National Institute for Health and Care Excellence

Cirrhosis in over 16s: assessment and management (update)

[A] Clinical and cost-effectiveness of non-selective beta-blockers and endoscopic variceal band ligation for the primary prevention of bleeding in people with oesophageal varices due to cirrhosis.

NICE guideline NG50

Evidence reviews underpinning recommendations 1.2.9, 1.3.1 to 1.3.2, 1.3.4 to 1.3.5 and research recommendations in the NICE guideline

September 2023

Final

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

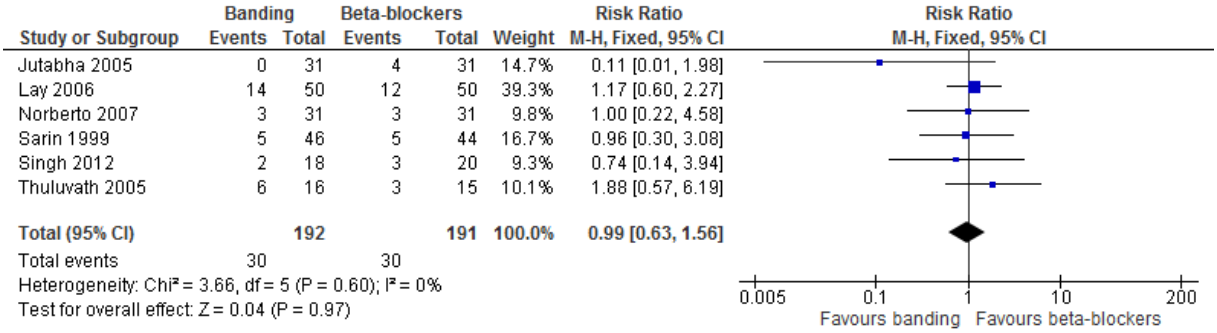
Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN: 978-1-4731-5350-9

Contents



Non-selective beta-blockers 140
Relative (95% CI) 140
Absolute 140
Survival (all follow up times) [>1 favours NSBB] 140
7[1] 140
randomised trials 140
very serious[2] 140
no serious inconsistency 140
no serious indirectness 140
very serious[3] 140
none 140
- 140
33.3%[4] 140
HR 1.03 (0.8 to 1.34) 140
8 more per 1000 (from 56 fewer to 86 more) 140
⊕OOO VERY LOW 140
Transplant free survival (follow-up 12 months) [>1 favours EVL] 140
1[5] 140
randomised trials 140
serious[6] 140
NA[7] 140
no serious indirectness 140
serious[8] 140
none 140
72/80 (90%) 140
61/80 (76.3%) 140
RR 1.18 (1.02 to 1.36) 140
137 more per 1000 (from 15 more to 275 more) 140
⊕⊕OO LOW 140
Mortality (all follow up times) [>1 favours NSBB] 140
6[9] 140
randomised trials 140
very serious[2] 140
no serious inconsistency 140
no serious indirectness 140
very serious[10] 140
none 140
30/192 (15.6%) 140
30/191 (15.7%) 140
RR 0.99 (0.63 to 1.56) 140
2 fewer per 1000 (from 58 fewer to 88 more) 140
⊕OOO VERY LOW 140
Free from variceal bleeding (all follow up times) [>1 favours NSBB] 140
7[11] 140
randomised trials 140
very serious[2] 140
serious[12] 140
no serious indirectness 140

1 Primary prophylaxis of oesophageal variceal haemorrhage

1.1 Review question

What is the clinical and cost-effectiveness of non-selective beta-blockers (NSBBs), endoscopic variceal band ligation (EVL) or NSBBs plus EVL compared to each other for the primary prevention of bleeding in people with medium to large oesophageal varices due to cirrhosis?

1.1.1 Introduction

NICE guideline NG50 recommends endoscopic oesophageal variceal band ligation (also known as endoscopic variceal ligation [EVL] as primary prophylaxis for preventing bleeding from medium-sized or large oesophageal varices. Evidence identified through surveillance shows that non-selective beta-blockers (NSBBs) may be an effective alternative to EVL for reducing bleeding or mortality. Feedback from stakeholders suggests that healthcare professionals currently use NSBBs for this purpose. New published evidence may also change the guideline's current cost-effectiveness estimates for EVL, which could impact on the existing recommendations.

As a result, a new review of the evidence has been undertaken to allow a committee to consider any changes that may need to be made to the recommendation.

