated Females: not stated Small varices: not stated High risk of bleeding: not stated Other features of decompensation: not stated Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other-causes for cirrhosis: not stated Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Inclusion: all cirrhotic patients with acute oesophageal variceal bleeding
Interventions	Group 1: Sclerotherapy plus somatostatin analogues (n = 64) Further details: somatostatin 3.5mcg/kg/hr infusion for 5 days or octreotide 0.1 mg/kg every 8 hours plus endoscopic sclerotherapy using 2% polidocanol (quantity not stated) Group 2: Sclerotherapy (n = 30) Further details: endoscopic sclerotherapy using 2% polidocanol (quantity not stated)
Outcomes	Outcomes reported: mortality, blood transfusion (RBC or whole blood) (quantity) Follow-up (months): 0.2
Notes	Source of funding: not stated Trial name/trial registry number: Not stated Attempts were made to contact the authors in October 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

Signorelli 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	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	Unclear risk	Comment: a prepublished protocol was not available, and adverse events and bleeding from oesophageal varices were not reported adequately
Other bias	Low risk	Comment: no other bias noted

Tsai 1986

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Taiwan, Republic of China Period of recruitment: 1983-1984 Number randomised: 39 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 39 Average age (years): 54 Females: 3 (7.7%) Other features of decompensation: not stated Alcohol-related cirrhosis: not stated Viral-related cirrhosis: 36 (92.3%) Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Inclusion: acute haemorrhage from esophageal varices confirmed by emergency endoscopy; decrease of a least 8% in hematocrit; active variceal bleeding was diagnosed when blood was directly seen by endoscopy to issue from a varix or when fresh blood was seen in the oesophagus of patients with cherry-red spots on large varices and no other potential site of bleeding was discovered Exclusion: patients who were known to have coronary artery disease or to have received therapy other than vasopressin, such as esophageal balloon tamponade
Interventions	Group 1: nitrates plus vasopressin analogues (n = 20) Further details: vasopressin 0.66 units/min until 1 hours after bleeding stops, and then 0.33 units/min for additional 24 hours Group 2: vasopressin analogues (n = 19) Further details: nitroglycerin 0.6 mg sublingually every 30 min for the first 6 hr and vasopressin 0.66 units/min until 1 hours after bleeding stops, and then 0.33 units/min for additional 24 hours
Outcomes	Outcomes reported: mortality, serious adverse events (number of participants), any adverse events (number of participants) Follow-up (months): 0.2
Notes	Source of funding (quote): "This study is supported by a grant (NSC73-0412-B075-18) from the National Science Council of the Republic of China" Trial name/trial registry number: not stated

Tsai 1986 *(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: "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	High risk	Quote: "This study was not performed blindly"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "This study was not performed blindly"
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 bleeding from oesophageal varices were not reported adequately
Other bias	Low risk	Comment: no other bias noted

VA Coop. Variceal Sclerotherapy Group 1994

Study characteristics

Methods	Randomised clinical trial
Participants	Country: USA Period of recruitment: 1985-1989 Number randomised: 49 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 49 Average age (years): not stated Females: 0 (0.0%) Other features of decompensation: not stated Alcohol-related cirrhosis: 49 (100.0%) Viral-related cirrhosis: 0 (0.0%) Autoimmune disease-related cirrhosis: 0 (0.0%) Other causes of cirrhosis: 0 (0.0%) Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Inclusion: 1. Male patients with alcoholic liver disease who manifested bleeding from esophageal varices 2. Consumption of at least 48 gm of alcohol per day for more than a year 3. Biopsy-proven or clinically diagnosed alcoholic liver disease

VA Coop. Variceal Sclerotherapy Group 1994 *(Continued)*

	Exclusion: 1. Inability to give informed consent 2. Contraindications to upper endoscopy 3. A positive test for Hepatitis B surface antigen in serum 4. A history of sclerotherapy or shunt surgery for varices 5. Esophageal or gastric malignancy 6. Myocardial infarction within the past 6 months 7. Need for beta-adrenergic antagonist drug therapy 8. Current bleeding from source other than esophageal varices 9. A decision by the treating physician to exclude the patient
Interventions	Group 1: no active intervention (n = 24) Further details: placebo Group 2: sclerotherapy (n = 25) Further details: sclerotherapy: sclerosant not stated; 0.5 to 2 ml, maximum of 20 ml per session
Outcomes	None of the outcomes of interest were reported
Notes	Source of funding (quote): "Elkins Sinn, Inc. for providing us with the sclerosant and matching placebo" 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 using sealed envelopes prepared centrally " Comment: although the details on sequence generation was not reported, the method of allocation concealment used makes it highly likely that the sequence was random
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was carried out using sealed envelopes prepared centrally "
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"
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 endoscopists do not appear to be the 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 none of the outcomes of interest for this review were not reported adequately
Other bias	Unclear risk	Comment: there were different proportion of people with number of previous variceal bleeds and in other signs of liver failure

Villanueva 1999

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Spain Period of recruitment: 1995-1996 Number randomised: 100 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 100 Average age (years): 60 Females: 34 (34.0%) Other features of decompensation: 20 (20.0%) Alcohol-related cirrhosis: 49 (49.0%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Prophylactic antibiotics for variceal bleeding: 100 (100.0%) Other inclusion/exclusion criteria: Inclusion: age over 18 years; presence of hematemesis and/or melena, confirmed by the hospital staff; clinical suspicion of chronic liver disease or portal hypertension; referred patients should be seen within 24 hours of admission at the referring hospital and not having received balloon tamponade or emergency sclerotherapy; rerandomization was only allowed if a separate bleeding episode occurred at least 45 days after the previous inclusion, but no more than twice; no decision had been made before bleeding to avoid specific medical therapy.
Interventions	Group 1: sclerotherapy plus somatostatin analogues (n = 50) Further details: sclerotherapy using 5% ethanolamine, maximum: 15 to 20 ml plus somatostatin 250 mcg IV bolus and then 250 mcg/h IV and additional boluses of 250 mcg every 6 hours for 5 days Group 2: somatostatin analogues (n = 50) Further details: somatostatin 250 mcg IV bolus and then 250 mcg/h IV and additional boluses of 250 mcg every 6 hours for 5 days
Outcomes	Outcomes reported: mortality, serious adverse events (number of participants), any adverse events (number of participants), additional treatment to control variceal bleeding, variceal rebleed (any) (number of patients), blood transfusion (RBC or whole blood) (quantity) Follow-up (months): 1.5
Notes	Source of funding (quote): "Supported in part by a grant from the Fundacio´ Investigacio´ Sant Pau" 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: "by means of sealed opaque envelopes containing the treatment option as derived from computer-generated random numbers"
Allocation concealment (selection bias)	Low risk	Quote: "by means of sealed opaque envelopes containing the treatment option as derived from computer-generated random numbers"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available

Villanueva 1999 *(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 the mortality, adverse events, and rebleeding adequately
Other bias	Unclear risk	Comment: patients were enrolled in a subsequent trial if they were alive at 5 days: this was done in both groups. however, it was not clear whether this was balanced in the two groups

