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


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

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ABSTRACT

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

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

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

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

Data collection and analysis
We performed a network meta-analysis with OpenBUGS using Bayesian methods and calculated the differences in treatments using hazard ratios (HR), odds ratios (OR), and rate ratios with 95% credible intervals (CrI) based on an available-case analysis, according to National
Institute for Health and Care Excellence Decision Support Unit guidance. We performed the direct comparisons from randomised clinical trials using the same codes and the same technical details.

**Main results**

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

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

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

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

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

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

**Authors’ conclusions**

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

**Plain language summary**

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

**What was the aim of this Cochrane Review?**

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

**Date of literature search**

December 2019

**Key messages**

We found that only one of the trials was conducted without flaws, and because of this, there is high to very high uncertainty in the findings. Approximately one in five trial participants with cirrhosis and oesophageal varices who never had bleeding previously and received the standard treatment of beta-blockers died within five years of treatment.
The funding source for the research was unclear in 50 trials; commercial organisations funded five trials. There were no concerns regarding the source of funding for the remaining 11 trials.

**What was studied in the review?**

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

**What were the main results of the review?**

The 66 studies included a relatively small number of participants (6653 people). Sixty studies with 6212 participants provided data for analyses. The follow-up of the trial ranged from six months to five years in studies that reported the outcomes that we were interested in. The review found the following:

- Approximately one in five people with cirrhosis and oesophageal varices (without previous bleeding) who receive the beta-blockers died within five years.
- Beta-blockers, variceal band ligation, sclerotherapy, and beta-blockers plus nitrates all may result in fewer deaths than no treatment.
- Variceal band ligation may result in a higher number of serious side effects than beta-blockers.
- Sclerotherapy, beta-blockers plus nitrates, and beta-blockers plus variceal band ligation may result in more side effects (when serious and non-serious adverse events were put together) than beta-blockers.
- Beta-blockers plus variceal band ligation may result in fewer people who develop bleeding than beta-blockers alone based on a single small trial.
- Nitrates alone may result in more people who develop bleeding than beta-blockers alone.
- The evidence indicates considerable uncertainty about the effect of the interventions in the remaining comparisons.
- None of the trials reported health-related quality of life.

**What are our conclusions?**

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

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

<table>
<thead>
<tr>
<th>Outcomes/Interventions</th>
<th>No active intervention</th>
<th>Variceal band ligation</th>
<th>Sclerotherapy</th>
<th>Beta-blockers + variceal band ligation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (follow-up: 8–60 months)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Beta-blockers</td>
<td>HR 2.04 (1.50 to 2.78)</td>
<td>HR 1.05 (0.80 to 1.38)</td>
<td>HR 1.35 (0.95 to 1.92)</td>
<td>HR 1.11 (0.56 to 2.19)</td>
</tr>
<tr>
<td>212 per 1000 (21.2%)</td>
<td>221 more per 1000 (107 more to 377 more)</td>
<td>11 more per 1000 (43 fewer to 81 more)</td>
<td>75 more per 1000 (10 fewer to 195 more)</td>
<td>23 more per 1000 (93 fewer to 252 more)</td>
</tr>
<tr>
<td>Network estimate</td>
<td>Network estimate</td>
<td>Network estimate</td>
<td>Network estimate</td>
<td></td>
</tr>
<tr>
<td>Low certainty</td>
<td>Very low certainty</td>
<td>Very low certainty</td>
<td>Very low certainty</td>
<td></td>
</tr>
<tr>
<td>Based on 1200 participants (10 RCTs)</td>
<td>Based on 1640 participants (17 RCTs)</td>
<td>Based on 320 participants (5 RCTs)</td>
<td>Based on 313 participants (2 RCTs)</td>
<td></td>
</tr>
</tbody>
</table>

#### Health-related quality of life

No trials reported health-related quality of life.

#### Serious adverse events (number of participants) (follow-up: 11–55 months)

<p>| Beta-blockers | OR 0.75 (0.02 to 23.24) | OR 0.55 (0.00 to 272.05) | — |
| 56 per 1000 (5.6%) | 13 fewer per 1000 (54 fewer to 522 more) | 24 fewer per 1000 (55 fewer to 886 more) | |
| Network estimate | Network estimate | |
| — | — | — | |</p>
<table>
<thead>
<tr>
<th>Serious adverse events (number of events) (follow-up: 13 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta-blockers</strong></td>
</tr>
<tr>
<td>24 per 1000 (2.4 per 100 participants)</td>
</tr>
<tr>
<td>Very low certainty (^a,,c,d)</td>
</tr>
<tr>
<td>Based on 372 participants (5 RCTs)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Any adverse events (number of participants) (follow-up: 11–55 months)</th>
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<tbody>
<tr>
<td><strong>Beta-blockers</strong></td>
</tr>
<tr>
<td>190 per 1000 (19%)</td>
</tr>
<tr>
<td>128 fewer per 1000 (185 fewer to 216 more)</td>
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<tr>
<td><strong>Network estimate</strong></td>
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<tr>
<td><strong>Network estimate</strong></td>
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<tr>
<td><strong>ΟΟΟΟ</strong></td>
</tr>
<tr>
<td>Very low certainty (^a,,c,e)</td>
</tr>
<tr>
<td>Based on 256 participants (2 RCTs)</td>
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<tr>
<td>No direct RCT</td>
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</table>

<table>
<thead>
<tr>
<th>Any adverse events (number of events) (follow-up: 12–52 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta-blockers</strong></td>
</tr>
<tr>
<td>610 per 1000 (61 per 100 participants)</td>
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<tr>
<td>16 fewer per 1000 (253 fewer to 415 more)</td>
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<tr>
<td><strong>Network estimate</strong></td>
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<tr>
<td><strong>Network estimate</strong></td>
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<tr>
<td><strong>ΟΟΟΟ</strong></td>
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<tr>
<td>Very low certainty (^a,,c,e)</td>
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<td><strong>ΟΟΟΟ</strong></td>
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<tr>
<td><strong>ΟΟΟΟ</strong></td>
</tr>
<tr>
<td>No direct RCT</td>
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<tr>
<td>Based on 90 participants (2 RCTs)</td>
</tr>
</tbody>
</table>
## Liver transplantation (follow-up: 11–52 months)

| Treatment | HR 1.36  
| (0.35 to 5.80) | 18 more per 1000  
| (31 fewer to 231 more) | HR 1.41  
| (0.83 to 2.43) | 20 more per 1000  
| (8 fewer to 69 more) | — | HR 2.40  
| (0.19 to 77.48) | 67 more per 1000  
| (39 fewer to 952 more) |

- Very low certainty

Based on 161 participants (1 RCT)

## Symptomatic variceal bleeding (follow-up: 15–44 months)

| Treatment | HR 1.14  
| (0.56 to 2.40) | 24 more per 1000  
| (79 fewer to 251 more) | HR 0.80  
| (0.47 to 1.36) | 36 fewer per 1000  
| (96 fewer to 64 more) | HR 0.91  
| (0.44 to 1.95) | 16 fewer per 1000  
| (100 fewer to 171 more) | HR 1.13  
| (0.45 to 2.87) | 23 more per 1000  
| (99 fewer to 337 more) |

- Very low certainty

Based on 140 participants (1 RCT)

Based on 380 participants (5 RCTs)

## Any variceal bleeding (follow-up: 6–55 months)

| Treatment | HR 2.71  
| (0.97 to 7.68) | 165 more per 1000  
| (3 fewer to 647 more) | HR 0.72  
| (0.33 to 1.51) | 27 fewer per 1000  
| (65 fewer to 49 more) | HR 1.02  
| (0.33 to 3.27) | 1 more per 1000  
| (65 fewer to 219 more) | HR 0.21  
| (0.04 to 0.71) | 76 fewer per 1000  
| (93 fewer to 28 fewer) |

- Very low certainty

Based on 208 participants (2 RCTs)

Based on 879 participants (9 RCTs)

Based on 175 participants (3 RCTs)

Based on 173 participants (1 RCT)
Other features of decompensation (follow-up: 18–55 months)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Relative effect (95% CrI)</th>
<th>Anticipated absolute effect* (95% CrI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers</td>
<td>—</td>
<td>18 more per 1000 (90 fewer to 302 more)</td>
</tr>
</tbody>
</table>

Notes:
- *Ranking was not provided because of the considerable uncertainty in the ranking.
- CrI: credible interval; HR: hazard ratio; OR: odds ratio; RaR: rate ratio; RCT: randomised clinical trial.

**GRADE Working Group grades of evidence**

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

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

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

**Patient or population**: people with liver cirrhosis and oesophageal varices with no history of bleeding

**Settings**: secondary or tertiary care

**Intervention**: various interventions

**Comparison**: beta-blockers

**Follow-up**: 6–60 months
### Mortality
**Total studies:** 58  
**Total participants:** 5936  
**Follow-up:** 8–60 months

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Reference</th>
<th>Mortality</th>
<th>Network estimate</th>
<th>Additional comments</th>
</tr>
</thead>
</table>
| Beta-blockers | No active intervention  
(10 RCTs, 1200 participants) | HR 2.04  
(1.50 to 2.78)  
Network estimate | 212 per 1000  
433 per 1000  
(319 to 589) | 221 more per 1000  
(107 more to 377 more) | ⬤⬤⬤⬤  
Low certainty a,b |
| | Variceal band ligation  
(17 RCTs, 1640 participants) | HR 1.05  
(0.80 to 1.38)  
Network estimate | 212 per 1000  
222 per 1000  
(169 to 293) | 11 more per 1000  
(43 fewer to 81 more) | ⬤⬤⬤  
Very low certainty a,b,c |
| | Sclerotherapy  
(5 RCTs, 320 participants) | HR 1.35  
(0.95 to 1.92)  
Network estimate | 212 per 1000  
286 per 1000  
(202 to 406) | 75 more per 1000  
(10 fewer to 195 more) | ⬤⬤⬤  
Very low certainty a,b,c |
| | Beta-blockers + variceal band ligation  
(2 RCTs, 313 participants) | HR 1.11  
(0.56 to 2.19)  
Network estimate | 212 per 1000  
235 per 1000  
(119 to 464) | 23 more per 1000  
(93 fewer to 252 more) | ⬤⬤⬤  
Very low certainty a,b,c |
| | Beta-blockers + nitrates  
(2 RCTs, 203 participants) | HR 0.84  
(0.44 to 1.64)  
Network estimate | 212 per 1000  
178 per 1000  
(92 to 347) | 34 fewer per 1000  
(119 fewer to 135 more) | ⬤⬤⬤  
Very low certainty a,b,c |
| | Nitrates  
(3 RCTs, 298 participants) | HR 1.19  
(0.66 to 2.11)  
Network estimate | 212 per 1000  
251 per 1000  
(139 to 447) | 39 more per 1000  
(72 fewer to 235 more) | ⬤⬤⬤  
Very low certainty a,b,c |
| | Beta-blockers + sclerotherapy  
(2 RCTs, 167 participants) | HR 2.08  
(1.03 to 4.08)  
Network estimate | 212 per 1000  
440 per 1000  
(218 to 864) | 228 more per 1000  
(6 more to 652 more) | ⬤⬤⬤  
Low certainty a,b |
| | Portocaval shunt  
(No direct RCT) | HR 0.51  
(0.06 to 2.92)  
Network estimate | 212 per 1000  
108 per 1000  
(12 to 620) | 103 fewer per 1000  
(200 fewer to 408 more) | ⬤⬤⬤  
Very low certainty a,b,c |
<table>
<thead>
<tr>
<th>Health-related quality of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>No trials reported health-related quality of life.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serious adverse events (number of participants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total studies: 6</td>
</tr>
<tr>
<td>Total participants: 457</td>
</tr>
<tr>
<td>Follow-up: 11–55 months</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Beta-blockers</th>
<th>Reference</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Variceal band ligation (5 RCTs, 372 participants)</td>
<td>OR 0.75 (0.02 to 23.24)</td>
<td>56 per 1000</td>
</tr>
<tr>
<td></td>
<td>Network estimate</td>
<td>42 per 1000 (1 to 578)</td>
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<tr>
<td></td>
<td></td>
<td>13 fewer per 1000 (54 fewer to 522 more)</td>
</tr>
<tr>
<td>Sclerotherapy (1 RCT, 85 participants)</td>
<td>OR 0.55 (0.00 to 272.05)</td>
<td>56 per 1000</td>
</tr>
<tr>
<td></td>
<td>Network estimate</td>
<td>32 per 1000 (0 to 941)</td>
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<tr>
<td></td>
<td></td>
<td>24 fewer per 1000 (55 fewer to 886 more)</td>
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</table>

<table>
<thead>
<tr>
<th>Serious adverse events (number of events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total studies: 1</td>
</tr>
<tr>
<td>Total participants: 168</td>
</tr>
<tr>
<td>Follow-up: 13 months</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Beta-blockers</th>
<th>Reference</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Variceal band ligation (1 RCT, 168 participants)</td>
<td>OR 10.49 (2.83 to 60.64)</td>
<td>24 per 1000</td>
</tr>
<tr>
<td></td>
<td>Network estimate</td>
<td>252 per 1000 (68 to 1455)</td>
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<td></td>
<td></td>
<td>228 more per 1000 (44 more to 1431 more)</td>
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</table>

<table>
<thead>
<tr>
<th>Any adverse events (number of participants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total studies: 12</td>
</tr>
<tr>
<td>Total participants: 1165</td>
</tr>
<tr>
<td>Follow-up: 11–55 months</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Beta-blockers</th>
<th>Reference</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No active intervention (2 RCTs, 256 participants)</td>
<td>OR 0.28 (0.02 to 2.91)</td>
<td>190 per 1000</td>
</tr>
<tr>
<td></td>
<td>Network estimate</td>
<td>62 per 1000 (6 to 407)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>128 fewer per 1000 (185 fewer to 216 more)</td>
</tr>
<tr>
<td>Variceal band ligation</td>
<td>OR 1.60</td>
<td>190 per 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>273 per 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>83 more per 1000</td>
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</tbody>
</table>
### Primary prevention of variceal bleeding in people with oesophageal varices due to liver cirrhosis: a network meta-analysis (Review)

#### (7 RCTs, 728 participants)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>OR (95% CI)</th>
<th>Event Rate 1000</th>
<th>Event Rate 1000 Confidence Interval</th>
<th>Very low certainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sclerotherapy (No direct RCT)</td>
<td>1.19 (0.02 to 80.24)</td>
<td>190</td>
<td>113 to 548</td>
<td>a,c,e</td>
</tr>
<tr>
<td>Beta-blockers + nitrates (1 RCT, 57 participants)</td>
<td>3.41 (1.11 to 11.28)</td>
<td>190</td>
<td>113 to 548</td>
<td>a,c,e</td>
</tr>
<tr>
<td>Any adverse events (number of events)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total studies: 11</td>
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<tr>
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<tr>
<td>Beta-blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No active intervention (No direct RCT)</td>
<td>0.97 (0.59 to 1.68)</td>
<td>610</td>
<td>357 to 1024</td>
<td>a,c,e</td>
</tr>
<tr>
<td>Variceal band ligation (4 RCTs, 480 participants)</td>
<td>0.77 (0.63 to 0.94)</td>
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<td>357 to 1024</td>
<td>a,c,e</td>
</tr>
<tr>
<td>Sclerotherapy (2 RCTs, 90 participants)</td>
<td>2.49 (1.53 to 4.22)</td>
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<td>357 to 1024</td>
<td>a,c,e</td>
</tr>
<tr>
<td>Beta-blockers + variceal band ligation (1 RCT, 140 participants)</td>
<td>1.65 (0.93 to 1.92)</td>
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<td>357 to 1024</td>
<td>a,c,e</td>
</tr>
<tr>
<td>Liver transplantation</td>
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<tr>
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<tr>
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<tr>
<td>Follow-up: 11–52 months</td>
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<td></td>
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</tr>
<tr>
<td>Beta-blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No active intervention (1 RCT, 161 participants)</td>
<td>1.36 (0.35 to 5.80)</td>
<td>48</td>
<td>17 to 280</td>
<td>a,c,e</td>
</tr>
</tbody>
</table>

---

**References**

- a
- c
- e
- d
- ⊗ ⊝ ⊝ ⊝
| Intervention                                         | Reference                          | HR (95% CI)       | Network estimate | HR (95% CI)       | Network estimate | HR (95% CI)       | Network estimate | HR (95% CI)       | Network estimate | HR (95% CI)       | Network estimate | HR (95% CI)       | Network estimate | HR (95% CI)       | Network estimate | HR (95% CI)       | Network estimate |
|-----------------------------------------------------|------------------------------------|-------------------|------------------|-------------------|------------------|-------------------|------------------|-------------------|------------------|-------------------|------------------|-------------------|------------------|-------------------|------------------|------------------|
| Variceal band ligation (5 RCTs, 380 participants)   |                                    |                   |                  |                   |                  |                   |                  |                   |                  |                   |                  |                   |                  |                   |                   |                  |
|                                                     | HR 1.41 (0.83 to 2.43)             |                   |                  |                   |                  | 48 per 1000       | 68 per 1000       | 20 more per 1000 | (8 fewer to 69 more) |
|                                                     | Network estimate                   |                   |                  |                   |                  |                   |                  |                   |                  |                   |                  |                   |                  |                   |                  |
| Beta-blockers + variceal band ligation (1 RCT, 140 participants) | HR 2.40 (0.19 to 77.48)           |                   |                  |                   |                  | 48 per 1000       | 116 per 1000      | 67 more per 1000 | (39 fewer to 952 more) |
|                                                     | Network estimate                   |                   |                  |                   |                  |                   |                  |                   |                  |                   |                  |                   |                  |                   |                  |
| Symptomatic variceal bleeding                        |                                    | 20 more per 1000  |                  |                   |                   | 40 to 117         |                   |                   |                   |                   |                   |                   |                   |                   |                   |
| Total studies: 7                                     |                                    |                   |                  |                   |                   |                   |                  |                   |                  |                   |                   |                   |                   |                   |                   |
| Total participants: 1007                              |                                    |                   |                  |                   |                   |                   |                  |                   |                  |                   |                   |                   |                   |                   |                   |
| Follow-up: 15–44 months                               |                                    |                   |                  |                   |                   |                   |                  |                   |                  |                   |                   |                   |                   |                   |                   |

**Beta-blockers**

- **No active intervention** (1 RCT, 140 participants)
  - HR 1.14 (0.56 to 2.40)  
  - Network estimate
  - 180 per 1000
  - 204 per 1000  
  - (101 to 431)
  - 24 more per 1000  
  - (79 fewer to 251 more)

**Variceal band ligation** (3 RCTs, 330 participants)

- HR 0.80 (0.47 to 1.36)  
  - Network estimate
  - 180 per 1000
  - 144 per 1000
  - (84 to 244)
  - 36 fewer per 1000
  - (96 fewer to 64 more)

**Sclerotherapy** (1 RCT, 141 participants)

- HR 0.91 (0.44 to 1.95)  
  - Network estimate
  - 180 per 1000
  - 164 per 1000
  - (80 to 351)
  - 16 fewer per 1000
  - (100 fewer to 171 more)

**Beta-blockers + variceal band ligation** (1 RCT, 140 participants)

- HR 1.13 (0.45 to 2.87)  
  - Network estimate
  - 180 per 1000
  - 203 per 1000
  - (81 to 517)
  - 23 more per 1000
  - (99 fewer to 337 more)

**Nitrites** (1 RCT, 118 participants)

- HR 1.27 (0.61 to 2.66)  
  - Network estimate
  - 180 per 1000
  - 228 per 1000
  - (110 to 478)
  - 48 more per 1000
  - (70 fewer to 298 more)

**Beta-blockers + sclerotherapy** (1 RCT, 141 participants)

- HR 0.92 (0.41 to 2.08)  
  - 180 per 1000
  - 166 per 1000
  - (73 to 375)
  - 14 fewer per 1000
  - (107 fewer to 195 more)
### Network estimate

<table>
<thead>
<tr>
<th>Any variceal bleeding</th>
<th>Total studies: 27</th>
<th>Total participants: 2460</th>
<th>Follow-up: 6–55 months</th>
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<tr>
<td>Beta-blockers</td>
<td>Reference</td>
<td></td>
<td></td>
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<tr>
<td>No active intervention</td>
<td>HR 2.71</td>
<td>97 per 1000</td>
<td>262 per 1000</td>
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<tr>
<td></td>
<td>(0.97 to 7.68)</td>
<td>(94 to 744)</td>
<td>(3 fewer to 647 more)</td>
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<td>Variceal band ligation</td>
<td>HR 0.72</td>
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<td>70 per 1000</td>
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<tr>
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<td>(0.33 to 1.51)</td>
<td>(32 to 146)</td>
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<td>Sclerotherapy</td>
<td>HR 1.02</td>
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<td>(0.33 to 3.27)</td>
<td>(31 to 316)</td>
<td>(65 fewer to 219 more)</td>
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<td>HR 0.21</td>
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<tr>
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<td>(0.04 to 0.71)</td>
<td>(4 to 69)</td>
<td>(93 fewer to 28 fewer)</td>
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<td>Direct estimate</td>
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<tr>
<td>Beta-blockers + nitrates</td>
<td>HR 0.93</td>
<td>97 per 1000</td>
<td>90 per 1000</td>
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<tr>
<td></td>
<td>(0.16 to 5.32)</td>
<td>(16 to 515)</td>
<td>(81 fewer to 418 more)</td>
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<td>Network estimate</td>
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<td>Nitrates</td>
<td>HR 6.40</td>
<td>97 per 1000</td>
<td>620 per 1000</td>
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<tr>
<td></td>
<td>(1.58 to 47.42)</td>
<td>(153 to 1000)</td>
<td>(56 more to 903 more)</td>
</tr>
<tr>
<td></td>
<td>Direct estimate</td>
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### Other features of decompensation

<table>
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<tr>
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<tr>
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Very low certainty a,c,d
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<tr>
<th>Intervention</th>
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<th>CrI</th>
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<th>CrI</th>
<th>Network estimate</th>
<th>Risk of bleeding per 1000</th>
<th>RaR</th>
<th>CrI</th>
<th>Network estimate</th>
<th>CrI</th>
<th>Network estimate</th>
<th>Number of additional bleeds per 1000</th>
<th>certainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers + nitrates</td>
<td>2 (RCTs, 203 participants)</td>
<td>(0.64 to 2.13)</td>
<td>162 per 1000</td>
<td>(103 to 345)</td>
<td>26 more per 1000</td>
<td>188 per 1000</td>
<td>1.16</td>
<td>(0.64 to 2.13)</td>
<td>162 per 1000</td>
<td>(103 to 345)</td>
<td>26 more per 1000</td>
<td>188 per 1000</td>
<td>Very low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.44 to 2.86)</td>
<td></td>
<td>(72 to 464)</td>
<td></td>
<td>(90 fewer to 302 more)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(90 fewer to 302 more)</td>
<td></td>
</tr>
</tbody>
</table>

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

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

**GRADE Working Group grades of evidence**

**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.

**Moderate certainty:** we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

**Low certainty:** our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

**Very low certainty:** we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

General comment: The GRADE classification was based on the main results.

a Downgraded one level for risk of bias because the trial(s) included in the analysis was/were at high risk of bias.

b Downgraded one level for inconsistency because there was evidence of statistical heterogeneity.

c Downgraded one level for imprecision because the credible intervals were wide (included clinical benefit and harms).

d Downgraded one level for imprecision because the sample size was small.

e Downgraded one level for indirectness because there was evidence of statistical inconsistency.
BACKGROUND

Description of the condition

Liver cirrhosis

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

Oesophageal varices

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

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

Pathophysiology of oesophageal varices

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

Description of the intervention

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

**How the intervention might work**

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

**Why it is important to do this review**

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

**Objectives**

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

**Methods**

Criteria for considering studies for this review

**Types of studies**

We considered only randomised clinical trials (including cross-over and cluster-randomised clinical trials) for this NMA irrespective of language, publication status, or date of publication. We excluded studies of other designs because of the risk of bias in such studies.

Inclusion of indirect observational evidence could weaken our NMA, but this could also be viewed as a strength for assessing rare adverse events. It is well-established that exclusion of non-randomised studies increases the focus on potential benefits and reduces the focus on the risks of serious adverse events and those of any adverse events. However, we did not include these studies because of the findings of this review (i.e. the treatment decision should be driven by effects on mortality rather than treatment-related adverse events).

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

**Types of participants**

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

**Types of interventions**

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

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

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

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

We evaluated the plausibility of the NMA transitivity assumption by looking at the inclusion and exclusion criteria in the trials. The transitivity assumption means that participants included in the different trials with different treatments (in this case, for primary
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 serious adverse events (as indicated in the protocol; Gurusamy 2018).
  * Proportion of people with one or more serious adverse events.
  * Number of serious adverse events per participant.

Other features of decompenstation (number of decompenstation events per participant at maximal follow-up).
discussion. We illustrated the study selection process in a PRISMA diagram (Figure 1).
Figure 1. Study flow diagram. Date of search 17 December 2019. RCT: randomised clinical trial.

8184 records identified through database searching

0 additional records identified through other sources

5764 records after duplicates removed

5764 records screened

5426 records excluded based on title and abstract

219 records (199 studies) excluded
- Not a population of interest for this review (114)
- Not an RCT (49)
- Not a comparison of interest for this review (21)
- Effect of randomisation was lost in a considerable proportion of participants because of trial-related procedures (1)
- Unclear if the studies included people without cirrhosis or gastric variceal bleeding (14)

2 records awaiting classification

338 full-text records assessed for eligibility

117 records (74 studies) identified in total
- 6 ongoing studies (7 records) awaiting results

66 studies (110 records) included in qualitative synthesis

60 trials included in quantitative
Data extraction and management

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

- Outcome data (for each outcome and for each intervention group whenever applicable):
  * number of participants randomised;
  * number of participants included for the analysis;
  * number of participants with events for binary outcomes, mean and standard deviation for continuous outcomes, number of events and the mean follow-up period for count outcomes, and number of participants with events and the mean follow-up period for time-to-event outcomes;
  * natural logarithm of hazard ratio (HR) and its standard error if this was reported rather than the number of participants with events and the mean follow-up period for time-to-event outcomes;
  * definition of outcomes or scale used if appropriate.

- Data on potential effect modifiers:
  * participant characteristics such as age, sex, size of varices, presence of high-risk factors such as those with red spots or red wale markings, presence of other features of decompensation such as ascites, the aetiology for cirrhosis, and the interval between diagnosis of varices and prophylactic treatment;
  * details of the intervention and control (including dose, frequency, and duration);
  * length of follow-up;
  * information related to risk of bias assessment (see below).

- Other data:
  * year and language of publication;
  * country in which the participants were recruited;
  * year(s) in which the trial was conducted;
  * inclusion and exclusion criteria.

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

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

Assessment of risk of bias in included studies

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

Allocation sequence generation

- Low risk of bias: sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were adequate if performed by an independent person not otherwise involved in the trial.

- Unclear risk of bias: the method of sequence generation was not specified.

- High risk of bias: the sequence generation method was not random or only quasi-randomised. We excluded such quasi-randomised studies.

Allocation concealment

- Low risk of bias: the allocation sequence was described as unknown to the investigators. Hence, the participants’ allocations could not have been foreseen in advance of, or during, enrolment. Allocation was controlled by a central and independent randomisation unit, an onsite locked computer, identical-looking numbered sealed opaque envelopes, drug bottles or containers prepared by an independent pharmacist, or an independent investigator.

- Unclear risk of bias: it was unclear if the allocation was hidden or if the block size was relatively small and fixed so that intervention allocations may have been foreseen in advance of, or during, enrolment.

- High risk of bias: the allocation sequence was likely to be known to the investigators who assigned the participants. We excluded such quasi-randomised studies.

Blinding of participants and personnel

- Low risk of bias: blinding of participants and key study personnel ensured, and it was unlikely that the blinding could have been broken; or rarely no blinding or incomplete blinding, but the review authors judged that the outcome was not likely to be influenced by lack of blinding.

- Unclear risk of bias: any of the following: insufficient information to permit judgement of ‘low risk’ or ‘high risk’; or the trial did not address this outcome.

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

Blinded outcome assessment

- Low risk of bias: blinding of outcome assessment ensured, and unlikely that the blinding could have been broken; or rarely no
blinding of outcome assessment, but the review authors judged that the outcome measurement was not likely to be influenced by lack of blinding.

- Unclear risk of bias: any of the following: insufficient information to permit judgement of ‘low risk’ or ‘high risk’; or the trial did not address this outcome.

- High risk of bias: any of the following: no blinding of outcome assessment, and the outcome measurement was likely to be influenced by lack of blinding; or blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.

Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. The study used sufficient methods, such as multiple imputation, to handle missing data.

- Unclear risk of bias: there was insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias on the results.

- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk of bias: the trial reported the following predefined outcomes: all-cause mortality, adverse events, and variceal bleeding. If the original trial protocol was available, the outcomes should have been those called for in that protocol. If we obtained the trial protocol from a trial registry (e.g. ClinicalTrials.gov), the outcomes sought should have been those enumerated in the original protocol if the trial protocol was registered before or at the time that the trial was begun. If the trial protocol was registered after the trial was begun, we did not consider those outcomes to be reliable.

- Unclear risk of bias: not all predefined, or clinically relevant and reasonably expected, outcomes were reported fully, or it was unclear whether data on these outcomes were recorded or not.

- High risk of bias: one or more predefined or clinically relevant and reasonably expected outcomes were not reported, even though data on these outcomes should have been available and even recorded.

Other bias

- Low risk of bias: the trial appeared free of other components that could have put it at risk of bias (e.g. inappropriate control or dose or administration of control, baseline differences, early stopping).

- Unclear risk of bias: the trial may or may not have been free of other components that could have put it at risk of bias.

- High risk of bias: there were other factors in the trial that could have put it at risk of bias (e.g. baseline differences, early stopping).

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

Measures of treatment effect

Relative treatment effects

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

Relative ranking

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

Unit of analysis issues

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

Cluster-randomised clinical trials

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

Cross-over randomised clinical trials

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

Trials with multiple intervention groups

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

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

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

Assessment of heterogeneity

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

We assessed statistical heterogeneity by comparing the results of the fixed-effect model meta-analysis and the random-effects model meta-analysis, lack of overlap of 95% CrIs of between-study variance (Tau²) with zero, and by calculating the NMA-specific I² statistic (Jackson 2014) using Stata/SE 15.1. When possible, we explored substantial clinical, methodological, or statistical heterogeneity and addressed the heterogeneity in subgroup analysis (see Subgroup analysis and investigation of heterogeneity).

Assessment of transitivity across treatment comparisons

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

Assessment of reporting biases

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

Data synthesis

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

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

Assessment of inconsistency

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

Direct comparison

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

Subgroup analysis and investigation of heterogeneity

We planned to perform the direct comparisons using the same codes and the same technical details. We performed the direct comparison by including only trials in which there was direct comparison (Dias 2010), that is, calculating the direct estimate for each pairwise comparison calculated from the direct comparisons and NMA. We planned to calculate a single common interaction term which assumes that each relative treatment effect compared to a common comparator treatment (i.e. beta-blockers) is impacted in the same way by the covariate in question, when applicable (Dias 2012a). If the 95% CrI of the interaction term did not overlap zero, we considered this statistically significant heterogeneity or inconsistency (depending upon the factor being used as covariate).