1.1.2 Summary of the protocol

Table 1: PICOS inclusion criteria

Population	Inclusion: People aged 16 years and older with cirrhosis, who have medium- sized or large oesophageal varices which have never bled.
Interventions	• Non-selective beta-blockers (NSBBs) -Nadolol, Timolol maleate, Sotalol, Carvedilol, Labetalol, Propranolol. • Endoscopic variceal band ligation (EVL) • NSBBs plus EVL
Comparator	Each other (including intraclass for NSBBs)
Outcomes	**Primary outcomes** • Primary variceal bleeding (at the longest and most frequently reported timepoints) • Mortality (including mortality caused by bleeding) (at the longest and most frequently reported timepoints) • Quality of life (using a validated scale) (at all reported timepoints)

	Secondary outcomes (All measured at the longest timepoint) • Liver transplant • Number of decompensation episodes • Hospitalisation (including length of hospital stay) • Other adverse events (for example, pain, low compliance/discontinuation with treatment due to side effects or for other reasons)
Study type	Randomised Controlled Trials (RCTs)

For the full protocol see appendix A.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the description of methods in the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

RevMan files of the previous version of this review were updated to generate the analysis for this review. Data from existing studies were not re-extracted, however new evidence tables were generated, and risk of bias was reassessed since Cochrane RoB 2.0 was not available at the last update.

Outcomes that have not changed during this update have been included in this review for completeness, however 10 conference abstracts that were included in the previous version of the guideline were excluded from this update and data associated with them were removed. These are detailed in appendix J.

Data for outcomes that were not prioritised for this review were not updated. They have been included in the appendices for reference but are not included in the summary of findings table.

1.1.3.1 Search methods

The searches for the clinical effectiveness evidence were run on 20th December 2022. The following databases were searched: Central Register of Controlled Trials (Wiley), Cochrane Database of Systematic Reviews (Wiley), Embase (Ovid), Epistemonikos and MEDLINE (Ovid), MEDLINE-in-Process (Ovid), MEDLINE Epub Ahead-of-Print (Ovid). The searches focused on the effectiveness of non-selective beta blockers and/or endoscopic variceal band ligation to prevent bleeding in those with medium to large oesophageal varices due to cirrhosis. Full search strategies for each database are provided in Appendix B.

The searches for the cost effectiveness evidence were run on 21st December 2022. The following databases were searched: EconLit (Ovid), Embase (Ovid), INAHTA and MEDLINE

(Ovid), MEDLINE-in-Process (Ovid), MEDLINE Epub Ahead-of-Print (Ovid). Full search strategies for each database are provided in Appendix B.

A NICE information specialist conducted the searches. The MEDLINE strategy was quality assured by a trained NICE information specialist and all translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2015 PRESS Guideline Statement.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A systematic search carried out to identify potentially relevant studies found 634 references (see appendix B for the literature search strategy).

These 634 references were screened at title and abstract level against the review protocol, with 616 excluded at this level. 10% of references were screened separately by two reviewers with >90% agreement. Discrepancies were resolved by discussion.

The full texts of 18 studies were ordered for closer inspection. 4 of these studies met the criteria specified in the review protocol (appendix A).

Additionally, 24 studies from the previous guideline were inspected and 14 of those were retained because they met the criteria specified in the review protocol (appendix A).

A total of 18 studies is included in this review.

For a summary of the 18 included studies see table_2 and table_3.

The clinical evidence study selection is presented as a PRISMA diagram in appendix C.

See section 1.1.14 References – included studies for the full references of the included studies.

1.1.4.2 Excluded studies

Details of studies excluded at full text, along with reasons for exclusion are given in appendix J.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2 Summary of new studies included in the effectiveness evidence

Study details	Population	Intervention 1	Intervention 2	Outcomes	Risk of bias
Abd ElRahim 2018 n=330 Egypt Follow up: 12 months	No history of bleeding; no prior endoscopic, radiological or surgical treatment of varices or ascites; no prior pharmacological treatment for primary variceal prophylaxis regimens **Exclusion**: Non-cirrhotic cause of portal hypertension; <18 or >75 years of age; Pregnant, lactating, or of childbearing age without use of contraception; Obstructive airways disease; Portal vein thrombosis; heart block; congestive cardiac failure; chronic renal insufficiency with plasma creatinine ≥ 150 µmol/l; history of variceal bleeding; hepatocellular carcinoma, previous primary or secondary prevention of varices,	**EVL** (n=88) Band ligation group received band ligation every 2 weeks using a multiband ligation device (sixshooter, Wilson-Cook Inc) up to six bands were placed per session from the distal oesophagus just above the gastroesophageal junction until oesophageal varices were eradicated.	**NSBB (2 groups)** **Carvedilol** (n= 92) Carvedilol group after assessment of baseline heart rate and blood pressure measurements, received a starting dosage of 6.25 mg daily, titrated up every 4 days to reach up to 12.5–50 mg, to achieve reduction of baseline heart rate by 25 %, but not below 55 beats/min. **Propranolol** (n=84) Propranolol group after assessment of baseline heart rate and blood pressure, received a starting	• Variceal bleed • Treatment related complications	**High** Lack of blinding; Variations in baseline characteristics not addressed; 20% drop-out at follow-up and no reference to an intention to treat analysis.