Villanueva 2006

Study characteristics	
Methods	Randomised clinical trial
Participants	Country: Spain Period of recruitment: 1999-2004 Number randomised: 182 Post-randomisation dropouts: 3 (1.6%) Revised sample size: 179 Reasons for post-randomisation dropouts: protocol violations Average age (years): 62 Females: 48 (26.8%) Other features of decompensation: 52 (29.1%) Alcohol-related cirrhosis: 71 (39.7%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes of cirrhosis: not stated Prophylactic antibiotics for variceal bleeding: 179 (100.0%) Other inclusion/exclusion criteria: Inclusion: all patients admitted to our hospital with hematemesis and/or melena, clinical suspicion of cirrhosis and age over 18 years; re-randomization was only allowed if a separate bleeding episode occurred at least 45 days after the previous inclusion, but not more than twice Exclusion criteria: bleeding from fundal varices or sources other than esophageal varices, previous emergency sclerotherapy or endoscopic variceal ligation within 2 weeks, previous TIPS or surgical shunt, advanced hepatocellular carcinoma, massive bleeding resulting in balloon tamponade or death before randomization, refusal to participate in the study, and previous decision to avoid specific medical therapy
Interventions	Group 1: variceal band ligation plus somatostatin analogues (n = 90) Further details: somatostatin 250 mcg IV bolus followed by 250 mcg/h and additional boluses of 250 mcg every 6 hours for 5 days plus variceal band ligation using multiband ligator Group 2: sclerotherapy plus somatostatin analogues (n = 89) Further details: somatostatin 250 mcg IV bolus followed by 250 mcg/h and additional boluses of 250 mcg every 6 hours for 5 days plus sclerotherapy 5% ethanolamine oleate, 15 to 25 ml
Outcomes	Outcomes reported: mortality, serious adverse events (number of participants), serious adverse events (number of events), any adverse events (number of participants), any adverse events (number of

Villanueva 2006 *(Continued)*

	events), additional treatment to control variceal bleeding, variceal rebleed (any) (number of patients), length of hospital stay (days), blood transfusion (RBC or whole blood) (quantity) Follow-up (months): 1.5
Notes	Source of funding (quote): "This study has been supported in part by a grant from the Fundacio´ Investigacio´ Sant Pau and by a grant from the Instituto de Salud Carlos III (CO3/02)" 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 with sealed and consecutively numbered opaque envelopes containing the treatment option as derived from computer-generated random numbers"
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed with sealed and consecutively numbered opaque envelopes containing the treatment option as 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	Unclear risk	Comment: there were post-randomisation dropouts; it was not clear if the dropouts were related to intervention and outcomes
Selective reporting (reporting bias)	Low risk	Comment: no prepublished protocol was available, but the authors reported the mortality, adverse events, and rebleeding adequately
Other bias	Unclear risk	Comment: patients were enrolled in a subsequent trial if they were alive at 5 days: this was done in both groups. however, it was not clear whether this was balanced in the two groups

Yousuf 2000

Study characteristics

Methods	Randomised clinical trial
Participants	Country: Pakistan Period of recruitment: 1996-1999 Number randomised: 96 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 96 Average age (years): 45 Females: 21 (21.9%) Other features of decompensation: not stated Alcohol-related cirrhosis: 0 (0.0%) Viral-related cirrhosis: 96 (100.0%)

Yousuf 2000 *(Continued)*

	Autoimmune disease-related cirrhosis: 0 (0.0%) Other causes of cirrhosis: 0 (0.0%) Prophylactic antibiotics for variceal bleeding: not stated Other inclusion/exclusion criteria: Exclusion: cirrhotic patients with bleeding from other sources; patients with coronary artery diseases, arrhythmias, malignant hypertension, congenital haemorrhagic diathesis, cerebrovascular accident, pregnancy, chronic respiratory failure
Interventions	Group 1: somatostatin analogues (n = 48) Further details: octreotide 50 mcg 6 hourly Group 2: sclerotherapy (n = 48) Further details: duration not stated
Outcomes	Outcomes reported: mortality, any adverse events (number of participants), variceal rebleed (any) (number of patients) Follow-up (months): 0.2
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)	Low risk	Comment: no prepublished protocol was available, but the authors reported the mortality, adverse events, and rebleeding adequately
Other bias	Low risk	Comment: no other bias noted

mcg = microgram
RBC = Red blood cells

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

Study	Reason for exclusion
Abd-Elsalam 2018	Not a RCT
ACTRN12611000049976	Comparison of variations in treatment
Adarsh 2011	All groups received endoscopic treatment, but did not state what the endoscopic treatments were and whether they were equal in the two groups (as there are different endoscopic treatments that were included as treatment nodes in this review,
Adson 1984	Not a RCT
Afdhal 2010	Not a RCT
Akriviadis 1989	Comparison of variations in treatment
Alexandrino 1990	Balloon tamponade was used in some participants in one of the groups and this was not done by a randomisation process
Altman 1993	Not a RCT
Al Traif 1999	Included patients with no acute bleeding
Altraif 2011	Not an intervention of interest
Am. Soc. Gastro. Endo. 1998	Not a RCT
Anonymous 1996	After failure of initial treatment
Arcidiacono 1992	Terlipressin and sclerotherapy were used in both groups during the initial phase (i.e. only variations in initial treatment were compared)
Armengol 1992	Not clear whether gastric only varices were included
Avgerinos 1997	Included patients with other causes of gastrointestinal bleeding; no separate data was available in people with acute variceal bleeding
Azam 2012	Comparison of variations in treatment
Bagarani 1987	Balloon tamponade was used in some participants in the groups and this was not done by a randomisation process i.e. the co-interventions were not equal between the groups at randomisation
Balatsos 1997	Includes people undergoing secondary prophylaxis; no separate data was available for those with acute bleed
Bambha 2008	Some of the participants also received balloon tamponade or sclerotherapy, which was not chosen at random
Barsoum 1982	Not all patients had cirrhosis
Becker 1995	Not clear what the co-interventions were and whether they were equal across groups at the time of randomisation
Berardi 1974	Not a RCT
Bernard 1994	Not a RCT

Study	Reason for exclusion
Bhuiyan 2007	Includes people undergoing secondary prophylaxis; no separate data was available for those with acute bleed
Biggs 1976	Includes mostly upper gastrointestinal bleeding from other causes
Blaise 1994	Not an intervention of interest
Blanc 1994	Includes people with gastric variceal bleeding
Bobadilla-Diaz 2002	Not clear whether people with active bleeding were included
Bockel 1981	Not an intervention of interest
Bonniere 1987	Not an intervention of interest
Bosch 1989	Not an intervention of interest
Bosch 2004	Included participants with other causes of bleeding
Bruha 2000	Included participants with other causes of bleeding
Brunswig 1973	Not a RCT
Burroughs 1983	Not an intervention of interest
Burroughs 1989	Not an intervention of interest
Burroughs 1998	Not a RCT
Cales 2001	Includes patients with gastric variceal bleeding without oesophageal variceal bleeding
Cardona 1989	Some participants had bleeding gastric varices and not bleeding oesophageal varices
Cello 1982	Not an intervention of interest
Chatterjee 2004	Not clear if patients had liver cirrhosis
Cheema 2004	Only patients not fit for immediate sclerotherapy or band ligation because of severe torrential haemorrhage were included in this trial; therefore, the population in this trial did not meet the inclusion criteria for this review
Chen 1996a	The intervention was targeted at gastric varices
Chen 2001	Not clear if patients had liver cirrhosis
Chen 2018	Not a RCT
Cheng 2000	Not an intervention of interest
Cheng 2001	Not clear if this is primary prophylaxis, secondary prophylaxis, or active bleeding
Cheng 2009	Not a RCT
ChiCTR1800015012	Included patients with gastric variceal bleeding

Study	Reason for exclusion
ChiCTR1800020347	Not an intervention of interest
ChiCTR1900021217	Not clear whether the endoscopic treatment was and whether it was one of the interventions considered for the review
Chiu 1990	Comparison of variations in treatment
Combier 1999	Not a RCT
Company 2001	Comparison of variations in treatment
Company 2002	Comparison of variations in treatment
Conn 1975	Included people with other causes of upper gastrointestinal bleeding
Conn 1986	Not a RCT
Conn 1987	Not a RCT
Conn 1993	Not a RCT
Copenhagen Esophag. Varices Sclero. Proj. 1984	There was variability in the treatments, some received balloon tamponade (and this was not random) i.e. the co-interventions were not equal between the groups at randomisation
CTRI/2016/11/007483	Includes children
D'Amico 1994	Included other sources of upper gastrointestinal bleeding
De 2008	Not an intervention of interest
de Franchis 1993	Comparison of variations in treatment
Djurdjevic 1996	Not clear whether patients with no acute bleed were included
Djurdjevic 1999	Included patients with no acute bleed
Dobrucali 1998	Not a RCT
Dong 2018	Not clear if patients had acute variceal bleeding
Dowidar 2005	Not clear if patients had liver cirrhosis
Dunne 2019	Not clear if patients had acute variceal bleeding
Durdevic 1997	Included patients with no acute bleed
El Amin 2010	Not clear if all patients had cirrhosis
El-Khavat 1997	Not clear if all patients had cirrhosis
El-Newihi 1991	Not clear if all patients had cirrhosis
Elsebaey 2019	Not an intervention of interest
El-Zayadi 1988	Not in people with cirrhosis