Sensitivity analysis

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

Presentation of results

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

Recommendations for future research

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

Summary of findings and assessment of the certainty of the evidence

Grading of evidence

We presented 'Summary of findings’ tables for all the primary and secondary outcomes (see Primary outcomes; Secondary outcomes). We followed the approach suggested by the GRADE Working Group (Brignardello-Petersen 2018; Yepes-Nunez 2019). First, we calculated the direct and indirect effect estimates (when possible) and 95% CrI using the node-splitting approach (Dias 2010), that is, calculating the direct estimate for each comparison by including only trials in which there was direct comparison of interventions and the indirect estimate for each
comparison by excluding the trials in which there was direct comparison of interventions (and ensuring a connected network). Next, we rated the quality of direct and indirect effect estimates using GRADE methodology, which takes into account the risk of bias, inconsistency (heterogeneity), directness of evidence (including incoherence, the term used in GRADE methodology for inconsistency in NMA), imprecision, and publication bias (Guyatt 2011). We then presented the relative and absolute estimates of the meta-analysis with the best certainty of evidence (Yepes-Nunez 2010). For illustration of the absolute measures, we used weighted median (Edgeworth 1887) control group proportion or mean. We also presented the 'Summary of findings' tables in a second format presenting all the outcomes for selected interventions (Yepes-Nunez 2019): we selected the four interventions (no active intervention, variceal band ligation, sclerotherapy, and beta-blockers plus variceal band ligation) that most trials compared (Table 1).

RESULTS

Description of studies

Results of the search

We identified 8184 records through electronic searches of CENTRAL (1855 records), MEDLINE Ovid (2725 records), Embase Ovid (1034 records), Science Citation Index Expanded (1902 records), ClinicalTrials.gov (83 records), World Health Organization Trials register (110 records), FDA (36 records), and EMA (439 records). After removing duplicates, there were 5765 records. We excluded 5426 clearly irrelevant records through reading titles and abstracts. We retrieved 339 full-text records for further assessment in detail. We excluded 220 records (199 studies) for the reasons stated in the Characteristics of excluded studies table. Two records are awaiting classification (Buuren 2003; euadract2011-006208-11). Seven records (six studies) are ongoing trials (ChicTR-1PR-5005816; NCT02066649; NCT03732625; NCT03776955; NCT04074473; Tripathi 2019). Thus, we included 66 trials described in 110 records (Characteristics of included studies table). The reference flow is shown in Figure 1.

Included studies


Participants

Forty-one trials reported the proportion of participants who had small varices: in 10 trials, none of the participants had small varices (Wordhoff 1987; Fleig 1988; Ideo 1988; Santangelo 1988; Sauerbruch 1988; Russo 1989; Paquet 1994; De 1999; D’Amico 2002; Singh 2012); in five trials, all participants had small varices.
who had autoimmune disease-related cirrhosis: in eight trials, none of the participants had autoimmune disease-related cirrhosis (Conn 1969; Snady 1988; Cales 1989a; Cales 1989b; VA Coop. Variceal Sclerotherapy Group 1991; Piscaglia 1998; Svoboda 1999; Tomikawa 2004); in the remaining 11 trials, the proportion of participants who had autoimmune disease-related cirrhosis ranged from 2.6% to 25.8% (Lebrec 1988; Santangelo 1988; Duhamel 1994; Paquet 1994; Jutabha 2005; Psilopoulos 2005; Thuluvath 2005; Perez-Ayuso 2010; Drastich 2011; Singh 2012). Thirty-nine trials reported the proportion of participants who had other causes of cirrhosis: in eight trials, none of the participants had other causes of cirrhosis (Conn 1969; Snady 1988; Cales 1989a; Cales 1989b; VA Coop. Variceal Sclerotherapy Group 1991; Piscaglia 1998; Svoboda 1999; Tomikawa 2004); in the remaining 31 trials, the proportion of participants who had other causes of cirrhosis ranged from 2.7% to 66.4% (Sauerbruch 1988; Quer 1991; D'Amico 2002; Lui 2002; Schepke 2004; Lay 2006; Wang 2006; Noorbeto 2007; Lo 2010; Perez-Ayuso 2010); in the remaining 10 trials, the proportion of participants who had risk of bleeding (Conn 1969; Snady 1988; Cales 1989a; Cales 1989b; VA Coop. Variceal Sclerotherapy Group 1991; Piscaglia 1998; Thuluvath 2005; Perez-Ayuso 2010; Drastich 2011; Fung 2012; Singh 2012; Sarin 2013; Shah 2014; Bonilha 2015; Bhardwaj 2017). Fifty-one trials reported the proportion of participants who had alcohol-related cirrhosis: in five trials, all participants had alcohol-related cirrhosis (Conn 1969; Snady 1988; Cales 1989a; Cales 1989b; VA Coop. Variceal Sclerotherapy Group 1991); in the remaining 46 trials, the proportion of participants who had alcohol-related cirrhosis ranged from 1.8% to 90.0% (Witzel 1985; Pascal 1987; Wordehoff 1987; Iode 1988). Thirty-eight trials reported the proportion of participants who had other causes of cirrhosis: in five trials, all participants had other causes of cirrhosis (Conn 1969; Snady 1988; Cales 1989a; Cales 1989b; VA Coop. Variceal Sclerotherapy Group 1991; Piscaglia 1998; Thuluvath 2005; Perez-Ayuso 2010; Drastich 2011). The proportion of participants who had small varices ranged from 4.5% to 88.9% (Witzel 1985; Pascal 1987; Andreani 1990; Conn 1991; PROVA study group 1991; Quer 1991; VA Coop. Variceal Sclerotherapy Group 1991; Angelico 1993; Kanazawa 1993; Duhamel 1994; Lay 1997; Piscaglia 1998; De 1999; Lo 1999; Song 1999; Merkel 2000; D'Amico 2002; Lui 2002; Lo 2004; Merkel 2004; Schepke 2004; Lay 2006; Wang 2006; Tripathi 2009; Lo 2010; Perez-Ayuso 2010; Drastich 2011; Fung 2012; Singh 2012; Sarin 2013; Shah 2014; Bonilha 2015; Bhardwaj 2017). Interventions Trials compared nine interventions (beta-blockers, no active intervention, variceal band ligation, sclerotherapy, beta-blockers plus variceal band ligation, beta-blockers plus nitrates, nitrates, beta-blockers plus sclerotherapy, portocaval shunt). Sixty trials reported one or more outcomes for this review (Conn 1969; Paquet 1982; Witzel 1985; Pascal 1987; Wordehoff 1987; Fleig 1988; Iode 1988; Lebrec 1988; Piai 1988; Santangelo 1988; Sauerbruch 1988; Snady 1988; Russo 1989; Andreani 1990; Conn 1991; De Franchis 1991; PROVA study group 1991; Quer 1991; Rossi 1991; VA Coop. Variceal Sclerotherapy Group 1991; Angelico 1993; Fassio 1993; Kanazawa 1993; Duhamel 1994; Paquet 1994; Lay 1997; De 1999; Lo 1999; Song 1999; Strauss 1999; Svoboda 1999; Chen 2000; Merkel 2000; Agarwal 2001; Borroni 2002; Lui 2002; Lo 2004; Merkel 2004; Schepke 2004; Tomikawa 2004; Jutabha 2005; Psilopoulos 2005; Thuluvath 2005; Lay 2006; Wang 2006; Tripathi 2009; Lo 2010; Perez-Ayuso 2010; Drastich 2011; Feng 2012; Singh 2012; Sarin 2013; Shah 2014; Bonilha 2015; Bhardwaj 2017).

Transitivity assumption

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

Excluded studies

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


- Not a comparison of interest for this review as the intervention was not listed in one of the ones mentioned and is not currently in common use for primary prophylaxis (21 studies: Jackson 1968; Italian Proj. Prop. Prev. Bleed. 1988; Pagliero 1989; Inokuchi 1990; Tincani 1993; Averginos 1994; Lin 1994; Tincani 1995; Lin 1996a; Abeches 2003; Agarwala 2011; Chandok 2012; Hamza 2012; Yattoo 2013; Bhardwaj 2014; Alvarado-Tapias 2016; Kim 2016; ChiCTR-IR-15007655; NCT01188733; NCT00493480; NCT01383044).

- Effect of randomisation was lost in a considerable proportion of participants because of trial-related procedures (one study: Averginos 2000).

- Unclear if the studies included non-cirrhotic participants or the prophylaxis was primarily against gastric variceal bleeding (14 studies: Lin 1996b; Madwar 1998; Siqueira 1998; Helmy 2015; PolloFlores 2015; ChiCTR-TRC-12002148; eudraCT2012-00236-26; eudraCT2012-002489-11; eudraCT2014-005523-27; eudraCT2014-002300-24; eudraCT2017-001762-13; NCT00409084; NCT02646202; NCT20695732).

Risk of bias in included studies

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

Figure 2. Risk of bias graph: review authors’ judgements about each risk of bias item presented as percentages across all included studies.
<table>
<thead>
<tr>
<th>Study</th>
<th>Random sequence generation (selection bias)</th>
<th>Allocation concealment (selection bias)</th>
<th>Blinding of participants and personnel (performance bias): All outcomes</th>
<th>Blinding of outcome assessment (detection bias): All outcomes</th>
<th>Incomplete outcome data (attrition bias): All outcomes</th>
<th>Selective reporting (reporting bias)</th>
<th>Other bias</th>
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## Figure 3. (Continued)

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Allocation


Blinding

Two trials were at low risk of performance bias as the participants and healthcare providers were blinded (Conn 1991; D’Amico 2002); 47 trials, which did not provide sufficient information, were at unclear risk of performance bias (Conn 1969; Paquet 1962; Witzel 1985; Wordehoff 1987; Fleig 1988; Ideo 1988; Piai 1988; Santangelo 1988; Sauерbruch 1988; Snady 1988; Cales 1989a; Cales 1989b; Russo 1989; De Franchis 1991; Quer 1991; Rossi 1991; VA Coop. Variceal Sclerotherapy Group 1991; Angelico 1993; Kanazawa 1993; Duhamel 1994; Paquet 1994; Piscaglia 1998; De 1999; Lo 1999; Song 1999; Strauss 1999; Svoobra 1999; Chen 2000; Agarwal 2001; Deplano 2001; Borrone 2002; Thuluvath 2005; Psilopoulos 2005; Mishra 2007; Feng 2012; Singh 2012; Bhardwaj 2017; Khan 2017; Seo 2017; NCT00337740; NCT00921349).

Incomplete outcome data

Forty-four trials were at low risk of attrition bias as there were no postrandomisation dropouts, the postrandomisation outputs were very few, or an intention-to-treat analysis was used (Conn 1969; Witzel 1985; Pascal 1987; Wordehoff 1987; Ideo 1988; Lebrech 1988; Piai 1988; Sauерbruch 1988; Russo 1989; Andreni 1990; Conn 1991; Quer 1991; PROVA study group 1991; Rossi 1991; VA Coop. Variceal Sclerotherapy Group 1991; Angelico 1993; Duhamel 1994; Paquet 1994; Lay 1997; Piscaglia 1998; De 1999; Merkel 2000; Borrone 2002; D’Amico 2002; Lui 2002; Lo 2004; Merkel 2004; Schepke 2004; Tomikawa 2004; Jutabha 2005; Psilopoulos 2005; Thuluvath 2005; Lay 2006; Wang 2006; Mishra 2007; Norbeto 2007; Tripathi 2009; Lo 2010; Perez-Ayuso 2010; Drastich 2011; Singh 2012; Shah 2014; Bonilha 2015; Bhardwaj 2017); 17 trials were at unclear risk of attrition bias (Paquet 1982; Fleig 1988; Snady 1988; Cales 1989a; Cales 1989b; De Franchis 1991; Fassio 1993; Kanazawa 1993; Lo 1999; Svoobra 1999; Chen 2000; Agarwal 2001; Feng 2012; Khan 2017; Seo 2017); 15 trials were at high risk of attrition bias as the postrandomisation dropouts were related to the outcomes (if there were postrandomisation dropouts); the remaining five trials were at high risk of attrition bias as the postrandomisation dropouts were probably related to the outcomes (Santangelo 1988; Song 1999; Strauss 1999; Sarin 2013; Bhardwaj 2017).

Selective reporting

Sixteen trials were at low risk of selective outcome reporting bias as the important clinical outcomes expected to be reported in such trials were reported (Paquet 1982; Lebrech 1988; Andreni 1990; VA Coop. Variceal Sclerotherapy Group 1991; Lay 1997; D’Amico 2002; Lo 2004; Tomikawa 2004; Lay 2006; Wang 2006; Norbeto 2007; Lo 2010; Perez-Ayuso 2010; Drastich 2011; Feng 2012; Bonilha 2015); 49 trials were at unclear risk of selective outcome reporting bias as a protocol published prior to recruitment was not available (Conn 1969; Witzel 1985; Pascal 1987; Wordehoff 1987; Fleig 1988; Ideo 1988; Piai 1988; Santangelo 1988; Sauерbruch 1988; Snady 1988; Cales 1989a; Cales 1989b; Russo 1989; De Franchis 1991; PROVA study group 1991; Fassio 1993; Lay 1997; Merkel 2000; Merkel 2004; Jutabha 2005; Perez-Ayuso 2010; Drastich 2011; Sarin 2013; Shah 2014; Bonilha 2015; Bhardwaj 2017; NCT00337740; NCT00921349), because it was unclear whether there were postrandomisation dropouts or whether the postrandomisation dropouts were related to the outcomes (if there were postrandomisation dropouts); the remaining five trials were at high risk of attrition bias as the postrandomisation dropouts were probably related to the outcomes (Santangelo 1988; Song 1999; Strauss 1999; Sarin 2013; Bhardwaj 2017).

Primary prevention of variceal bleeding in people with oesophageal varices due to liver cirrhosis: a network meta-analysis (Review)
NCT00337740; NCT00921349); the remaining one trial was at high risk of selective outcome reporting bias as the outcomes were changed from the protocol published prior to recruitment without sufficient justification (Bhardwaj 2017).

Other potential sources of bias

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

Effects of interventions

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

The network plots (where relevant) are available in Figure 4. The inconsistency factor plots (where relevant) are available in Figure 5. The NMA results for mortality, adverse events, and any variceal bleed and the differences in the fixed-effect versus random-effects model, where relevant, are available in Figure 6. The model fit is available in Table 3. The effect estimates are available in Table 4.
Figure 4. Network plots: a high resolution version of this image can be found at https://doi.org/10.5281/zenodo.4409371. The network plots showing the outcomes for which network meta-analysis was performed. The size of the node (circle) provides a measure of the number of trials in which the particular intervention was included as one of the intervention groups. The thickness of the line provides a measure of the number of direct comparisons between two nodes (interventions). BT: balloon tamponade; PC_shunt: portocaval shunt; Sclero: sclerotherapy;
Som: somatostatin analogues; TIPS: transjugular intrahepatic portosystemic shunt; Vas: vasopressin analogues; VBL: variceal band ligation.
Figure 5. Inconsistency factor plots showing the inconsistency factors for the outcomes with direct and indirect evidence available for one or more comparisons. There was no evidence of inconsistency for any of the outcomes where this could be assessed (i.e. the confidence intervals of all the inconsistency factors for all outcomes overlap zero). A higher resolution image of this picture is available at https://doi.org/10.5281/zenodo.4441270. BT: balloon tamponade; PC_shunt: portocaval shunt; Sclero: sclerotherapy; Som: somatostatin analogues; TIPS: transjugular intrahepatic portosystemic shunt; Vas: vasopressin analogues; VBL: variceal band ligation.
Figure 6. Forest plots showing mortality and the outcomes for which the random-effects model were different from the fixed-effect model. The more conservative random-effects model was used. BBlock: beta-blockers; Sclero: sclerotherapy; VBL: variceal band ligation.

**Mortality**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Odds Ratio IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC_shunt</td>
<td>-0.733</td>
<td>1.007</td>
<td>0.51 [0.07, 3.68]</td>
</tr>
<tr>
<td>BBlock+Nitrates</td>
<td>-0.173</td>
<td>0.337</td>
<td>0.84 [0.43, 1.63]</td>
</tr>
<tr>
<td>VBL</td>
<td>0.049</td>
<td>0.140</td>
<td>1.05 [0.00, 1.76]</td>
</tr>
<tr>
<td>BBlock+VBL</td>
<td>0.103</td>
<td>0.347</td>
<td>1.11 [0.56, 2.19]</td>
</tr>
<tr>
<td>Nitrates</td>
<td>0.178</td>
<td>0.297</td>
<td>1.19 [0.86, 2.12]</td>
</tr>
<tr>
<td>Sclero</td>
<td>0.301</td>
<td>0.179</td>
<td>1.35 [0.95, 1.92]</td>
</tr>
<tr>
<td>No active intervention</td>
<td>0.714</td>
<td>0.156</td>
<td>2.04 [1.50, 2.78]</td>
</tr>
<tr>
<td>BBlock+Sclero</td>
<td>0.733</td>
<td>0.351</td>
<td>2.08 [1.04, 4.14]</td>
</tr>
</tbody>
</table>

**Any adverse events (number of participants)**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Odds Ratio IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2.1 Network meta-analysis (fixed-effect model)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No active intervention</td>
<td>-1.199</td>
<td>0.623</td>
<td>0.33 [0.09, 1.03]</td>
</tr>
<tr>
<td>Sclero</td>
<td>0.205</td>
<td>1.144</td>
<td>1.23 [0.13, 11.57]</td>
</tr>
<tr>
<td>VBL</td>
<td>0.227</td>
<td>0.184</td>
<td>1.26 [0.91, 1.73]</td>
</tr>
<tr>
<td>BBlock+Nitrates</td>
<td>0.650</td>
<td>0.459</td>
<td>1.92 [0.78, 4.71]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Odds Ratio IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2.2 Network meta-analysis (random-effects model)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No active intervention</td>
<td>-1.262</td>
<td>1.214</td>
<td>0.29 [0.03, 3.96]</td>
</tr>
<tr>
<td>Sclero</td>
<td>0.172</td>
<td>2.124</td>
<td>1.19 [0.02, 78.44]</td>
</tr>
<tr>
<td>VBL</td>
<td>0.460</td>
<td>0.575</td>
<td>1.50 [0.52, 4.94]</td>
</tr>
<tr>
<td>BBlock+Nitrates</td>
<td>0.566</td>
<td>1.184</td>
<td>1.76 [0.17, 17.96]</td>
</tr>
</tbody>
</table>

**Any variceal bleed**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Hazard Ratio IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3.1 Network meta-analysis (fixed-effect model)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BBlock+Nitrates</td>
<td>-0.180</td>
<td>0.573</td>
<td>0.84 [0.27, 2.55]</td>
</tr>
<tr>
<td>BBlock+VBL</td>
<td>-1.512</td>
<td>22.927</td>
<td>0.22 [0.00, 1.24]</td>
</tr>
<tr>
<td>Nitrates</td>
<td>1.888</td>
<td>0.081</td>
<td>6.48 [1.15, 30.33]</td>
</tr>
<tr>
<td>No active intervention</td>
<td>1.142</td>
<td>66.583</td>
<td>3.13 [0.00, 1.42]</td>
</tr>
<tr>
<td>Sclero</td>
<td>0.191</td>
<td>66.924</td>
<td>1.03 [0.00, 1.21]</td>
</tr>
<tr>
<td>VBL</td>
<td>-0.209</td>
<td>22.927</td>
<td>0.75 [0.00, 4.22]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Hazard Ratio IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3.2 Network meta-analysis (random-effects model)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BBlock+Nitrates</td>
<td>-0.273</td>
<td>0.897</td>
<td>0.39 [0.16, 6.29]</td>
</tr>
<tr>
<td>BBlock+VBL</td>
<td>-1.417</td>
<td>0.338</td>
<td>0.24 [0.05, 1.25]</td>
</tr>
<tr>
<td>Nitrates</td>
<td>1.897</td>
<td>1.339</td>
<td>6.57 [0.48, 91.95]</td>
</tr>
<tr>
<td>No active intervention</td>
<td>0.906</td>
<td>5.271</td>
<td>2.71 [0.66, 10.1]</td>
</tr>
<tr>
<td>Sclero</td>
<td>0.031</td>
<td>5.593</td>
<td>1.03 [0.32, 3.22]</td>
</tr>
<tr>
<td>VBL</td>
<td>-0.330</td>
<td>0.397</td>
<td>0.72 [0.34, 1.53]</td>
</tr>
</tbody>
</table>
We would like to note that no cluster- or cross-over randomised trials contributed to the effects of interventions. We would also like to note that there were several multiple arm trials. The codes that we used for analysis accounted for the correlation between the effect sizes from studies with more than two groups.

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

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

Mortality

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

Direct comparisons

- Beta-blockers had lower mortality than no active intervention: HR 0.59 (95% CI 0.42 to 0.83); 10 trials, 1200 participants; low-certainty evidence (because of the way information is presented in Table 4 and Summary of findings 1 where beta-blockers were used as the reference treatment, the HR of no active intervention versus beta-blockers was: HR 1.70 (95% CI 1.21 to 2.39).}

- Sclerotherapy had lower mortality than no active intervention: 
  HR 0.61 (95% CI 0.41 to 0.90); 18 trials, 1666 participants; low-certainty evidence.

- Sclerotherapy had higher mortality than beta-blockers: HR 1.88 (95% CI 1.01 to 3.69); 5 trials, 320 participants; low-certainty evidence.

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

Network meta-analysis

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

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

- Beta-blockers versus no active intervention: HR 0.49 (95% CI 0.36 to 0.67); direct comparison: HR 0.59 (95% CI 0.42 to 0.83); 10 trials, 1200 participants; low-certainty evidence (because beta-blockers was the reference treatment, the HR of no active intervention versus beta-blockers in Table 4 and Summary of findings 1 was: HR 2.04 (95% CI 1.50 to 2.78).

- Variceal band ligation versus no active intervention: HR 0.51 (95% CI 0.35 to 0.74); direct comparison HR 0.49 (95% CI 0.12 to 2.14); 3 trials, 355 participants; low-certainty evidence.

- Sclerotherapy versus no active intervention: HR 0.66 (95% CI 0.51 to 0.85); direct comparison HR 0.61 (95% CI 0.41 to 0.90); 18 trials, 1666 participants; low-certainty evidence.

- Beta-blockers plus nitrates versus no active intervention: HR 0.41 (95% CI 0.20 to 0.85); no direct comparison; low-certainty evidence.

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

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

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

Health-related quality of life

No trials reported health-related quality of life.

Serious adverse events

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

**Serious adverse events (number of participants)**

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

**Direct comparisons**

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

**Network meta-analysis**

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

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

**Serious adverse events (number of events)**

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

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

**Any adverse events**

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

**Any adverse events (number of participants)**

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

**Direct comparisons**

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

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

**Network meta-analysis**

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

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

**Any adverse events (number of events)**

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

**Direct comparisons**

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

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

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

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

**Network meta-analysis**

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

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

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

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

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

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

**Liver transplantation**

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

**Direct comparisons**

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

**Network meta-analysis**

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

**Variceal bleeding**

**Symptomatic variceal bleeding**

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

**Direct comparisons**

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

**Network meta-analysis**

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

**Any variceal bleeding**

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

**Direct comparisons**

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

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

**Network meta-analysis**

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

In the NMA, in the following pairwise comparisons, the first intervention had lower 'any variceal bleeding' than second intervention.
• Variceal band ligation versus no active intervention: HR 0.27 (95% CrI 0.09 to 0.76); direct comparison: HR 0.33 (95% CrI 0.01 to 10.90); 2 trials, 253 participants; low-certainty evidence.

• Sclerotherapy versus no active intervention: HR 0.38 (95% CrI 0.16 to 0.88); direct comparison: HR 0.36 (95% CrI 0.05 to 2.45); 6 trials, 530 participants; low-certainty evidence.

• Beta-blockers plus variceal band ligation versus no active intervention: HR 0.09 (95% CrI 0.01 to 0.54); no direct comparison; low-certainty evidence.

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

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

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

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

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

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

Number of days of lost work
No trials reported number of days of lost work.

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

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

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

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

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

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

Any variceal bleeding
• Sclerotherapy versus no active intervention:
  * main analysis: lower in sclerotherapy than no active intervention;
  * worst–best analysis: lower in sclerotherapy than no active intervention;
  * best–worst analysis: no evidence of difference between groups.

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

**Imputation of standard deviations**

We did not perform any imputation of standard deviations.

**Assessment of reporting biases**

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

**Post hoc analyses**

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

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

**Baseline risk-adjusted analysis**

Mortality

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

**Subset of trials published from the year 2000 onwards**

Mortality

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

Any variceal bleeding

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

**DISCUSSION**

**Summary of main results**

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

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

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

Based on low-certainty evidence, any variceal bleeding was lower in beta-blockers plus variceal band ligation than beta-blockers (direct comparison: HR 0.21, 95% CrI 0.04 to 0.71; 1 trial, 173 participants), variceal band ligation than no active intervention (HR 0.27, 95% CrI 0.09 to 0.76; direct comparison: HR 0.32, 95% CrI 0.01 to 10.90; 2 trials, 253 participants), sclerotherapy than no active intervention (HR 0.38, 95% CrI 0.16 to 0.88; direct comparison: HR 0.36, 95% CrI 0.05 to 2.45; 6 trials, 530 participants), and beta-blockers plus variceal band ligation than no active intervention (HR 0.09, 95% CrI 0.01 to 0.54; no direct comparison). Based on low-certainty
evidence, any variceal bleeding was higher in nitrates than beta-blockers (direct comparison: HR 6.40, 95% CrI 1.58 to 47.42; 1 trial, 52 participants) and in beta-blockers plus variceal band ligation (HR 28.02, 95% CrI 1.46 to 719.82; no direct comparison). When a subset of trials published from 2000 onwards were analysed, there was no evidence of differences in any of the comparisons.

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

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

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

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

- NCT03776955 and NCT03736265 are comparing beta-blockers with placebo for people with small oesophageal varices (although NCT03736265 is including only hepatitis B virus-related cirrhosis and does not have mortality as one of its outcomes).
- NCT0206649 and Tripathi 2019 are comparing beta-blockers versus variceal band ligation in people with medium or large oesophageal varices.
- NCT03776955 and Tripathi 2019 plan to measure health-related quality of life and, therefore, can address the uncertainty around it.

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

Overall completeness and applicability of evidence

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

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

Quality of the evidence

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

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

We used clinical outcomes; therefore, there is no issue of indirectness due to outcomes. There was no suggestion that the potential effect modifiers were systematically different across comparisons (i.e. there was no concern about the transitivity assumption) for most outcomes. However, it should be noted that some of the comparisons were downgraded as they were solely made up of indirect comparisons. One cannot rule out inconsistency (‘incoherence’ according to GRADE terminology) despite finding no evidence of this in most analyses.
There was no meaningful way to rank these studies (i.e. there was no specific change in the risk of bias in the studies, sample size, or the control group used over time); we have completed a thorough search for studies on effectiveness. However, different sets of trials were included for different outcomes: while 85% of trials reported mortality, only about 15% of trials reported serious adverse events adequately; only about 40% of trials reported variceal bleeding adequately; and less than 10% of trials described other decomposition events. These are outcomes that should have been recorded in trials of this nature, but were not reported. This may suggest reporting bias for these outcomes.

Potential biases in the review process

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

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

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

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

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

Agreements and disagreements with other studies or reviews

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

Authors’ conclusions

Implications for practice

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

Implications for research

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

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

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Danish State and The Copenhagen Trial Unit disclaimer
The views and opinions expressed in this review are those of the authors and do not necessarily reflect those of the Danish State or the Copenhagen Trial Unit.
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Bonilha 2010 (published data only)

Bosch 2005 (published data only)

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Burroughs 1992 (published data only)

Cales 1990b (published data only)

Cales 1999 (published data only)

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**Conn 1987** *(published data only)*


**Conn 1993** *(published data only)*


**Copaci 2012** *(published data only)*


**Chandok 2012** *(published data only)*


**Cheng 2001** *(published data only)*


**ChiCTR-IIR-15007655** *(published data only)*


**ChiCTR-PRRC-08000228** *(published data only)*


**ChiCTR-TRC-12002148** *(published data only)*


**Cirera 1995** *(published data only)*


**Conn 1986** *(published data only)*


**Escorsell 1997b** *(published data only)*


**Escorsell 2001** *(published data only)*


**Estevens 1996** *(published data only)*


**eudract2006-006393-14** *(published data only)*

**eudract2012-000236-26** *(published data only)*

**eudract2012-002489-11** *(published data only)*

**eudract2014-000102-35** *(published data only)*

**eudract2014-002018-21** *(published data only)*
Primary prevention of variceal bleeding in people with oesophageal varices due to liver cirrhosis: a network meta-analysis (Review)

Gallant 1992 (published data only)

Garcia-Pagán 1991 (published data only)

Garcia-Pagán 1996 (published data only)

Garcia-Pagán 2001 (published data only)

Garcia-Pagán 2003 (published data only)

Gawrieh 2005 (published data only)

Gheorghe 2006 (published data only)


Gilbert 1991 (published data only)

Gong 1998 (published data only)

Gong 2010 (published data only)

Gotoh 1999 (published data only)

Gregory 1991 (published data only)

Groszmann 2005 (published data only)

Group Francais de la Prevention Pre-Primaire 1995 (published data only)

Gupta 1993 (published data only)

Hamza 2012 (published data only)

Hanno 2016 (published data only)

Hashizume 1993 (published data only)

Helmy 2015 (published data only)
Hidaka 2011 (published data only)


Hua 2007 (published data only)


Hutteroth 1983 (published data only)


Inokuchi 1990 (published data only)


Iwakiri 2000 (published data only)


Iwao 1996 (published data only)


Jackson 1968 (published data only)


Kainth 2017 (published data only)


Kalambokis 2005 (published data only)


Kanazawa 1988 (published data only)


Kim 2016 (published data only)


Kitano 1989 (published data only)


Kitano 1992 (published data only)


Kleber 1987 (published data only)


Kleber 1991 (published data only)

Kobe 1990 (published data only)


Koch 1994 (published data only)


Kong 2013 (published data only)

Korula 1991 (published data only)

Kuwayama 2005 (published data only)

Lashner 1988 (published data only)

Lee 2001 (published data only)

Li 1995 (published data only)

Li 2016a (published data only)

Lin 1994 (published data only)

Lin 1996a (published data only)

Lin 1996b (published data only)

Lin 2002 (published data only)

Lin 2005 (published data only)

Liu 2004 (published data only)

Madwar 1998 (published data only)

Mann 2004 (published data only)

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Masumoto 1998 (published data only)

McCormick 1992 (published data only)
McCormick PA, Biagini MR, Dick R, Greenslade L, Chin J, Cardin F, et al. Octreotide inhibits the meal-induced increases...
in the portal venous-pressure of cirrhotic patients with portal-hypertension – a double-blind placebo-controlled study. 


McCormick 1993 (published data only)


Mcke 1990 (published data only)


Mino 1995 (published data only)


Miyoshi 1997 (published data only)


Mo 2014 (published data only)


NCT00006398 (published data only)


NCT00409084 (published data only)

NCT00409084. Beta blockers versus variceal band ligation and beta blockers for primary prophylaxis of variceal bleeding. clinicaltrials.gov/ct2/show/NCT00409084 (first received 8 December 2006).

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NCT00799851. A randomized controlled trial comparing band ligation and cyanoacrylate injection for esophageal varices. clinicaltrials.gov/show/NCT00799851 (first received 1 December 2008).

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NCT01188733 (published data only)


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NCT02646202. Scleroligation for eradication of gastroesophageal varices [Scleroligation is a safe and effective new technique for eradication of gastroesophageal varices]. clinicaltrials.gov/ct2/show/NCT02646202 (first received 27 December 2017).