Study details	Population	Intervention 1	Intervention 2	Outcomes	Risk of bias
	sick sinus syndrome; bradycardia under 60 beats/min; asthma; uncontrolled diabetes mellitus; drugs affecting portal pressure (betablockers, vasopressors, nitrates, and vasodilators); active schistosomiasis; chronic alcoholism.		dosage of 40 mg daily, adjusted in 20–40 mg increments at 2-weekly intervals, to achieve reduction of baseline heart rate by 25 %, but not below 55 beats/min.		
Kanwal 2022 n= 254 Pakistan Follow up: 3 months	Patients aged 18 – 75 years of both genders with cirrhosis and oesophageal varices. **Exclusion**: previous history of variceal bleeding or undergone EVL, allergy to carvedilol, history of obstructive airway disease, already on NSBB.	**EVL** (n=127) Saeed Six Shooter Multi-Band Ligator® connected to a video endoscope (Olympus, Tokyo, Japan) was used. Procedure was repeated every 3 weeks until variceal obliteration.	**Carvedilol** (n=127) Started on dose of once daily 6.25mg initially for 1 week and subsequently titrated to twice daily 6.25mg	• Variceal bleeding Sub-groups for • Age (18-40/40-75) • Gender • Duration of disease <12m/>12m	**Moderate** Lack of blinding and general lack of study detail reported.
Khan 2017 n-250 Pakistan	Patients aged 30–80 years with cirrhosis and oesophageal varices on endoscopy (grade I &II). **Exclusion**: previous variceal bleed; pregnant or lactating; allergic to carvedilol; already taking β-	**EVL** (n=125) EVL was performed using a multibander device. All EVBL was done by a single consultant gastroenterologist.	**Carvedilol** (n=125) Carvedilol 12.5mg daily	• Variceal bleeding Sub-groups for • Age (<50/>50) • Gender	**Moderate** Lack of blinding and general lack of study detail reported.

Study details	Population	Intervention 1	Intervention 2	Outcomes	Risk of bias
Follow up: 6 months	blockers; cancer or presence of severe systemic illness; BP>140/90mmHg; DM (SBR>200mg/dl); h/o psychiatric disease; COPD or asthma; Mean Arterial Pressure <55mmHg or HR <50 bpm; portal vein thrombosis				
Singh 2022 n=160 India Follow up: 12 months	Patients with cirrhosis (Child-Turcotte-Pugh, CTP-B or C), age ≥ 18 years and ≤ 75 years, and ≥ grade2 ascites with oesophageal varices needing primary prophylaxis. **Exclusion**: patients with active/recent infection within 2 weeks; hepatic encephalopathy; renal dysfunction; HCC; portal vein thrombosis; active alcoholism; past-VH or NSBB use or EVL; R.A.; pregnancy; HIV infection; contraindications for beta-blockers (severe COPD; severe asthma; uncontrolled diabetes; bradyarrhythmia, peripheral	**EVL** (n=80) EVL (+standard treatment) - group underwent regular sessions of EVL using a multi-band ligation device (six shooter) till variceal eradication every 4 weeks followed by 3 monthly for the initial 6 months and 6 monthly thereafter. Recurrent oesophageal varices were banded till eradication. Standard treatment was low sodium diet (2 g/day) and a combination of furosemide (20–160 mg/day) and spironolactone (50–400 mg/day) with dose escalation by one step at a time.	**Propranolol** (n=80) Propranolol +standard treatment: Long-acting PPL orally at 40 mg/day, with weekly dose titration with a target heart rate of 55–60 beats/min or 20–25% reduction or maximum tolerated dose. Compliance with PPL was assessed by monthly pill counts and/or self-reporting. Standard treatment was low sodium diet (2 g/day) and a combination of furosemide (20–160 mg/day) and spironolactone (50–400 mg/day) with dose	• Variceal bleeding • Adverse events • Transplant free survival • Hospital admission	**Moderate** No blinding.

Study details	Population	Intervention 1	Intervention 2	Outcomes	Risk of bias
	vascular disease) and patients refusing to give consent.		escalation by one step at a time.		

EVL: Endoscopic variceal band ligation; NSBB: Non-selective beat blocker; D: outcome reported as a dichotomous outcome; TTE: outcome reported as a time-to-event outcome

Table 3 Summary of studies included in the previous effectiveness evidence (NG50)

Study details	Population	Intervention	Comparison	Outcomes	Risk of bias
De 1999 India Follow up: mean 18 months (range not reported)	Cirrhosis and III to IV oesophageal varices and no history of bleeding (HVPG ≥12 mmHg)	**EVL** (n=15) EVL weekly to fortnightly until obliteration	**propranolol** (n=15) Propranolol starting dose 40 mg 3 times daily then titrated to achieve a 25% reduction in pulse rate	• Variceal bleeding (D) • Gastrointestinal bleeding* (D)	**Moderate** Method for randomisation unclear. No blinding. Study states that there were no significant differences between study arms but there is no reference to how this was established.
Drastich 2011 Czech Republic Follow up:	Portal hypertension due to liver cirrhosis and large oesophageal varices (>5 mm) **Excluded**: non-cirrhotic cause of portal hypertension; history of gastrointestinal bleeding; sclerotherapy, EVL	**EVL** (n=40) EVL using multiband ligator device (Six shooter, Wilson-Cook), up to 6 bands placed in each session. Performed at 2-week intervals until	**Propranolol** (n=33) Propranolol starting dose 20 mg twice daily. Adjusted in 20–40 mg increments at weekly intervals to achieve a HR reduction of 25%	• Mortality (TTE) • Variceal bleeding (TTE) • Gastrointestinal bleeding – variceal only* (D)	**Moderate** No blinding. There were deviations and adaptions in each arm because of adverse effects during the follow-up period which are outlined in the results section.