Study	Reason for exclusion
El-Zayadi 1998	Not clear if all patients had cirrhosis
Escorsell 2016	Not an intervention of interest
eudract2007-002237-37	Not an intervention of interest
eudract2009-016500-24	Not an intervention of interest
eudract2012-000236-26	Not clear if patients had oesophageal varices
eudract2012-002489-11	Not clear if patients had oesophageal varices
eudract2014-002300-24	Not clear if patients had oesophageal varices
EVASP Study Group 1978	Not clear what the conventional treatment was
Fakhry 1997	Not clear if patients had liver cirrhosis
Feu 1996	Included gastric variceal only bleeding
Flati 1986	Included patients with other causes of gastrointestinal bleeding; no separate data was available in people with acute variceal bleeding
Fleischer 1985	Not an intervention of interest
Fogel 1982	Included patients with other causes of gastrointestinal bleeding; no separate data was available in people with acute variceal bleeding
Fort 1990b	Not a RCT
Freeman 1982	Comparison of variations in treatment
Garcia-Compean 1997	Included patients with gastric variceal bleeding without oesophageal variceal bleeding
Garcia-Pagan 2010	The control group received a range of treatments to be included in this review and this was not based on randomisation (i.e. the co-interventions were not equal between the groups at randomisation)
Garden 1992	Not a RCT
Geng 2015	Included patients with no active bleeding
Gilbert 1991	Not a RCT
Gimson 1993	Patients without acute bleeding were included
Gong 1998	Not a RCT
Gong 2010	Not clear if this is primary prophylaxis, secondary prophylaxis, active bleeding or all three
Gotzsche 1995	Included patients without oesophageal varices
Gralnek 1999	Included patients without acute variceal bleeding
Gronbaek 2003	Not a RCT

Study	Reason for exclusion
Gupta 1991	Not an intervention of interest
Gupta 2016	Comparison of variations in treatment
Hecker 1983	The medical treatment was not described (i.e. the interventions were not described)
Hecketsweiler 1978	Included patients with other causes of gastrointestinal bleeding; no separate data was available in people with acute variceal bleeding
Henderson 2006	Included people without acute bleed
Hosking 1988	Not an intervention of interest
Hou 1995	Included people with and without acute bleed
Hou 2001	Included people with and without acute bleed
Hu 2008	Comparison of variations in treatment
Huang 2007	Included gastric variceal only bleeding
Huang 2013	Comparison of variations in treatment
Huizinga 1985	Not a comparison of interest
Ibrahim 2019	Not clear if gastric only variceal bleeding was included
Ihre 1981	Included other sources of upper gastrointestinal bleeding
Iso 1997	Include patients without acute bleed
Jaramillo 1991	Both groups received a Sengstaken-Blakemore tube; the tube was inflated in only one of the groups (i.e. the co-interventions were not equal between the groups at randomisation)
Jenkins 1985	Not clear if acute bleeding from gastric varices only were included
Jenkins 1997	Patients in both groups received sclerotherapy, but the timing differed. One group also received octreotide, but non-randomly in some patients (i.e. the co-interventions were not equal between the groups at randomisation)
Jensen 1989	The control group received different treatments, which do not appear to be chosen at random
Jensen 1993	Includes patients with gastric variceal bleeding without oesophageal variceal bleeding
Johnston 2019	Not a RCT
Junquera 2000	Included patients with gastric variceal bleeding without oesophageal variceal bleeding
Kim 2005	Some patients received balloon tamponade, which does not appear to be at random (i.e. the co-interventions were not equal between the groups at randomisation)
Kochman 1992	Not a RCT
Korula 1985	Included patients who did not have acute bleed

Study	Reason for exclusion
Korula 1994	Not a RCT
Krag 2009	Not a RCT
Kravetz 1984	Included patients with gastric variceal bleeding without oesophageal variceal bleeding
Kullavanijaya 2001	Included patients with other causes of gastrointestinal bleeding; no separate data was available in people with acute variceal bleeding
Kusumobroto 1986	Not clear if patients had liver cirrhosis
Kusumobroto 1994	Not clear if patients had liver cirrhosis
Larson 1986	Standard treatment included vasopressin and/or balloon tamponade which was not determined at random
Lee 1998	Not a RCT
Lee 1999b	Not clear whether this was a RCT
Lee 2003	Not clear if this was oesophageal variceal bleeding
Levacher 1995	Included other sources of upper gastrointestinal bleeding
Li 1996	Not clear if it included gastric only varices
Li 1997	Not a comparison of interest for this review
Lin 1996	Not clear if patients had liver cirrhosis
Lin 2018	Not clear if gastric only variceal bleeding was included
Ling 2000	Not clear whether this was a RCT
Liu 1998	Not an intervention of interest
Ljubicic 2011	Not an intervention of interest
Lo 1991	Not a RCT
Lo 1994	Not all patients had cirrhosis
Lo 1997	Some participants received vasoconstrictors and this was not decided at random (i.e. the co-interventions were not equal at randomisation)
Lo 2004	Not a RCT
Lo 2011	Not an intervention of interest
Loperfido 1987	Not a comparison of interest
Ludwig 2000	Included people without oesophageal varices or bleeding
Luz 2011	Included patients without cirrhosis

Study	Reason for exclusion
Ma 2007	Not an intervention of interest
Mallory 1980	Included other sources of upper gastrointestinal bleeding
Mansour 2017	Not clear whether the bleeding was from oesophageal varices or gastric varices
Marbet 1988	Not an intervention of interest
Merli 1998	Included patients without acute variceal bleeding
Mezick 1994	Not a RCT
Mino 1995	Not a RCT
Mishin 1999	Not an intervention of interest
Moller 1992	In the medical regimen, some people received vasopressin, which was not determined at random
Moloney 2000	Not a RCT
Monescillo 2004	Included patients with gastric variceal bleeding without oesophageal variceal bleeding
Morales 2000	Not clear whether participants had acute bleeding
Moreto 1988	Included patients without cirrhosis
Mostafa 1996	Included patients without cirrhosis
Nakamura 2001	Included patients without acute variceal bleeding
Nakase 1996	Included patients without acute variceal bleeding
NCT00161915	Not an intervention of interest
NCT00331188	Not a RCT
NCT00369694	Comparison of variations in treatment
NCT00371943	Not an intervention of interest
NCT00563602	Comparison of variations in treatment
NCT00863837	Not a comparison of interest
NCT00966355	Not clear whether this Includes patients with gastric variceal bleeding without oesophageal variceal bleeding
NCT01103154	Included patients without acute variceal bleeding
NCT01131962	Not clear if patients had cirrhosis
NCT01242280	Not a comparison of interest
NCT01335516	Not a RCT