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NCT02695732. The effect of carvedilol vs endoscopic therapy in primary prophylaxis of high-risk esophageal gastric variceal bleeding [Primary prophylaxis of high-risk esophageal gastric variceal bleeding comparing carvedilol and endoscopic therapy: a multicenter randomized controlled trial]. clinicaltrials.gov/show/NCT02695732 (first received 1 March 2016).

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**Nevans 1996b** *(published data only)*


**Nevans 1996c** *(published data only)*


**Nishikawa 1999** *(published data only)*


**Oberti 1999** *(published data only)*


**Ohmoto 2006** *(published data only)*


**Okano 2003a** *(published data only)*


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**Orloff 1962** *(published data only)*


**Orloff 1974** *(published data only)*


**Orloff 2014** *(published data only)*


**Pagliaro 1989** *(published data only)*


**Pagliaro 2003a** *(published data only)*


**Pang 1997** *(published data only)*


**Paquet 1983** *(published data only)*


**Paquet 1993** *(published data only)*


**Pfisterer 2018** *(published data only)*


**Phillips 1975** *(published data only)*


**Plevris 1994** *(published data only)*


**Pollo-Flores 2015** *(published data only)*

Resnick 1974

Resnick 1969

Resnick 2005

Pozzi 2005 (published data only)


Qi 2007 (published data only)


Ramond 1999 (published data only)


Resnick 1969 (published data only)


Resnick 1974 (published data only)


Reynolds 1991 (published data only)


Romero 2000 (published data only)


Santambrogio 1990 (published data only)


Santos 2011 (published data only)


Sarin 1996 (published data only)


Sarin 1999 (published data only)


Sarin 2005 (published data only)


Sarin 2010 (published data only)


Schepe 2001 (published data only)


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**Schiedermair 2003** *(published data only)*


**Sen 2002** *(published data only)*


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**Sharara 2003** *(published data only)*

Sharara AI, Rockey DC, Tripathi D, Hayes PC. Therapy for primary prophylaxis of varices: and, the winner is …? *Hepatology (Baltimore, Md.)* 2003;37(2):473-6.

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**Siqueira 1998** *(published data only)*


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**Sohn 2013** *(published data only)*


**Sotto 1989** *(published data only)*


**Stiegmann 1999** *(published data only)*


**Sugano 1997** *(published data only)*


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**Sussman 2003** *(published data only)*


**Taniai 2002** *(published data only)*


**Taranto 1990** *(published data only)*


**Testa 1991** *(published data only)*


**Thiel 1993** *(published data only)*

References to ongoing studies

ChicTR-IPR-15005816 {published data only}

NCT02066649 {published data only}

NCT03736265 {published data only}

References to studies awaiting assessment

Buuren 2003 {published data only}
eudact2011-006208-11 {published data only}

References

Tincani 1993 {published data only}

Tincani 1995 {published data only}

Triantos 2005 {published data only}

Triger 1991 {published data only}


Umehara 1999 {published data only}

Vanruyswyk 1992 {published data only}

Vorobioff 2002 {published data only}

Vorobioff 2007 {published data only}

Yattoo 2013 {published data only}

Zalepuga 2000 {published data only}

Zargar 2008 {published data only}

Zironi 1996 {published data only}
NCT03776955 (published data only)


NCT04074473 (published data only)

Tripathi 2019 (published data only)

Additional references

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Beppu 1981

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Brignardello-Petersen 2018

Cales 1990a

Chaimani 2012

Chaimani 2013

Chawla 2012

D’Amico 2010

D’Amico 2014

de Franchis 1992

de Franchis 2015

Dias 2010

Dias 2012a
Jackson 2014

Kjaergard 2001

Li 2016b


Mccarty 2017

McPherson 2016

Merlon 2010

Merli 2003

Mills 2012

Moher 1998

Mokdad 2014

Moore 2013

NCBI 2018a

NCBI 2018b

Newell 1992

NIEC 1988

Optum 2018

Puhan 2014

QI 2015

Ratib 2015

Read 1972
Rios 2015

Royle 2003

Salanti 2011

Salanti 2012

Sass 2009

Savović 2012a

Savović 2012b

Savović 2018

Scaglione 2015

Schulz 1995

Setiawan 2016

Severini 1993

Sharma 2019

Stata/SE 15.1 [Computer program]

Thabut 2007

Tripathi 2015

Tsochatzis 2014

van Valkenhoef 2012

Williams 2014

Wood 2008
References to other published versions of this review

Gurusamy 2018

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Agarwal 2001

Study characteristics

<table>
<thead>
<tr>
<th>Study characteristics</th>
<th>Randomised clinical trial</th>
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<td>Methods</td>
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<tr>
<td>Participants</td>
<td>Country: India</td>
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<tr>
<td></td>
<td>Period of recruitment: not stated</td>
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<tr>
<td></td>
<td>Number randomised: 92</td>
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<td>Postrandomisation dropouts: 0 (0.0%)</td>
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<td>Revised sample size: 92</td>
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<td>Mean age (years): not stated</td>
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<td>Small varices: not stated</td>
</tr>
<tr>
<td></td>
<td>High risk of bleeding: not stated</td>
</tr>
<tr>
<td></td>
<td>Other features of decompensation: not stated</td>
</tr>
<tr>
<td></td>
<td>Alcohol-related cirrhosis: not stated</td>
</tr>
<tr>
<td></td>
<td>Viral-related cirrhosis: not stated</td>
</tr>
<tr>
<td></td>
<td>Autoimmune disease-related cirrhosis: not stated</td>
</tr>
<tr>
<td></td>
<td>Other causes of cirrhosis: not stated</td>
</tr>
<tr>
<td></td>
<td>Other inclusion/exclusion criteria: not stated</td>
</tr>
<tr>
<td>Interventions</td>
<td>Group 1: beta-blockers and variceal band ligation (n = 46)</td>
</tr>
<tr>
<td></td>
<td>Further details: propranolol (mean dose 92 mg/day) + variceal band ligation every 1–2 weeks until obliteration</td>
</tr>
<tr>
<td></td>
<td>Group 2: variceal band ligation (n = 46)</td>
</tr>
<tr>
<td></td>
<td>Further details: variceal band ligation every 1–2 weeks until obliteration</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Mortality at maximal follow-up, variceal bleed at maximal follow-up (any) (number of participants)</td>
</tr>
<tr>
<td></td>
<td>Follow-up (months): 8</td>
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### Agarwal 2001 (Continued)

**Notes**

Source of funding: not stated

Trial name/trial registry number: not stated

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

#### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
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<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Comment: no information of postrandomisation dropouts; authors stated that an intention to treat analysis was used.</td>
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<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Comment: no prepublished protocol available</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Comment: no other bias noted</td>
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### Andreani 1990

#### Study characteristics

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<th>Randomised clinical trial</th>
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<tbody>
<tr>
<td>Participants</td>
<td>Country: France</td>
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<tr>
<td></td>
<td>Period of recruitment: 1985–1988</td>
</tr>
<tr>
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<td>Number randomised: 85</td>
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<td>Postrandomisation dropouts: 0 (0.0%)</td>
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<td></td>
<td>Revised sample size: 85</td>
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<tr>
<td></td>
<td>Mean age (years): 56</td>
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<tr>
<td></td>
<td>Females: 32 (37.6%)</td>
</tr>
<tr>
<td></td>
<td>Small varices: 72 (84.7%)</td>
</tr>
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<td></td>
<td>High risk of bleeding: not stated</td>
</tr>
<tr>
<td></td>
<td>Other features of decompensation: 5 (5.9%)</td>
</tr>
</tbody>
</table>
Alcohol-related cirrhosis: 67 (78.8%)
Viral-related cirrhosis: not stated
Autoimmune disease-related cirrhosis: not stated
Other causes of cirrhosis: not stated
Other exclusion criteria: existence of hepatocellular carcinoma; contraindication to use of propranolol; serious associated illness reducing life expectancy to < 1 year; previous treatment with endoscopic sclerotherapy, propranolol, or surgery for portal hypertension

Interventions
Group 1: sclerotherapy (n = 42)
Further details: sclerosant, 1% or 2% polidocanol 15–40 mL repeated every 1 or 2 weeks until complete disappearance
Group 2: beta-blockers (n = 43)
Further details: propranolol doses titrated to achieve a 25% reduction in resting heart rate
Group 3: vitamin K. Excluded as vitamin K was not an intervention of interest – although the authors used this as placebo, vitamin K may have procoagulant properties

Outcomes
Mortality at maximal follow-up, serious adverse events (number of participants), liver transplantation at maximal follow-up, variceal bleed at maximal follow-up (any) (number of participants)
Follow-up (months): 24

Notes
Source of funding (quote): "the study was funded by INSERM (Institut National de la Santé et de la Recherche Médicale) (author reply)."
Trial name/trial registry number: not stated
Attempted to contact the authors in February 2020; received no additional information

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Quote: &quot;the allocation was in sealed envelopes&quot; (author reply).</td>
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<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Quote: &quot;the allocation was in sealed envelopes&quot; (author reply). Comment: further details were not available.</td>
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<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>Quote: &quot;these treatments were not administered blindly.&quot;</td>
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<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>High risk</td>
<td>Quote: &quot;these treatments were not administered blindly.&quot;</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Comment: no postrandomisation dropouts</td>
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</table>
### Andreani 1990 (Continued)

<table>
<thead>
<tr>
<th>Selective reporting (reporting bias)</th>
<th>Low risk</th>
<th>Comment: no prepublished protocol available, but authors reported mortality, adverse events, and variceal bleed adequately.</th>
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</thead>
<tbody>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Comment: no other bias noted</td>
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### Angelico 1993

#### Study characteristics

<table>
<thead>
<tr>
<th>Methods</th>
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<td>Participants</td>
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<td>Country: Italy</td>
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<td>Period of recruitment: 1988–1990</td>
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<td>Number randomised: 118</td>
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<td>Postrandomisation dropouts: 0 (0.0%)</td>
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<td>Revised sample size: 118</td>
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<td>Mean age (years): 58</td>
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<td>Females: 47 (39.8%)</td>
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<td>Small varices: 83 (70.3%)</td>
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<td>High risk of bleeding: not stated</td>
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<tr>
<td>Other features of decompensation: 51 (43.2%)</td>
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<tr>
<td>Alcohol-related cirrhosis: 32 (27.1%)</td>
<td></td>
</tr>
<tr>
<td>Viral-related cirrhosis: not stated</td>
<td></td>
</tr>
<tr>
<td>Autoimmune disease-related cirrhosis: not stated</td>
<td></td>
</tr>
<tr>
<td>Other causes of cirrhosis: not stated</td>
<td></td>
</tr>
<tr>
<td>Other inclusion/exclusion criteria: no history of previous bleeding, and a risk of bleeding more than 11% at 1 year and 16% at 2 years according to the North Italian Endoscopic Club (NIEC) predictive scoring system</td>
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<tr>
<td>Interventions</td>
<td></td>
</tr>
<tr>
<td>Group 1: nitrates (n = 57)</td>
<td></td>
</tr>
<tr>
<td>Further details: isosorbide-5-mononitrate 3 times daily up to a maximum tolerated dose</td>
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<tr>
<td>Group 2: beta-blockers (n = 61)</td>
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<tr>
<td>Further details: propranolol up to a maximum tolerated dose (median 60 mg/day)</td>
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<tr>
<td>Outcomes</td>
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<tr>
<td>Mortality at maximal follow-up, variceal bleed at maximal follow-up (symptomatic recovery) (number of participants)</td>
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<td>Follow-up (months): 44</td>
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<td>Notes</td>
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<td>Source of funding: not stated</td>
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<td>Trial name/trial registry number: not stated</td>
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### Angelico 1993 (Continued)

#### Risk of bias

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

#### Bhardwaj 2017

#### Study characteristics

<table>
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<tr>
<th>Methods</th>
<th>Randomised clinical trial</th>
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<tr>
<td>Participants</td>
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<td>Period of recruitment: 2010–2012</td>
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<td>Number randomised: 140</td>
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<td>Postrandomisation dropouts: not stated</td>
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<td>Revised sample size: 140</td>
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<tr>
<td></td>
<td>Mean age (years): 49</td>
</tr>
<tr>
<td></td>
<td>Females: 21 (15.0%)</td>
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<tr>
<td></td>
<td>Small varices: 140 (100.0%)</td>
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<td></td>
<td>High risk of bleeding: not stated</td>
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<tr>
<td></td>
<td>Other features of decompensation: 17 (12.1%)</td>
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<tr>
<td></td>
<td>Alcohol-related cirrhosis: 33 (23.6%)</td>
</tr>
<tr>
<td></td>
<td>Viral-related cirrhosis: 35 (25.0%)</td>
</tr>
</tbody>
</table>
### Interventions

**Group 1:** no active intervention (n = 70)  
Further details: for 2 years

**Group 2:** beta-blockers (n = 70)  
Further details: carvedilol 3.125–12.5 mg twice daily to ensure systolic blood pressure < 100 mmHg and heart rate < 55 bpm

### Outcomes

Mortality at maximal follow-up  
Follow-up (months): 21

### Notes

Source of funding: not stated  
Trial name/trial registry number: NCT01196507  
Attempted to contact authors in February 2020; received no additional information

### Risk of bias

<table>
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<th>Support for judgement</th>
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</table>
| Random sequence generation (selection bias) | Low risk           | Quote: "An independent statistician generated allocation sequence."  
Comment: although the details on sequence generation were not reported, as an independent statistician generated allocation sequence, the sequence was probably random (and not based on hospital numbers, date of birth, alternation, or other quasi-random methods of sequence generation). |
| Allocation concealment (selection bias)   | Unclear risk       | Comment: information not available                                                    |
| Blinding of participants and personnel (performance bias) All outcomes | High risk          | Quote: "We decided, in agreement with the ethics committee, to use a single-blind design, also because it was considered unrealistic that blindness could be kept with a drug with an evident effect on heart rate."  
Comment: only the participant was blinded. |
| Blinding of outcome assessment (detection bias) All outcomes | High risk          | Quote: "We decided, in agreement with the ethics committee, to use a single-blind design, also because it was considered unrealistic that blindness could be kept with a drug with an evident effect on heart rate." |
| Incomplete outcome data (attrition bias) All outcomes | High risk          | Comment: although the participant flow was reported, an earlier abstract published 4 years previously had greater number of participants. |
| Selective reporting (reporting bias)      | High risk          | Comment: a prepublished protocol available prior to the start of the study showed that the authors had changed the timing of the primary outcome, removed important clinical outcomes as secondary endpoints, and replaced them with surrogate endpoints. |
Comment: although the full text and abstract were linked to the same trial registry number and the period of recruitment was the same, and the abstract was published 4 years prior to the full text, the abstract mentioned randomising 175 participants (subsequent abstracts also refer to 175 participants), but the consort flow diagram showed only 140 participants without any reference about including or excluding the remaining 35 participants and an intention to treat analysis included only 140 participants.
Follow-up (months): 12

Source of funding: not stated

Trial name/trial registry number: NCT01893541

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

Individual participants had multiple cirrhosis aetiologies

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
</table>
| Random sequence generation (selection bias) | Low risk           | Quote: "Randomization was performed by an independent physician by sequentially opening numbered opaque and sealed envelopes containing group allocation cards in a random sequence."
 |
| Allocation concealment (selection bias)   | Low risk           | Quote: "Randomization was performed by an independent physician by sequentially opening numbered opaque and sealed envelopes containing group allocation cards in a random sequence."
 |
| Blinding of participants and personnel (performance bias) | High risk          | Quote: "The endoscopic diagnosis of oesophageal varices eradication or recurrence was always defined on the basis of the analysis of one physician who was blinded to patients' group assignments (only this physician was blinded)."
 |
| Blinding of outcome assessment (detection bias) | High risk          | Quote: "The endoscopic diagnosis of oesophageal varices eradication or recurrence was always defined on the basis of the analysis of one physician who was blinded to patients' group assignments (only this physician was blinded)."
 |
| Incomplete outcome data (attrition bias)   | Low risk           | Comment: no postrandomisation dropouts                                                |
| Selective reporting (reporting bias)       | Low risk           | Comment: a prepublished protocol was not available, but the authors reported mortality, adverse events, and variceal bleed adequately. |
| Other bias                                 | Low risk           | Comment: no other bias noted                                                            |

**Study characteristics**

Methods: Randomised clinical trial

Participants: Country: Italy

Period of recruitment: 1994–1998
<table>
<thead>
<tr>
<th>Number randomised: 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postrandomisation dropouts: 0 (0.0%)</td>
</tr>
<tr>
<td>Revised sample size: 52</td>
</tr>
<tr>
<td>Mean age (years): 60</td>
</tr>
<tr>
<td>Females: 15 (28.8%)</td>
</tr>
<tr>
<td>Small varices: not stated</td>
</tr>
<tr>
<td>High risk of bleeding: not stated</td>
</tr>
<tr>
<td>Other features of decompensation: 52 (100.0%)</td>
</tr>
<tr>
<td>Alcohol-related cirrhosis: 23 (44.2%)</td>
</tr>
<tr>
<td>Viral-related cirrhosis: 37 (71.2%)</td>
</tr>
<tr>
<td>Autoimmune disease-related cirrhosis: not stated</td>
</tr>
<tr>
<td>Other causes of cirrhosis: 2 (3.8%)</td>
</tr>
<tr>
<td>Other exclusion criteria: use of vasoactive drugs or other prophylactic treatments; hepatocellular carcinoma; renal failure; portal vein thrombosis; active alcohol drinking; refractory ascites defined according to the criteria of the International Ascites Club</td>
</tr>
</tbody>
</table>

**Interventions**

<table>
<thead>
<tr>
<th>Group 1: nitrates (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Further details: isosorbide mononitrate 20 mg, increased to 40 mg twice daily</td>
</tr>
<tr>
<td>Group 2: beta-blockers (n = 25)</td>
</tr>
<tr>
<td>Further details: nadolol 40 mg increased until the resting heart rate fell by 25% or below 55 bpm</td>
</tr>
</tbody>
</table>

**Outcomes**

| Mortality at maximal follow-up, variceal bleed at maximal follow-up (any) (number of participants) |
| Follow-up (months): 18 |

**Notes**

Source of funding (quote): "A. Maggi and A. Panzeri received fellowship grants from the ‘Istituto di Ricovero e Cura a Carattere Scientifico’ (IRCCS) Ospedale Maggiore di Milano. This work was supported in part by a grant of the Ministero della Università Italiano."

Trial name/trial registry number: not stated

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

Individual participants had multiple cirrhosis aetiologies

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
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</table>
### Borroni 2002 (Continued)

<table>
<thead>
<tr>
<th>Study characteristics</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised clinical trial</td>
</tr>
<tr>
<td>Participants</td>
<td>Country: France</td>
</tr>
<tr>
<td></td>
<td>Period of recruitment: not stated</td>
</tr>
<tr>
<td></td>
<td>Number randomised: 24</td>
</tr>
<tr>
<td></td>
<td>Postrandomisation dropouts: not stated</td>
</tr>
<tr>
<td></td>
<td>Revised sample size: 24</td>
</tr>
<tr>
<td></td>
<td>Mean age (years): not stated</td>
</tr>
<tr>
<td></td>
<td>Females: not stated</td>
</tr>
<tr>
<td></td>
<td>Small varices: not stated</td>
</tr>
<tr>
<td></td>
<td>High risk of bleeding: not stated</td>
</tr>
<tr>
<td></td>
<td>Other features of decompenation: not stated</td>
</tr>
<tr>
<td></td>
<td>Alcohol-related cirrhosis: 24 (100.0%)</td>
</tr>
<tr>
<td></td>
<td>Viral-related cirrhosis: 0 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>Autoimmune disease-related cirrhosis: 0 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>Other causes of cirrhosis: 0 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>Other inclusion criteria: people with alcoholic cirrhosis and large oesophageal varices</td>
</tr>
<tr>
<td></td>
<td>Other exclusion criteria: previous haemorrhage of gastrointestinal tract or hepatic encephalopathy</td>
</tr>
<tr>
<td>Interventions</td>
<td>Group 1: no active intervention (n = 8)</td>
</tr>
<tr>
<td></td>
<td>Further details: placebo</td>
</tr>
<tr>
<td></td>
<td>Group 2: beta-blockers (n = 16)</td>
</tr>
<tr>
<td></td>
<td>Further details: propranolol 160 mg daily (conventional or long-acting) – no further details</td>
</tr>
</tbody>
</table>
**Cales 1989a** (Continued)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No outcomes of interest reported</th>
</tr>
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</table>

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

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
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<th>Support for judgement</th>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Comment: no prepublished protocol available</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Comment: no other bias noted</td>
</tr>
</tbody>
</table>

### Study characteristics

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised clinical trial</th>
</tr>
</thead>
</table>
| Participants | Country: France  
|       | Period of recruitment: not stated  
|       | Number randomised: 16  
|       | Postrandomisation dropouts: not stated  
|       | Revised sample size: 16  
|       | Mean age (years): 50  
|       | Females: not stated  
|       | Small varices: not stated |
### Cales 1989b (Continued)

- High risk of bleeding: not stated
- Other features of decompensation: 6 (37.5%)
- Alcohol-related cirrhosis: 16 (100.0%)
- Viral-related cirrhosis: 0 (0.0%)
- Autoimmune disease-related cirrhosis: 0 (0.0%)
- Other causes of cirrhosis: 0 (0.0%)
- Other exclusion criteria: contraindication to beta-blockers; treatment with any cardiovascular drug in the 15 days before entry into the study; concomitant drugs apart from vitamins

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Group 1: no active intervention (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Further details: placebo</td>
</tr>
<tr>
<td></td>
<td>Group 2: beta-blockers (n = 8)</td>
</tr>
<tr>
<td></td>
<td>Further details: propranolol 160 mg daily (no further details)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No outcomes of interest reported</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
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<td></td>
<td>Attempted to contact the authors in February 2020; received no additional information</td>
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### Risk of bias

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<thead>
<tr>
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<th>Support for judgement</th>
</tr>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
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<td>Comment: information not available</td>
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<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
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<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Comment: no prepublished protocol available</td>
</tr>
<tr>
<td>Other bias</td>
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<td>Comment: no other bias noted</td>
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</table>
### Study characteristics

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

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
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</table>
### Chen 2000 (Continued)

<table>
<thead>
<tr>
<th>Bias Type</th>
<th>Risk Level</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Comment: no prepublished protocol available</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Comment: no other bias noted</td>
</tr>
</tbody>
</table>

### Conn 1969

**Study characteristics**

**Methods**
- Randomised clinical trial

**Participants**
- Country: USA
- Period of recruitment: 1965–1968
- Number randomised: 29
- Post-randomisation dropouts: 0 (0.0%)
- Revised sample size: 29
- Mean age (years): 47
- Females: not stated
- Small varices: not stated
- High risk of bleeding: not stated
- Other features of decompensation: 29 (100.0%)
- Alcohol-related cirrhosis: 29 (100.0%)
- Viral-related cirrhosis: 0 (0.0%)
- Autoimmune disease-related cirrhosis: 0 (0.0%)
- Other causes of cirrhosis: 0 (0.0%)
- Other exclusion criteria: aged > 65 years

**Interventions**
- Group 1: portocaval shunt (n = 13)
- Further details: portocaval shunt
- Group 2: no active intervention (n = 16)
### Conn 1969 (Continued)

Further details: no treatment

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Mortality at maximal follow-up, other features of decompensation at maximal follow-up, variceal bleed at maximal follow-up (any) (number of rebleeds)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Follow-up (months): 19.1</td>
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</tbody>
</table>

**Notes**

Source of funding: not stated

Trial name/trial registry number: not stated

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

### Risk of bias

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

### Conn 1991

#### Study characteristics

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised clinical trial</th>
</tr>
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<tbody>
<tr>
<td>Participants</td>
<td>Country: multicentre; Spain, USA</td>
</tr>
<tr>
<td></td>
<td>Period of recruitment: 1982–1986</td>
</tr>
<tr>
<td></td>
<td>Number randomised: 102</td>
</tr>
<tr>
<td></td>
<td>Postrandomisation dropouts: 0 (0.0%)</td>
</tr>
</tbody>
</table>
Revised sample size: 102
Mean age (years): 54
Females: 29 (28.4%)
Small varices: 55 (53.9%)
High risk of bleeding: not stated
Other features of decompensation: 11 (10.8%)
Alcohol-related cirrhosis: 80 (78.4%)
Viral-related cirrhosis: not stated
Autoimmune disease-related cirrhosis: not stated
Other causes of cirrhosis: not stated
Other inclusion criteria: well-established clinical diagnosis of cirrhosis, oesophageal varices on endoscopy and portal hypertension
Other exclusion criteria: previous gastrointestinal bleed

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Group 1: no active intervention (n = 51)</th>
<th>Further details: placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 2: beta-blockers (n = 51)</td>
<td>Further details: propranolol: dosage based on titration median dosage 80 mg; duration not stated clearly, but ≥ 6 months</td>
</tr>
</tbody>
</table>

| Outcomes | Mortality at maximal follow-up, variceal bleed at maximal follow-up (any) (number of participants) | Follow-up (months): 17 |

| Notes | Source of funding (quote): "Supported by Ayerst Laboratories, New York, New York; Imperial Chemical industries, Spain; and the Veterans Administration Merit Review Program" |
|       | Trial name/trial registry number: CT 06510-8056 |
|       | Attempted to contact the authors in February 2020; received no additional information |

<table>
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<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;the patients were randomly selected using a sealed envelope technique and computer-generated randomization to receive either placebo or propranolol therapy.&quot;</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;the patients were randomly selected using a sealed envelope technique and computer-generated randomization to receive either placebo or propranolol therapy.&quot;</td>
</tr>
<tr>
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<td>Low risk</td>
<td>Quote: &quot;The placebo and the propranolol tablets were identical in appearance. To maintain the double-blind nature of the investigation, the patients were examined on each visit by a nurse and the postdoctoral fellow assigned to the study.&quot;</td>
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</tbody>
</table>
### Conn 1991 (Continued)

<table>
<thead>
<tr>
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<th>Low risk</th>
<th>Quote: &quot;The placebo and the propranolol tablets were identical in appearance. To maintain the double-blind nature of the investigation, the patients were examined on each visit by a nurse and the postdoctoral fellow assigned to the study.&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Comment: no postrandomisation dropouts</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Comment: no prepublished protocol available</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Comment: no other bias noted</td>
</tr>
</tbody>
</table>

### D’Amico 2002

**Study characteristics**

<table>
<thead>
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<th>Randomised clinical trial</th>
</tr>
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<td>Participants</td>
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</tr>
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<td></td>
<td>Period of recruitment: 1992–1996</td>
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<tr>
<td></td>
<td>Number randomised: 57</td>
</tr>
<tr>
<td></td>
<td>Postrandomisation dropouts: 0 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>Revised sample size: 57</td>
</tr>
<tr>
<td></td>
<td>Mean age (years): 56</td>
</tr>
<tr>
<td></td>
<td>Females: 27 (47.4%)</td>
</tr>
<tr>
<td></td>
<td>Small varices: 0 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>High risk of bleeding: 57 (100.0%)</td>
</tr>
<tr>
<td></td>
<td>Other features of decompensation: 9 (15.8%)</td>
</tr>
<tr>
<td></td>
<td>Alcohol-related cirrhosis: not stated</td>
</tr>
<tr>
<td></td>
<td>Viral-related cirrhosis: 49 (86.0%)</td>
</tr>
<tr>
<td></td>
<td>Autoimmune disease-related cirrhosis: not stated</td>
</tr>
<tr>
<td></td>
<td>Other causes of cirrhosis: not stated</td>
</tr>
<tr>
<td></td>
<td>Other exclusion criteria: large varices known for &gt; 1 year; hepatocellular carcinoma; serum creatinine &gt; 2 mg/dL; aged &gt; 75 years; features of decompensation such as hepatic encephalopathy; contraindications to beta-blockers</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Group 1: beta-blockers + nitrates (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Further details: nadolol 20 mg daily increased by 20 mg until maximum tolerated dose (heart rate &gt; 55 bpm) was reached + isosorbide mononitrate 10 mg twice daily increased to 40 mg twice daily until maximum tolerated dose (systolic blood pressure &gt; 90 mmHg) was reached</td>
</tr>
<tr>
<td></td>
<td>Group 2: beta-blockers (n = 27)</td>
</tr>
</tbody>
</table>
Further details: nadolol 20 mg daily increased by 20 mg until maximum tolerated dose (heart rate > 55 bpm) was reached + placebo

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Mortality at maximal follow-up, any adverse events (number of participants), variceal bleed at maximal follow-up (any) (number of participants), other features of decompensation at maximal follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up (months):</td>
<td>31</td>
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<table>
<thead>
<tr>
<th>Notes</th>
<th>Source of funding (quote): &quot;The trial drug and placebo were kindly provided by Chiesi Farmaceutici, Florence, Italy&quot;</th>
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**Risk of bias**

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

**Methods**
- Randomised clinical trial

**Participants**
- **Country:** India
- **Period of recruitment:** 1994–1996
- **Number randomised:** 30
- **Postrandomisation dropouts:** 0 (0.0%)
- **Revised sample size:** 30
- **Mean age (years):** 40
- **Females:** 8 (26.7%)
- **Small varices:** 0 (0.0%)
- **High risk of bleeding:** not stated
- **Other features of decompensation:** 4 (13.3%)
- **Alcohol-related cirrhosis:** 5 (16.7%)
- **Viral-related cirrhosis:** not stated
- **Autoimmune disease-related cirrhosis:** not stated
- **Other causes of cirrhosis:** not stated
- **Other inclusion criteria:** hepatic venous pressure gradient ≥ 12 mmHg

**Interventions**
- **Group 1:** variceal band ligation (n = 15)
  - Further details: variceal band ligation: weekly to fortnightly until variceal eradication
- **Group 2:** beta-blockers (n = 15)
  - Further details: propranolol to decrease heart rate by 25%

**Outcomes**
- **Variceal bleed at maximal follow-up (any) (number of participants), other features of decompensation at maximal follow-up**
- **Follow-up (months):** 17.6

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

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
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</table>
**De 1999 (Continued)**

<table>
<thead>
<tr>
<th>Blinding of participants and personnel (performance bias)</th>
<th>Unclear risk</th>
<th>Comment: information not available</th>
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</thead>
<tbody>
<tr>
<td>All outcomes</td>
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</tr>
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</table>

<table>
<thead>
<tr>
<th>Blinding of outcome assessment (detection bias)</th>
<th>Unclear risk</th>
<th>Comment: information not available</th>
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<tbody>
<tr>
<td>All outcomes</td>
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</table>

<table>
<thead>
<tr>
<th>Incomplete outcome data (attrition bias)</th>
<th>Low risk</th>
<th>Comment: no postrandomisation dropouts</th>
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<tbody>
<tr>
<td>All outcomes</td>
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<table>
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<tr>
<th>Selective reporting (reporting bias)</th>
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<tbody>
<tr>
<td>All outcomes</td>
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</table>

<table>
<thead>
<tr>
<th>Other bias</th>
<th>Low risk</th>
<th>Comment: no other bias noted</th>
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<tbody>
<tr>
<td>All outcomes</td>
<td></td>
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</tr>
</tbody>
</table>

**De Franchis 1991**

**Study characteristics**

**Methods**
- Randomised clinical trial

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

**Interventions**
- Group 1: sclerotherapy (n = 55)
Further details: sclerotherapy: ethanolamine oleate 5% or 1% polidocanol, repeated at 7 days, 30 days, and then monthly under eradication

Group 2: no active intervention (n = 51)

Further details: no treatment

Outcomes
Mortality at maximal follow-up, variceal bleed at maximal follow-up (any) (number of participants)
Follow-up (months): 24