Study details	Population	Intervention	Comparison	Outcomes	Risk of bias
median 10 months.	or shunt; malignant disease; gastric or duodenal ulcer; congestive heart failure; renal insufficiency; treatment with beta-blockers, nitrates, ACE inhibitors or verapamil; antiviral therapy; AV block, sick-sinus syndrome, bradycardia; decompensated diabetes; pregnancy, lactation.	oesophageal varices eradicated (complete disappearance or too small to be ligated). EVL continued in patients with recurrence.	(not below 55 bpm or systolic BP <80 mmHg).	• Bleeding mortality (D) • Weakness (D)	
Jutabha 2005 USA mean 12 months (range 1 to 61 months)	Cirrhosis and large (>5 mm or Paquet grade 3-4) or high-risk (medium size 3–5mm with red signs) non-bleeding varices. Cirrhosis was biopsy-proven or clinically evident. No previous upper Gastrointestinal bleeding; no prior sclerotherapy or EVL, TIPS or surgical; no current beta-blocker; life expectancy at least 24 months. **Excluded**: serious recurrent or ongoing comorbid illness and	**EVL** (n=31) EVL using a multiband ligating device (Saeed Six-Shooter). Follow up banding performed at 4–5 weeks. EVL performed until obliteration or reduction to a small size and EVL not possible. Recurrent varices also underwent EVL. In EVL group, patients prescribed proton pump inhibitors once daily	**Propranolol** (n=31) Propranolol – either long acting at starting dose of 80 mg and seen weekly to adjust dose by 80 mg increments (max 400mg) to reduce HR by 25% OR 40 mg twice daily and increased every 2 weeks by 40–80 mg as tolerated.	• Mortality (D) • Variceal bleeding (D) • Gastrointestinal bleeding – variceal only* (D) • Bleeding mortality (D)	**High** No blinding. Significant difference in participant characteristics post randomisation (at interim analysis) that led to study recruitment being stopped before all recruitment had been completed. The results of this study represent the findings of the interim analysis. Further there were some issues with the supply of propranolol at year 3 leading to participants being moved onto a different treatment regimen - this deviation may have had some impact but did not need to be

Study details	Population	Intervention	Comparison	Outcomes	Risk of bias
	contraindication to beta-blockers. Other exclusion criteria detailed including moderate or large gastric or duodenal ulcers, large-volume or tense ascites or HCC.	until obliteration of varices.			balanced across both arms as interventions were different. Both these factors introduce bias and findings should be treated with some caution.
Lay 2006 Taiwan Follow up: mean 35 months (range 1 to 72 months)	Cirrhosis and oesophageal varices (risk score from Beppu et al., corresponded to all patients having blue varices of F2 or F3 size with at least 1 red colour sign) at high risk and no previous upper Gastrointestinal bleeding. **Excluded**: other disease reducing life expectancy	**EVL** (n=50) EVL with 1–3 rubber bands on each varix until the varices were too small to ligate (max 10 rubber bands per session).	**Propranolol** (n=50) Propranolol at a starting dose of 40 mg twice daily. Increased by 10 mg twice daily until either a reduction in the resting HR of 20% or to the maximum dose.	• Mortality (D) • Variceal bleeding (D) • Gastrointestinal bleeding* (D) • Bleeding mortality (D)	**Moderate** No blinding. Some concerns due to lack of consideration of participant withdrawals from study and mortality in the analysis and conclusion sections. It is unclear in the paper how the participant withdrawals were considered.
Lui 2002 UK mean 20 months	Cirrhosis and grade II or III oesophageal varices that had never bled. Cirrhosis diagnosed based on histology or a combination of radiology, laboratory, and clinical parameters.	**EVL** (n=44) EVL performed every 2 weeks until eradication (complete or grade I only) with single or multiband. Further EVL	**Propranolol** (n=66) Propranolol starting dose of 40mg twice daily and incremental dosing used to achieve the	• Mortality (TTE) • Variceal bleeding (TTE) • Gastrointestinal bleeding –	**Moderate** No blinding.