Study	Reason for exclusion
NCT01426087	Not clear if gastric only variceal bleeding was included
NCT01851564	The standard therapy was not defined (i.e. the control intervention was not clearly defined)
NCT02311608	Not a RCT
NCT02361593	Comparison of variations in treatment
NCT02377141	Only those who had haemostasis after initial endoscopy were included. Therefore, this is not the type of participants that were not of interest for this review.
NCT03583996	Not a RCT
Nevens 1997	Not a RCT
O'Connor 1989	Included patients without acute variceal bleeding
Okano 2003a	Not a RCT
Okano 2003b	Not a RCT
Orloff 1962	Not a RCT
Orloff 1974	Not a RCT
Orloff 1994	The co-interventions in the groups was administered at different times in the groups, which is likely to affect the effect estimates for the research objectives of this review
Orloff 2009	The study also included referrals from other hospital. Although the interval between last bleed and the study entry was not described in this study, another trial by the same research team suggests that people whose last bleed was up to 3 to 4 days were included. This group of patients do not fit in with the objectives of this review
Orloff 2012	Patients were included up to 3 to 4 days after last bleeding
Orloff 2014	Not a RCT
Orloff 2015	Not a RCT
Otte 1983	Included patients without acute variceal bleeding
Paquet 1983	Not a RCT
Pedretti 1994	Included gastric variceal only bleeding
Peng 2013	Not an intervention of interest
Pinto Correia 1984	Included patients with gastric variceal bleeding without oesophageal variceal bleeding
Piqueras 2004	Not clear if all patients had cirrhosis
Prindiville 1986	Not a RCT
Prioton 1988	Included patients without acute variceal bleeding

Study	Reason for exclusion
Priyadarshi 2011	Not clear if patients had liver cirrhosis
Rabeneck 1989	Not a RCT
Ramage 1993	Not clear if patients had liver cirrhosis
Ramires 2000	Included patients without cirrhosis
Reynolds 1981	Included patients without acute variceal bleeding
Rikkers 1993	Included patients without acute variceal bleeding
Rosemurgy 1996	Included patients with other causes of upper gastrointestinal bleeding
Saeed 1997	Included patients without acute variceal bleeding
Sahu 2014	Not clear whether the trial included only patients with acute oesophageal variceal bleed
Salem 1999	Included patients without cirrhosis
Santambrogio 2006	Not in patients with acute variceal bleeding
Sarin 1993	Not a RCT
Sayed 1995	Not clear if patients had liver cirrhosis
Seo 2006	It was not clear whether participants with gastric varices only bleeding were included
Seo 2014	Included patients with gastric variceal bleeding without oesophageal variceal bleeding
Shafqat 1998	Included patients without liver cirrhosis
Shaikh 2002	Not clear if this included patients with gastric varices only bleeding
Shields 1992	Included patients without liver cirrhosis
Shigemitsu 2000	Included patients without acute variceal bleeding
Shiha 1996	Not clear if patients had liver cirrhosis
Shin 1998	Not clear if this included patients with acute variceal bleeding
Silva 2004	The endoscopic therapy was variceal band ligation or sclerotherapy, which was not determined at random
Silvain 1991	Not a RCT
Silvain 1993	Included patients with gastric variceal bleeding without oesophageal variceal bleeding
Siqueira 1998	Not clear if patients had liver cirrhosis
Sivri 2000	Included patients with gastric variceal bleeding without oesophageal variceal bleeding
Smith-Laing 1981	Included patients without liver cirrhosis

Study	Reason for exclusion
Soderlund 1985	Quasi-randomised study (allocation by birth date)
Soderlund 1990	The placebo was mannitol, which cannot be considered an inactive treatment, but is not an intervention of interest for this review
Soderlund 1996	Not a RCT
Souza 2003	Not clear if patients had liver cirrhosis
Spina 1990	Included patients with and without acute variceal bleed
Stiegmann 1992	It was not clear whether all participants had acute variceal bleed
Sun 2013	Not clear if patients had acute variceal bleeding
Sung 1993	Not all patients had cirrhosis
Sung 1995	Not all patients had cirrhosis
Sung 1998	Not clear if patients had liver cirrhosis
Taniai 2002	Not a RCT
Terblanche 1979	Not all patients had cirrhosis
Terblanche 1986	Not a RCT
Teres 1987	Included patients with gastric variceal bleeding without oesophageal variceal bleeding
Teres 1989	Not a RCT
Terés 1990	Included patients with gastric variceal bleeding without oesophageal variceal bleeding
Thiel 1993	Not a RCT
Tricerri 1995	Not clear if this was a RCT
Valenzuela 1989	Not clear if patients had liver cirrhosis
Villanueva 2001	Included only patients in whom haemostasis was achieved with endoscopic sclerotherapy
Villanueva 2005	Only people who did not respond to high dose somatostatin were included in this study
Vlachogiannakos 2007	Included other sources of upper gastrointestinal bleeding
Walker 1986	Some patients received balloon tamponade, which does not appear to be at random (i.e. co-interventions were not equal at randomisation)
Walker 1992	Included gastric variceal only bleeding
Westaby 1983	Included patients without liver cirrhosis
Westaby 1989	Included patients without liver cirrhosis
Westaby 1994	Not a RCT

Study	Reason for exclusion
Wong 2001	Not a RCT
Ximing 2013	Not clear if patients had liver cirrhosis
Xu 1993	Included patients without liver cirrhosis
Xu 1998	Not clear if this was a RCT
Xu 2012	Not a RCT
Yan 2019	Includes patients with gastric variceal bleeding without oesophageal variceal bleeding
Yang 1998	Not a comparison of interest for this review
Yang 2001	Comparison of variations in treatment
Yassin 1983	Included patients without liver cirrhosis
Yol 2003	Included patients without liver cirrhosis
Yoshida 2004	Not a RCT
Zargar 2008	Not in patients with cirrhosis
Zhang 2000	Included patients with cirrhosis
Zhang 2002	Included patients with gastric variceal bleeding without oesophageal variceal bleeding
Zhang 2006	Not a RCT
Zhang 2008	Included patients without acute variceal bleeding
Zhao 1998	Not clear if patients had acute variceal bleeding
Zhou 2002	Not in patients with bleeding oesophageal varices
Zhou 2013	Not a RCT
Zhu 2005	Not clear if patients had liver cirrhosis
Zoller 1995	Not a RCT
Zuberi 2000	Included patients with gastric variceal bleeding without oesophageal variceal bleeding
Zuckerman 2016	Included patients without acute variceal bleeding

RCT = randomised clinical trial

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

Chen 1996b

Methods	Not stated

Chen 1996b *(Continued)*

Participants	Not stated
Interventions	Not stated
Outcomes	Not stated
Notes	Full text not available

Khan 2002

Methods	Not stated
Participants	Not stated
Interventions	Not stated
Outcomes	Not stated
Notes	Full text not available

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

CTRI/2018/03/012860

Study name	Comparison of a drug (Octreotide) which reduces bleeding by decreasing blood pressure with a control agent in stopping blood vomiting in patients with alcoholic liver disease after band occlusion of the bleeding vessels
Methods	Randomised clinical trial
Participants	Inclusion criteria: All patients presenting with bleeding esophageal varices due to cirrhosis to the emergency department during the study period Exclusion criteria: 1) Non-cirrhotic patients with portal hypertension 2) Extremes of ages (<18 and >60 years) 3) Patients in hepatic encephalopathy grades 3 and 4 4) Patients with source of bleeding in addition to or other than esophageal varices which includes gastritis, ulcers, ectasias, gastric varices, portal gastropathy 5) Patients already on vasoactive drugs for current episode of bleeding 6) Patients already received endoscopic ligation for the current episode elsewhere 7) Patients requiring Sengstaken-Blakemore tube insertion 8) Any history of past surgeries for portal hypertension 9) Patients associated with severe cardiopulmonary disease or malignancy 10) Patients not willing to participate in the study

CTRI/2018/03/012860 *(Continued)*

Interventions	Group 1: octreotide 100 mcg is given intravenously followed by Octreotide infusion 500mcg in one unit of 5% dextrose. After endoscopic band ligation of esophageal varices, octreotide is given subcutaneously for 3 days Group 2: placebo used is Normal saline. After endoscopic band ligation, normal saline is given subcutaneously for 3 days
Outcomes	Re-bleeding rates in both the octreotide and the placebo groups are compared at the end of three days
Starting date	2018
Contact information	Raj KN Department of Surgery (Office), Jawaharlal Institute of Post Graduate Medical Education and Research, Gorimedu, Pondicherry raj.jipmer@gmail.com
Notes	