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

Risk of bias

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

Deplano 2001

Study characteristics

Methods
Randomised clinical trial

Participants
Country: Italy
Period of recruitment: not stated
Deplano 2001 (Continued)

Number randomised: 36
Postrandomisation dropouts: not stated
Revised sample size: 36
Mean age (years): not stated
Females: not stated
Small varices: not stated
High risk of bleeding: not stated
Other features of decompenation: not stated
Alcohol-related cirrhosis: not stated
Viral-related cirrhosis: not stated
Autoimmune disease-related cirrhosis: not stated
Other causes of cirrhosis: not stated
Other exclusion criteria: no previous bleeding

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<tbody>
<tr>
<td>Group 1: beta-blockers + nitrates (n = 14)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
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<tr>
<td>Further details: nadolol + isosorbide mononitrates (no further details)</td>
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<td></td>
</tr>
<tr>
<td>Group 2: beta-blockers (n = 22)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Further details: nadolol (no further details)</td>
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<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>None of the outcomes of interest were reported.</td>
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<tr>
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<td>Unclear risk</td>
<td>Comment: information not available</td>
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<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
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<tr>
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<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
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Deplano 2001
All outcomes

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<th>Selective reporting (reporting bias)</th>
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</thead>
<tbody>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Comment: no other bias noted</td>
</tr>
</tbody>
</table>

Dрастич 2011

Study characteristics

Methods
Randomised clinical trial

Participants
Country: Czech Republic
Period of recruitment: not stated
Number randomised: 73
Post-randomisation dropouts: 0 (0.0%)
Revised sample size: 73
Mean age (years): 57
Females: 22 (30.1%)
Small varices: not stated
High risk of bleeding: 28 (38.4%)
Other features of decompensation: 20 (27.4%)
Alcohol-related cirrhosis: 46 (63.0%)
Viral-related cirrhosis: 9 (12.3%)
Autoimmune disease-related cirrhosis: 2 (2.7%)
Other causes of cirrhosis: 16 (21.9%)
Other exclusion criteria: congestive heart failure, renal failure, malignancy, history of sclerotherapy, endoscopic variceal band ligation or portosystemic shunt, gastric or duodenal ulcer

Interventions
Group 1: variceal band ligation (n = 40)
Further details: variceal band ligation: 6 Shooter, Wilson-Cook; 2-weekly intervals until eradication of varices
Group 2: beta-blockers (n = 33)
Further details: propranolol started at 20 mg twice daily and increased to reduce heart rate by 25%, but not < 55 bpm

Outcomes
Mortality at maximal follow-up, serious adverse events (number of participants), any adverse events (number of participants), liver transplantation at maximal follow-up, variceal bleed at maximal follow-up (any) (number of participants)
Follow-up (months): 11
**Dрастич 2011 (Continued)**

**Notes**
Source of funding (quote): "Study was funded by Grant Agency of Ministry of Health of the Czech Republic" (author reply)

Trial name/trial registry number: not stated

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

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### Risk of bias

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<tr>
<th>Bias</th>
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<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;computer-generated table of random numbers.&quot;</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;randomization was centralized&quot; (author reply).</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performace bias) All outcomes</td>
<td>High risk</td>
<td>Quote: &quot;Study was not blinded&quot; (author reply).</td>
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<td>High risk</td>
<td>Quote: &quot;Study was not blinded&quot; (author reply).</td>
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<tr>
<td>Incomplete outcome data (attrition bias)</td>
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<td>Comment: no postrandomisation dropouts</td>
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<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Comment: a prepublished protocol was not available, but the authors reported mortality, adverse events, and variceal bleed adequately.</td>
</tr>
<tr>
<td>Other bias</td>
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<td>Comment: no other bias noted</td>
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**Duhamel 1994**

**Study characteristics**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Country: France</td>
</tr>
<tr>
<td></td>
<td>Period of recruitment: 1985–1988</td>
</tr>
<tr>
<td></td>
<td>Number randomised: 117</td>
</tr>
<tr>
<td></td>
<td>Postrandomisation dropouts: 0 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>Revised sample size: 117</td>
</tr>
<tr>
<td></td>
<td>Mean age (years): 56</td>
</tr>
<tr>
<td></td>
<td>Females: 29 (24.8%)</td>
</tr>
<tr>
<td></td>
<td>Small varices: 103 (88.0%)</td>
</tr>
<tr>
<td></td>
<td>High risk of bleeding: 32 (27.4%)</td>
</tr>
</tbody>
</table>
### Duhamel 1994 (Continued)

<table>
<thead>
<tr>
<th>Other features of decompensation: 75 (64.1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol-related cirrhosis: 94 (80.3%)</td>
</tr>
<tr>
<td>Viral-related cirrhosis: 8 (6.8%)</td>
</tr>
<tr>
<td>Autoimmune disease-related cirrhosis: 4 (3.4%)</td>
</tr>
<tr>
<td>Other causes of cirrhosis: 10 (8.5%)</td>
</tr>
</tbody>
</table>

Other exclusion criteria: aged > 80 years, hepatocellular carcinoma, heart failure, respiratory failure, previous variceal haemorrhage, previous gastrointestinal bleed of unknown cause, use of beta-blockers

### Interventions

<table>
<thead>
<tr>
<th>Group 1: sclerotherapy (n = 57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Further details: sclerotherapy: up to 30 mL of 1% polidocanol repeated every 3 weeks until obliteration of varices</td>
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<table>
<thead>
<tr>
<th>Group 2: no active intervention (n = 60)</th>
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<tbody>
<tr>
<td>Further details: no treatment</td>
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### Outcomes

<table>
<thead>
<tr>
<th>Mortality at maximal follow-up, variceal bleed at maximal follow-up (any) (number of participants)</th>
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<tbody>
<tr>
<td>Follow-up (months): 30</td>
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### Notes

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

### Risk of bias

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<tr>
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</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Quote: “Each centre was in possession of numbered sealed envelopes.” Comment: further details were not available.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Quote: “Each centre was in possession of numbered sealed envelopes.” Comment: further details were not available.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Comment: although the study authors excluded 1 participant, the outcome for this person was reported; therefore, we included them in the analysis.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Comment: no prepublished protocol available</td>
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### Duhamel 1994

<table>
<thead>
<tr>
<th>Other bias</th>
<th>Low risk</th>
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### Fassio 1993

#### Study characteristics

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
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<tr>
<td>Country: Argentina</td>
<td></td>
</tr>
<tr>
<td>Number randomised: 42</td>
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<tr>
<td>Postrandomisation dropouts: not stated</td>
<td></td>
</tr>
<tr>
<td>Revised sample size: 42</td>
<td></td>
</tr>
<tr>
<td>Mean age (years): 53</td>
<td></td>
</tr>
<tr>
<td>Females: 8 (19.0%)</td>
<td></td>
</tr>
<tr>
<td>Small varices: not stated</td>
<td></td>
</tr>
<tr>
<td>High risk of bleeding: 42 (100.0%)</td>
<td></td>
</tr>
<tr>
<td>Other features of decompensation: 24 (57.1%)</td>
<td></td>
</tr>
<tr>
<td>Alcohol-related cirrhosis: 35 (83.3%)</td>
<td></td>
</tr>
<tr>
<td>Viral-related cirrhosis: not stated</td>
<td></td>
</tr>
<tr>
<td>Autoimmune disease-related cirrhosis: not stated</td>
<td></td>
</tr>
<tr>
<td>Other causes of cirrhosis: not stated</td>
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</tr>
<tr>
<td>Other exclusion criteria: hepatocellular carcinoma, renal failure, cardiac failure, treatments that could change survival (steroids for autoimmune hepatitis, interferon for hepatitis B virus/hepatitis C virus) or other disease limiting survival</td>
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</tr>
<tr>
<td>Interventions</td>
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<tr>
<td>Group 1: nitrates (n = 23)</td>
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<tr>
<td>Further details: isosorbide mononitrate 20 mg twice daily (duration not stated, probably until the follow-up)</td>
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<tr>
<td>Group 2: no active intervention (n = 19)</td>
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<tr>
<td>Further details: placebo</td>
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<td>Outcomes</td>
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<td>Notes</td>
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### Risk of bias
### Fassio 1993 (Continued)

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<th>Support for judgement</th>
</tr>
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<td>Low risk</td>
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<td>Allocation concealment (selection bias)</td>
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<td>Comment: information not available</td>
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<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>High risk</td>
<td>Quote: &quot;The patients were not aware of the treatment received. In contrast, the treating doctors were not blind with respect to which patients received drugs or placebo.&quot;</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Comment: no prepublished protocol available</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Comment: no other bias noted</td>
</tr>
</tbody>
</table>

### Feng 2012

#### Study characteristics

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td></td>
</tr>
<tr>
<td>Country: China</td>
<td></td>
</tr>
<tr>
<td>Number randomised: 168</td>
<td></td>
</tr>
<tr>
<td>Postrandomisation dropouts: not stated</td>
<td></td>
</tr>
<tr>
<td>Revised sample size: 168</td>
<td></td>
</tr>
<tr>
<td>Mean age (years): 54</td>
<td></td>
</tr>
<tr>
<td>Females: 63 (37.5%)</td>
<td></td>
</tr>
<tr>
<td>Small varices: not stated</td>
<td></td>
</tr>
<tr>
<td>High risk of bleeding: not stated</td>
<td></td>
</tr>
<tr>
<td>Other features of decompensation: 39 (23.2%)</td>
<td></td>
</tr>
<tr>
<td>Alcohol-related cirrhosis: 14 (8.3%)</td>
<td></td>
</tr>
<tr>
<td>Viral-related cirrhosis: 140 (83.3%)</td>
<td></td>
</tr>
<tr>
<td>Autoimmune disease-related cirrhosis: not stated</td>
<td></td>
</tr>
<tr>
<td>Other causes of cirrhosis: 14 (8.3%)</td>
<td></td>
</tr>
</tbody>
</table>
### Feng 2012 (Continued)

Other exclusion criteria: aged > 75 years or < 18 years; with malignant tumours, uraemia, or other serious life-threatening diseases; complicated with refractory ascites, hepatic encephalopathy, and severe jaundice; previously treated with shunt or endoscopic treatment

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Group 1: variceal band ligation (n = 84)</th>
<th>Further details: variceal band ligation (no further details) repeated every 2 weeks until eradication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 2: beta-blockers (n = 84)</td>
<td>Further details: propranolol 30–160 mg/day to maintain heart rate just above 25% from baseline, 60 bpm and systolic blood pressure at 90 mmHg; duration not reported, probably until follow-up</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Mortality at maximal follow-up, any adverse events (number of participants), variceal bleed at maximal follow-up (symptomatic recovery) (number of participants)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Follow-up (months): 23.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Notes</th>
<th>Source of funding: not stated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trial name/trial registry number: not stated</td>
</tr>
<tr>
<td></td>
<td>Attempted to contact the authors in February 2020; received no additional information</td>
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### Risk of bias

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

### Fleig 1988

**Study characteristics**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised clinical trial</th>
</tr>
</thead>
</table>
Fleig 1988 (Continued)

**Participants**
- Country: Germany
- Period of recruitment: not stated
- Number randomised: 49
- Postrandomisation dropouts: 9 (18.4%)
- Revised sample size: 40
- Reasons for postrandomisation dropouts: protocol violations
- Mean age (years): not stated
- Females: not stated
- Small varices: 0 (0.0%)
- High risk of bleeding: not stated
- Other features of decompensation: not stated
- Alcohol-related cirrhosis: not stated
- Viral-related cirrhosis: not stated
- Autoimmune disease-related cirrhosis: not stated
- Other causes of cirrhosis: not stated
- Other inclusion/exclusion criteria: not stated

**Interventions**
- Group 1: sclerotherapy (n = 16)
  - Further details: sclerotherapy: 1% polidocanol until the varices were eradicated or covered by fibrous tissue
- Group 2: no active intervention (n = 24)
  - Further details: no active treatment until bleeding

**Outcomes**
- Mortality at maximal follow-up
- Follow-up (months): 28.8

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

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
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<th>Support for judgement</th>
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<tbody>
<tr>
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<td>Unclear risk</td>
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<tr>
<td>Allocation concealment (selection bias)</td>
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<td>Blinding of participants and personnel (performance bias)</td>
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### Fleig 1988 (Continued)

**All outcomes**

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

### Ideo 1988

#### Study characteristics

**Methods**

- Randomised clinical trial

**Participants**

- Country: Italy
- Period of recruitment: 1982–1986
- Number randomised: 57
- Postrandomisation dropouts: 0 (0.0%)
- Revised sample size: 57
- Mean age (years): 53
- Females: 15 (26.3%)
- Small varices: 0 (0.0%)
- High risk of bleeding: not stated
- Other features of decompensation: 4 (7.0%)
- Alcohol-related cirrhosis: 30 (52.6%)
- Viral-related cirrhosis: not stated
- Autoimmune disease-related cirrhosis: not stated
- Other causes of cirrhosis: not stated
- Other exclusion criteria: prior variceal bleed, not large varices, contraindication to beta-blockers, cardiopulmonary disease, erosive gastroduodenitis, peptic ulcer disease, hepatocellular carcinoma, other neoplasia, intractable ascites

**Interventions**

- Group 1: no active intervention (n = 27)
- Further details: placebo
- Group 2: beta-blockers (n = 30)
Further details: nadolol at doses that reduced resting heart rate by approximately 25%

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Mortality at maximal follow-up, variceal bleed at maximal follow-up (any) (number of rebleeds)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Follow-up (months): 22.8</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Notes</th>
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<td>Trial name/trial registry number: not stated</td>
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<td>Attempted to contact the authors in February 2020; received no additional information</td>
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### Risk of bias

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

### Jutabha 2005

#### Study characteristics

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Country: USA</td>
</tr>
<tr>
<td></td>
<td>Period of recruitment: 1996–2001</td>
</tr>
<tr>
<td></td>
<td>Number randomised: 62</td>
</tr>
<tr>
<td></td>
<td>Postrandomisation dropouts: 0 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>Revised sample size: 62</td>
</tr>
<tr>
<td></td>
<td>Mean age (years): 55</td>
</tr>
</tbody>
</table>
Females: 18 (29.0%)

Small varices: 4 (6.5%)

High risk of bleeding: 21 (33.9%)

Other features of decompensation: not stated

Alcohol-related cirrhosis: 7 (11.3%)

Viral-related cirrhosis: 47 (75.8%)

Autoimmune disease-related cirrhosis: 6 (9.7%)

Other causes of cirrhosis: 12 (19.4%)

Clinical exclusion criteria: people who were unco-operative, unable to give written informed consent, or could not return for routine follow-up; serious recurrent or outgoing comorbid illness (e.g. severe renal, cardiac, or respiratory failure; peritonitis; or sepsis); contraindication to beta-blockers (e.g. severe congestive heart failure, severe chronic obstructive pulmonary disease, severe asthma, or severe insulin-dependent diabetes mellitus)

Biochemical exclusion criteria: severe coagulopathy unresponsive to blood product transfusions (e.g. prothrombin time 3 seconds over control or international normalised ratio 1.6); severe thrombocytopenia, defined as a platelet count 40,000/μL; increased alpha-fetoprotein level; positive beta-human chorionic gonadotropin (women only)

Diagnostic imaging exclusion criteria: documented hepatoma (by scanning and increased alpha-fetoprotein, histology, or both); portal or hepatic vein thrombosis; large-volume or tense ascites that could not be controlled with diuretics and sodium restriction and required repeated therapeutic paracentesis

Endoscopic exclusion criteria: contraindication to therapeutic endoscopy; presence of moderate or large gastric or duodenal varices; severe erosive oesophagitis, oesophageal stricture requiring dilation, active duodenal or gastric ulceration, or upper gastrointestinal tumour; severe upper gastrointestinal angiomatous syndrome (watermelon stomach or upper gastrointestinal angiomas) or severe portal hypertensive gastropathy with spontaneous or contact bleeding, severe recurrent upper gastrointestinal bleeding, or severe anaemia with haemoccult-positive stools thought to be secondary to the upper gastrointestinal angiomatous syndrome or portal hypertensive gastropathy because of an otherwise negative gastrointestinal evaluation (including push enteroscopy, colonoscopy, and small-bowel x-ray) that excluded another source of gastrointestinal haemorrhage

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Group 1: variceal band ligation (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Further details: variceal band ligation using Saeed 6 Shooter, performed monthly until varices were eradicated</td>
</tr>
<tr>
<td></td>
<td>Group 2: beta-blockers (n = 31)</td>
</tr>
<tr>
<td></td>
<td>Further details: propranolol titrated to reducing resting pulse by ≥ 25%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Mortality at maximal follow-up, serious adverse events (number of participants), liver transplantation at maximal follow-up, variceal bleed at maximal follow-up (symptomatic recovery) (number of participants), treatment costs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Follow-up (months): 15</td>
</tr>
</tbody>
</table>

| Notes                  | Source of funding (quote): "The study and investigators were supported in part by the following grants: NIH Clinical Associate Physician Award (R.J.), American Society for Gastrointestinal Endoscopy Research Award (R.J.), NIH NIDDK IK24 DK 02650 Grant (D.M.J.), NIH NIDDK 41301 (CURE CORE grant), and NIH General Clinical Research Center-PHS Grant 5 MO1-RR00865825."
|                        | Trial name/trial registry number: not stated |
|                        | Attempted to contact the authors in February 2020; received no additional information |
Individual participants had multiple cirrhosis aetiologies

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;Treatment assignment was by opening a sealed opaque envelope that designated 1 of 2 treatments.&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;Treatment assignment was by opening a sealed opaque envelope that designated 1 of 2 treatments.&quot;</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>Quote: &quot;not blinded&quot; (author reply).</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>High risk</td>
<td>Quote: &quot;not blinded&quot; (author reply).</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Comment: no postrandomisation dropouts</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Comment: no prepublished protocol available</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Comment: no other bias noted</td>
</tr>
</tbody>
</table>

Kanazawa 1993

Study characteristics

Methods
Randomised clinical trial

Participants
Country: Japan
Period of recruitment: 1987–1992
Number randomised: 65
Postrandomisation dropouts: 4 (6.2%)
Revised sample size: 61
Reasons for postrandomisation dropouts: lost to follow-up
Mean age (years): 58
Females: 19 (31.1%)
Small varices: 36 (59.0%)
High risk of bleeding: 65 (100.0%)
### Kanazawa 1993 (Continued)

Other features of decompensation: 8 (13.1%)
- Alcohol-related cirrhosis: not stated
- Viral-related cirrhosis: 39 (63.9%)
- Autoimmune disease-related cirrhosis: not stated
- Other causes of cirrhosis: not stated

Other inclusion criteria: liver cirrhosis; no history of vomiting blood; not having been treated for oesophageal varices; no liver cancer; oesophageal varices of ≥ F2 RC sign positive, Beppu score < 1.14; hepatovenous pressure gradient ≥ 12 mmHg; Child-Pugh score ≤ 13; aged < 75 years

### Interventions

<table>
<thead>
<tr>
<th>Group 1: sclero therapy (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Further details: sclero therapy: ethanolamine oleate, repeated weekly to reduce it to F1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 2: beta-blockers (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Further details: propranolol started at 30 mg titrated to reduce the heart rate by 25%</td>
</tr>
</tbody>
</table>

### Outcomes

Mortality at maximal follow-up, any adverse events (number of events), variceal bleed at maximal follow-up (any) (number of participants)

Follow-up (months): 31

### Notes

Source of funding: not stated

Trial name/trial registry number: not stated

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

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: “subjects were divided into propranolol group or sclero therapy group by envelope method.”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: although details on sequence generation were not reported, the method of allocation concealment used makes it highly likely that the sequence was random.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: “subjects were divided into propranolol group or sclero therapy group by envelope method.”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: although details on allocation concealment were not reported (as sealed envelope technique or shuffled envelope technique), the authors are likely to have used a method that was likely to result in randomisation.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Comment: there were postrandomisation dropouts; unclear whether these were related to the intervention and outcomes. Our sensitivity analysis indi-</td>
</tr>
</tbody>
</table>
### Kanazawa 1993 (Continued)

<table>
<thead>
<tr>
<th>All outcomes</th>
<th>cated the results of the network meta-analysis were sensitive to postrandomisation dropouts.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### Khan 2017

#### Study characteristics

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<tr>
<th>Methods</th>
<th>Randomised clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Country: Pakistan</td>
</tr>
<tr>
<td>Period of recruitment: not stated</td>
<td></td>
</tr>
<tr>
<td>Number randomised: 250</td>
<td></td>
</tr>
<tr>
<td>Postrandomisation dropouts: not stated</td>
<td></td>
</tr>
<tr>
<td>Revised sample size: 250</td>
<td></td>
</tr>
<tr>
<td>Mean age (years): 53</td>
<td></td>
</tr>
<tr>
<td>Females: 103 (41.2%)</td>
<td></td>
</tr>
<tr>
<td>Small varices: not stated</td>
<td></td>
</tr>
<tr>
<td>High risk of bleeding: not stated</td>
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</tr>
<tr>
<td>Other features of decompensation: not stated</td>
<td></td>
</tr>
<tr>
<td>Alcohol-related cirrhosis: not stated</td>
<td></td>
</tr>
<tr>
<td>Viral-related cirrhosis: not stated</td>
<td></td>
</tr>
<tr>
<td>Autoimmune disease-related cirrhosis: not stated</td>
<td></td>
</tr>
<tr>
<td>Other causes of cirrhosis: not stated</td>
<td></td>
</tr>
<tr>
<td>Other exclusion criteria: previous variceal bleed, pregnancy or lactating, allergy to carvedilol, already receiving beta-blocker, cancer, severe systemic illness, hypertension, diabetes, psychiatric disease, chronic obstructive pulmonary disease, asthma, mean arterial pressure &lt; 55 mmHg, heart rate &lt; 50 bpm, and portal vein thrombosis</td>
<td></td>
</tr>
<tr>
<td>Interventions</td>
<td>Group 1: variceal band ligation (n = 125)</td>
</tr>
<tr>
<td>Further details: variceal band ligation (multiband device): unclear if it was repeated</td>
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</tr>
<tr>
<td>Group 2: beta-blockers (n = 125)</td>
<td></td>
</tr>
<tr>
<td>Further details: carvedilol 12.5 mg once daily for 6 months</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>Variceal bleed at maximal follow-up (any) (number of participants)</td>
</tr>
<tr>
<td>Follow-up (months): 6</td>
<td></td>
</tr>
<tr>
<td>Notes</td>
<td>Source of funding: not stated</td>
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</tbody>
</table>
Khan 2017 (Continued)

Trial name/trial registry number: not stated

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

### Risk of bias

<table>
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<tr>
<th>Bias</th>
<th>Authors' judgement</th>
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<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
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<tr>
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<td>Low risk</td>
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Lay 1997

### Study characteristics

<table>
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<th>Randomised clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
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<td>Period of recruitment: 1993–1995</td>
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</tr>
<tr>
<td>Number randomised: 126</td>
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<tr>
<td>Postrandomisation dropouts: 0 (0.0%)</td>
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<tr>
<td>Revised sample size: 126</td>
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<tr>
<td>Mean age (years): 55</td>
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<tr>
<td>Females: 25 (19.8%)</td>
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<tr>
<td>Small varices: not stated</td>
<td></td>
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<tr>
<td>High risk of bleeding: 126 (100.0%)</td>
<td></td>
</tr>
<tr>
<td>Other features of decompensation: 65 (51.6%)</td>
<td></td>
</tr>
<tr>
<td>Alcohol-related cirrhosis: 23 (18.3%)</td>
<td></td>
</tr>
</tbody>
</table>
### Lay 1997 (Continued)

Viral-related cirrhosis: 96 (76.2%)
Autoimmune disease-related cirrhosis: not stated
Other causes of cirrhosis: 7 (5.6%)

Other inclusion criteria: no known previous bleeding from the upper gastrointestinal tract; presence of high-risk oesophageal varices; cirrhosis with no other diseases restricting life expectancy
Other exclusion criteria: gastric or ectopic varices

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Group 1: variceal band ligation (n = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Further details: variceal band ligation using an endoscopic ligation device weekly for first 3 weeks and then every 2 weeks until obliteration of varices</td>
</tr>
<tr>
<td></td>
<td>Group 2: no active intervention (n = 64)</td>
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<td></td>
<td>Further details: no treatment</td>
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</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Mortality at maximal follow-up, any adverse events (number of participants), any adverse events (number of events), variceal bleed at maximal follow-up (any) (number of participants)</th>
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<tbody>
<tr>
<td></td>
<td>Follow-up (months): 13.5</td>
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### Risk of bias

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<th>Bias</th>
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<th>Support for judgement</th>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;sealed-envelope method.&quot;</td>
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<tr>
<td></td>
<td></td>
<td>Comment: although the details on sequence generation were not reported, the method of allocation concealment used makes it highly likely that the sequence was random.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;sealed-envelope method.&quot;</td>
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<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>Quote: &quot;At the time of endoscopy, the patients in the EVL [endoscopic variceal ligation] group returned for visits more frequently than the non-EVL group. The follow-up was indeed different in these two groups of patients.&quot;</td>
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<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Quote: &quot;At the time of endoscopy, the patients in the EVL group returned for visits more frequently than the non-EVL group. The follow-up was indeed different in these two groups of patients.&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: although the follow-up was different between the groups, there is a possibility that outcome assessors were blinded. However, information on blinding or lack of blinding was not provided.</td>
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<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Comment: no postrandomisation dropouts</td>
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Lay 1997 (Continued)

<table>
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<tr>
<th>Selective reporting (reporting bias)</th>
<th>Low risk</th>
<th>Comment: prepublished protocol not available, but the authors reported mortality, adverse events, and variceal bleed adequately.</th>
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<tbody>
<tr>
<td>Other bias</td>
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</table>

Lay 2006

Study characteristics

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised clinical trial</th>
</tr>
</thead>
</table>

Participants

| Country: China |
| Period of recruitment: 1998–2002 |
| Number randomised: 100 |
| Postrandomisation dropouts: 0 (0.0%) |
| Revised sample size: 100 |
| Mean age (years): 56 |
| Females: 22 (22.0%) |
| Small varices: not stated |
| High risk of bleeding: 100 (100.0%) |
| Other features of decompensation: 17 (17.0%) |
| Alcohol-related cirrhosis: 21 (21.0%) |
| Viral-related cirrhosis: 73 (73.0%) |
| Autoimmune disease-related cirrhosis: not stated |
| Other causes of cirrhosis: 6 (6.0%) |
| Other inclusion criteria: no known previous bleeding from the upper gastrointestinal tract; presence of high-risk oesophageal varices; cirrhosis with no other diseases restricting life expectancy |
| Other exclusion criteria: gastric or ectopic varices |

Interventions

| Group 1: variceal band ligation (n = 50) |
| Further details: variceal band ligation using an endoscopic ligation device weekly for first 3 weeks and then every 2 weeks until obliteration of varices |
| Group 2: beta-blockers (n = 50) |
| Further details: propranolol initial dose 40 mg twice daily titrated to reduce the resting heart rate by 20% |

Outcomes

| Mortality at maximal follow-up, any adverse events (number of participants), any adverse events (number of events), variceal bleed at maximal follow-up (any) (number of participants), other features of decompensation at maximal follow-up |
| Follow-up (months): 34.9 |

Notes

| Source of funding: not stated |

---

Lay 2006

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

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Risk of bias

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<tr>
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<td>Unclear risk</td>
<td>Comment: information not available</td>
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<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
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<tr>
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<td>Low risk</td>
<td>Comment: no postrandomisation dropouts</td>
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<tr>
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Lebrec 1988

Study characteristics

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<td>Participants</td>
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<tr>
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<td>Mean age (years): 56</td>
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<td>Females: 27 (25.5%)</td>
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<tr>
<td></td>
<td>Small varices: not stated</td>
</tr>
<tr>
<td></td>
<td>High risk of bleeding: not stated</td>
</tr>
</tbody>
</table>
Other features of decompensation: not stated

Alcohol-related cirrhosis: 78 (73.6%)
Viral-related cirrhosis: 12 (11.3%)
Autoimmune disease-related cirrhosis: 4 (3.8%)
Other causes of cirrhosis: 12 (11.3%)

Other inclusion criteria: no history of gastrointestinal bleeding; presence of ≥ 1 oesophageal varix measuring ≥ 4 mm; serum bilirubin < 100 μmol/L; absent or only mild and transient ascites; no hepatic encephalopathy

Other exclusion criteria: Child-Pugh C; heart failure; asthma; hepatocellular carcinoma

Interventions

Group 1: no active intervention (n = 53)
Further details: placebo

Group 2: beta-blockers (n = 53)
Further details: nadolol dose titrated to decrease the resting heart rate by approximately 25%

Outcomes

Mortality at maximal follow-up, any adverse events (number of participants), variceal bleed at maximal follow-up (any) (number of participants)
Follow-up (months): 12

Notes

Source of funding (quote): "We had no special fund for the study" (author reply)
Trial name/trial registry number: not stated
Attempted to contact the authors in February 2020; received no additional information

Risk of bias

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<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>Quote: &quot;The patients did not know whether they were receiving nadolol or placebo; the physicians caring for the patients did know.&quot;</td>
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<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
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<td>Quote: &quot;The patients did not know whether they were receiving nadolol or placebo; the physicians caring for the patients did know.&quot;</td>
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<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
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<td>Comment: no postrandomisation dropouts</td>
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<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Comment: prepublished protocol not available, but the authors reported mortality, adverse events, and variceal bleed adequately.</td>
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### Study characteristics

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

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<th>Bias</th>
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<td>Quote: “The method of randomization was based on a system of random numbers.”</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
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<td>Comment: information not available</td>
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<tr>
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<td>Incomplete outcome data (attrition bias) All outcomes</td>
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**Study characteristics**

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<td>Participants</td>
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<tr>
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<td>Postrandomisation dropouts: 0 (0.0%)</td>
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<tr>
<td>Revised sample size: 100</td>
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<tr>
<td>Mean age (years): 56</td>
<td></td>
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<tr>
<td>Females: 23 (23.0%)</td>
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</tr>
<tr>
<td>Small varices: 61 (61.0%)</td>
<td></td>
</tr>
<tr>
<td>High risk of bleeding: 100 (100.0%)</td>
<td></td>
</tr>
<tr>
<td>Other features of decompensation: 41 (41.0%)</td>
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<tr>
<td>Alcohol-related cirrhosis: 20 (20.0%)</td>
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</tbody>
</table>
Viral-related cirrhosis: 73 (73.0%)
Autoimmune disease-related cirrhosis: not stated
Other causes of cirrhosis: 7 (7.0%)

Other exclusion criteria: aged > 75 years or < 20 years; presence of malignancy, uraemia, or other serious medical illness that could reduce life expectancy; refractory ascites, hepatic encephalopathy, or marked jaundice (bilirubinaemia > 10 mg/dL); history of shunt operation, TIPS, or endoscopic therapy (ligation or sclerotherapy); contraindication to treatment with beta-blockers

Interventions
Group 1: variceal band ligation (n = 50)
Further details: variceal band ligation using multiband ligator repeated at 3- to 4-week intervals until obliteration
Group 2: beta-blockers (n = 50)
Further details: nadolol started at 40 mg once daily and titrated to reduce resting pulse rate to 25% or 55/minute

Outcomes
Mortality at maximal follow-up, serious adverse events (number of participants), any adverse events (number of participants), variceal bleed at maximal follow-up (symptomatic recovery) (number of participants)
Follow-up (months): 22.2

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

Risk of bias

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<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
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<td>Comment: information not available</td>
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<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Comment: no postrandomisation dropouts</td>
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<td>Low risk</td>
<td>Comment: prepublished protocol not available, but the authors reported mortality, adverse events, and variceal bleed adequately.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Comment: no other bias noted</td>
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</table>
**Study characteristics**