Study details	Population	Intervention	Comparison	Outcomes	Risk of bias
(range 1 to 48 months)	**Excluded** if <18 or >75 years; advanced systemic illness; non-cirrhotic cause of portal hypertension; on vasoactive agents; contraindications to beta-blockers.	if grade II or larger varices recurred.	target daily dose of 160mg.	variceal only* (D) • Bleeding mortality (D)	
Norberto 2007 Italy 14 months (range not reported).	Cirrhosis and studied for liver transplant. Oesophageal varices F3 or F2 blue with red signs according to Beppu, and no previous bleeding. Cirrhosis diagnosed based on clinical, biochemical or histological analysis. **Excluded** if <18 or >85 years; gastric varices; previous endoscopic, radiological, or surgical treatment of varices; HCC; portal vein thrombosis; heart, respiratory or renal failure; contraindications to beta-blockers; treatment with nitrates, Ca antagonists or	**EVL** (n=31) EVL performed using a multiband ligator with 6 or 7 bands (Six shooter, Wilson-Cook). Performed every 2 weeks until varices completely eradicated. EVL performed again on recurrent varices. EVL group also received proton pump inhibitors.	**Propranolol** (n=31) Propranolol started at 10mg twice daily and increased by 20mg/day until a 25% reduction in HR. Maximum dose 160 mg/day.	• Mortality (D) • Variceal bleeding (D) • Gastrointestinal bleeding – variceal only* (D) • Bleeding mortality (D)	**Moderate** No blinding. The trial was ended early due to recorded deaths.

Study details	Population	Intervention	Comparison	Outcomes	Risk of bias
	anti-arrhythmic drugs; pregnancy; neoplasia.				
Perez-Ayuso 2010 Mexico Follow up 55 months (range 1 to 119 months).	Cirrhosis, high-risk oesophageal varices (large or medium size, 3–5 mm, with red colour signs), no history of bleeding from varices and no current treatment with beta-blockers. Cirrhosis diagnosed based on clinical, biochemical, histological or ultrasonographic evidence. **Excluded**: younger than 18 and older than 70; big gastric varices, evidence of portal thrombosis, malignancy, contraindication to beta-blockers, previous variceal endoscopic treatment, TIPS, surgical shunt or renal failure.	**EVL** (n=39) EVL performed at 3-week intervals until eradication (absence of ligable varices). Up to 6 bands placed in each session using a multiband ligator (Six shooter, Wilson-Cook). Religation performed if at least 1 varix >5mm reoccurred.	**Propranolol** (n=36) Propranolol starting dose 20 mg twice daily and increased every 3 days to achieve a 25% reduction in heart rate, to a heart rate <55 bpm, to a systolic blood pressure <90 mmHg or a maximum of 320 mg daily.	• Mortality (TTE) • Variceal bleeding (D) • Gastrointestinal bleeding* (D) • Bleeding mortality (D)	**High** Deviations from intended intervention post randomisation with 2 patients in the propranolol arm suffering adverse events and being crossed over to the EVL arm of the study. This deviation does not appear to have been balanced across the study (or is not documented). There was approximately 15% loss to follow-up with no reference to an analysis to consider the impact of a lack of adherence to the interventions under study.
Psilopoulos 2005	Portal hypertension caused by cirrhosis, grade II or III oesophageal varices (F2 or F3	**EVL** (n=30) EVL performed using multiband ligation	**Propranolol** (n=30) Propranolol received 40 mg and dose	• Mortality (TTE) • Variceal bleeding (TTE)	**High** No blinding which is a potential source of bias. During the study 2

Study details	Population	Intervention	Comparison	Outcomes	Risk of bias
Greece Follow up: 28 months (range 0.5 to 52 months).	according to Beppu) with red signs and no history of variceal bleeding. **Excluded** treatment with nitrates or beta-blockers; <20 or >70 years; gastric or ectopic varices; severe comorbidity; refractory ascites; HCC; marked jaundice; contraindications to beta-blockers; history of EVL, sclerotherapy or TIPS or shunts.	device (Speedband or Six shooter). 1 or 2 bands applied to each varix, and up to 6 bands per session. Sessions repeated every 2–3 weeks until variceal eradication or too small to be ligated. EVL patients treated with proton pump inhibitors until variceal eradication.	adjusted to achieve 25% reduction in HR.	• Gastrointestinal bleeding* (D) • Bleeding mortality (D)	participants in the EVL arm developed variceal bleeding post first and second EVL session and were treated with endoscopic sclerotherapy which was outlined as an exclusion criteria. In the PPL arm treatment was discontinued for 4 participants. It is unclear how the analysis accounted for these deviations from the study protocol.
Sarin 1999 India mean not reported (range 0.5 to 18 months)	Portal hypertension and large grade 3 (3–6 mm) or 4 (>6 mm) varices with no history of bleeding. Cirrhosis was diagnosed on the basis of clinical, biochemical, histologic or ultrasonographic evidence (cirrhosis was not an entry criterion and 6 patients had extrahepatic portal vein obstruction and 1 patient had non-cirrhotic portal fibrosis)	**EVL** (n=46) EVL performed using a single rubber band for each varix and as many bands as possible in each session (average 3–9). Performed every week until obliterated or reduced to grade I size. EVL repeated if varices recurred and	**Propranolol** (n=44) Propranolol started with 40 mg and increased the dose by 2–40 mg/day until a 25% reduction in HR achieved.	• Mortality (D) • Variceal bleeding (TTE) • Gastrointestinal bleeding – variceal only* (D) • Bleeding mortality (D) • Lethargy (D)	**Moderate** No blinding.