NCT02646202

Study name	NCT02646202
Methods	Randomised clinical trial
Participants	Cirrhotic patients presenting with an acute or recent episode of gastro-esophageal variceal bleeding
Interventions	Endocopic sclerotherapy versus endoscopic variceal band ligation versus combination of endoscopic sclerotherapy and endoscopic variceal band ligation
Outcomes	None of the outcomes of interest for this review were included in this trial
Starting date	January 2015
Contact information	Sherief Abd-Elsalam (sherif_tropical@yahoo.com)
Notes	This may be eligible if the trial reports data for only those with acute bleeding in participants with oesophageal varices bleeding (i.e. excluding those with gastric only varices bleeding if such participants were included)

ADDITIONAL TABLES

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

Study name	Intervention 1 (number of participants) versus Intervention 2 (number of participants)	Included participants with other features of decompensation	Alcohol-related cirrhosis	Viral-related cirrhosis	Autoimmune disease-related cirrhosis	Prophylactic antibiotics for variceal bleeding given routinely	Low risk of bias	Period of recruitment	Follow-up in months
Bildozola 2000	Somatostatin analogues (39) versus sclerotherapy (37)	Yes (ascites)	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Not stated	Not stated	Yes	No	1994 - 1997	0.1
Freitas 1995	Somatostatin analogues (58) versus sclerotherapy (53)	Not stated	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Not stated	Not stated	Not stated	No	1989 - 1994	1
Planas 1994	Somatostatin analogues (35) versus sclerotherapy (35)	Yes (encephalopathy)	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Not stated	Not stated	Yes	No	1990 - 1993	1.5
Yousuf 2000	Somatostatin analogues (48) versus sclerotherapy (48)	Not stated	No participants had alcohol-related cirrhosis	All participants had viral-related cirrhosis	No participants had autoimmune disease-related cirrhosis	Not stated	No	1996 - 1999	0.2
Escorsell 2000	Vasopressin analogues (105) versus sclerotherapy (114)	Not stated	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Not stated	Not stated	Not stated	No	1994 - 1996	1.5
Ramon 1997	Vasopressin analogues (105) versus sclerotherapy (114)	Not stated	Not stated	Not stated	Not stated	Not stated	No	Not stated	1.5
Abid 2009	Vasopressin analogues (163) versus somatostatin analogues (161)	Yes (not stated)	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Participants with viral-related cirrhosis and without vi-	Not stated	Yes	No	2003-2005	0.17

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

				ral-related cirrhosis					
Chon 2000	Vasopressin analogues (13) versus somatostatin analogues (15)	Not stated	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Not stated	Not stated	Not stated	No	1997 - 1998	0.5
Hsia 1990	Vasopressin analogues (24) versus somatostatin analogues (22)	Not stated	Not stated	Participants with viral-related cirrhosis and without viral-related cirrhosis	Not stated	Not stated	No	Not stated	1.5
Huang 1992	Vasopressin analogues (21) versus somatostatin analogues (20)	Not stated	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Participants with viral-related cirrhosis and without viral-related cirrhosis	Not stated	Yes	No	1991	0.25
Hwang 1992	Vasopressin analogues (24) versus somatostatin analogues (24)	Not stated	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Participants with viral-related cirrhosis and without viral-related cirrhosis	Not stated	Not stated	No	1990 - 1991	1.5
NCT00534677	Vasopressin analogues (not stated) versus somatostatin analogues (not stated)	Not stated	Not stated	Not stated	Not stated	Not stated	No	2004-2005	not stated
Pauwels 1994	Vasopressin analogues (17) versus somatostatin analogues (18)	Not stated	Not stated	Not stated	Not stated	Only in participants with clinical indication	No	1986 - 1988	1
Saari 1990	Vasopressin analogues (22) versus somatostatin analogues (32)	Not stated	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Not stated	Not stated	Not stated	No	1985 - 1988	0.25

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

Besson 1995	Sclerotherapy plus somatostatin analogues (98) versus sclerotherapy (101)	Yes (encephalopathy)	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Not stated	Not stated	Not stated	No	1992 - 1994	0.5
Farooqi 2000	Sclerotherapy plus somatostatin analogues (72) versus sclerotherapy (69)	Not stated	No participants had alcohol-related cirrhosis	All participants had viral-related cirrhosis	No participants had autoimmune disease-related cirrhosis	Not stated	No	1994 - 1998	0.5
Freitas 2000	Sclerotherapy plus somatostatin analogues (44) versus sclerotherapy (42)	Not stated	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Not stated	Not stated	Not stated	No	1989 - 1994	1
Morales 2007	Sclerotherapy plus somatostatin analogues (40) versus sclerotherapy (28)	Not stated	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Participants with viral-related cirrhosis and without viral-related cirrhosis	Not stated	Yes	No	2001-2004	0.25
Shah 2005	Sclerotherapy plus somatostatin analogues (51) versus sclerotherapy (54)	Yes (encephalopathy)	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Participants with viral-related cirrhosis and without viral-related cirrhosis	No participants had autoimmune disease-related cirrhosis	Not stated	No	1997 - 1998	0.2
Signorelli 1996	Sclerotherapy plus somatostatin analogues (64) versus sclerotherapy (30)	Not stated	Not stated	Not stated	Not stated	Not stated	No	Not stated	0.2
Patsanas 2002	Sclerotherapy plus somatostatin analogues (15) versus somatostatin analogues (15)	Not stated	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Participants with viral-related cirrhosis and without viral-related cirrhosis	Participants with autoimmune disease-related cirrhosis and without autoimmune disease-related cirrhosis	Not stated	No	Not stated	1.5

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

Villanueva 1999	Sclerotherapy plus somatostatin analogues (50) versus somatostatin analogues (50)	Yes (encephalopathy)	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Not stated	Not stated	Yes	No	1995 - 1996	1.5
Armonis 2000	Variceal band ligation (13) versus sclerotherapy (12)	Not stated	Not stated	Not stated	Not stated	not stated	No	not stated	1.5
Cipolletta 1997	Variceal band ligation (41) versus sclerotherapy (40)	Not stated	Not stated	Not stated	Not stated	Not stated	No	1994 - 1996	0.5
Laine 1993	Variceal band ligation (38) versus sclerotherapy (39)	Not stated	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Participants with viral-related cirrhosis and without viral-related cirrhosis	Participants with autoimmune disease-related cirrhosis and without autoimmune disease-related cirrhosis	Not stated	No	1990 - 1992	0.3
Lo 1995	Variceal band ligation (61) versus sclerotherapy (59)	Yes (ascites)	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Participants with viral-related cirrhosis and without viral-related cirrhosis	Participants with autoimmune disease-related cirrhosis and without autoimmune disease-related cirrhosis	Not stated	No	1992 - 1993	3
Paquet 1985	Balloon tamponade (22) versus sclerotherapy (21)	Not stated	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Participants with viral-related cirrhosis and without viral-related cirrhosis	Not stated	Yes	No	1980 - 1981	1
Avgerinos 1991	Balloon tamponade (30) versus somatostatin analogues (31)	Not stated	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Participants with viral-related cirrhosis and without viral-related cirrhosis	Participants with autoimmune disease-related cirrhosis and without	Only in participants with clinical indication	No	not stated	0.25

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

					autoimmune disease-related cirrhosis				
Liu 2009	Somatostatin analogues plus variceal band ligation (51) versus somatostatin analogues (50)	Not stated	Not stated	Not stated	Not stated	Not stated	No	2003 - 2008	0.3
Chen 2006	Somatostatin analogues plus variceal band ligation (63) versus variceal band ligation (62)	Yes (encephalopathy)	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Participants with viral-related cirrhosis and without viral-related cirrhosis	Not stated	Yes	No	2000 - 2004	1.5
Kumar 2015	Somatostatin analogues plus variceal band ligation (31) versus variceal band ligation (30)	Yes (encephalopathy)	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Participants with viral-related cirrhosis and without viral-related cirrhosis	Not stated	All patients received prophylactic intravenous antibiotics (third generation cephalosporins).	No	2005 - 2009	0.25
Gimson 1986	Nitrates plus vasopressin analogues (32) versus vasopressin analogues (30)	Not stated	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Participants with viral-related cirrhosis and without viral-related cirrhosis	Participants with autoimmune disease-related cirrhosis and without autoimmune disease-related cirrhosis	Not stated	No	1982 - 1984	0.5
Lee 1988	Nitrates plus vasopressin analogues (24) versus vasopressin analogues (21)	Not stated	Not stated	Participants with viral-related cirrhosis and without viral-related cirrhosis	Not stated	Not stated	No	1987 - 1988	1.5