**Methods**
Randomised clinical trial

**Participants**
Country: Taiwan
Period of recruitment: not stated
Number randomised: 140
Postrandomisation dropouts: 0 (0.0%)
Revised sample size: 140
Mean age (years): 56
Females: 53 (37.9%)
Small varices: 122 (87.1%)
High risk of bleeding: 140 (100.0%)
Other features of decompensation: 3 (2.1%)
Alcohol-related cirrhosis: 24 (17.1%)
Viral-related cirrhosis: 101 (72.1%)
Autoimmune disease-related cirrhosis: not stated
Other causes of cirrhosis: 15 (10.7%)
Other exclusion criteria: aged > 75 years or < 20 years; malignancy, uraemia, or other serious medical illness that may reduce life expectancy; refractory ascites, hepatic encephalopathy stage > 2 or deep jaundice (bilirubin > 10 mg/dL); history of shunt operation, TIPS, or endoscopic therapy; contraindications to beta-blockers; unable to co-operate; declined to participate

**Interventions**
Group 1: beta-blockers + variceal band ligation (n = 70)
Further details: nadolol titrated to reduce pulse rate by 25%, duration until follow-up + variceal band ligation using multiband ligators repeated every 4 weeks until variceal obliteration
Group 2: beta-blockers (n = 70)
Further details: nadolol titrated to reduce pulse rate by 25%, until follow-up

**Outcomes**
Mortality at maximal follow-up, any adverse events (number of events), liver transplantation at maximal follow-up, variceal bleed at maximal follow-up (symptomatic recovery) (number of participants)
Follow-up (months): 26

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

**Risk of bias**

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

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<table>
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</tr>
<tr>
<td>Other bias</td>
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</table>

**Lui 2002**

**Study characteristics**

**Methods**

Randomised clinical trial

**Participants**

Country: Scotland

Period of recruitment: 1994–1999

Number randomised: 172

Postrandomisation dropouts: 0 (0.0%)

Revised sample size: 172

Mean age (years): 55

Females: 75 (43.6%)

Small varices: 144 (83.7%)

High risk of bleeding: 8 (4.7%)

Other features of decompensation: 5 (2.9%)

Alcohol-related cirrhosis: 112 (65.1%)

Viral-related cirrhosis: not stated

Autoimmune disease-related cirrhosis: not stated

Other causes of cirrhosis: not stated

Other exclusion criteria: aged < 18 years or > 75 years; failure or inability to provide informed consent; advanced systemic illness; non-cirrhotic portal hypertension; person receiving existing vasoactive
agents; contraindications to beta-blockers; systolic blood pressure < 100 mmHg or diastolic < 50 mmHg or pulse rate < 56/minute; allergy to either trial medication

### Interventions

**Group 1: beta-blockers (n = 66)**
- Further details: propranolol started at 40 mg twice daily and increased to 80 mg twice daily after 3 days if well tolerated, systolic blood pressure was > 100 mmHg, and pulse rate was > 50/minute

**Group 2: nitrates (n = 62)**
- Further details: isosorbide mononitrate started at 20 mg twice daily and increased to 40 mg twice daily after 3 days if well tolerated and systolic blood pressure was > 100 mmHg

**Group 3: variceal band ligation (n = 44)**
- Further details: variceal band ligation, initially by single band device later by multiband device every 2 weeks until variceal obliteration

### Outcomes

- Mortality at maximal follow-up, variceal bleed at maximal follow-up (any) (number of rebleeds)
- Follow-up (months): 19.7

### Notes

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

### Risk of bias

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</thead>
</table>
| Random sequence generation (selection bias) | Low risk           | Quote: "Serially numbered opaque envelopes containing cards with randomly assigned treatment arms were used."
|                                     |                    | Comment: although the details on sequence generation were not reported, the method of allocation concealment used makes it highly likely that the sequence was random. |
| Allocation concealment (selection bias) | Low risk           | Quote: "Serially numbered opaque envelopes containing cards with randomly assigned treatment arms were used." |
|                                     |                    | Comment: information not available                                                     |
| Blinding of participants and personnel (performance bias) All outcomes | Unclear risk       | Comment: information not available                                                     |
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk       | Comment: information not available                                                     |
| Incomplete outcome data (attrition bias) All outcomes | Low risk           | Comment: no postrandomisation dropouts                                                |
| Selective reporting (reporting bias) | Unclear risk       | Comment: no prepublished protocol available                                           |
| Other bias                          | Low risk           | Comment: no other bias noted                                                          |
### Merkel 2000

**Study characteristics**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised clinical trial</th>
</tr>
</thead>
</table>
| Participants | Country: Italy  
Number randomised: 146  
Postrandomisation dropouts: 0 (0.0%)  
Revised sample size: 146  
Mean age (years): 57  
Females: 55 (37.7%)  
Small varices: 101 (69.2%)  
High risk of bleeding: 97 (66.4%)  
Other features of decompensation: 16 (11.0%)  
Alcohol-related cirrhosis: 79 (54.1%)  
Viral-related cirrhosis: 53 (36.3%)  
Autoimmune disease-related cirrhosis: not stated  
Other causes of cirrhosis: 4 (2.7%)  
Other exclusion criteria: previous treatment for portal hypertension; Child-Pugh score > 11; presence of any malignancy; inability to attend follow-up; contraindications to beta-blockers or long acting nitrates; concomitant or recent treatment with interferon for hepatitis B virus or hepatitis C virus |

| Interventions | Group 1: beta-blockers + nitrates (n = 72)  
Further details: nadolol dose titrated to achieve a 20–25% decrease in resting heart rate + isosorbide mononitrate starting with 10 mg twice daily, which was increased to 20 mg twice daily, unless hypotension (systolic blood pressure < 85 mmHg) or severe headache occurred  
Group 2: beta-blockers (n = 74)  
Further details: nadolol dose titrated to achieve a 20–25% decrease in resting heart rate |

| Outcomes | Mortality at maximal follow-up, other features of decompensation at maximal follow-up  
Follow-up (months): 55 |

| Notes | Source of funding (quote): "Supported in part by a grant from the Italian Ministry of University and Scientific Research (National Project "Liver Cirrhosis and Virus Hepatitis")"  
Trial name/trial registry number: not stated  
Attempted to contact the authors in February 2020; received no additional information |

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
</table>

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Primary prevention of variceal bleeding in people with oesophageal varices due to liver cirrhosis: a network meta-analysis (Review)
### Merkel 2000 (Continued)

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

### Merkel 2004

#### Study characteristics

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Country: Italy</td>
</tr>
<tr>
<td></td>
<td>Period of recruitment: 1996–2000</td>
</tr>
<tr>
<td></td>
<td>Number randomised: 161</td>
</tr>
<tr>
<td></td>
<td>Postrandomisation dropouts: 0 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>Revised sample size: 161</td>
</tr>
<tr>
<td></td>
<td>Mean age (years): 56</td>
</tr>
<tr>
<td></td>
<td>Females: 78 (48.4%)</td>
</tr>
<tr>
<td></td>
<td>Small varices: 161 (100.0%)</td>
</tr>
<tr>
<td></td>
<td>High risk of bleeding: 0 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>Other features of decompensation: 41 (25.5%)</td>
</tr>
<tr>
<td></td>
<td>Alcohol-related cirrhosis: 92 (57.1%)</td>
</tr>
<tr>
<td></td>
<td>Viral-related cirrhosis: 62 (38.5%)</td>
</tr>
<tr>
<td></td>
<td>Autoimmune disease-related cirrhosis: not stated</td>
</tr>
<tr>
<td></td>
<td>Other causes of cirrhosis: 7 (4.3%)</td>
</tr>
</tbody>
</table>
Merkel 2004 (Continued)

Other exclusion criteria: previous variceal bleeding; previous medical, surgical, or endoscopic treatment for portal hypertension; Child-Pugh score > 11; neoplastic disease in any site; inability to perform follow-up; contraindications to beta-blockers

### Interventions

<table>
<thead>
<tr>
<th>Group 1: no active intervention (n = 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Further details: placebo</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 2: beta-blockers (n = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Further details: nadolol, target of a 25% decrease or a heart rate of 50 bpm</td>
</tr>
</tbody>
</table>

### Outcomes

| Mortality at maximal follow-up, liver transplantation at maximal follow-up |
| Follow-up (months): 36 |

### Notes

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

### Risk of bias

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

**Methods**  
Randomised clinical trial

**Participants**  
Country: India  
Period of recruitment: not stated  
Number randomised: 85  
Postrandomisation dropouts: 0 (0.0%)  
Revised sample size: 85  
Mean age (years): not stated  
Females: not stated  
Small varices: 85 (100.0%)  
High risk of bleeding: not stated  
Other features of decompensation: not stated  
Alcohol-related cirrhosis: not stated  
Viral-related cirrhosis: not stated  
Autoimmune disease-related cirrhosis: not stated  
Other causes of cirrhosis: not stated  
Other inclusion criteria: cirrhosis; small varices; no previous bleeding

**Interventions**  
Group 1: no active intervention (n = 42)  
Further details: placebo  
Group 2: beta-blockers (n = 43)  
Further details: propranolol dose titrated to decrease resting heart rate to 55 bpm

**Outcomes**  
Mortality at maximal follow-up  
Follow-up (months): 18

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

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
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</tbody>
</table>

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Primary prevention of variceal bleeding in people with oesophageal varices due to liver cirrhosis: a network meta-analysis (Review)  
Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
### Mishra 2007 (Continued)

<table>
<thead>
<tr>
<th>Risk of Bias</th>
<th>Decision</th>
<th>Comment</th>
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<tbody>
<tr>
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<td>Information not available</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Information not available</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>No postrandomisation dropouts</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No prepublished protocol available</td>
</tr>
<tr>
<td>Other bias</td>
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</table>

### NCT00337740

**Study characteristics**

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

Outcomes
None of the outcomes of interest were reported.

Notes
Source of funding: not stated
Trial name/trial registry number: NCT00337740
Attempted to contact the authors in February 2020; received no additional information

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
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<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
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</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>Quote: “open label.”</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>High risk</td>
<td>Quote: “open label.”</td>
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<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Comment: a prepublished protocol was not available.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Comment: no other bias noted</td>
</tr>
</tbody>
</table>

NCT00921349

Study characteristics

Methods
Randomised clinical trial

Participants
Country: Taiwan
Period of recruitment: 2004–2009
Number randomised: 140
Postrandomisation dropouts: not stated
Revised sample size: 140
Mean age (years): not stated
Females: not stated
Small varices: not stated
High risk of bleeding: not stated
Other features of decompensation: not stated
Alcohol-related cirrhosis: not stated
Viral-related cirrhosis: not stated
Autoimmune disease-related cirrhosis: not stated
Other causes of cirrhosis: not stated

Interventions

Group 1: beta-blockers + variceal band ligation (n = not stated)
Further details: variceal band ligation: multiband ligation device, repeated at intervals of 3–4 weeks until all varices were obliterated + nadolol (no further details)

Group 2: beta-blockers (n = not stated)
Further details: nadolol (no further details)

Outcomes

None of the outcomes of interest were reported.

Notes

Source of funding: not stated
Trial name/trial registry number: NCT00921349
Attempted to contact the authors in February 2020; received no additional information

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>Quote: &quot;open label.&quot;</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>High risk</td>
<td>Quote: &quot;open label.&quot;</td>
</tr>
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<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
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<td>Comment: prepublished protocol not available.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Comment: no other bias noted</td>
</tr>
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### Study characteristics

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Country: Italy</td>
</tr>
<tr>
<td></td>
<td>Period of recruitment: 2001–2005</td>
</tr>
<tr>
<td></td>
<td>Number randomised: 62</td>
</tr>
<tr>
<td></td>
<td>Postrandomisation dropouts: 0 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>Revised sample size: 62</td>
</tr>
<tr>
<td></td>
<td>Mean age (years): 53</td>
</tr>
<tr>
<td></td>
<td>Females: not stated</td>
</tr>
<tr>
<td></td>
<td>Small varices: 53 (85.5%)</td>
</tr>
<tr>
<td></td>
<td>High risk of bleeding: 62 (100.0%)</td>
</tr>
<tr>
<td></td>
<td>Other features of decompensation: not stated</td>
</tr>
<tr>
<td></td>
<td>Alcohol-related cirrhosis: not stated</td>
</tr>
<tr>
<td></td>
<td>Viral-related cirrhosis: 32 (51.6%)</td>
</tr>
<tr>
<td></td>
<td>Autoimmune disease-related cirrhosis: not stated</td>
</tr>
<tr>
<td></td>
<td>Other causes of cirrhosis: not stated</td>
</tr>
<tr>
<td></td>
<td>Other exclusion criteria: oesophageal varices not less than F3 or F2 with red signs; presence of gastric varices; previous endoscopic, radiological, surgical, treatment of oesophageal varices; hepatocellular carcinoma; severe heart, respiratory, or renal failure; portal vein thrombosis; contraindications to beta-blockers; treatment with nitrates, calcium antagonists, or other antiarrhythmic drugs; pregnancy; neoplasias; an unco-operative attitude or suspicion for non-compliance to follow-up</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Group 1: variceal band ligation (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Further details: variceal band ligation multiband ligator, repeated every 2 weeks until the varices were completely eradicated</td>
</tr>
<tr>
<td></td>
<td>Group 2: beta-blockers (n = 31)</td>
</tr>
<tr>
<td></td>
<td>Further details: propranolol titrated to ensure systolic blood pressure ≥ 90 mmHg and heart rate ≥ 50 bpm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Mortality at maximal follow-up, serious adverse events (number of participants), liver transplantation at maximal follow-up, variceal bleed at maximal follow-up (any) (number of participants), treatment costs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Follow-up (months): 14.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Notes</th>
<th>Source of funding: not stated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trial name/trial registry number: not stated</td>
</tr>
<tr>
<td></td>
<td>Attempted to contact the authors in February 2020; received no additional information</td>
</tr>
</tbody>
</table>

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
</table>

---

---
**Norbeto 2007 (Continued)**

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

**Paquet 1982**

**Study characteristics**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Country: Germany</td>
</tr>
<tr>
<td></td>
<td>Period of recruitment: 1978–1980</td>
</tr>
<tr>
<td></td>
<td>Number randomised: 71</td>
</tr>
<tr>
<td></td>
<td>Postrandomisation dropouts: 8 (11.3%)</td>
</tr>
<tr>
<td></td>
<td>Revised sample size: 63</td>
</tr>
<tr>
<td></td>
<td>Reasons for postrandomisation dropouts: lost to follow-up</td>
</tr>
<tr>
<td></td>
<td>Mean age (years): not stated</td>
</tr>
<tr>
<td></td>
<td>Females: not stated</td>
</tr>
<tr>
<td></td>
<td>Small varices: not stated</td>
</tr>
<tr>
<td></td>
<td>High risk of bleeding: not stated</td>
</tr>
<tr>
<td></td>
<td>Other features of decompensation: not stated</td>
</tr>
<tr>
<td></td>
<td>Alcohol-related cirrhosis: not stated</td>
</tr>
<tr>
<td></td>
<td>Viral-related cirrhosis: not stated</td>
</tr>
<tr>
<td></td>
<td>Autoimmune disease-related cirrhosis: not stated</td>
</tr>
<tr>
<td></td>
<td>Other causes of cirrhosis: not stated</td>
</tr>
</tbody>
</table>
Other inclusion criteria: liver cirrhosis confirmed histologically; degree III or IV varices bearing telangiectasias on top and degree II-IV varices without telangiectasias but coagulation factors < 30%, or both

**Interventions**

- **Group 1:** sclerotherapy (n = 31)
  - Further details: sclerotherapy: aethoxysclerol 30–50 mL, 2–4 sessions at an interval of 6–7 days
- **Group 2:** no active intervention (n = 32)
  - Further details: no treatment

**Outcomes**

- Mortality at maximal follow-up, any adverse events (number of participants), variceal bleed at maximal follow-up (any) (number of participants)
  - Follow-up (months): 18

**Notes**

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

**Risk of bias**

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

**Paquet 1984**

**Study characteristics**

<table>
<thead>
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<th>Methods</th>
<th>Randomised clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Country: Germany</td>
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</table>
Period of recruitment: 1987–1992
Number randomised: 89
Postrandomisation dropouts: 0 (0.0%)
Revised sample size: 89
Mean age (years): 51
Females: 32 (36.0%)
Small varices: 0 (0.0%)
High risk of bleeding: 89 (100.0%)
Other features of decompensation: not stated
Alcohol-related cirrhosis: 63 (70.8%)
Viral-related cirrhosis: 15 (16.9%)
Autoimmune disease-related cirrhosis: 4 (4.5%)
Other causes of cirrhosis: 7 (7.9%)
Other inclusion criteria: no history of upper gastrointestinal bleeding; no previous endoscopic evidence of oesophageal varices degrees III and IV with telangiectasias (minivarices); hepatovenous pressure gradient > 16 mmHg; liver cirrhosis histologically confirmed with no other disease reducing life expectancy to < 1 year; full consent to participate in the study

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Group 1: sclerotherapy (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Further details: sclerotherapy: 0.5–1% aethoxysclero l repeated every week until varices were reduced in size and covered by fibrous tissue</td>
</tr>
<tr>
<td></td>
<td>Group 2: no active intervention (n = 45)</td>
</tr>
<tr>
<td></td>
<td>Further details: no treatment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Mortality at maximal follow-up, variceal bleed at maximal follow-up (any) (number of participants)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Follow-up (months): 33</td>
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<tr>
<th>Notes</th>
<th>Source of funding (quote): &quot;Dr. Gad received grants from the Egyptian Government (1988 – 90 and 1994).&quot;</th>
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<td>Trial name/trial registry number: not stated</td>
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### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
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### Paquet 1994

(Continued)

<table>
<thead>
<tr>
<th>All outcomes</th>
<th>Blinding of outcome assessment (detection bias)</th>
<th>Unclear risk</th>
<th>Comment: information not available</th>
</tr>
</thead>
<tbody>
<tr>
<td>All outcomes</td>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Comment: no postrandomisation dropouts</td>
</tr>
<tr>
<td>All outcomes</td>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Comment: no prepublished protocol available</td>
</tr>
<tr>
<td></td>
<td>Other bias</td>
<td>Low risk</td>
<td>Comment: no other bias noted</td>
</tr>
</tbody>
</table>

### Pascal 1987

**Study characteristics**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Country: France</td>
</tr>
<tr>
<td></td>
<td>Period of recruitment: 1983–1984</td>
</tr>
<tr>
<td></td>
<td>Number randomised: 230</td>
</tr>
<tr>
<td></td>
<td>Postrandomisation dropouts: 0 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>Revised sample size: 230</td>
</tr>
<tr>
<td></td>
<td>Mean age (years): 54</td>
</tr>
<tr>
<td></td>
<td>Females: not stated</td>
</tr>
<tr>
<td></td>
<td>Small varices: 171 (74.3%)</td>
</tr>
<tr>
<td></td>
<td>High risk of bleeding: not stated</td>
</tr>
<tr>
<td></td>
<td>Other features of decompensation: not stated</td>
</tr>
<tr>
<td></td>
<td>Alcohol-related cirrhosis: 207 (90.0%)</td>
</tr>
<tr>
<td></td>
<td>Viral-related cirrhosis: not stated</td>
</tr>
<tr>
<td></td>
<td>Autoimmune disease-related cirrhosis: not stated</td>
</tr>
<tr>
<td></td>
<td>Other causes of cirrhosis: not stated</td>
</tr>
<tr>
<td></td>
<td>Other inclusion criteria: adults aged &lt; 75 years; cirrhosis with Child-Pugh score &lt; 14; grade II or III oesophageal varices</td>
</tr>
<tr>
<td></td>
<td>Other exclusion criteria: contraindications to beta-blockers; history of upper gastrointestinal bleed; evidence of gastroduodenal ulcer, hepatocellular carcinoma; receiving treatment that altered portal haemodynamics</td>
</tr>
<tr>
<td>Interventions</td>
<td>Group 1: no active intervention (n = 112)</td>
</tr>
<tr>
<td></td>
<td>Further details: placebo</td>
</tr>
<tr>
<td></td>
<td>Group 2: beta-blockers (n = 118)</td>
</tr>
</tbody>
</table>
Further details: propranolol to reduce the heart rate by 20–25%  

Outcomes  
Mortality at maximal follow-up  
Follow-up (months): 14.3  

Notes  
Source of funding (quote): "We are indebted to … Dr C Dupont (ICI Pharma, France) for her help.”  
Trial name/trial registry number: not stated  
Attempted to contact the authors in February 2020; received no additional information  

Risk of bias  

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

Perez-Ayuso 2010  

Study characteristics  

Methods  
Randomised clinical trial  

Participants  
Country: Chile  
Number randomised: 75  
Postrandomisation dropouts: 0 (0.0%)
Revised sample size: 75
Mean age (years): 59
Females: 38 (50.7%)
Small varices: not stated
High risk of bleeding: 75 (100.0%)
Other features of decompensation: 8 (10.7%)
Alcohol-related cirrhosis: 18 (24.0%)
Viral-related cirrhosis: 11 (14.7%)
Autoimmune disease-related cirrhosis: 13 (17.3%)
Other causes of cirrhosis: 42 (56.0%)
Other inclusion criteria: cirrhosis; no history of haemorrhage from oesophageal varices; high-risk varices; non-current treatment with beta-blocker
Other exclusion criteria: aged < 18 years or > 70 years; evidence of portal thrombosis, malignancy, contraindication to beta-blockers; previous variceal endoscopic treatment, TIPS, surgical shunt, renal failure, or denial to participate in the study

Interventions
Group 1: variceal band ligation (n = 39)
Further details: variceal band ligation using a multiband ligator, repeated every 3 weeks until eradication of varices
Group 2: beta-blockers (n = 36)
Further details: propranolol increased to achieve a reduction of 25% of the pretreatment resting heart rate, heart rate was 55 bpm or systolic blood pressure was < 90 mmHg

Outcomes
Mortality at maximal follow-up, serious adverse events (number of participants), any adverse events (number of participants), variceal bleed at maximal follow-up (any) (number of participants)
Follow-up (months): 55

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

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: “Stratified randomization was centrally performed according to Child-Pugh classification (Child-Pugh score &lt;9 or ≥9).”</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: “Random allocation sequence was generated using numerated sealed envelopes.”</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>High risk</td>
<td>Quote: “After the randomization the patient and physicians were informed.”</td>
</tr>
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</table>
Perez-Ayuso 2010 (Continued)

<table>
<thead>
<tr>
<th>Study characteristics</th>
<th></th>
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<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Randomised clinical trial</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td></td>
</tr>
<tr>
<td>Country: Italy</td>
<td></td>
</tr>
<tr>
<td>Period of recruitment: 1983–1985</td>
<td></td>
</tr>
<tr>
<td>Number randomised: 140</td>
<td></td>
</tr>
<tr>
<td>Postrandomisation dropouts: 0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Revised sample size: 140</td>
<td></td>
</tr>
<tr>
<td>Mean age (years): 56</td>
<td></td>
</tr>
<tr>
<td>Females: 41 (29.3%)</td>
<td></td>
</tr>
<tr>
<td>Small varices: not stated</td>
<td></td>
</tr>
<tr>
<td>High risk of bleeding: 140 (100.0%)</td>
<td></td>
</tr>
<tr>
<td>Other features of decompensation: not stated</td>
<td></td>
</tr>
<tr>
<td>Alcohol-related cirrhosis: 47 (33.6%)</td>
<td></td>
</tr>
<tr>
<td>Viral-related cirrhosis: 57 (40.7%)</td>
<td></td>
</tr>
<tr>
<td>Autoimmune disease-related cirrhosis: not stated</td>
<td></td>
</tr>
<tr>
<td>Other causes of cirrhosis: 19 (13.6%)</td>
<td></td>
</tr>
<tr>
<td>Other inclusion criteria: no known previous bleeding from the upper gastrointestinal tract; oesophageal varices at high risk of bleeding; liver cirrhosis with no other disease reducing life expectancy</td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Interventions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1: sclerotherapy (n = 71)</td>
<td></td>
</tr>
<tr>
<td>Further details: sclerotherapy: polidocanol 1% maximum 20–40 mL, 7- to 10-day interval between sessions</td>
<td></td>
</tr>
<tr>
<td>Group 2: no active intervention (n = 69)</td>
<td></td>
</tr>
<tr>
<td>Further details: no treatment</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality at maximal follow-up</td>
<td></td>
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</table>

Piai 1988

Study characteristics

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<tr>
<td>Number randomised: 140</td>
<td></td>
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<tr>
<td>Postrandomisation dropouts: 0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Revised sample size: 140</td>
<td></td>
</tr>
<tr>
<td>Mean age (years): 56</td>
<td></td>
</tr>
<tr>
<td>Females: 41 (29.3%)</td>
<td></td>
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<tr>
<td>Small varices: not stated</td>
<td></td>
</tr>
<tr>
<td>High risk of bleeding: 140 (100.0%)</td>
<td></td>
</tr>
<tr>
<td>Other features of decompensation: not stated</td>
<td></td>
</tr>
<tr>
<td>Alcohol-related cirrhosis: 47 (33.6%)</td>
<td></td>
</tr>
<tr>
<td>Viral-related cirrhosis: 57 (40.7%)</td>
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</tr>
<tr>
<td>Autoimmune disease-related cirrhosis: not stated</td>
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</tr>
<tr>
<td>Other inclusion criteria: no known previous bleeding from the upper gastrointestinal tract; oesophageal varices at high risk of bleeding; liver cirrhosis with no other disease reducing life expectancy</td>
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<td></td>
</tr>
<tr>
<td>Group 2: no active intervention (n = 69)</td>
<td></td>
</tr>
<tr>
<td>Further details: no treatment</td>
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</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality at maximal follow-up</td>
<td></td>
</tr>
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</table>
### Piai 1988 (Continued)

Follow-up (months): 13

Source of funding: not stated

Trial name/trial registry number: not stated

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

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: “Patients were randomly allocated either to a treatment group or to a control group (using a sealed envelope method).” Comment: although the details on sequence generation was not reported, the method of allocation concealment used makes it highly likely that the sequence was random.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: “Patients were randomly allocated either to a treatment group or to a control group (using a sealed envelope method).”</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
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<td>Comment: information not available</td>
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<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Comment: no postrandomisation dropouts</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Comment: no prepublished protocol available</td>
</tr>
<tr>
<td>Other bias</td>
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<td>Comment: no other bias noted</td>
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### Piscaglia 1998

**Study characteristics**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised clinical trial</th>
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</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Country: Italy</td>
</tr>
<tr>
<td></td>
<td>Period of recruitment: not stated</td>
</tr>
<tr>
<td></td>
<td>Number randomised: 18</td>
</tr>
<tr>
<td></td>
<td>Postrandomisation dropouts: 0 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>Revised sample size: 18</td>
</tr>
<tr>
<td></td>
<td>Mean age (years): 58</td>
</tr>
<tr>
<td></td>
<td>Females: 7 (38.9%)</td>
</tr>
</tbody>
</table>
Small varices: 16 (88.9%)
High risk of bleeding: not stated
Other features of decompensation: 3 (16.7%)
Alcohol-related cirrhosis: 4 (22.2%)
Viral-related cirrhosis: 14 (77.8%)
Autoimmune disease-related cirrhosis: 0 (0.0%)
Other causes of cirrhosis: 0 (0.0%)
Other inclusion criteria: absence of previous episodes of gastrointestinal bleeding; no previous prophylaxis of variceal bleeding by sclerotherapy, banding ligation, or TIPS; exclusion of any cardiovascular disease; absence of portal vein thrombosis or portal vein hepatofugal flow; technical feasibility of duplex-Doppler

Interventions

<table>
<thead>
<tr>
<th>Group 1: beta-blockers and nitrates (n = 10)</th>
<th>Further details: propranolol 40 mg once daily increased to 40 mg twice daily for 1 month + single dose of isosorbide mononitrate 20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 2: no active intervention (n = 8)</td>
<td>Further details: placebo</td>
</tr>
</tbody>
</table>

Outcomes

None of the outcomes of interest were reported.

Notes

Source of funding (quote): “This study was supported by 60% Funds of Ministero dell’Università e Ricerca Scientifica e Tecnologica (MURST).”

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

Risk of bias

<table>
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<th>Support for judgement</th>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
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<td>Comment: information not available</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>Comment: placebo used, but it was unclear whether blinding was achieved.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Comment: placebo used, but it was unclear whether blinding was achieved.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Comment: no postrandomisation dropouts</td>
</tr>
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</table>
### Piscaglia 1998 (Continued)

<table>
<thead>
<tr>
<th>Study characteristics</th>
<th>Reporting bias</th>
<th>Unclear risk</th>
<th>Comment: no prepublished protocol available</th>
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<tbody>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Comment: no other bias noted</td>
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</table>

### PROVA study group 1991

#### Study characteristics

<table>
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<th>Methods</th>
<th>Randomised clinical trial</th>
</tr>
</thead>
</table>

<table>
<thead>
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<th>Participants</th>
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<tr>
<td>Period of recruitment: 1985–1989</td>
<td></td>
</tr>
<tr>
<td>Number randomised: 286</td>
<td></td>
</tr>
<tr>
<td>Postrandomisation dropouts: 0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Revised sample size: 286</td>
<td></td>
</tr>
<tr>
<td>Mean age (years): 54</td>
<td></td>
</tr>
<tr>
<td>Females: 86 (30.1%)</td>
<td></td>
</tr>
<tr>
<td>Small varices: 245 (85.7%)</td>
<td></td>
</tr>
<tr>
<td>High risk of bleeding: not stated</td>
<td></td>
</tr>
<tr>
<td>Other features of decompensation: 23 (8.0%)</td>
<td></td>
</tr>
<tr>
<td>Alcohol-related cirrhosis: 235 (82.2%)</td>
<td></td>
</tr>
<tr>
<td>Viral-related cirrhosis: not stated</td>
<td></td>
</tr>
<tr>
<td>Autoimmune disease-related cirrhosis: not stated</td>
<td></td>
</tr>
<tr>
<td>Other causes of cirrhosis: not stated</td>
<td></td>
</tr>
<tr>
<td>Other exclusion criteria: previous sclero therapy of oesophageal varices, current beta-blocker treatment or impossibility for it to be replaced by another medication, repeated sclero therapy not technically feasible, and permanent beta-blocker treatment not feasible</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Group 1: beta-blockers (n = 68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Further details: propranolol: starting dose 160 mg adjusted to decrease heart rate by 25%</td>
<td></td>
</tr>
<tr>
<td>Group 2: sclero therapy (n = 73)</td>
<td></td>
</tr>
<tr>
<td>Further details: sclero therapy: polidocanol 10 mg/mL, maximum of 30 mL repeated in 1- to 2-week intervals</td>
<td></td>
</tr>
<tr>
<td>Group 3: beta-blockers and sclero therapy (n = 73)</td>
<td></td>
</tr>
<tr>
<td>Further details: sclero therapy: polidocanol 10 mg/mL, maximum of 30 mL repeated in 1- to 2-week intervals + propranolol: starting dose 160 mg adjusted to decrease heart rate by 25%</td>
<td></td>
</tr>
<tr>
<td>Group 4: no active intervention (n = 72)</td>
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</tr>
<tr>
<td>Further details: no active treatment</td>
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</tr>
</tbody>
</table>
### PROVA study group 1991 (Continued)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Mortality at maximal follow-up, variceal bleed at maximal follow-up (symptomatic recovery) (number of participants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up (months): 15.4</td>
<td></td>
</tr>
</tbody>
</table>

**Notes**
- Source of funding (quote): "The study was supported by the Danish Medical Research Council (grant no. 12-55991, ICI Pharmaceuticals Inc. and Kreussler Inc."
- Trial name/trial registry number: PROVA study group
- Attempted to contact the authors in February 2020; received no additional information

### Risk of bias

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

### Psilopoulos 2005

**Study characteristics**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td></td>
</tr>
<tr>
<td>Country: Greece</td>
<td></td>
</tr>
<tr>
<td>Period of recruitment: 1999–2003</td>
<td></td>
</tr>
<tr>
<td>Number randomised: 60</td>
<td></td>
</tr>
<tr>
<td>Postrandomisation dropouts: 0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Revised sample size: 60</td>
<td></td>
</tr>
</tbody>
</table>
Psilopoulos 2005 (Continued)

Mean age (years): 60
Females: 18 (30.0%)
Small varices: 46 (76.7%)
High risk of bleeding: 60 (100.0%)
Other features of decompensation: not stated
Alcohol-related cirrhosis: 15 (25.0%)
Viral-related cirrhosis: 36 (60.0%)
Autoimmune disease-related cirrhosis: 4 (6.7%)
Other causes of cirrhosis: 5 (8.3%)

Other inclusion criteria: portal hypertension caused by cirrhosis, irrespectively of aetiology and Child–Pugh class; grade II or grade III oesophageal varices (F2, F3 according to Beppu classification), with ≥1 sign of increased risk of bleeding (red wale markings, cherry red spots, haematocystic spots); no history of variceal bleeding; no treatment with beta-blockers or nitrates; written informed consent

Other exclusion criteria: aged > 70 years or < 20 years; gastric or ectopic varices; severe comorbidity that could substantially reduce life expectancy; refractory ascites, hepatic encephalopathy, or marked jaundice (serum bilirubin > 10 mg/dL); known contraindications to propranolol treatment such as heart failure, obstructive airway disease, hypotension (systolic pressure < 90 mmHg), bradycardia (pulse rate < 60/minute), diabetes mellitus, severe peripheral vascular disease; history of endoscopic sclerotherapy, endoscopic variceal ligation, TIPSs, or surgical portacaval shunt

Interventions

Group 1: variceal band ligation (n = 30)
Further details: variceal band ligation using a multiband ligator repeated

Group 2: beta-blockers (n = 30)
Further details: propranolol, adjusted to achieve a 25% maximal reduction of the pretreatment pulse rate

Outcomes

Mortality at maximal follow-up, any adverse events (number of participants), any adverse events (number of events)
Follow-up (months): 27.5

Notes

Source of funding (quote): "The study was partially funded by a grant of the Hellenic Society of Gastroenterology."