Study details	Population	Intervention	Comparison	Outcomes	Risk of bias
		became grade II or larger.		• Hospitalisation (D)	
Schepke 2004 Germany Follow up: mean 34 months (0,1 to 73 months).	Cirrhosis and 2 or more oesophageal varices >5 mm, no previous bleeding, and a Child-Pugh score below 12. Cirrhosis diagnosis made on histology or unequivocal clinical, sonographic and laboratory findings. **Excluded**: prehepatic portal hypertension, bradycardia, systolic BP <100 mmHg, contraindications to beta-blockers, severe comorbidities, listed for liver transplantation, treatment with beta-blockers or nitrates, TIPS, or surgical shunt.	**EVL** (n=75) EVL performed using a multiband ligator (Six shooter, Wilson-Cook), up to 10 bands in each session. Performed weekly until eradication. Religation preformed when at least 1 varix >5 mm recurred.	**Propranolol** (n=77) Propranolol started at 40 mg twice daily and increased by 10 mg twice daily until HR reduction of 20% or to the maximum dose.	• Mortality (TTE) • Variceal bleeding (TTE) • Gastrointestinal bleeding – variceal only* (D) • Bleeding mortality (D)	**High** No blinding. Some concerns regarding adherence to intervention. In the propranolol group, 25% (n=19) participants withdrew from the treatment, 12 due to side effects which did not resolve with dose reduction and a further 7 due to incompliance despite no side effects. Trial ended early because at the interim analysis, virtually no difference was seen between the 2 arms and it was clear that 200 participants in each arm would be insufficient to detect a difference in bleeding rates between the two groups.
Shah 2014 Pakistan	Cirrhosis without history of variceal bleed; medium or large sized oesophageal varices (grade II-IV). Diagnosis of cirrhosis made based on	**EVL** (n=86) EVL performed using Saeed Six Shooter Multiband ligator (Wilson-Cook).	**Carvedilol** (n=82) Carvedilol initial dose 6.25mg once a day increased to twice a	• Mortality (TTE) • Variceal bleeding (TTE)	**Moderate** No blinding.

Study details	Population	Intervention	Comparison	Outcomes	Risk of bias
Follow up: mean 13.2 months	clinical, radiological, biochemical features and liver histology where available. **Excluded**: Pregnant or lactating; allergy to carvedilol or reactive airway disease; already on beta-blocker treatment; presence of hepatic or other malignancy which could impair longevity or presence of severe systemic illness which could impair the subject's ability to participate in the trial; people with mental ill-health or learning disabilities; gastric varices alone.	Repeated every 3 weeks until obliteration of varices achieved (no varices or only small varices which were flattened on air insuffations). Procedure repeated if varices recurred.	day after a period of 1 week.	• Gastrointestinal bleeding – variceal only* (D) • Bleeding mortality (D)	
Singh 2012 India Follow up:	Patients with portal hypertension and oesophageal varices at high risk of bleeding, who had never had bleeding from varices. Large, grade 3 or 4 varices at high risk (Conn's criteria: grade 3, varices of 3	**EVL** (n=18) EVL carried using PentaGun Multiband Ligator - as many bands as possible (3–6 bands). Performed weekly until varices obliterated or	**Propranolol** (n=20) Propranolol started with 40 mg. Dose increased by increments of 20– 40 mg/day until a 25%	• Mortality (D) • Gastrointestinal bleeding* (D) • Bleeding mortality (D)	**High** No information is provided on whether allocation was concealed until participants enrolled and assigned to intervention. No blinding. Few details on patient characteristics are given. There

Study details	Population	Intervention	Comparison	Outcomes	Risk of bias
12 months	to 6 mm; grade 4, varices of > 6 mm). Eligibility criteria does not specify cirrhosis, but results report all patients had cirrhosis and cirrhosis was diagnosed based on clinical-biochemical, histologic, or ultrasonographic evidence. **Excluded**: receiving antiviral therapy or concomitant hepatoma or tumour, severe cardio-pulmonary or renal disease, bradycardia, bronchial asthma, diabetes mellitus, heart failure, peripheral vascular disease, a psychiatric disorder, glaucoma, or prostatic hypertrophy	reduced to size grade 1. Procedure repeated if varices recurred or became grade 2 or larger.	decrease in HR achieved.		are also some concerns that not all outcomes listed as end points appear to be reported.
Thuluvath 2005 USA Follow up:	Cirrhosis and large oesophageal varices (F2 or F3), no previous bleeding and HVPG ≥12 mmHg. Cirrhosis diagnosis made by clinical or histologic evidence.	**EVL** (n=16) EVL using a multiband ligator every 2–3 weeks until variceal eradication.	**Propranolol** (n=15) Propranolol titrated to achieve a HR of <60 bpm or a 25% reduction, or until	• Mortality (D) • Variceal bleeding (D) • Gastrointestinal bleeding –	**High** No blinding. Compliance was self-reported by patients rather than by a validated measure. The study was terminated early due to realisation that the required