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

Tsai 1986	Nitrates plus vasopressin analogues (20) versus vasopressin analogues (19)	Not stated	Not stated	Participants with viral-related cirrhosis and without viral-related cirrhosis	Not stated	Only in participants with clinical indication	No	1983 - 1984	0.2
Fort 1990a	Nitrates plus vasopressin analogues (20) versus balloon tamponade (22)	Not stated	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Not stated	Not stated	Not stated	No	1987 - 1989	0.25
VA Coop. Variceal Sclerotherapy Group 1994	No active intervention (24) versus sclerotherapy (25)	Yes (not stated)	All participants had alcohol-related cirrhosis	No participants had viral-related cirrhosis	No participants had autoimmune disease-related cirrhosis	not stated	No	1985-1989	3
Burroughs 1990	No active intervention (59) versus somatostatin analogues (61)	Yes (encephalopathy)	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Not stated	Participants with autoimmune disease-related cirrhosis and without autoimmune disease-related cirrhosis	not stated	No	1985-1987	1
Pauwels 1994	No active intervention (14) versus somatostatin analogues (18)	Not stated	Not stated	Not stated	Not stated	Only in participants with clinical indication	No	1986 - 1988	1
Freeman 1989	No active intervention (16) versus vasopressin analogues (15)	Not stated	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Participants with viral-related cirrhosis and without viral-related cirrhosis	Participants with autoimmune disease-related cirrhosis and without autoimmune disease-related cirrhosis	Yes	No	Not stated	0.25

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

Pauwels 1994	No active intervention (14) versus vasopressin analogues (17)	Not stated	Not stated	Not stated	Not stated	Only in participants with clinical indication	No	1986 - 1988	1
Jensen 1998	Sclerotherapy plus variceal band ligation (29) versus sclerotherapy (28)	Not stated	Not stated	Not stated	Not stated	Not stated	No	not stated	3
Villanueva 2006	Variceal band ligation plus somatostatin analogues (90) versus sclerotherapy plus somatostatin analogues (89)	Yes (encephalopathy)	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Not stated	Not stated	Yes	No	1999 - 2004	1.5
Laine 1996	Sclerotherapy plus variceal band ligation (21) versus variceal band ligation (20)	Not stated	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Not stated	Not stated	Not stated	No	1993 - 1995	0.3
Lo 1992	Balloon tamponade plus sclerotherapy (31) versus sclerotherapy (29)	Not stated	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Participants with viral-related cirrhosis and without viral-related cirrhosis	Participants with autoimmune disease-related cirrhosis and without autoimmune disease-related cirrhosis	Not stated	No	1988 - 1990	0.6
McKee 1990	Balloon tamponade plus sclerotherapy (20) versus sclerotherapy plus somatostatin analogues (20)	Not stated	Not stated	Not stated	Not stated	Not stated	No	1986 - 1988	0.2
Avgerinos 1991	Balloon tamponade plus somatostatin analogues (31) versus somatostatin analogues (31)	Not stated	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Participants with viral-related cirrhosis and without viral-related cirrhosis	Participants with autoimmune disease-related cirrhosis and without autoimmune	Only in participants with clinical indication	No	not stated	0.25

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

					disease-related cirrhosis				
Avgerinos 1991	Balloon tamponade plus somatostatin analogues (31) versus balloon tamponade (30)	Not stated	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Participants with viral-related cirrhosis and without viral-related cirrhosis	Participants with autoimmune disease-related cirrhosis and without autoimmune disease-related cirrhosis	Only in participants with clinical indication	No	not stated	0.25
Clanet 1978	Balloon tamponade plus vasopressin analogues (26) versus balloon tamponade (18)	Not stated	Not stated	Not stated	Not stated	Not stated	No	Not stated	0.5
Colin 1987	Balloon tamponade plus vasopressin analogues (26) versus balloon tamponade (26)	Not stated	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Not stated	Not stated	Not stated	No	1984 - 1986	0.2
Cho 2006	Variceal band ligation plus vasopressin analogues (43) versus somatostatin analogues plus Variceal band ligation (45)	Yes (encephalopathy)	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Participants with viral-related cirrhosis and without viral-related cirrhosis	No participants had autoimmune disease-related cirrhosis	Not stated	No	2005	1.5
Asad 2014	Variceal band ligation plus vasopressin analogues (40) versus sclerotherapy plus variceal band ligation (40)	Not stated	Not stated	Not stated	Not stated	Not stated	No	Not stated	1
Chelarescu 2001	Balloon tamponade plus nitrates plus vasopressin analogues (32) versus balloon tamponade plus somatostatin analogues (27)	Not stated	Not stated	Not stated	Not stated	Not stated	No		0.06
Lee 1999a	Balloon tamponade plus variceal band ligation (18) versus somatostatin ana-	Not stated	Not stated	Not stated	Not stated	Not stated	No	Not stated	0.25

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

	logues plus variceal band ligation (20)								
Cello 1987	Portocaval shunt (32) versus sclerotherapy (32)	Yes (ascites)	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Not stated	Not stated	Not stated	No	1980 - 1984	1
Cello 1997	Sclerotherapy plus TIPS (24) versus sclerotherapy (25)	Yes (encephalopathy)	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Not stated	Not stated	Not stated	No	1991 - 1995	1
Hafta 2001	Sclerotherapy plus vasopressin analogues (17) versus sclerotherapy plus somatostatin analogues (17)	Not stated	Participants with alcohol-related cirrhosis and without alcohol-related cirrhosis	Participants with viral-related cirrhosis and without viral-related cirrhosis	No participants had autoimmune disease-related cirrhosis	Yes	No	1999 - 2000	0.1

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
Bildozola 2000	Somatostatin analogues (39) versus sclerotherapy (37)	Low	Unclear	Unclear	Unclear	Unclear	Low	Low	HIgh
Freitas 1995	Somatostatin analogues (58) versus sclerotherapy (53)	Low	Unclear	Unclear	Unclear	Low	Unclear	Low	HIgh
Planas 1994	Somatostatin analogues (35) versus sclerotherapy (35)	Low	Low	Unclear	Unclear	Low	Low	Unclear	HIgh
Yousuf 2000	Somatostatin analogues (48) versus sclerotherapy (48)	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	HIgh

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

Escorsell 2000	Vasopressin analogues (105) versus sclerotherapy (114)	Low	Low	Unclear	Unclear	Unclear	Low	Low	HIgh
Ramon 1997	Vasopressin analogues (105) versus sclerotherapy (114)	Low	Low	Unclear	Unclear	Unclear	Low	Low	HIgh
Abid 2009	Vasopressin analogues (163) versus somatostatin analogues (161)	Low	Low	Low	Low	Low	Unclear	Unclear	HIgh
Chon 2000	Vasopressin analogues (13) versus somatostatin analogues (15)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	HIgh
Hsia 1990	Vasopressin analogues (24) versus somatostatin analogues (22)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	HIgh
Huang 1992	Vasopressin analogues (21) versus somatostatin analogues (20)	Low	Low	Unclear	Unclear	Low	Low	Low	HIgh
Hwang 1992	Vasopressin analogues (24) versus somatostatin analogues (24)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	HIgh
NCT00534677	Vasopressin analogues (not stated) versus somatostatin analogues (not stated)	Unclear	Unclear	Low	Low	Unclear	Unclear	Low	HIgh
Pauwels 1994	Vasopressin analogues (17) versus somatostatin analogues (18)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	HIgh
Saari 1990	Vasopressin analogues (22) versus somatostatin analogues (32)	Low	Low	Unclear	Unclear	High	Unclear	Unclear	HIgh
Besson 1995	Sclerotherapy plus somatostatin analogues (98) versus sclerotherapy (101)	Low	Low	Low	Low	Low	Unclear	Low	HIgh
Farooqi 2000	Sclerotherapy plus somatostatin analogues (72) versus sclerotherapy (69)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	HIgh
Freitas 2000	Sclerotherapy plus somatostatin analogues (44) versus sclerotherapy (42)	Low	Unclear	Unclear	Unclear	Low	Unclear	Low	HIgh
Morales 2007	Sclerotherapy plus somatostatin analogues (40) versus sclerotherapy (28)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear	HIgh