Trial name/trial registry number: not stated

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

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Low risk</td>
<td>Quote: &quot;table of random numbers.&quot;</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Unclear risk</td>
<td>Quote: &quot;A resident doctor gave a number from the table to each patient entering the study.&quot;</td>
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<tr>
<td></td>
<td></td>
<td>Comment: further details were not available.</td>
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### Psilopoulos 2005 (Continued)

<table>
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<tr>
<th>Blinding of participants and personnel (performance bias)</th>
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<th>Comment: information not available</th>
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<tbody>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Blinding of outcome assessment (detection bias)</th>
<th>Unclear risk</th>
<th>Comment: information not available</th>
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<td>All outcomes</td>
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</table>

<table>
<thead>
<tr>
<th>Incomplete outcome data (attrition bias)</th>
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<th>Comment: no postrandomisation dropouts</th>
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<tbody>
<tr>
<td>All outcomes</td>
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<table>
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<td>All outcomes</td>
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<table>
<thead>
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<th>Other bias</th>
<th>Low risk</th>
<th>Comment: no other bias noted</th>
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<tbody>
<tr>
<td>All outcomes</td>
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</table>

### Quer 1991

#### Study characteristics

<table>
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<th>Methods</th>
<th>Randomised clinical trial</th>
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<td></td>
<td>Number randomised: 47</td>
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<td></td>
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<td></td>
<td>Revised sample size: 46</td>
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<tr>
<td></td>
<td>Reasons for postrandomisation dropouts: refused therapy</td>
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<tr>
<td></td>
<td>Mean age (years): 56</td>
</tr>
<tr>
<td></td>
<td>Females: 16 (34.8%)</td>
</tr>
<tr>
<td></td>
<td>Small varices: 30 (65.2%)</td>
</tr>
<tr>
<td></td>
<td>High risk of bleeding: 7 (15.2%)</td>
</tr>
<tr>
<td></td>
<td>Other features of decompenstation: 4 (8.7%)</td>
</tr>
<tr>
<td></td>
<td>Alcohol-related cirrhosis: 31 (67.4%)</td>
</tr>
<tr>
<td></td>
<td>Viral-related cirrhosis: not stated</td>
</tr>
<tr>
<td></td>
<td>Autoimmune disease-related cirrhosis: not stated</td>
</tr>
<tr>
<td></td>
<td>Other causes of cirrhosis: not stated</td>
</tr>
<tr>
<td></td>
<td>Other inclusion criteria: hepatic cirrhosis and varices type B or greater</td>
</tr>
<tr>
<td></td>
<td>Other exclusion criteria: previous episodes of digestive haemorrhage</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Group 1: sclerotherapy (n = 22)</th>
</tr>
</thead>
</table>
Further details: sclerotherapy: 1% polidocanol 30–50 mL per session, every 2 weeks to start with and later every 4 weeks until obliteration

Group 2: no active intervention (n = 24)

Further details: no treatment

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Mortality at maximal follow-up, variceal bleed at maximal follow-up (any) (number of participants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up (months): 16</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Notes</th>
<th>Source of funding: not stated</th>
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<tbody>
<tr>
<td></td>
<td>Trial name/trial registry number: not stated</td>
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<td></td>
<td>Attempted to contact the authors in February 2020; received no additional information</td>
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### Risk of bias

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

### Rossi 1991

<table>
<thead>
<tr>
<th>Study characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
</tr>
<tr>
<td>Participants</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
Revised sample size: 37
Mean age (years): 63
Females: 20 (54.1%)
Small varices: not stated
High risk of bleeding: not stated
Other features of decompensation: not stated
Alcohol-related cirrhosis: 18 (48.6%)
Viral-related cirrhosis: 11 (29.7%)
Autoimmune disease-related cirrhosis: not stated
Other causes of cirrhosis: 8 (21.6%)
Other inclusion criteria: cirrhosis; high-risk varices; partial thromboplastin time > 50%; platelet count > 70,000/µL
Other exclusion criteria: previous haemorrhage; peptic ulcer; neoplasia

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Group 1: sclerotherapy (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Further details: sclerotherapy 1% polidocanol at weekly intervals until obliteration of varices</td>
</tr>
<tr>
<td></td>
<td>Group 2: no active intervention (n = 19)</td>
</tr>
<tr>
<td></td>
<td>Further details: no treatment</td>
</tr>
</tbody>
</table>

| Outcomes                          | Mortality at maximal follow-up                                                               |
|                                   | Follow-up (months): 36.6                                                                     |

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

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
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<td>Comment: information not available</td>
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<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
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### Rossi 1991 (Continued)

<table>
<thead>
<tr>
<th>Incomplete outcome data (attrition bias) All outcomes</th>
<th>Low risk</th>
<th>Comment: no postrandomisation dropouts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Comment: no prepublished protocol available</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Comment: no other bias noted</td>
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</tbody>
</table>

### Russo 1989

#### Study characteristics

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td></td>
</tr>
<tr>
<td>Country: Italy</td>
<td></td>
</tr>
<tr>
<td>Period of recruitment: 1984–1985</td>
<td></td>
</tr>
<tr>
<td>Number randomised: 41</td>
<td></td>
</tr>
<tr>
<td>Postrandomisation dropouts: 0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Revised sample size: 41</td>
<td></td>
</tr>
<tr>
<td>Mean age (years): 62</td>
<td></td>
</tr>
<tr>
<td>Females: 17 (41.5%)</td>
<td></td>
</tr>
<tr>
<td>Small varices: 0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>High risk of bleeding: not stated</td>
<td></td>
</tr>
<tr>
<td>Other features of decompensation: not stated</td>
<td></td>
</tr>
<tr>
<td>Alcohol-related cirrhosis: 0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Viral-related cirrhosis: 31 (75.6%)</td>
<td></td>
</tr>
<tr>
<td>Autoimmune disease-related cirrhosis (e.g. primary sclerosing cholangitis, primary biliary cirrhosis, autoimmune hepatitis): not stated</td>
<td></td>
</tr>
<tr>
<td>Other causes for cirrhosis: 10 (24.3%)</td>
<td></td>
</tr>
<tr>
<td>Other inclusion criteria: only non-alcoholic liver cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Other exclusion criteria: alcohol intake &gt; 80 g/day</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1: sclerotherapy (n = 21)</td>
<td></td>
</tr>
<tr>
<td>Further details: sclerotherapy: 1% polidocanol mean 22.5 mL per session repeated every 7–10 days until obliteration of varices</td>
<td></td>
</tr>
<tr>
<td>Group 2: no active intervention (n = 20)</td>
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<tr>
<td>Further details: no treatment</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality at maximal follow-up</td>
<td></td>
</tr>
<tr>
<td>Follow-up (months): 18</td>
<td></td>
</tr>
</tbody>
</table>
Russo 1989 (Continued)

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

Risk of bias

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

Santangelo 1988

Study characteristics

Methods
Randomised clinical trial

Participants
Country: USA
Period of recruitment: 1985–1987
Number randomised: 101
Postrandomisation dropouts: 6 (5.9%)
Revised sample size: 95
Reasons for postrandomisation dropouts: did not want to continue sclerotherapy or lost to follow-up
Mean age (years): 42
Females: 25 (26.3%)
Small varices: 0 (0.0%)
High risk of bleeding: not stated
Other features of decompensation: 22 (23.0%)
Alcohol-related cirrhosis: 85 (89.5%)
Viral-related cirrhosis: 3 (3.2%)
Autoimmune disease-related cirrhosis: 4 (4.2%)
Other causes of cirrhosis: 3 (3.2%)
Other exclusion criteria: ≤ grade 2 or lower varices, or no varices

Interventions
Group 1: sclerotherapy (n = 49)
Further details: sclerotherapy: 1% sodium tetradecyl 10–20 mL per treatment session, repeated every 10–14 days until varices decrease markedly in size or were obliterated
Group 2: no active intervention (n = 46)
Further details: no treatment

Outcomes
Mortality at maximal follow-up, length of hospital stay (days) (all admissions until maximal follow-up)
Follow-up (months): 13

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

Risk of bias

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

**Methods**  
Randomised clinical trial

**Participants**  
Country: India  
Period of recruitment: 2004–2007  
Number randomised: 164  
Postrandomisation dropouts: 14 (8.5%)  
Revised sample size: 150  
Reasons for postrandomisation dropouts: dropped out before the completion of 6 months of study  
Mean age (years): 43  
Females: 30 (20.0%)  
Small varices: 150 (100.0%)  
High risk of bleeding: not stated  
Other features of decompensation: 3 (2.0%)  
Alcohol-related cirrhosis: 53 (35.3%)  
Viral-related cirrhosis: 80 (53.3%)  
Autoimmune disease-related cirrhosis: not stated  
Other causes of cirrhosis: 17 (11.3%)  
Other inclusion criteria: cirrhosis; aged 18–70 years, grade 1 or 2 varices or small per Bavano classification  
Other exclusion criteria: history of variceal bleeding

**Interventions**  
Group 1: no active intervention (n = 73)  
Further details: placebo  
Group 2: beta-blockers (n = 77)  
Further details: propranolol titrated to achieve a target heart rate of 55 bpm or maximal dose 360 mg/day, if the medication was well tolerated and the systolic blood pressure remained at least 90 mmHg

**Outcomes**  
Mortality at maximal follow-up, any adverse events (number of participants)  
Follow-up (months): 25

**Notes**  
Source of funding: not stated  
Trial name/trial registry number: NCT00772057  
Attempted to contact the authors in February 2020; received no additional information

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
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<th>Support for judgement</th>
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</thead>
</table>

Primary prevention of variceal bleeding in people with oesophageal varices due to liver cirrhosis: a network meta-analysis (Review)  
Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
### Sarin 2013 (Continued)

<table>
<thead>
<tr>
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<th>Risk</th>
<th>Description</th>
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</thead>
<tbody>
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<td>Quote: &quot;All randomizations were done by computer-generated random numbers.&quot;</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low</td>
<td>Quote: &quot;The randomization sequence remained with the statistician, and the sequence remained concealed from the investigators until the intervention was assigned.&quot;</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>High</td>
<td>Quote: &quot;Single blind…The endoscopists were blinded to the treatment protocol.&quot;</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td>Comment: the primary outcome of this trial was growth of oesophageal varices, which an endoscopist assessed.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>High</td>
<td>Quote: &quot;Single blind…The endoscopists were blinded to the treatment protocol.&quot;</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td>Comment: the primary outcome of this trial was growth of oesophageal varices, which an endoscopist assessed. However, the endoscopist assessed none of the outcomes of interest for this review.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High</td>
<td>Comment: there were postrandomisation dropouts that were probably related to the intervention and outcome.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear</td>
<td>Comment: no prepublished protocol available</td>
</tr>
<tr>
<td>Other bias</td>
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<td>Comment: no other bias noted</td>
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### Sauerbruch 1988

#### Study characteristics

<table>
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<th>Randomised clinical trial</th>
</tr>
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<td>Participants</td>
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<tr>
<td></td>
<td>Period of recruitment: 1982–1986</td>
</tr>
<tr>
<td></td>
<td>Number randomised: 133</td>
</tr>
<tr>
<td></td>
<td>Postrandomisation dropouts: 0 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>Revised sample size: 133</td>
</tr>
<tr>
<td></td>
<td>Mean age (years): 56</td>
</tr>
<tr>
<td></td>
<td>Females: 44 (33.1%)</td>
</tr>
<tr>
<td></td>
<td>Small varices: 0 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>High risk of bleeding: 48 (36.1%)</td>
</tr>
<tr>
<td></td>
<td>Other features of decompensation: 63 (47.4%)</td>
</tr>
<tr>
<td></td>
<td>Alcohol-related cirrhosis: 88 (66.2%)</td>
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<tr>
<td></td>
<td>Viral-related cirrhosis: 34 (25.6%)</td>
</tr>
<tr>
<td></td>
<td>Autoimmune disease-related cirrhosis: not stated</td>
</tr>
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Other causes of cirrhosis: not stated
Other inclusion criteria: liver cirrhosis; ≥ 2 varices in the distal part of the oesophagus, each with a diameter ≥ 5 mm; no previous intestinal bleeding; no extrahepatic disease; no gastrointestinal ulcer at the time of randomisation; a Child-Pugh score < 12; no current treatment with steroids, beta-blockers, and penicillamine; aged 18–75 years

Interventions
Group 1: sclerotherapy (n = 68)
Further details: sclerotherapy: 1% polidocanol repeated every 7–10 days until obliteration
Group 2: no active intervention (n = 65)
Further details: no treatment

Outcomes
Mortality at maximal follow-up, variceal bleed at maximal follow-up (symptomatic recovery) (number of participants)
Follow-up (months): 22

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

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
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<th>Support for judgement</th>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: “Randomisation was subsequently carried out by a Central trial secretariat according to the Efron biased coin method.”</td>
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<tr>
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<td>Quote: “Randomisation was subsequently carried out by a Central trial secretariat according to the Efron biased coin method.”</td>
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<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
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<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
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<td>Comment: no postrandomisation dropouts</td>
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<td>Selective reporting (reporting bias)</td>
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<tr>
<td>Other bias</td>
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</table>

Sauerbruch 1988

Schepke 2004

Study characteristics
### Methods
Randomised clinical trial

### Participants
- **Country:** Germany
- **Period of recruitment:** 1996–2001
- **Number randomised:** 157
- **Postrandomisation dropouts:** 5 (3.2%)
- **Revised sample size:** 152
- **Reasons for postrandomisation dropouts:** wrongly included despite meeting exclusion criteria
- **Mean age (years):** 56
- **Females:** 48 (31.6%)
- **Small varices:** 67 (44.1%)
- **High risk of bleeding:** 59 (38.8%)
- **Other features of decompensation:** 19 (12.5%)
- **Alcohol-related cirrhosis:** 78 (51.3%)
- **Viral-related cirrhosis:** 47 (30.9%)
- **Autoimmune disease-related cirrhosis:** 8 (5.3%)
- **Other causes of cirrhosis:** 18 (11.8%)
- **Other inclusion criteria:** ≥ 2 oesophageal varices with diameter > 5 mm; confirmed liver cirrhosis; Child-Pugh score < 12; aged 18–75 years
- **Other exclusion criteria:** previous variceal bleeding; prehepatic portal hypertension; heart rate < 64 bpm; systolic blood pressure < 100 mmHg; contraindications to propranolol; severe comorbidity reducing life expectancy; being listed for liver transplantation; long-term anticoagulant treatment; treatment with beta-blockers or nitrates 30 days before randomisation; existing transjugular intrahepatic porto-systemic or surgical shunt; non-compliance with the study protocol

### Interventions
- **Group 1:** variceal band ligation (n = 75)
  - Further details: variceal band ligation using multiband ligator at weekly sessions until obliteration
- **Group 2:** beta-blockers (n = 77)
  - Further details: propranolol, until a reduction of the resting heart rate of 20% compared to the pre-treatment heart rate

### Outcomes
- **Mortality at maximal follow-up,** any adverse events (number of participants), any adverse events (number of events), liver transplantation at maximal follow-up
- **Follow-up (months):** 51.8

### Notes
- **Source of funding (quote):** "Supported by the German Association for the Study of the Liver (GASL) and the Ernst und Berta Grimmke Stiftung, Dusseldorf, Germany"
- **Trial name/trial registry number:** not stated
- **Attempted to contact the authors in February 2020; received no additional information**
### Schepke 2004 (Continued)

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<td>Quote: “Patients were centrally assigned to the 2 treatment arms at the Institute of Medical Biometry, University of Bonn, Germany, by a block randomization with blocks of 6 patients for each centre.” Comment: although the details on sequence generation were not reported, the method of allocation concealment used makes it highly likely that the sequence was random.</td>
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<td>Comment: although there were postrandomisation dropouts, these did not appear to be related to the intervention or outcome.</td>
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### Seo 2017

**Study characteristics**

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<td>Participants</td>
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<tr>
<td></td>
<td>Period of recruitment: not stated</td>
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<tr>
<td></td>
<td>Number randomised: 260</td>
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<td></td>
<td>Postrandomisation dropouts: 1 (0.4%)</td>
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<td></td>
<td>Revised sample size: 259</td>
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<tr>
<td></td>
<td>Reasons for postrandomisation dropouts: not stated</td>
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<tr>
<td></td>
<td>Mean age (years): 53</td>
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<tr>
<td></td>
<td>Females: 70 (27.0%)</td>
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<tr>
<td></td>
<td>Small varices: 146 (56.4%)</td>
</tr>
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<td></td>
<td>High risk of bleeding: not stated</td>
</tr>
<tr>
<td></td>
<td>Other features of decompensation: not stated</td>
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</table>
Alcohol-related cirrhosis: not stated
Viral-related cirrhosis: not stated
Autoimmune disease-related cirrhosis: not stated
Other causes of cirrhosis: not stated

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

Risk of bias

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<th>Support for judgement</th>
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<td>Comment: information not available</td>
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<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
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<td>Comment: information not available</td>
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<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
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<td>Comment: information not available</td>
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<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Comment: 1 participant was excluded from analysis; unclear whether this was related to the outcomes, but was unlikely to alter the effect estimates considerably.</td>
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</tr>
<tr>
<td>Other bias</td>
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</table>
### Study characteristics

**Methods**
Randomised clinical trial

**Participants**
Country: Pakistan  
Period of recruitment: 2007–2011  
Number randomised: 168  
Postrandomisation dropouts: 0 (0.0%)  
Revised sample size: 168  
Mean age (years): 48  
Females: 46 (27.4%)  
Small varices: 91 (54.2%)  
High risk of bleeding: not stated  
Other features of decompensation: 65 (38.7%)  
Alcohol-related cirrhosis: 3 (1.8%)  
Viral-related cirrhosis: 151 (89.9%)  
Autoimmune disease-related cirrhosis: not stated  
Other causes of cirrhosis: 14 (8.3%)  
Other inclusion criteria: liver cirrhosis; large size oesophageal varices  
Other exclusion criteria: pregnant or lactating; allergy to carvedilol or reactive airway disease; already on beta-blocker treatment; presence of any hepatic or other malignancy; people with psychiatric or mental disabilities that would prevent them giving informed consent and refusal to give consent; gastric varices alone

**Interventions**
Group 1: variceal band ligation (n = 86)  
Further details: variceal band ligation using multiband ligator, repeated every 3 weeks until obliteration of varices  
Group 2: beta-blockers (n = 82)  
Further details: carvedilol 6.25 mg once daily increased to 6.25 mg twice daily after 1 week

**Outcomes**
Mortality at maximal follow-up, serious adverse events (number of events), any adverse events (number of events)  
Follow-up (months): 13.3

**Notes**
Source of funding (quote): "The research team acknowledges the unconditional support of Ferozsons Laboratories (BF Bio-Sciences)"

Trial name/trial registry number: NCT01070641  
Attempted to contact the authors in February 2020; received no additional information
### Shah 2014 (Continued)

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

### Singh 2012

#### Study characteristics

<table>
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<th>Methods</th>
<th>Randomised clinical trial</th>
</tr>
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<tbody>
<tr>
<td>Participants</td>
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</tr>
<tr>
<td></td>
<td>Period of recruitment: not stated</td>
</tr>
<tr>
<td></td>
<td>Number randomised: 38</td>
</tr>
<tr>
<td></td>
<td>Postrandomisation dropouts: 0 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>Revised sample size: 38</td>
</tr>
<tr>
<td></td>
<td>Mean age (years): not stated</td>
</tr>
<tr>
<td></td>
<td>Females: not stated</td>
</tr>
<tr>
<td></td>
<td>Small varices: 0 (0.0%)</td>
</tr>
</tbody>
</table>

Primary prevention of variceal bleeding in people with oesophageal varices due to liver cirrhosis: a network meta-analysis (Review)
Singh 2012 (Continued)

High risk of bleeding: not stated
Other features of decompensation: 23 (60.5%)
Alcohol-related cirrhosis: 19 (50.0%)
Viral-related cirrhosis: 15 (39.5%)
Autoimmune disease-related cirrhosis: 1 (2.6%)
Other causes of cirrhosis: 3 (7.9%)
Other inclusion criteria: liver cirrhosis; large size varices (grade 3–4)
Other exclusion criteria: receiving antiviral therapy; concomitant hepatoma or another tumour; severe cardio-pulmonary or renal disease; bradycardia; bronchial asthma; diabetes mellitus; heart failure; peripheral vascular disease; a psychiatric disorder; glaucoma; prostatic hypertrophy

Interventions

Group 1: variceal band ligation (n = 18)
Further details: variceal band ligation using multiband ligator every week until the varices were obliterated
Group 2: beta-blockers (n = 20)
Further details: propranolol, at a dose sufficient to decrease the baseline heart rate by 25%, until the varices were obliterated

Outcomes
Mortality at maximal follow-up
Follow-up (months): 12

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

Risk of bias

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### Snady 1988

#### Study characteristics

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<tr>
<td><strong>Participants</strong></td>
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<td>Small varices: not stated</td>
</tr>
<tr>
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<td>High risk of bleeding: not stated</td>
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<tr>
<td></td>
<td>Other features of decompensation: not stated</td>
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<tr>
<td></td>
<td>Alcohol-related cirrhosis: 56 (100.0%)</td>
</tr>
<tr>
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<td>Viral-related cirrhosis: 0 (0.0%)</td>
</tr>
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<td></td>
<td>Autoimmune disease-related cirrhosis: 0 (0.0%)</td>
</tr>
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<td>Other causes of cirrhosis: 0 (0.0%)</td>
</tr>
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<td></td>
<td>Other inclusion criteria: people with cirrhosis with alcoholic liver disease and oesophageal varices that never bled</td>
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<td><strong>Interventions</strong></td>
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<td>Group 1: beta-blockers</td>
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<td>Further details:</td>
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<td>Group 2: no active intervention</td>
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<td>Further details:</td>
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<td>Group 3: sclerotherapy</td>
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<td>Further details:</td>
<td>sclerotherapy (no further details)</td>
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<tr>
<td>Group 4: beta-blockers + sclerotherapy</td>
<td>(n = 12)</td>
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<td>Further details:</td>
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#### Outcomes

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<td><strong>Mortality at maximal follow-up</strong></td>
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<tr>
<td><strong>Follow-up (months): 12</strong></td>
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Snady 1988 (Continued)

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

Risk of bias

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</tbody>
</table>

Song 1999

Study characteristics

Methods
Randomised clinical trial

Participants
Country: Korea
Number randomised: 64
Postrandomisation dropouts: 3 (4.7%)
Revised sample size: 61
Reasons for postrandomisation dropouts: transferred to different hospital or discontinued therapy after complications
Mean age (years): 55
Females: 6 (9.8%)
Small varices: 39 (63.9%)
High risk of bleeding: not stated
Other features of decompensation: 7 (11.5%)
Alcohol-related cirrhosis: 22 (36.1%)
Viral-related cirrhosis: 35 (57.4%)
Autoimmune disease-related cirrhosis: not stated
Other causes of cirrhosis: 4 (6.6%)
Other inclusion criteria: high-risk varices
Other exclusion criteria: previous bleeding, cardiopulmonary disease, hepatocellular carcinoma

Interventions
Group 1: variceal band ligation (n = 31)
Further details: variceal band ligation using Stieglmann-Goff endoscopic ligator kit, repeated at 2-week to 3-month intervals until obliteration of varices
Group 2: beta-blockers (n = 30)
Further details: propranolol titrated to decrease the heart rate to 25% of the participant’s basal heart rate

Outcomes
Mortality at maximal follow-up, variceal bleed at maximal follow-up (any) (number of participants)
Follow-up (months): 12

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

Risk of bias

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### Strauss 1999

#### Study characteristics

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| Participants | Country: Brazil  
Period of recruitment: 1984–1989  
Number randomised: 43  
Postrandomisation dropouts: 3 (7.0%)  
Revised sample size: 40  
Reasons for postrandomisation dropouts: lost to follow-up or did not complete sclerotherapy  
Mean age (years): 51  
Females: not stated  
Small varices: 40 (100.0%)  
High risk of bleeding: not stated  
Other features of decompensation: not stated  
Alcohol-related cirrhosis: not stated  
Viral-related cirrhosis: not stated  
Autoimmune disease-related cirrhosis: not stated  
Other causes of cirrhosis: not stated  
Other inclusion criteria: liver cirrhosis, no previous bleeding, small oesophageal varices |

| Interventions | Group 1: sclerotherapy (n = 19)  
Further details: sclerotherapy: ethanolamine oleate up to 20 mL per session, repeated every 30 days until obliteration  
Group 2: no active intervention (n = 21)  
Further details: no treatment |
| Outcomes | Mortality at maximal follow-up  
Follow-up (months): 60 |

### Notes

- Source of funding: not stated
- Trial name/trial registry number: not stated
- Attempted to contact the authors in February 2020; received no additional information
### Strauss 1999 (Continued)

<table>
<thead>
<tr>
<th>Bias</th>
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<td>Blinding of participants and personnel (performance bias) All outcomes</td>
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<td>Incomplete outcome data (attrition bias) All outcomes</td>
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### Svoboda 1999

**Study characteristics**

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<tr>
<td></td>
<td>Period of recruitment: 1994–1997</td>
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<tr>
<td></td>
<td>Number randomised: 186</td>
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<tr>
<td></td>
<td>Postrandomisation dropouts: 29 (15.6%)</td>
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<td>Revised sample size: 157</td>
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<td>Reasons for postrandomisation dropouts: lost to follow-up</td>
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<td></td>
<td>Mean age (years): 46</td>
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<tr>
<td></td>
<td>Females: 35 (22.3%)</td>
</tr>
<tr>
<td></td>
<td>Small varices: 7 (4.5%)</td>
</tr>
<tr>
<td></td>
<td>High risk of bleeding: not stated</td>
</tr>
<tr>
<td></td>
<td>Other features of decompensation: not stated</td>
</tr>
<tr>
<td></td>
<td>Alcohol-related cirrhosis: 109 (69.4%)</td>
</tr>
<tr>
<td></td>
<td>Viral-related cirrhosis: 48 (30.6%)</td>
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<tr>
<td></td>
<td>Autoimmune disease-related cirrhosis: 0 (0.0%)</td>
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</table>
Other causes of cirrhosis: 0 (0.0%)

Other inclusion criteria: people with cirrhosis with alcoholic liver disease and oesophageal varices that never bled

Interventions

Group 1: sclerotherapy (n = 55)

Further details: sclerotherapy: 1% polidocanol, maximum of 20 mL per session initially every 2 weeks, and then every month until eradication of varices

Group 2: variceal band ligation (n = 52)

Further details: variceal band ligation using multiband ligator until eradication of varices

Group 3: no active intervention (n = 50)

Further details: no treatment

Outcomes

Mortality at maximal follow-up, serious adverse events (number of participants), any adverse events (number of events)

Follow-up (months): 25

Notes

Source of funding (quote): "This work was supported by grant IGA MZ CR 5187 of Internal Grant Agency of Ministry of Health of the Czech Republic ND 5 187-3"

Trial name/trial registry number: not stated

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

Risk of bias

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<tr>
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</table>
Thuluvath 2005

Study characteristics

Methods
Randomised clinical trial

Participants
Country: Brazil
Period of recruitment: 2000–2002
Number randomised: 31
Postrandomisation dropouts: 0 (0.0%)
Revised sample size: 31
Mean age (years): 52
Females: 14 (45.2%)
Small varices: not stated
High risk of bleeding: not stated
Other features of decompensation: not stated
Alcohol-related cirrhosis: 6 (19.4%)
Viral-related cirrhosis: 13 (41.9%)
Autoimmune disease-related cirrhosis: 8 (25.8%)
Other causes of cirrhosis: 4 (12.9%)
Other inclusion criteria: liver cirrhosis, no previous bleeding, small oesophageal varices

Interventions
Group 1: variceal band ligation (n = 16)
Further details: variceal band ligation using multiband ligator every 2–3 weeks until obliteration
Group 2: beta-blockers (n = 15)
Further details: propranolol dose was titrated to achieve a resting heart rate < 60 bpm, or a 25% reduction from baseline, or until the maximum tolerated dose was achieved

Outcomes
Mortality at maximal follow-up, liver transplantation at maximal follow-up
Follow-up (months): 27.4

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

Risk of bias

Bias Authors' judgement Support for judgement
Random sequence generation (selection bias) Unclear risk Quote: “using sealed envelopes.”
Comment: further details were not available
### Thuluvath 2005 (Continued)

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### Tomikawa 2004

#### Study characteristics

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<td>Participants</td>
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<td></td>
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<td></td>
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<tr>
<td></td>
<td>Postrandomisation dropouts: 0 (0.0%)</td>
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<tr>
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<tr>
<td></td>
<td>Females: 10 (40.0%)</td>
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<tr>
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<td>Small varices: not stated</td>
</tr>
<tr>
<td></td>
<td>High risk of bleeding: 25 (100.0%)</td>
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<tr>
<td></td>
<td>Other features of decompensation: not stated</td>
</tr>
<tr>
<td></td>
<td>Alcohol-related cirrhosis: 2 (8.0%)</td>
</tr>
<tr>
<td></td>
<td>Viral-related cirrhosis: 23 (92.0%)</td>
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<tr>
<td></td>
<td>Autoimmune disease-related cirrhosis: 0 (0.0%)</td>
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<tr>
<td></td>
<td>Other causes of cirrhosis: 0 (0.0%)</td>
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<tr>
<td></td>
<td>Other inclusion criteria: cirrhosis with large varices and sign of high risk of bleeding</td>
</tr>
<tr>
<td>Interventions</td>
<td>Group 1: sclerotherapy (n = 13)</td>
</tr>
</tbody>
</table>
Further details: sclerotherapy: 5% ethanolamine oleate at weekly intervals until the whole lower oesophageal mucosa was replaced with an iatrogenic shallow ulcer

Group 2: beta-blockers (n = 12)
Further details: propranolol, dose titrated until the heart rate at rest was reduced by approximately 25%

Outcomes
Any adverse events (number of events), variceal bleed at maximal follow-up (any) (number of participants)
Follow-up (months): 13.5

Notes
Source of funding (quote): "This study was supported in part by health research grants from the “Health Science Research Including Drug Innovation” from the Japan Health Sciences Foundation.”