Study details	Population	Intervention	Comparison	Outcomes	Risk of bias
mean 27 months.	**Excluded** large gastric varices; previous EVL or sclerotherapy; HCC; contraindications to beta-blockers.		maximum dose reached.	variceal only* (D) • Bleeding mortality (D)	sample size to show a difference between the trial arms had been grossly underestimated.
Tripathi 2009 UK Follow up: mean 26 months (range not reported)	Cirrhosis and oesophageal varices grade II or larger in size without previous bleeding. Cirrhosis diagnosis made based on clinical, radiological or laboratory evidence and/or liver biopsy. Excluded: <18 or >75 years; pregnant or lactating; childbearing age not on contraception; carvedilol allergy; malignancy affecting survival; systemic illness; psychiatric disease; obstructive airway disease; portal vein thrombosis; mean arterial pressure <55 mmHg or pulse <50 bpm.	**EVL** (n=75) EVL performed using a multiband ligator (Speedbander or Six shooter). Performed every 2 weeks until eradication or grade I in size. EVL repeated on recurrence of varices.	**Carvedilol** (n=77) Carvedilol starting dose of 6.25 mg per day, increased to a target dose of 12.5 mg/day if systolic BP did not fall below 90 mmHg.	• Mortality (TTE) • Variceal bleeding (TTE) • Gastrointestinal bleeding – variceal only* (D) • Bleeding mortality (D)	**High** Loss of approxmately1/3 participants in each arm. Some concerns about lack of blinding for participants, relatives and clinicians. People in EVL arm given NSBB if unable to tolerate EVL.

EVL: Endoscopic variceal band ligation; HCC: Hepatocellular carcinoma; HVPG: Hepatic venous pressure gradient; TIPS: transjugular intrahepatic portosystemic shunt; D: outcome reported as a dichotomous outcome; TTE: outcome reported as a time-to-event outcome.

* Not included as an outcome in this update, however the data have been preserved in the appendices for continuity.

See appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Only outcomes related to the PICO for this update are summarised here. GRADE tables for other outcomes considered in the previous version of this guideline are in appendix F.

1.1.6.1 Endoscopic variceal band ligation versus non-selective beta-blockers for the primary prevention of variceal bleeding

Should EVL or NSBB be used in people with cirrhosis for the primary prophylaxis of variceal bleeding?

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Interpretation of effect
				Risk with control	Risk difference with Medium/large varices Banding ligation versus non-selective beta-blockers (95% CI)	
Mortality	383 (6 studies[6])	⨁⊖⊖⊖ **VERY LOW**[7,8] due to risk of bias, imprecision	**RR 0.99** (0.63 to 1.56)	**157 per 1000**	**2 fewer per 1000** (from 58 fewer to 88 more)	**Could not differentiate**
Variceal bleeding	1288 (10 studies[10])	⨁⊖⊖⊖ **VERY LOW**[7,11,12] due to risk of bias, inconsistency, imprecision	**RR 0.86** (0.52 to 1.43)	**128 per 1000**	**18 fewer per 1000** (from 62 fewer to 55 more)	**Could not differentiate**
• **Variceal bleeding - All NSBB**	264 (1 study[13]) 12 months	⨁⊖⊖⊖ **VERY LOW**[8,12] due to risk of bias, imprecision	**RR 0.78** (0.38 to 1.62)	**131 per 1000**	**29 fewer per 1000** (from 81 fewer to 81 more)	**Could not differentiate**
• **Variceal bleeding - Carvedilol**	504 (2 studies[14]) 3-6 months	⨁⊖⊖⊖ **VERY LOW**[5,11,15] due to risk of bias, inconsistency, imprecision	**RR 1.66** (0.84 to 3.28)	**131 per 1000**	**86 more per 1000** (from 21 fewer to 299 more)	**Could not differentiate**
• **Variceal bleeding - Propranolol**	520 (7 studies[16])	⨁⊖⊖⊖ **VERY LOW**[5,7]	**RR 0.51** (0.28 to 0.95)	**124 per 1000**	**61 fewer per 1000** (from 6 fewer to 89 fewer)	**Favours EVL**