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

Shah 2005	Sclerotherapy plus somatostatin analogues (51) versus sclerotherapy (54)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	HIgh
Signorelli 1996	Sclerotherapy plus somatostatin analogues (64) versus sclerotherapy (30)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	HIgh
Patsanas 2002	Sclerotherapy plus somatostatin analogues (15) versus somatostatin analogues (15)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	HIgh
Villanueva 1999	Sclerotherapy plus somatostatin analogues (50) versus somatostatin analogues (50)	Low	Low	Unclear	Unclear	Low	Low	Unclear	HIgh
Armonis 2000	Variceal band ligation (13) versus sclerotherapy (12)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	HIgh
Cipolletta 1997	Variceal band ligation (41) versus sclerotherapy (40)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	HIgh
Laine 1993	Variceal band ligation (38) versus sclerotherapy (39)	Low	Low	High	High	Low	Low	Low	HIgh
Lo 1995	Variceal band ligation (61) versus sclerotherapy (59)	Low	Low	High	High	Low	Unclear	Low	HIgh
Paquet 1985	Balloon tamponade (22) versus sclerotherapy (21)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	HIgh
Avgerinos 1991	Balloon tamponade (30) versus somatostatin analogues (31)	Low	Unclear	Unclear	Unclear	Low	Low	Low	HIgh
Liu 2009	Somatostatin analogues plus variceal band ligation (51) versus somatostatin analogues (50)	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	HIgh
Chen 2006	Somatostatin analogues plus variceal band ligation (63) versus variceal band ligation (62)	Low	Low	Unclear	Unclear	Low	Low	Low	HIgh
Kumar 2015	Somatostatin analogues plus variceal band ligation (31) versus variceal band ligation (30)	Low	Low	Low	Low	Low	Unclear	Low	HIgh
Gimson 1986	Nitrates plus vasopressin analogues (32) versus vasopressin analogues (30)	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	HIgh

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

Lee 1988	Nitrates plus vasopressin analogues (24) versus vasopressin analogues (21)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	HIgh
Tsai 1986	Nitrates plus vasopressin analogues (20) versus vasopressin analogues (19)	Low	Unclear	High	High	Low	Unclear	Low	HIgh
Fort 1990a	Nitrates plus vasopressin analogues (20) versus balloon tamponade (22)	Low	Unclear	Unclear	Unclear	Low	Low	Low	HIgh
VA Coop. Variceal Sclerotherapy Group 1994	No active intervention (24) versus sclerotherapy (25)	Low	Low	Low	Low	Low	Unclear	Unclear	HIgh
Burroughs 1990	No active intervention (59) versus somatostatin analogues (61)	Low	Low	Low	Low	Low	Unclear	Low	HIgh
Pauwels 1994	No active intervention (14) versus somatostatin analogues (18)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	HIgh
Freeman 1989	No active intervention (16) versus vasopressin analogues (15)	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	HIgh
Pauwels 1994	No active intervention (14) versus vasopressin analogues (17)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	HIgh
Jensen 1998	Sclerotherapy plus variceal band ligation (29) versus sclerotherapy (28)	Low	Low	Low	High	Low	Unclear	Low	HIgh
Villanueva 2006	Variceal band ligation plus somatostatin analogues (90) versus sclerotherapy plus somatostatin analogues (89)	Low	Low	Unclear	Unclear	Unclear	Low	Unclear	HIgh
Laine 1996	Sclerotherapy plus variceal band ligation (21) versus variceal band ligation (20)	Low	Low	High	High	Low	Low	Low	HIgh
Lo 1992	Balloon tamponade plus sclerotherapy (31) versus sclerotherapy (29)	Low	Low	High	High	Low	Low	Low	HIgh
McKee 1990	Balloon tamponade plus sclerotherapy (20) versus sclerotherapy plus somatostatin analogues (20)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	HIgh

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

Avgerinos 1991	Balloon tamponade plus somatostatin analogues (31) versus somatostatin analogues (31)	Low	Unclear	Unclear	Unclear	Low	Low	Low	HIgh
Avgerinos 1991	Balloon tamponade plus somatostatin analogues (31) versus balloon tamponade (30)	Low	Unclear	Unclear	Unclear	Low	Low	Low	HIgh
Clanet 1978	Balloon tamponade plus vasopressin analogues (26) versus balloon tamponade (18)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	HIgh
Colin 1987	Balloon tamponade plus vasopressin analogues (26) versus balloon tamponade (26)	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear	HIgh
Cho 2006	Variceal band ligation plus vasopressin analogues (43) versus somatostatin analogues plus variceal band ligation (45)	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	HIgh
Asad 2014	Variceal band ligation plus vasopressin analogues (40) versus sclerotherapy plus variceal band ligation (40)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	HIgh
Chelarescu 2001	Balloon tamponade plus nitrates plus vasopressin analogues (32) versus balloon tamponade plus somatostatin analogues (27)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	HIgh
Lee 1999a	Balloon tamponade plus variceal band ligation (18) versus somatostatin analogues plus variceal band ligation (20)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	HIgh
Cello 1987	Portocaval shunt (32) versus sclerotherapy (32)	Low	Low	Unclear	Unclear	Low	Unclear	Low	HIgh
Cello 1997	Sclerotherapy plus TIPS (24) versus sclerotherapy (25)	Low	Low	Unclear	Unclear	Low	Unclear	Low	HIgh
Hafta 2001	Sclerotherapy plus vasopressin analogues (17) versus sclerotherapy plus somatostatin analogues (17)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	HIgh

TIPS = Transjugular Intrahepatic Portosystemic Shunt

Table 3. Network meta-analysis: model fit

Mortality	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	391.5	391.9	397.1
DIC	454.8	456.6	468.9
pD	63.32	64.64	71.84
Serious adverse events (number of people)	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	39.26	39.65	-
DIC	48.06	49.06	-
pD	8.803	9.405	-
Any adverse events (number of people)	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	155.3	133.4	133.6
DIC	177.3	161.6	162.4
pD	22.08	28.19	28.77
Any adverse events (number of events)	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	97.32	-	-
DIC	114.1	-	-
1pD	16.75	-	-
Variceal rebleed (symptomatic recovery) (number of patients)	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	35.38	36.03	-
DIC	42.4	43.69	-
pD	7.018	7.659	-
Variceal rebleed (any) (number of patients)	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	178.4	175.6	176.5
DIC	210.3	211.2	214.9
pD	31.93	35.59	38.41
Other features of decompensation	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**

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

Dbar	16.72	-	-
DIC	20.62	-	-
pD	3.9	-	-
Additional treatment to control variceal bleeding	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	70.21	68.28	68.34
DIC	84.84	84.64	84.89
pD	14.62	16.36	16.56
Blood transfusion (RBC or whole blood) (quantity)	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	146.2	121.6	120.8
DIC	188.1	172.7	171.6
pD	41.98	51.02	50.74
Length of hospital stay (days)	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	72.37	70.34	69.45
DIC	93.37	93.43	92.94
pD	21	23.1	23.49
Treatment costs	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	315.8	-	-
DIC	315.8	-	-
pD	0.005305	-	-

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

Table 4. Effect estimates

This table is too wide to be displayed in RevMan. This table can be found here.