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

Risk of bias

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Tripathi 2009

Study characteristics

Methods
Randomised clinical trial

Participants
Country: UK
Period of recruitment: 2000–2006
Tripathi 2009 (Continued)

Number randomised: 152
Postrandomisation dropouts: 0 (0.0%)
Revised sample size: 152
Mean age (years): 54
Females: 43 (28.3%)
Small varices: not stated
High risk of bleeding: 7 (4.6%)
Other features of decompensation: 78 (51.3%)
Alcohol-related cirrhosis: 111 (73.0%)
Viral-related cirrhosis: not stated
Autoimmune disease-related cirrhosis: not stated
Other causes of cirrhosis: not stated
Other inclusion criteria: presence of cirrhosis and oesophageal varices grade II or larger in size without previous variceal bleeding
Other exclusion criteria: aged < 18 years or > 75 years; pregnant or lactating women; people of child-bearing age not receiving contraception; allergy to carvedilol; already on beta-blockers or nitrates; presence of malignancy that significantly affects survival; presence of severe systemic illness (cardiorespiratory, active sepsis); psychiatric disease or learning difficulty that will prevent the granting of informed consent; presence of obstructive airways disease; mean arterial pressure 55 mmHg or pulse 50 bpm at baseline; and portal vein thrombosis

Interventions

Group 1: variceal band ligation (n = 75)
Further details: variceal band ligation using multibander devices every 2 weeks until eradication of varices
Group 2: beta-blockers (n = 77)
Further details: carvedilol 12.5 mg once daily (initial dose 6.25 mg and increased to 12.5 mg per day if systolic blood pressure did not fall below 90 mmHg)

Outcomes
Mortality at maximal follow-up
Follow-up (months): 20

Notes
Source of funding (quote): "Supported by the University of Edinburgh"
Trial name/trial registry number: ISRCTN26269039
Attempted to contact the authors in February 2020; received no additional information

Risk of bias

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<td>Comment: although the details on sequence generation were not reported, the method of allocation concealment used makes it highly likely that the sequence was random.</td>
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### Tripathi 2009 (Continued)

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### VA Coop. Variceal Sclerotherapy Group 1991

**Study characteristics**

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<td>Number randomised: 281</td>
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<td>Postrandomisation dropouts: 0 (0.0%)</td>
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<td>Revised sample size: 281</td>
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<td>Mean age (years): 58</td>
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<tr>
<td></td>
<td>Females: 0 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>Small varices: 181 (64.4%)</td>
</tr>
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<td></td>
<td>Other features of decompensation: 140 (49.8%)</td>
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<tr>
<td></td>
<td>Alcohol-related cirrhosis: 281 (100.0%)</td>
</tr>
<tr>
<td></td>
<td>Viral-related cirrhosis: 0 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>Autoimmune disease-related cirrhosis: 0 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>Other causes of cirrhosis: 0 (0.0%)</td>
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<td>Other exclusion criteria: hepatitis B surface antigen positivity; hepatocellular carcinoma; previous sclerotherapy or shunt surgery; history of malignancies or cardiovascular disease</td>
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<tr>
<td>Interventions</td>
<td>Group 1: sclerotherapy (n = 143)</td>
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</table>
Further details: sclerotherapy: 1.5% sodium tetradecyl sulphate up to 20 mL per session until obliteration; frequency unclear

Group 2: no active intervention (n = 138)

Further details: placebo

Outcomes

Mortality at maximal follow-up, any adverse events (number of events), variceal bleed at maximal follow-up (any) (number of rebleeds)

Follow-up (months): 47

Notes

Source of funding (quote): "Supported by the Cooperative Services Program of the Medical Research Service, Department of Veterans Affairs"

Trial name/trial registry number: not stated

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

### Risk of bias

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<td>Quote: &quot;Randomisation was carried out according to permuted-blocks design.&quot;</td>
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<td>Blinding of participants and personnel (performance bias)</td>
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<td>Quote: &quot;Only the members of the endoscopy-sclerotherapy team were aware of the patient’s assignments; all other care givers remained unaware of the treatment assignment.&quot;</td>
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</table>
## Study characteristics

### Methods
- Randomised clinical trial

### Participants
- **Country:** Taiwan
  - **Period of recruitment:** 2002–2004
  - **Number randomised:** 61
  - **Postrandomisation dropouts:** 0 (0.0%)
  - **Revised sample size:** 61
  - **Mean age (years):** 61
  - **Females:** 23 (37.7%)
  - **Small varices:** 39 (63.9%)
  - **High risk of bleeding:** 61 (100.0%)
  - **Other features of decompensation:** 1 (1.6%)
  - **Alcohol-related cirrhosis:** 11 (18.0%)
  - **Viral-related cirrhosis:** 47 (77.0%)
  - **Autoimmune disease-related cirrhosis:** not stated
  - **Other causes of cirrhosis:** 3 (4.9%)
  - **Other inclusion criteria:** portal hypertension caused by cirrhosis; oesophageal varices of moderate or severe grade, associated with any red colour signs (red wale marking, cherry red spots, haematocystic spots); no history of haemorrhage from oesophageal varices; no current treatment with beta-blockers or nitrates, diagnosis of cirrhosis was based on liver biopsy or clinical examination, biochemical tests, and imaging studies
  - **Other exclusion criteria:** aged > 75 years or < 20 years; presence of malignancy, uraemia, or other serious medical illness that could reduce life expectancy; refractory ascites, hepatic encephalopathy, or marked jaundice (serum bilirubin > 10 mg/dL); history of shunt operation, transjugular intrahepatic portosystemic stent shunt, or endoscopic therapy (sclerotherapy or endoscopic variceal ligation); contraindications to beta-blockers or nitrates, e.g. asthma, chronic obstructive airway disease, diabetes mellitus with documented hypoglycaemic episodes, congestive heart failure, peripheral vascular disease, hypotension (systolic blood pressure < 90 mmHg) and bradycardia

### Interventions
- **Group 1:** beta-blockers + nitrates (n = 31)
  - Further details: nadolol to reduce the pulse rate by 25% and isosorbide mononitrate 20 mg once or twice daily
- **Group 2:** variceal band ligation (n = 30)
  - Further details: variceal band ligation using multiband ligator repeated at 4-weekly intervals until obliteration

### Outcomes
- **Mortality at maximal follow-up,** serious adverse events (number of participants), any adverse events (number of participants), variceal bleed at maximal follow-up (any) (number of participants)
  - **Follow-up (months):** 23.3
### Wang 2006 (Continued)

**Notes**

Source of funding (quote): "The study was supported by a grant from the Medical Research and Advancement Foundation in Memory of Dr Chi-Shuen Tsou in Taiwan."

Trial name/trial registry number: not stated

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

### Risk of bias

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<th>Support for judgement</th>
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### Witzel 1985

**Study characteristics**

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<td>Number randomised: 109</td>
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<tr>
<td>Postrandomisation dropouts: 0 (0.0%)</td>
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</tr>
<tr>
<td>Revised sample size: 109</td>
<td></td>
</tr>
<tr>
<td>Mean age (years): 53</td>
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</tr>
<tr>
<td>Females: 37 (33.9%)</td>
<td></td>
</tr>
<tr>
<td>Small varices: 75 (68.8%)</td>
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<tr>
<td>High risk of bleeding: not stated</td>
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</table>
Other features of decompensation: not stated
Alcohol-related cirrhosis: 88 (80.7%)
Viral-related cirrhosis: 16 (14.7%)
Autoimmune disease-related cirrhosis: not stated
Other causes of cirrhosis: 5 (4.6%)
Other inclusion criteria: liver cirrhosis, no previous bleeding

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Group 1: sclerotherapy (n = 56)</th>
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<tr>
<td></td>
<td>Further details: sclerotherapy 1% polidocanol repeated monthly until variceal obliteration</td>
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<tr>
<td></td>
<td>Group 2: no active intervention (n = 53)</td>
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<tr>
<th>Outcomes</th>
<th>Mortality at maximal follow-up, variceal bleed at maximal follow-up (any) (number of participants)</th>
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<td>Follow-up (months): 25</td>
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### Risk of bias

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<tr>
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<th>Authors’ judgement</th>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
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</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
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<td>Comment: information not available</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
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<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Comment: information not available</td>
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<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Comment: no postrandomisation dropouts</td>
</tr>
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<td>Selective reporting (reporting bias)</td>
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<td>Other bias</td>
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## Study characteristics

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<th>Randomised clinical trial</th>
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<tr>
<td>Number randomised: 49</td>
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<td>Mean age (years): 54</td>
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<td>Females: 12 (24.5%)</td>
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<tr>
<td>Small varices: 0 (0.0%)</td>
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<td>Other features of decompensation: not stated</td>
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<tr>
<td>Alcohol-related cirrhosis: 22 (44.9%)</td>
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<tr>
<td>Viral-related cirrhosis: 18 (36.7%)</td>
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<td>Autoimmune disease-related cirrhosis: not stated</td>
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<tr>
<td>Other causes of cirrhosis: 9 (18.4%)</td>
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<tr>
<td>Other inclusion criteria: people with stage III or IV varices with confirmed liver cirrhosis and no previous bleeding</td>
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<tr>
<td>Interventions</td>
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<tr>
<td>Group 1: sclerotherapy (n = 25)</td>
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<tr>
<td>Further details: sclerotherapy using 1% polidocanol, maximum 30 mL per session, repeated every 8–10 days until obliteration</td>
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<td>Mortality at maximal follow-up</td>
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Wordhoff 1987 (Continued)

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

Characteristics of excluded studies [ordered by study ID]

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<tr>
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<tr>
<td>Avgerinos 2000</td>
<td>Compared endoscopic sclerotherapy + propranolol vs propranolol alone. Measured intraoesophageal variceal pressure. During this procedure, a considerable proportion of the control group who were randomised to propranolol received endoscopic sclerotherapy because of bleeding during measurement of intraoesophageal variceal pressure. Therefore, the effect of randomisation was lost.</td>
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RCT: randomised clinical trial.

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

**Buuren 2003**

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

- Randomised clinical trial

**Participants**

- Adults with oesophageal variceal bleeding with cirrhosis

**Interventions**

- **Group 1:** endoscopic band ligation
  - Further details: no further details
- **Group 2:** oral carvedilol
  - Further details: no further details

**Outcomes**

- Not stated

**Notes**

- No published data

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

**ChiCTR-IPR-15005816**

- **Study name:** Multicenter, randomized, comparative, prospective study on efficacy of EVL-EVS sequential therapy in preventing esophageal variceal hemorrhage

- **Methods**
  - Randomised clinical trial

- **Participants**
  - **Inclusion criteria:** written informed consent; aged 18–65 years; history of liver cirrhosis, endoscopy confirmed by gastroesophageal varices exist and have indication of endoscopic therapy; percutaneous transluminal angioplasty ≥ 40%; without other complications of liver cirrhosis
  - **Exclusion criteria:** with light to moderate oesophageal varices; with gastric varices; percutaneous transluminal angioplasty < 40%; combined with malignant tumour of liver or other organs; cannot give written informed consent

- **Interventions**
  - **Group 1:** control group
    - Further details: no further details
  - **Group 2:** EVL
    - Further details: no further details
  - **Group 3:** EVS
    - Further details: no further details
  - **Group 4:** EVL + EVS
    - Further details: no further details

- **Outcomes**
  - Outcomes planned: 5 year survival rate, oesophageal varices bleeding, rebleeding, oesophageal varices elimination

- **Starting date**
  - July 2017

- **Contact information**
  - Bin Wu: binwu001@hotmail.com
  - Department of Gastroenterology, The Third Affiliated Hospital of Sun Yat-sen University. No. 600, Tianhe Rd, Tianhe District, Guangzhou, Guangdong, China
### ChiCTR-IPR-15005816

**Notes**

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

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### NCT02066649

**Study name**

Carvedilol vs band ligation vs combination therapy for primary prophylaxis of variceal bleeding

**Methods**

Randomised clinical trial

**Participants**

Inclusion criteria: aged > 18 years with diagnosis of cirrhosis (by history, serology, or imaging), with medium or large oesophageal varices on variceal screening oesophagogastroduodenoscopy, and no history of gastrointestinal bleeding, as related to portal hypertension

Exclusion criteria: pregnant women; receiving beta-blockers or nitrates for any underlying condition; allergies to carvedilol; mean arterial pressure < 55 mmHg or heart rate < 55 beats per minute at baseline; presence of hepatocellular carcinoma; presence of portal vein thrombosis; severe, uncontrolled respiratory disease (asthma, chronic obstructive pulmonary disease); complete heart block or other significant arrhythmias; significant renal disease (Chronic Kidney Disease stage III or higher); unable to provide consent; and people who in the opinion of the principal investigator are not suitable for participation in the trial

**Interventions**

- **Group 1: beta-blocker**
  
  Further details: initiating participant on carvedilol after diagnosis of varices made on endoscopy

- **Group 2: variceal band ligation**
  
  Further details: performing variceal band ligation during endoscopy on participant after diagnosis of oesophageal varices made on endoscopy

- **Group 3: beta-blocker + variceal band ligation**
  
  Further details: once participant has confirmed large oesophageal varices on endoscopy, he/she will be started on carvedilol (postprocedure) in addition to having variceal band ligation performed during endoscopy

**Outcomes**

Planned primary outcomes: incidence of first variceal bleed (time frame: within 2-year follow-up)

Planned secondary outcomes: bleed-related mortality; overall mortality; recurrence of varices (time frame: within 2-year follow-up)

**Starting date**

Estimated study start date: July 2018

**Contact information**

Nikolaos T Pyrsopoulos

Rutgers, The State University of New Jersey

**Notes**

- Planned sample size: not stated
- Planned study time: July 2018 to September 2021

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### NCT03736265

**Study name**

Carvedilol for prevention of oesophageal varices progression

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

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### Methods

**Randomised clinical trial**

### Participants

**Inclusion criteria:** males or females; people with hepatitis B virus-related liver cirrhosis with ≥ 2 years of antiviral therapy; presence of small or medium oesophageal varices without red colour sign; hepatitis B virus-DNA < $1 \times 10^{3}$ IU/mL; signature of informed consent

**Exclusion criteria:** previous presence of decompensated cirrhosis including ascites, bleeding and hepatic encephalopathy; any contraindications to beta-blockers including asthma, chronic obstructive pulmonary disease, allergic rhinitis, New York Heart Association class IV heart failure, atrioventricular block, sinus bradycardia (heart rate < 50 beats per minute), cardiogenic shock, hypotension (systolic blood pressure < 90 mmHg), sick sinus syndrome, insulin dependent diabetes, peripheral vascular disease; allergy to carvedilol; any malignancy that affects survival; renal dysfunction; history of beta-blockers within last 3 months; history of surgery for portal hypertension; history of prior EVL or sclerotherapy, history of surgery for portal hypertension including portosystemic shunts, disconnection and spleen resection and TIPS; severe systemic diseases; refusal to participate in the study

### Interventions

**Group 1: beta-blocker + nucleos(t)ide analogue**

Further details: based on nucleoside analogue, carvedilol will be given to the participants. Carvedilol started at 6.25 mg once per day. After 1 week, will be increased to 6.25 mg twice daily. Target dose 12.5 mg twice daily will be started after 2 weeks if systolic blood pressure does not fall below 90 mmHg and heart rate 55 beats per minute.

**Group 2: nucleos(t)ide analogues**

Further details: continuing take nucleoside analogue including lamivudine, adefovir dipivoxil, entecavir, telbivudine, tenofovir disoproxil fumarate and tenofovir alafenamide

### Outcomes

**Planned primary outcomes:** progression incidence of oesophageal varices (time frame: 2 years) (defined as varices developed from small (F1) to medium or large (F2/F3); varices developed from medium (F2) to large (F3); bleeding from oesophageal varices)

**Planned secondary outcomes:** cumulative rate of liver decompensation (including ascites, hepatic encephalopathy) after 2 years; cumulative rate of hepatic cellular carcinoma, death, or liver transplantation after 2 years; progression rate of non-invasive scores (Child-Pugh, Model for End-Stage Liver Disease, aspartate transaminase to platelet ratio index, Fibrosis-4 score) after 2 years; dynamic change of liver stiffness quantified by transient elastography after 2 years; dynamic change of haemodynamics parameter (heart rate and mean arterial pressure) after 2 years

### Starting date

Study start date: 26 August 2017

### Contact information

Xiaojuan Ou, Beijing Friendship Hospital

### Notes

Planned sample size: 240 participants

Planned study time: August 2017 to December 2021
brosis score > stage 4 on liver biopsy; 4. Fibroscan liver stiffness measurement > 15 kilopascal without other explanation; small oesophageal varices diagnosed within the last 3 months (defined as < 5 mm in diameter or varices which completely disappear on moderate insufflation at gastroscopy); not received a beta-blocker in the last week; capacity to provide informed consent

Exclusion criteria: non-cirrhotic portal hypertension; medium/large oesophageal varices (current or history of; (defined as > 5 mm in diameter); isolated gastric, duodenal, rectal varices with or without evidence of recent bleeding; previous variceal haemorrhage; red signs accompanying varices at endoscopy; known intolerance to beta-blockers; contraindication to beta-blocker (heart rate < 50 bpm, known 2nd degree or higher heart block, sick sinus syndrome, systolic blood pressure < 85 mmHg, chronic airways obstruction (asthma/chronic obstructive pulmonary disease), floppy iris syndrome, CYP2D6 poor metaboliser, history of cardiogenic shock, history of severe hypersensitivity reaction to beta-blockers, untreated pheochromocytoma, severe peripheral vascular disease, priazmetal angina, New York Heart Association IV heart failure); unable to provide informed consent; Child-Pugh C cirrhosis; already receiving a beta-blocker for another reason that cannot be discontinued; graft cirrhosis after liver transplantation; evidence of active malignancy without curative therapy planned; pregnant or lactating women; women of child bearing potential unwilling to use adequate contraception during the trial; people who have been on another clinical trial within the previous 3 months

Interventions

Group 1: beta-blocker
Further details: 6.25 mg or 12.5 mg if tolerated
Group 2: placebo
Further details: oral placebo

Outcomes

Planned primary outcomes: time to first variceal haemorrhage; assessment of the cost effectiveness of early intervention with non-specific beta-blockers in this patient population

Planned secondary outcomes: variceal bleed rate (time frame: 1 and 3 years); variceal bleeding needing intervention (time frame: 3 years; number of participants that progress to medium/large varices requiring clinical intervention); composite of variceal bleed rate and bleeding needing intervention (time frame: 3 years; i.e. unit less measure of rate of ((number of participants who bled) + (number of participants who progressed without bleeding))/(number of participants in that arm at randomisation) at 3 years ranging from 0 to 1; clinical decompensation (time frame: 3 years; spontaneous bacterial peritonitis, new ascites, new hepatic encephalopathy); Child-Pugh Score for Cirrhosis mortality (time frame: 3 years; range 5–15; higher scores represent worse outcomes); model for end-stage liver disease score (time frame: 3 years; range 6–40; higher scores represent worse outcomes); survival (overall, liver-related, cardiovascular-related; time frame: 3 years); quality of life assessment (time frame: 3 years; using EQ-5D-5L; range 5–25; higher scores represent worse outcomes)

Starting date
Actual study start date: 17 June 2019

Contact information
Vishal Patel: vishal.patel@nhs.net
Kieran Brack: kch-tr.bopptrial@nhs.net

Notes
Planned sample size: 1200 participants
Planned study time: June 2019 to December 2024
**Methods**
- **Randomised clinical trial**

**Participants**
- **Inclusion criteria:** aged 20–85 years; people with cirrhosis with oesophageal varices regardless of bleeding event or not will be enrolled in this study
- **Exclusion criteria:** terminal stage hepatocellular carcinoma; other malignancy; stroke; active sepsis; chronic kidney disease stage 4 under renal replacement therapy; contraindications to non-selective beta-blockers; history of non-selective beta-blockers use, sclerotherapy, banding ligation, transjugular intrahepatic porto-systemic shunt, or shunt surgery; serum total bilirubin > 10 mg/dL; refractory ascites; hepatorenal syndrome; pregnancy; severe heart failure (New York Heart Association (F class III/IV)); bronchial asthma or chronic obstructive pulmonary disease; second or third degree atrioventricular block; severe hypotension; refusal to participate

**Interventions**
- **Group 1: beta-blocker**
  - Further details: propranolol 10 mg twice daily initially and titrated every week to achieve 25% reduction in heart rate (heart rate > 55 bpm or systemic blood pressure > 90 mmHg)
- **Group 2: oesophageal variceal ligation**
  - Further details: oesophageal variceal ligation every 3–4 weeks to achieve variceal eradication under endoscopy. After eradication, follow-up endoscopy every 3 months and variceal ligation again if recurrence
- **Group 3: oesophageal variceal ligation (discontinue propranolol after oesophageal variceal eradication)**
  - Further details: participants randomised to banding ligation group discontinue propranolol after eradication of oesophageal varices

**Outcomes**
- Planned primary outcomes: acute kidney injury; hepatorenal syndrome; overall survival (time frame for all: 3 years)
- Planned secondary outcomes: oesophageal varices bleeding/rebleeding; infection rate (time frame for both: 3 years)

**Starting date**
- Actual study start date: 13 April 2015

**Contact information**
- Ming-Chih Hou: mchou@vghtpe.gov.tw
- Han-Chieh Lin: hclin@vghtpe.gov.tw

**Notes**
- Planned sample size: 170 participants
- Planned study time: April 2015 to July 2020

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**Tripathi 2019**

**Study name**
- Study protocol for a randomised controlled trial of carvedilol vs variceal band ligation in primary prevention of variceal bleeding in liver cirrhosis (CALIBRE trial)

**Methods**
- Randomised clinical trial

**Participants**
- Inclusion criteria: person with cirrhosis and medium varices (Grade II varices that do not flatten on air insufflation and do not occlude the lumen) or large varices (Grade III varices which are larger than Grade II varices and occupy the whole lumen) that have never bled as defined in the British Society of Gastroenterology guidelines
### Exclusion criteria:
- receiving propranolol, carvedilol, or nadolol for primary prevention or have had band ligation.

### Interventions

- **Group 1**: beta-blocker
  - Further details: carvedilol 12.5 mg once daily
- **Group 2**: oesophageal variceal ligation
  - Further details: as per the British Society of Gastroenterology guidelines

### Outcomes

**Planned primary outcomes:**
- any variceal bleeding within 1 year of randomisation (first variceal bleed defined as haematemesis or melena (or both) with either endoscopic evidence of variceal bleeding or stigmata of recent haemorrhage and ≥ 2 g/L reduction in haemoglobin within 24 hours of admission or massive upper gastrointestinal bleeding leading to death. The definition includes bleeding from banding ulceration.
- Planned secondary outcomes:
  - time to first variceal bleed in days (from randomisation); mortality at 1 year (from randomisation; all-cause mortality, liver-related mortality, cardiovascular mortality); transplant free survival at 1 year (from randomisation); adverse events related to treatment (up to 12 months after randomisation; dysphagia requiring discontinuation of treatment, symptomatic hypotension requiring change in treatment, dyspnoea, gastrointestinal upset); other complications of cirrhosis (new onset ascites confirmed clinically or on imaging and graded as per International Club of Ascites recommendations, new onset encephalopathy defined using West Haven Criteria, spontaneous bacterial peritonitis, hepatocellular carcinoma, any renal dysfunction as per International Club of Ascites – Acute Kidney Injury definitions; health-related quality of life (EQ-5D-5L) from randomisation to 6 and 12 months; use of healthcare resources (costs and cost-effectiveness based on the outcomes of cost per variceal bleeding avoided within 1 year of randomisation, cost per quality-adjusted life-year estimated using the EQ-5D-5L, and cost per death avoided at 1 year); patient preference (qualitative interviews with patients and staff during the pilot phase that will explore patients' experience of and preferences related to treatment (carvedilol or oesophageal variceal ligation); use of alternative therapies; cross-over therapies.

**Starting date**
- Quote: "Patient enrollment is expected to start in early 2019"

**Contact information**
- Dr Dhiraj Tripathi: d.tripathi@bham.ac.uk

**Notes**
- Planned sample size: 2630 participants
- Planned study time: early 2019 to end 2022

EVL: endoscopic variceal ligation; EVS: endoscopic variceal sclerotherapy.
### Table 1. Characteristics of included studies (ordered by comparisons)

<table>
<thead>
<tr>
<th>Study name</th>
<th>Intervention</th>
<th>Small varices</th>
<th>High risk of bleeding</th>
<th>Aetiology of cirrhosis</th>
<th>Period of recruitment</th>
<th>Follow-up in months</th>
<th>Overall risk of bias</th>
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</thead>
<tbody>
<tr>
<td>PROVA study group 1991</td>
<td>No active intervention (72) vs beta-blockers (68)</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Alcohol-related: participants with and without alcohol-related cirrhosis</td>
<td>1985–1989</td>
<td>15.4</td>
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<td>Bhardwaj 2017</td>
<td>No active intervention (70) vs beta-blockers (70)</td>
<td>All participants had small varices</td>
<td>Participants with and without high risk of bleeding</td>
<td>Alcohol-related: participants with and without alcohol-related cirrhosis</td>
<td>2010–2012</td>
<td>21</td>
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<tr>
<td>Cales 1989a</td>
<td>No active intervention (8) vs beta-blockers (16)</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Alcohol-related: all participants had alcoholic cirrhosis</td>
<td>Not stated</td>
<td>0.25</td>
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<td>Cales 1989b</td>
<td>No active intervention (8) vs beta-blockers (8)</td>
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<td>Yes (ascites)</td>
<td>Alcohol-related: all participants had alcoholic cirrhosis</td>
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<td>0.15</td>
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Table 1. Characteristics of included studies (ordered by comparisons)

<table>
<thead>
<tr>
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<th>Intervention</th>
<th>Control</th>
<th>Autoimmune-related</th>
<th>Other</th>
<th>Circumstances</th>
<th>Year</th>
<th>No.</th>
<th>Quality</th>
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<td>No active intervention (51) vs beta-blockers (51)</td>
<td>Not stated</td>
<td>Yes (encephalopathy)</td>
<td>Alcohol-related: participants with and without alcohol-related cirrhosis</td>
<td>1982–1986</td>
<td>17</td>
<td>High</td>
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<td>Ideo 1988</td>
<td>No active intervention (27) vs beta-blockers (30)</td>
<td>No participants had small varices</td>
<td>Yes (encephalopathy)</td>
<td>Alcohol-related: participants with and without alcohol-related cirrhosis</td>
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<td>Yes (not stated)</td>
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<td>Merkel 2004</td>
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<td>All participants had small varices</td>
<td>No participants had high risk of bleeding</td>
<td>Alcohol-related: participants with and without alcohol-related cirrhosis</td>
<td>1996–2000</td>
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<td>Intervention 2</td>
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<tr>
<td>Mishra 2007</td>
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|                |                                 |                                 | 1998–2002 34.9 High                                                               |
|                |                                 |                                 | 1997–2000 22.2 High                                                               |
|                |                                 |                                 | 1994–1999 19.7 High                                                               |
|                |                                 |                                 | High                                                                              |
|                |                                 |                                 | High                                                                              |
|                |                                 |                                 | High                                                                              |

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

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

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<td>Alcohol-related: all participants had alcohol-related cirrhosis Viral-related: no participants had viral-related cirrhosis Autoimmune-related: no participants had autoimmune disease-related cirrhosis Other: no participants had other causes of cirrhosis</td>
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<td>PROVA study group 1991</td>
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<td>De Franchis 1991</td>
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Viral-related: participants with and without viral-related cirrhosis
Autoimmune-related: participants with and without autoimmune disease-related cirrhosis
Other: participants with and without other causes of cirrhosis
Alcohol-related: participants with and without alcohol-related cirrhosis

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Participants</th>
<th>Risk of Bleeding</th>
<th>Alcohol-related</th>
<th>Viral-related</th>
<th>Autoimmune-related</th>
<th>Other Causes of Cirrhosis</th>
<th>Year</th>
<th>Follow-up</th>
<th>Grade</th>
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<td>Quer 1991</td>
<td>Sclerotherapy (22) vs no active intervention (24)</td>
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<td>Alcohol-related: participants with and without alcohol-related cirrhosis</td>
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<td>Russo 1989</td>
<td>Sclerotherapy (21) vs no active intervention (20)</td>
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<td>Sauerbruch 1988</td>
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### Table 1. Characteristics of included studies (ordered by comparisons) (Continued)

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<th>Variceal Size</th>
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<th>Cirrhosis Type</th>
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<td>Strauss 1999</td>
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<td>Svoboda 1999</td>
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<td>Witzel 1985</td>
<td>Sclerotherapy (56) vs no active intervention (53)</td>
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### Table 1. Characteristics of included studies (ordered by comparisons) (Continued)

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<th>Characteristics</th>
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<td>Lo 2010</td>
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<td>Beta-blockers + variceal band ligation (87) vs</td>
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No participants had small varices

No participants had high risk of bleeding

Yes (encephalopathy)
<table>
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<tr>
<th>Study</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Type</th>
<th>Study Duration</th>
<th>Participants</th>
<th>Odds Ratio</th>
<th>Evidence Quality</th>
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<td>Beta-blockers (22)</td>
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Table 1. Characteristics of included studies (ordered by comparisons) (Continued)

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<th>Intervention 1</th>
<th>Intervention 2</th>
<th>Participants</th>
<th>Primary Prevention of Asymptomatic Variceal Bleeding (%)</th>
<th>Allocation</th>
<th>Study period</th>
<th>Year of publication</th>
<th>Risk of Bias</th>
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<td>Merkel 2000</td>
<td>Beta-blockers + nitrates (72) vs beta-blockers (74)</td>
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<td>Participants with and without high risk of bleeding</td>
<td>Yes (encephalopathy)</td>
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<td>Autoimmune-related: not stated</td>
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<td>Other: participants with and without other causes of cirrhosis</td>
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<td>Piscaglia 1998</td>
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<td>Autoimmune-related: no participants had autoimmune disease-related cirrhosis</td>
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<td>Other: no participants had other causes of cirrhosis</td>
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<td>Wang 2006</td>
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<td>Other: participants with and without other causes of cirrhosis</td>
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<td>Angelico 1993</td>
<td>Nitrates (57) vs beta-blockers (61)</td>
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<td>Not stated</td>
<td>Yes (ascites)</td>
<td>Alcohol-related: participants with and without alcohol-related cirrhosis</td>
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### Table 1. Characteristics of included studies (ordered by comparisons) (Continued)

Viral-related: participants with and without viral-related cirrhosis
Autoimmune-related: not stated
Other: participants with and without other causes of cirrhosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Therapy 1</th>
<th>Therapy 2</th>
<th>Comparator 1</th>
<th>Comparator 2</th>
<th>Setting</th>
<th>Year</th>
<th>HR (95% CI)</th>
<th>Quality</th>
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<tr>
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<td>Nitrates (23) vs No active intervention (19)</td>
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<td>Snady 1988</td>
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Table 1. Characteristics of included studies (ordered by comparisons) (Continued)

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<th>Study name</th>
<th>Intervention 1 (number of participants) vs intervention 2 (number of participants)</th>
<th>Sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants and health-care providers</th>
<th>Blinding of outcome assessors</th>
<th>Missing outcome bias</th>
<th>Selective outcome reporting</th>
<th>Other bias</th>
<th>Overall risk of bias</th>
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<tr>
<td>Conn 1969</td>
<td>Portocaval shunt (13) vs no active intervention (16)</td>
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Table 2. Risk of bias (ordered by comparison)

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<th>Allocation concealment</th>
<th>Blinding of participants and health-care providers</th>
<th>Blinding of outcome assessors</th>
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<th>Selective outcome reporting</th>
<th>Other bias</th>
<th>Overall risk of bias</th>
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<td>Bhardwaj 2017</td>
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<td>vs variceal band ligation (86)</td>
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<tr>
<td>D’Amico 2002</td>
<td>Beta-blockers + nitrates (30) vs beta-blockers (27)</td>
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<td>Low</td>
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<td>Low</td>
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<td>Deplano 2001</td>
<td>Beta-blockers + nitrates (14) vs beta-blockers (22)</td>
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<td>Merkel 2000</td>
<td>Beta-blockers + nitrates (72) vs beta-blockers (74)</td>
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<tr>
<td>Piscaglia 1998</td>
<td>Beta-blockers + nitrates (10) vs no active intervention (8)</td>
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<td>Wang 2006</td>
<td>Beta-blockers + nitrates (31) vs variceal band ligation (30)</td>
<td>Low</td>
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<tr>
<td>Angelico 1993</td>
<td>Nitrates (57) vs beta-blockers (61)</td>
<td>Unclear</td>
<td>Unclear</td>
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<td>Borroni 2002</td>
<td>Nitrates (27) vs beta-blockers (25)</td>
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<tr>
<td>Lui 2002</td>
<td>Nitrates (62) vs beta-blockers (66)</td>
<td>Low</td>
<td>Low</td>
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<td>Low</td>
<td>Unclear</td>
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<td>Fassio 1993</td>
<td>Nitrates (23) vs no active intervention (19)</td>
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<td>Unclear</td>
<td>Unclear</td>
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<td>Low</td>
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<tr>
<td>Lui 2002</td>
<td>Nitrates (62) vs variceal band ligation (44)</td>
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<td>PROVA study group 1991</td>
<td>Beta-blockers + sclerotherapy (73) vs beta-blockers (68)</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Unclear</td>
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<td>Snady 1988</td>
<td>Beta-blockers + sclerotherapy (12) vs beta-blockers (14)</td>
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<td>Unclear</td>
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Table 2. Risk of bias (ordered by comparison) (Continued)

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<th>Study Group</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>Risk of Bias</th>
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<tr>
<td>1969 Conn</td>
<td>Portocaval shunt vs no active intervention</td>
<td>Low</td>
<td>Low</td>
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<td>1988 Snady</td>
<td>Beta-blockers + sclerotherapy vs no active intervention</td>
<td>Unclear</td>
<td>Low</td>
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<td>1991 PROVA study group</td>
<td>Beta-blockers + sclerotherapy vs sclerotherapy</td>
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<td>1991 PROVA study group</td>
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<td>1988 Snady</td>
<td>Beta-blockers + sclerotherapy vs no active intervention</td>
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<td>1969 Conn</td>
<td>Portocaval shunt vs no active intervention</td>
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<td>1988 Snady</td>
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<td>1991 PROVA study group</td>
<td>Beta-blockers + sclerotherapy vs sclerotherapy</td>
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<td>1991 PROVA study group</td>
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Legend: Low risk, High risk, Unclear.
Table 3. Model fit

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Fixed-effect model</th>
<th>Random-effects model</th>
<th>Inconsistency model</th>
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<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Dbar</td>
<td>—</td>
<td>572.7</td>
<td>573</td>
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<tr>
<td>DIC</td>
<td>—</td>
<td>662.4</td>
<td>666.2</td>
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<tr>
<td>pD</td>
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<td>89.69</td>
<td>93.15</td>
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<td><strong>Serious adverse events (number of participants)</strong></td>
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<td></td>
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<td>Dbar</td>
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<td>33.38</td>
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<td>DIC</td>
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<td>pD</td>
<td>6.814</td>
<td>8.737</td>
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<tr>
<td><strong>Any adverse events (number of participants)</strong></td>
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<tr>
<td>Dbar</td>
<td>156.2</td>
<td>110.9</td>
<td>111.1</td>
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<tr>
<td>DIC</td>
<td>172.2</td>
<td>133.5</td>
<td>134</td>
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<tr>
<td>pD</td>
<td>15.99</td>
<td>22.61</td>
<td>22.94</td>
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<tr>
<td><strong>Any adverse events (number of events)</strong></td>
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<td>Dbar</td>
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<td>185.9</td>
<td>135.1</td>
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<td>DIC</td>
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<td>200.9</td>
<td>157.6</td>
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<td>pD</td>
<td>14.92</td>
<td>14.95</td>
<td>22.51</td>
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<td><strong>Liver transplantation</strong></td>
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<tr>
<td>Dbar</td>
<td>47.89</td>
<td>48.85</td>
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<tr>
<td>DIC</td>
<td>56.61</td>
<td>58.62</td>
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<tr>
<td>pD</td>
<td>8.717</td>
<td>9.773</td>
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<td><strong>Symptomatic variceal bleeding</strong></td>
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<tr>
<td>Dbar</td>
<td>81.84</td>
<td>78.92</td>
<td>78.21</td>
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<tr>
<td>DIC</td>
<td>94.73</td>
<td>94.48</td>
<td>93.86</td>
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<tr>
<td>pD</td>
<td>12.88</td>
<td>15.55</td>
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<td><strong>Any variceal bleeding</strong></td>
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<tr>
<td>Dbar</td>
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<td>226.3</td>
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Table 3. Model fit (Continued)

<table>
<thead>
<tr>
<th></th>
<th>Fixed-effect model</th>
<th>Random-effects model</th>
<th>Inconsistency model</th>
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<tbody>
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<td><strong>DIC</strong></td>
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<td>273.3</td>
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<td><strong>pD</strong></td>
<td>45.1</td>
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<td><strong>Other features of decompensation</strong></td>
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<td>Random-effects model</td>
<td>Inconsistency model</td>
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<td>37.02</td>
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<td>DIC</td>
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<td>pD</td>
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<td>5.916</td>
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Dbar: posterior mean of deviance; DIC: deviance information criteria; pD: effective number of parameters or leverage.
### Table 4. Effect estimates

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Beta-blockers</th>
<th>No active intervention</th>
<th>Variceal band ligation</th>
<th>Sclerotherapy</th>
<th>Beta-blockers + variceal band ligation</th>
<th>Beta-blockers + nitrates</th>
<th>Nitrates</th>
<th>Beta-blockers + sclerotherapy</th>
<th>Portocaval shunt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers</td>
<td>—</td>
<td>1.70 (1.21 to 2.39)</td>
<td>1.06 (0.82 to 1.36)</td>
<td>1.88 (1.01 to 3.69)</td>
<td>1.05 (0.04 to 26.55)</td>
<td>0.88 (0.04 to 22.35)</td>
<td>1.37 (0.27 to 6.48)</td>
<td>2.03 (0.04 to 75.04)</td>
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<tr>
<td>No active intervention</td>
<td>2.04 (1.50 to 2.76)</td>
<td>—</td>
<td>0.49 (0.12 to 2.14)</td>
<td>0.61 (0.41 to 0.90)</td>
<td>—</td>
<td>—</td>
<td>0.34 (0.04 to 1.99)</td>
<td>1.02 (0.02 to 51.47)</td>
<td>0.25 (0.03 to 1.15)</td>
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<tr>
<td>Variceal band ligation</td>
<td>1.05 (0.80 to 1.38)</td>
<td>0.51 (0.35 to 0.74)</td>
<td>—</td>
<td>0.84 (0.36 to 1.97)</td>
<td>1.21 (0.11 to 11.26)</td>
<td>0.69 (0.22 to 2.06)</td>
<td>0.90 (0.44 to 1.86)</td>
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<td>—</td>
</tr>
<tr>
<td>Sclerotherapy</td>
<td>1.35 (0.95 to 1.92)</td>
<td>0.66 (0.51 to 0.85)</td>
<td>1.29 (0.86 to 1.94)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1.19 (0.02 to 43.38)</td>
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<tr>
<td>Beta-blockers + variceal band ligation</td>
<td>1.11 (0.56 to 2.19)</td>
<td>0.54 (0.26 to 1.12)</td>
<td>1.06 (0.53 to 2.09)</td>
<td>0.82 (0.39 to 1.73)</td>
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<tr>
<td>Beta-blockers + nitrates</td>
<td>0.84 (0.44 to 1.64)</td>
<td>0.41 (0.20 to 0.85)</td>
<td>0.80 (0.40 to 1.62)</td>
<td>0.62 (0.30 to 1.32)</td>
<td>0.76 (0.30 to 1.97)</td>
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<tr>
<td>Nitrates</td>
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<td>0.88 (0.45 to 1.69)</td>
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<td>1.41 (0.59 to 3.37)</td>
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<tr>
<td>Beta-blockers + sclerotherapy</td>
<td>2.08 (1.03 to 4.08)</td>
<td>1.02 (0.52 to 1.93)</td>
<td>1.98 (0.95 to 4.00)</td>
<td>1.54 (0.77 to 2.94)</td>
<td>1.86 (0.72 to 4.80)</td>
<td>2.45 (0.94 to 6.29)</td>
<td>1.75 (0.71 to 4.22)</td>
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<tr>
<td>Portocaval shunt</td>
<td>0.51 (0.06 to 2.92)</td>
<td>0.25 (0.03 to 1.38)</td>
<td>0.49 (0.05 to 2.80)</td>
<td>0.38 (0.04 to 2.14)</td>
<td>0.46 (0.05 to 2.93)</td>
<td>0.61 (0.06 to 3.90)</td>
<td>0.43 (0.05 to 2.71)</td>
<td>0.25 (0.03 to 1.57)</td>
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</tr>
</tbody>
</table>

**Serious adverse events (number of participants)**

<table>
<thead>
<tr>
<th>Beta-blockers</th>
<th>Variceal band ligation</th>
<th>Sclerotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers</td>
<td>—</td>
<td>0.71 (0.24 to 1.98)</td>
</tr>
<tr>
<td>Variceal band ligation</td>
<td>0.70 (0.23 to 2.01)</td>
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Table 4. Effect estimates a (Continued)

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

<table>
<thead>
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<th>Any adverse events (number of events)</th>
<th>Beta-blockers</th>
<th>No active intervention</th>
<th>Variceal band ligation</th>
<th>Sclerotherapy</th>
<th>Beta-blockers + variceal band ligation</th>
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</thead>
<tbody>
<tr>
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<td>0.73 (0.59 to 0.90)</td>
<td>2.47 (1.27 to 5.06)</td>
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<td><strong>No active intervention</strong></td>
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<td>0.65 (0.29 to 1.45)</td>
<td>2.61 (2.18 to 3.18)</td>
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<td><strong>Variceal band ligation</strong></td>
<td>0.77 (0.63 to 0.94)</td>
<td>0.79 (0.46 to 1.31)</td>
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<td>1.99 (0.95 to 4.45)</td>
<td>1.18 (0.66 to 2.06)</td>
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<tr>
<td><strong>Sclerotherapy</strong></td>
<td>2.49 (1.53 to 4.22)</td>
<td>2.56 (2.13 to 3.08)</td>
<td>3.24 (1.99 to 5.49)</td>
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Table 4. Effect estimates \(^a\) (Continued)

<table>
<thead>
<tr>
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<th>Beta-blockers + variceal band ligation</th>
<th>Beta-blockers + variceal band ligation</th>
<th>Beta-blockers + variceal band ligation</th>
<th>Beta-blockers + variceal band ligation</th>
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</thead>
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<tr>
<td><strong>Liver transplantation</strong></td>
<td>Beta-blockers</td>
<td>No active intervention</td>
<td>Variceal band ligation</td>
<td>Beta-blockers + variceal band ligation</td>
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<tr>
<td>Beta-blockers</td>
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<td>1.37 (0.34 to 5.64)</td>
<td>1.40 (0.84 to 2.34)</td>
<td>2.46 (0.19 to 80.40)</td>
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<tr>
<td>No active intervention</td>
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<td>Variceal band ligation</td>
<td>1.41 (0.83 to 2.43)</td>
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<tr>
<td>Beta-blockers + variceal band ligation</td>
<td>2.40 (0.19 to 77.48)</td>
<td>1.79 (0.09 to 70.11)</td>
<td>1.71 (0.12 to 56.32)</td>
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<tr>
<td><strong>Symptomatic variceal bleed</strong></td>
<td>Beta-blockers</td>
<td>No active intervention</td>
<td>Variceal band ligation</td>
<td>Sclerotherapy</td>
</tr>
<tr>
<td>Beta-blockers</td>
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<td>1.03 (0.46 to 2.29)</td>
<td>0.79 (0.47 to 1.34)</td>
<td>1.01 (0.46 to 2.27)</td>
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<tr>
<td>Variceal band ligation</td>
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<td>0.70 (0.28 to 1.71)</td>
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<tr>
<td>Sclerotherapy</td>
<td>0.91 (0.44 to 1.95)</td>
<td>0.80 (0.49 to 1.29)</td>
<td>1.15 (0.46 to 2.89)</td>
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<td>Beta-blockers + variceal band ligation</td>
<td>1.13 (0.45 to 2.87)</td>
<td>0.99 (0.30 to 3.20)</td>
<td>1.42 (0.49 to 4.15)</td>
<td>1.24 (0.38 to 4.00)</td>
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</tbody>
</table>
Table 4. Effect estimates \(a\) (Continued)

<table>
<thead>
<tr>
<th></th>
<th>Beta-blockers</th>
<th>No active intervention</th>
<th>Variceal band ligation</th>
<th>Sclerotherapy</th>
<th>Beta-blockers + variceal band ligation</th>
<th>Beta-blockers + nitrates</th>
<th>Nitrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrates</td>
<td>1.27 (0.61 to 2.66)</td>
<td>1.12 (0.39 to 3.11)</td>
<td>1.59 (0.64 to 3.96)</td>
<td>1.39 (0.49 to 3.90)</td>
<td>1.12 (0.34 to 3.62)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Beta-blockers + sclerotherapy</td>
<td>0.92 (0.41 to 2.08)</td>
<td>0.81 (0.38 to 1.65)</td>
<td>1.15 (0.44 to 3.04)</td>
<td>1.01 (0.47 to 2.09)</td>
<td>0.81 (0.24 to 2.79)</td>
<td>0.72 (0.24 to 2.18)</td>
<td>—</td>
</tr>
</tbody>
</table>

Any variceal bleeding

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

Other features of decompensation

|                  | Beta-blockers | Variceal band ligation | Beta-blockers + nitrates | — |
|------------------|---------------|------------------------|--------------------------|—|
| Beta-blockers    | —             | 1.11 (0.45 to 2.80)   | 1.16 (0.64 to 2.12) | — |
| Variceal band ligation | 1.11 (0.44 to 2.86) | — | — | — |
### Table 4. Effect estimates $^a$ (Continued)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Beta-blockers + nitrates</th>
<th>Beta-blockers + variceal band ligation</th>
<th>Beta-blockers + sclerotherapy</th>
<th>No active intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers + nitrates</td>
<td>1.16 (0.64 to 2.13)</td>
<td>1.04 (0.34 to 3.16)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Beta-blockers + variceal band ligation</td>
<td>0.55 (0.38 to 0.80)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Beta-blockers + sclerotherapy</td>
<td>1.14 (0.75 to 1.73)</td>
<td>0.63 (0.48 to 0.81)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Variceal band ligation</td>
<td>2.33 (1.28 to 4.51)</td>
<td>0.55 (0.38 to 0.80)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Sclerotherapy</td>
<td>2.65 (1.50 to 4.95)</td>
<td>0.63 (0.48 to 0.81)</td>
<td>1.14 (0.75 to 1.73)</td>
<td>—</td>
</tr>
<tr>
<td>No active intervention</td>
<td>4.24 (2.39 to 8.04)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Nitrates</td>
<td>2.56 (1.18 to 5.92)</td>
<td>0.61 (0.31 to 1.16)</td>
<td>1.10 (0.58 to 2.08)</td>
<td>—</td>
</tr>
</tbody>
</table>

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

#### Effect measures

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

### Table 5. Effect estimates (baseline risk-adjusted) $^a$

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Beta-blockers</th>
<th>No active intervention</th>
<th>Variceal band ligation</th>
<th>Sclerotherapy</th>
<th>Beta-blockers + variceal band ligation</th>
<th>Beta-blockers + nitrates</th>
<th>Nitrates</th>
<th>Beta-blockers + sclerotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>No active intervention</td>
<td>4.24 (2.39 to 8.04)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Variceal band ligation</td>
<td>2.33 (1.28 to 4.51)</td>
<td>0.55 (0.38 to 0.80)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Sclerotherapy</td>
<td>2.65 (1.50 to 4.95)</td>
<td>0.63 (0.48 to 0.81)</td>
<td>1.14 (0.75 to 1.73)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Beta-blockers + variceal band ligation</td>
<td>2.57 (1.06 to 6.61)</td>
<td>0.61 (0.28 to 1.30)</td>
<td>1.11 (0.55 to 2.23)</td>
<td>0.97 (0.44 to 2.13)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Beta-blockers + nitrates</td>
<td>1.88 (0.79 to 4.78)</td>
<td>0.45 (0.21 to 0.95)</td>
<td>0.81 (0.39 to 1.67)</td>
<td>0.71 (0.33 to 1.56)</td>
<td>0.73 (0.28 to 1.94)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Nitrates</td>
<td>2.56 (1.18 to 5.92)</td>
<td>0.61 (0.31 to 1.16)</td>
<td>1.10 (0.58 to 2.08)</td>
<td>0.97 (0.49 to 1.92)</td>
<td>1.00 (0.40 to 2.47)</td>
<td>1.36 (0.54 to 3.37)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Beta-blockers + sclerotherapy</td>
<td>4.17 (1.80 to 10.01)</td>
<td>0.99 (0.49 to 1.91)</td>
<td>1.80 (0.84 to 3.71)</td>
<td>1.58 (0.79 to 3.07)</td>
<td>1.62 (0.59 to 4.29)</td>
<td>2.22 (0.81 to 5.84)</td>
<td>1.63 (0.65 to 4.02)</td>
<td>—</td>
</tr>
</tbody>
</table>
Table 5. Effect estimates (baseline risk-adjusted) a (Continued)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Beta-blockers</th>
<th>Variceal band ligation</th>
<th>Beta-blockers + variceal band ligation</th>
<th>No active intervention</th>
<th>Beta-blockers + nitrates</th>
<th>Nitrates</th>
<th>Sclerotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portocaval shunt</td>
<td>1.06 (0.11 to 6.77)</td>
<td>0.25 (0.03 to 1.42)</td>
<td>0.46 (0.05 to 2.69)</td>
<td>0.40 (0.04 to 2.31)</td>
<td>0.41 (0.04 to 2.75)</td>
<td>0.56 (0.06 to 3.75)</td>
<td>0.41 (0.04 to 2.66)</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Beta-blockers</th>
<th>Variceal band ligation</th>
<th>Beta-blockers + variceal band ligation</th>
<th>No active intervention</th>
<th>Beta-blockers + nitrates</th>
<th>Nitrates</th>
<th>Sclerotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>Beta-blockers</td>
<td>Variceal band ligation</td>
<td>Beta-blockers + variceal band ligation</td>
<td>No active intervention</td>
<td>Beta-blockers + nitrates</td>
<td>Nitrates</td>
<td>Sclerotherapy</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>---------------</td>
<td>------------------------</td>
<td>----------------------------------------</td>
<td>------------------------</td>
<td>--------------------------</td>
<td>----------</td>
<td>--------------</td>
</tr>
<tr>
<td>Mortality</td>
<td>Beta-blockers</td>
<td>Variceal band ligation</td>
<td>Beta-blockers + variceal band ligation</td>
<td>No active intervention</td>
<td>Beta-blockers + nitrates</td>
<td>Nitrates</td>
<td>Sclerotherapy</td>
</tr>
<tr>
<td>Mortality</td>
<td>Beta-blockers</td>
<td>Variceal band ligation</td>
<td>Beta-blockers + variceal band ligation</td>
<td>No active intervention</td>
<td>Beta-blockers + nitrates</td>
<td>Nitrates</td>
<td>Sclerotherapy</td>
</tr>
<tr>
<td>Mortality</td>
<td>Beta-blockers</td>
<td>Variceal band ligation</td>
<td>Beta-blockers + variceal band ligation</td>
<td>No active intervention</td>
<td>Beta-blockers + nitrates</td>
<td>Nitrates</td>
<td>Sclerotherapy</td>
</tr>
<tr>
<td>Mortality</td>
<td>Beta-blockers</td>
<td>Variceal band ligation</td>
<td>Beta-blockers + variceal band ligation</td>
<td>No active intervention</td>
<td>Beta-blockers + nitrates</td>
<td>Nitrates</td>
<td>Sclerotherapy</td>
</tr>
<tr>
<td>Mortality</td>
<td>Beta-blockers</td>
<td>Variceal band ligation</td>
<td>Beta-blockers + variceal band ligation</td>
<td>No active intervention</td>
<td>Beta-blockers + nitrates</td>
<td>Nitrates</td>
<td>Sclerotherapy</td>
</tr>
<tr>
<td>Mortality</td>
<td>Beta-blockers</td>
<td>Variceal band ligation</td>
<td>Beta-blockers + variceal band ligation</td>
<td>No active intervention</td>
<td>Beta-blockers + nitrates</td>
<td>Nitrates</td>
<td>Sclerotherapy</td>
</tr>
<tr>
<td>Mortality</td>
<td>Beta-blockers</td>
<td>Variceal band ligation</td>
<td>Beta-blockers + variceal band ligation</td>
<td>No active intervention</td>
<td>Beta-blockers + nitrates</td>
<td>Nitrates</td>
<td>Sclerotherapy</td>
</tr>
<tr>
<td>Mortality</td>
<td>Beta-blockers</td>
<td>Variceal band ligation</td>
<td>Beta-blockers + variceal band ligation</td>
<td>No active intervention</td>
<td>Beta-blockers + nitrates</td>
<td>Nitrates</td>
<td>Sclerotherapy</td>
</tr>
<tr>
<td>Mortality</td>
<td>Beta-blockers</td>
<td>Variceal band ligation</td>
<td>Beta-blockers + variceal band ligation</td>
<td>No active intervention</td>
<td>Beta-blockers + nitrates</td>
<td>Nitrates</td>
<td>Sclerotherapy</td>
</tr>
<tr>
<td>Mortality</td>
<td>Beta-blockers</td>
<td>Variceal band ligation</td>
<td>Beta-blockers + variceal band ligation</td>
<td>No active intervention</td>
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<td>Nitrates</td>
<td>Sclerotherapy</td>
</tr>
<tr>
<td>Mortality</td>
<td>Beta-blockers</td>
<td>Variceal band ligation</td>
<td>Beta-blockers + variceal band ligation</td>
<td>No active intervention</td>
<td>Beta-blockers + nitrates</td>
<td>Nitrates</td>
<td>Sclerotherapy</td>
</tr>
<tr>
<td>Mortality</td>
<td>Beta-blockers</td>
<td>Variceal band ligation</td>
<td>Beta-blockers + variceal band ligation</td>
<td>No active intervention</td>
<td>Beta-blockers + nitrates</td>
<td>Nitrates</td>
<td>Sclerotherapy</td>
</tr>
<tr>
<td>Mortality</td>
<td>Beta-blockers</td>
<td>Variceal band ligation</td>
<td>Beta-blockers + variceal band ligation</td>
<td>No active intervention</td>
<td>Beta-blockers + nitrates</td>
<td>Nitrates</td>
<td>Sclerotherapy</td>
</tr>
<tr>
<td>Mortality</td>
<td>Beta-blockers</td>
<td>Variceal band ligation</td>
<td>Beta-blockers + variceal band ligation</td>
<td>No active intervention</td>
<td>Beta-blockers + nitrates</td>
<td>Nitrates</td>
<td>Sclerotherapy</td>
</tr>
<tr>
<td>Mortality</td>
<td>Beta-blockers</td>
<td>Variceal band ligation</td>
<td>Beta-blockers + variceal band ligation</td>
<td>No active intervention</td>
<td>Beta-blockers + nitrates</td>
<td>Nitrates</td>
<td>Sclerotherapy</td>
</tr>
<tr>
<td>Mortality</td>
<td>Beta-blockers</td>
<td>Variceal band ligation</td>
<td>Beta-blockers + variceal band ligation</td>
<td>No active intervention</td>
<td>Beta-blockers + nitrates</td>
<td>Nitrates</td>
<td>Sclerotherapy</td>
</tr>
<tr>
<td>Mortality</td>
<td>Beta-blockers</td>
<td>Variceal band ligation</td>
<td>Beta-blockers + variceal band ligation</td>
<td>No active intervention</td>
<td>Beta-blockers + nitrates</td>
<td>Nitrates</td>
<td>Sclerotherapy</td>
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<tr>
<td>Mortality</td>
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<td>Variceal band ligation</td>
<td>Beta-blockers + variceal band ligation</td>
<td>No active intervention</td>
<td>Beta-blockers + nitrates</td>
<td>Nitrates</td>
<td>Sclerotherapy</td>
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<td>Mortality</td>
<td>Beta-blockers</td>
<td>Variceal band ligation</td>
<td>Beta-blockers + variceal band ligation</td>
<td>No active intervention</td>
<td>Beta-blockers + nitrates</td>
<td>Nitrates</td>
<td>Sclerotherapy</td>
</tr>
<tr>
<td>Mortality</td>
<td>Beta-blockers</td>
<td>Variceal band ligation</td>
<td>Beta-blockers + variceal band ligation</td>
<td>No active intervention</td>
<td>Beta-blockers + nitrates</td>
<td>Nitrates</td>
<td>Sclerotherapy</td>
</tr>
<tr>
<td>Mortality</td>
<td>Beta-blockers</td>
<td>Variceal band ligation</td>
<td>Beta-blockers + variceal band ligation</td>
<td>No active intervention</td>
<td>Beta-blockers + nitrates</td>
<td>Nitrates</td>
<td>Sclerotherapy</td>
</tr>
</tbody>
</table>

aThe table provides the effect estimates (hazard ratio) with 95% credible intervals of each pairwise comparison for mortality. The top half of the table is empty because this is the location for effect estimates from the direct comparisons, which we have presented in the main analysis (Table 4). The bottom half of the table indicates the effect estimates from the network meta-analysis adjusted for baseline risk. For network meta-analysis, to identify the effect estimate of a comparison, for example A versus B, use the cell that occupies the row corresponding to intervention A and the column corresponding to intervention B. If that cell is empty (indicated by ‘—’), use the row corresponding to intervention B and the column corresponding to intervention A. Take the inverse of this number (i.e. 1/number) to arrive at the treatment effect of A versus B. Statistically significant results are shown in italics.
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Hazard Ratio (95% CI)</th>
<th>Hazard Ratio (95% CI)</th>
<th>Hazard Ratio (95% CI)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers + variceal band ligation</td>
<td>0.25 (0.04 to 1.09)</td>
<td>0.35 (0.07 to 1.40)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Beta-blockers + nitrates</td>
<td>0.92 (0.18 to 4.83)</td>
<td>1.26 (0.25 to 7.15)</td>
<td>3.65 (0.46 to 37.23)</td>
<td>—</td>
</tr>
<tr>
<td>Nitrates</td>
<td>6.65 (0.63 to 100.69)</td>
<td>9.21 (0.79 to 165.50)</td>
<td>27.09 (1.70 to 688.83)</td>
<td>7.32 (0.41 to 172.95)</td>
</tr>
</tbody>
</table>

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

### Appendix 1. Search strategies

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

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**Appendix 2. Data**

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

**HISTORY**

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

**CONTRIBUTIONS OF AUTHORS**

**Protocol**
Conceiving the protocol: KG
Designing the protocol: KG
Co-ordinating the protocol: KG
Designing search strategies: KG
Writing the protocol: KG
Providing general advice on the protocol: ET
Securing funding for the protocol: KG
Both authors approved of the current protocol version
Performing previous work that was the foundation of the current study: not applicable

**Review**
Co-ordinating the review: KG
Study selection: KG, Danielle R, MC
Data extraction: KG, Davide R, MPT, AB, LP, NW, LB, SA, TB, MC
Writing the review: KG, LB
Providing advice on the review: SF, AJS, NC, EJM, MT, CSP, BRD, ET
Securing funding for the review: KG
All authors approved of the review for publication.

**DECLARATIONS OF INTEREST**

Davide R: none.
LB: none.
SF: none.
Danielle R: none.
NC: none.
AJS: none.
AB: none.
MPT: none.
LP: none.
MC: none.
SA: none.
TB: none.
EJM: none.
MT: none.
CSP: none.
BRD: none.
ET: none.
NW: none.
KG: none.

**SOURCES OF SUPPORT**

Internal sources
- University College London, UK
  Writing equipment, software, etc.

External sources
- National Institute for Health Research, UK
  Payment for writing reviews, writing equipment, and software.

**DIFFERENCES BETWEEN PROTOCOL AND REVIEW**

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

• At the protocol stage, we did not expect any studies where randomisation was performed without informed consent; therefore, we did not specify that we would exclude such trials. However, during the systematic review process, we identified one trial in which randomisation was performed without informed consent. Therefore, we excluded this trial.

• We added information about the definition of treatment nodes and added clarification of the 'decision set.'

• We indicated how we planned to interpret standardised mean differences (SMD) if we calculated the SMD.

• We did not perform Trial Sequential Analysis because the risk of false-positive results with Bayesian meta-analysis is usually less or at least equivalent to Trial Sequential Analysis.

• We used the latest guidance from the GRADE Working group (Brignardello-Petersen 2018; Yepes-Nunez 2019), rather than the previous guidance (Puhan 2014), for presenting the 'Summary of Findings' tables.

• The trials did not report the proportion of people with other episodes of decompensation but reported the number of episodes of decompensation. Therefore, we treated this as a count outcome and used the Poisson likelihood to calculate the rate ratio.

• In the absence of a protocol published prior to the start of the study, we classified the risk of bias as low for selective reporting bias only when mortality, adverse events, and bleeding were reported, as we anticipated these outcomes to be routinely measured in clinical trials of this nature.

• We used 30,000 iterations (instead of 10,000 iterations) as a minimum for burn-in of the simulation sampler used to estimate quantities in the statistical models to ensure convergence of the simulation sampler.

• We did not present some information such as ranking probability tables, rankograms, and surface area under the curve (SUCRA plots) because of the concern about the misinterpretation of the results. We highlighted this clearly within the text of the review along with the reasons for not presenting them.

• We performed additional meta-regression analyses based on baseline risk and presented results from trials published since 2000 to account for the change in baseline risk over time.

NOTES

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