Please note the extremely wide credible intervals for additional treatment. Despite achieving convergence, the credible intervals were wide regardless of whether the model used was fixed-effects model or random-effects model. The most likely explanation for these wide credible intervals is the sparse data for this outcome.

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 obtain the effect estimate 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. Red colour indicates that the A has worse outcome than B and green colour indicates that A has better outcomes than B.

APPENDICES

Appendix 1. Search strategies

Database	Time span	Search strategy
Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	2019, Issue 12	#1 MeSH descriptor: [Esophageal and Gastric Varices] explode all trees #2 *esophageal varic* #3 #1 or #2
MEDLINE Ovid	January 1947 to December 2019	1. exp "Esophageal and Gastric Varices"/ 2. *esophageal varic*/.ti,ab. 3. 1 or 2 4. randomized controlled trial.pt. 5. controlled clinical trial.pt. 6. randomized.ab. 7. placebo.ab. 8. drug therapy.fs. 9. randomly.ab. 10. trial.ab. 11. groups.ab. 12. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 13. exp animals/ not humans.sh. 14. 12 not 13 15. 3 and 14
Embase Ovid	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.

(Continued)

		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. List of comparisons for which the interpretation was altered by worst-best and best-worst analysis for 'any' variceal bleed

- Sclerotherapy plus somatostatin analogues versus sclerotherapy:
  - Main analysis: no evidence of difference between groups
  - Worst-best analysis: lower in sclerotherapy plus somatostatin analogues than sclerotherapy
  - Best-worst analysis: no evidence of difference between groups
- Somatostatin analogues plus variceal band ligation versus sclerotherapy:
  - Main analysis: no evidence of difference between groups
  - Worst-best analysis: lower in somatostatin analogues plus variceal band ligation than sclerotherapy
  - Best-worst analysis: no evidence of difference between groups
- Balloon tamponade plus sclerotherapy versus sclerotherapy:
  - Main analysis: no evidence of difference between groups
  - Worst-best analysis: lower in balloon tamponade plus sclerotherapy than sclerotherapy
  - Best-worst analysis: no evidence of difference between groups
- Sclerotherapy plus somatostatin analogues versus somatostatin analogues:
  - Main analysis: no evidence of difference between groups
  - Worst-best analysis: lower in sclerotherapy plus somatostatin analogues than somatostatin analogues
  - Best-worst analysis: no evidence of difference between groups
- Somatostatin analogues plus variceal band ligation versus somatostatin analogues:
  - Main analysis: no evidence of difference between groups
  - Worst-best analysis: lower in somatostatin analogues plus variceal band ligation than somatostatin analogues
  - Best-worst analysis: no evidence of difference between groups
- Balloon tamponade plus sclerotherapy versus somatostatin analogues:
  - Main analysis: no evidence of difference between groups
  - Worst-best analysis: lower in balloon tamponade plus sclerotherapy than somatostatin analogues
  - Best-worst analysis: no evidence of difference between groups
- Sclerotherapy plus somatostatin analogues versus vasopressin analogues:
  - Main analysis: no evidence of difference between groups
  - Worst-best analysis: lower in sclerotherapy plus somatostatin analogues than vasopressin analogues
  - Best-worst analysis: no evidence of difference between groups

- Somatostatin analogues plus variceal band ligation versus vasopressin analogues:
  * Main analysis: no evidence of difference between groups
  * Worst-best analysis: lower in somatostatin analogues plus variceal band ligation than vasopressin analogues
  * Best-worst analysis: no evidence of difference between groups
- Balloon tamponade plus sclerotherapy versus vasopressin analogues:
  * Main analysis: no evidence of difference between groups
  * Worst-best analysis: lower in balloon tamponade plus sclerotherapy than vasopressin analogues
  * Best-worst analysis: no evidence of difference between groups
- Balloon tamponade plus vasopressin analogues versus variceal band ligation:
  * Main analysis: higher in balloon tamponade plus vasopressin analogues than variceal band ligation
  * Worst-best analysis: higher in balloon tamponade plus vasopressin analogues than variceal band ligation
  * Best-worst analysis: no evidence of difference between groups

Appendix 3. Differences in results between standard model and baseline-risk adjusted model

Mortality

- Somatostatin analogues versus sclerotherapy
  * Standard analysis: higher in somatostatin analogues than sclerotherapy
  * Baseline risk-adjusted analysis: no evidence of difference between groups
- Variceal band ligation plus vasopressin analogues versus balloon tamponade plus sclerotherapy:
  * Standard analysis: no evidence of difference between groups
  * Baseline risk-adjusted analysis: lower in variceal band ligation plus vasopressin analogues than balloon tamponade plus sclerotherapy

Any variceal bleed

- Balloon tamponade versus variceal band ligation:
  * Standard analysis: higher in balloon tamponade than variceal band ligation
  * Baseline risk-adjusted analysis: no evidence of difference between groups
- Balloon tamponade plus vasopressin analogues versus variceal band ligation:
  * Standard analysis: higher in balloon tamponade plus vasopressin analogues than variceal band ligation
  * Baseline risk-adjusted analysis: no evidence of difference between groups
- Variceal band ligation plus vasopressin analogues versus balloon tamponade:
  * Standard analysis: lower in variceal band ligation plus vasopressin analogues than balloon tamponade
  * Baseline risk-adjusted analysis: no evidence of difference between groups
- Variceal band ligation plus vasopressin analogues versus balloon tamponade plus vasopressin analogues:
  * Standard analysis: lower in variceal band ligation plus vasopressin analogues than balloon tamponade plus vasopressin analogues
  * Baseline risk-adjusted analysis: no evidence of difference between groups

Appendix 4. Data

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HISTORY

Protocol first published: Issue 10, 2018
Review first published: Issue 4, 2021

CONTRIBUTIONS OF AUTHORS

Protocol

Conceiving the protocol: KG, DR, ET
Designing the protocol: KG, DR
Co-ordinating the protocol: KG
Designing search strategies: KG
Writing the protocol: DR, KG
Providing general advice on the protocol: ET
Securing funding for the protocol: KG
All 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, DR, MC
Data extraction: KG, DR, NW, LB, SA, TB, MC, DW
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 approved the current review for publication.

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, software

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. We clarified that we are evaluating the initial treatments rather than treatment of refractory acute bleeding.
2. We also excluded trials in which the haemostasis was achieved prior to randomisation: this was because we were evaluating the initial treatments for bleeding oesophageal varices rather than treatment of varices where bleeding was controlled.
3. We added information about treatment nodes and the decision set in the Types of interventions section.
4. We changed the follow-up time at which the outcomes were measured to be at 6 weeks. This was because most trials reported the outcomes only up to this period, but those that provided longer follow-up had started interventions related to secondary prophylaxis which would have affected the treatment estimates.
5. We removed the sentence "In general, we will classify the risk of bias as low if the method used for allocation concealment suggested that it was extremely likely that the sequence was generated randomly (for example, use of interactive voice response system)". We have also removed: 'For profit bias'. These were done following the current guidance for risk of bias classification of the CHB Group.
6. We used the 'sclerotherapy' (endoscopic sclerotherapy) as the reference group (changed from 'vasoactive drugs plus endoscopic ligation'), as sclerotherapy was the commonest intervention compared in the trials.
7. We did not perform Trial Sequential Analysis (TSA) because the risk of false positive results with Bayesian meta-analysis is usually less or at least equivalent to TSA.
8. We used the latest guidance from the GRADE Working Group (Brignardello-Petersen 2018; Yepes-Nunez 2019) rather than the previous guidance (Puhan 2014) for presenting the 'Summary of findings' 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 a trial, 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 template used by Cochrane Hepato-Biliary Group modified for network meta-analysis used by the author group based on advice provided by the Complex Reviews Support Unit for a network meta-analysis protocol (Best 2018).