		due to risk of bias, imprecision				
Variceal bleeding by length of disease - Variceal bleeding < 12 months disease	227 (1 study[17]) 3 months	⨁⊖⊖⊖ **VERY LOW**[4,12] due to risk of bias, imprecision	**RR 1.31** (0.75 to 2.3)	**157 per 1000**	**49 more per 1000** (from 39 fewer to 203 more)	**Could not differentiate**
Variceal bleeding by length of disease - Variceal bleeding >12 months disease	27 (1 study[17]) 3 months	⨁⊖⊖⊖ **VERY LOW**[4,12] due to risk of bias, imprecision	**RR 1.07** (0.71 to 1.61)	**750 per 1000**	**53 more per 1000** (from 218 fewer to 458 more)	**Could not differentiate**
Variceal bleeding by age - Variceal bleeding 18 - 40 years	18 (1 study[17]) 3 months	⨁⊖⊖⊖ **VERY LOW**[4,12] due to risk of bias, imprecision	**RR 2** (0.22 to 18.33)	**111 per 1000**	**111 more per 1000** (from 87 fewer to 1000 more)	**Could not differentiate**
Variceal bleeding by age - Variceal bleeding <50 years	131 (1 study[18]) 6 months	⨁⊖⊖⊖ **VERY LOW**[4,12] due to risk of bias, imprecision	**RR 2.61** (0.74 to 9.22)	**49 per 1000**	**79 more per 1000** (from 13 fewer to 404 more)	**Could not differentiate**
Variceal bleeding by age - Variceal bleeding 40-75 years	236 (1 study[17]) 3 months	⨁⨁⊖⊖ **LOW**[4,5] due to risk of bias, imprecision	**RR 1.27** (0.81 to 1.98)	**220 per 1000**	**59 more per 1000** (from 42 fewer to 216 more)	**Could not differentiate**
Variceal bleeding by age - Variceal bleeding >50 years	119 (1 study[18]) 6 months	⨁⊖⊖⊖ **VERY LOW**[4,12] due to risk of bias, imprecision	**RR 2.72** (0.74 to 10)	**47 per 1000**	**81 more per 1000** (from 12 fewer to 422 more)	**Could not differentiate**
Variceal bleeding by gender - Male	335 (2 studies[14]) 3-6 months	⨁⨁⊖⊖ **LOW**[5,15] due to risk of bias, imprecision	**RR 1.5** (0.89 to 2.53)	**112 per 1000**	**56 more per 1000** (from 12 fewer to 172 more)	**Could not differentiate**
Variceal bleeding by gender - Female	169 (2 studies[14]) 3-6 months	⨁⊖⊖⊖ **VERY LOW**[5,11,15] due to risk of bias, inconsistency, imprecision	**RR 1.62** (0.89 to 2.93)	**169 per 1000**	**105 more per 1000** (from 19 fewer to 326 more)	**Could not differentiate**
Upper gastrointestinal bleeding	1203 (14 studies[19])	⨁⊖⊖⊖ **VERY LOW**[5,7] due to risk of bias, imprecision	**RR 0.8** (0.62 to 1.04)	**175 per 1000**	**35 fewer per 1000** (from 66 fewer to 7 more)	**Could not differentiate**

Bleeding-related mortality	1202 (14 studies[19]) 12 months	⊕⊖⊖⊖ **VERY LOW**[5,7] due to risk of bias, imprecision	**RR 0.67** (0.42 to 1.08)	**66 per 1000**	**22 fewer per 1000** (from 38 fewer to 5 more)	**Favours EVL**
Hospitalisation	249 (2 studies[20]) 12 months	⊕⊕⊖⊖ **LOW**[5,15] due to risk of bias, imprecision	**RR 0.64** (0.44 to 0.93)	**379 per 1000**	**136 fewer per 1000** (from 27 fewer to 212 fewer)	**Favours EVL**
Adverse events - All adverse events	424 (2 studies[21]) 12 months	⊕⊖⊖⊖ **VERY LOW**[5,7,22] due to risk of bias, inconsistency, imprecision	**RR 0.53** (0.34 to 0.81)	**270 per 1000**	**127 fewer per 1000** (from 51 fewer to 178 fewer)	**Favours EVL**

*The basis for the **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **HR:** Hazard ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Calculated from the median control group rate at the end of the study
[2] Drastlich 2005; Lui 2002; Perez-Ayuso 2010; Psilopoulos 2005; Schepke 2004; Shah 2014; Tripathi 2009
[3] Singh 2022
[4] Single study at moderate risk of bias
[5] Downgraded once for crossing 1 MID
[6] Jutabha 2005; Lay 2006; Norbeto 2007; Sarin 1999; Singh 2012; Thuluvath 2005
[7] Downgraded twice because greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias
[8] Single study at high risk of bias
[9] Drastich 2005; Lui 2002; Psilopoulos 2005; Sarin 1999; Schepke 2004; Shah 2014; Tripathi 2009
[10] Abd El Rahim 2018; Kanwal 2022; Khan 2017; De 1999; Jutabha 2005; Lay 2006; Norberto 2007; Perez-Ayuso 2010; Singh 2022; Thuluvath 2005
[11] Downgraded once because I2 >33% and less than 66%
[12] Downgraded twice for crossing both MIDs
[13] Abd El Rahim 2018
[14] Kanwal 2022; Khan 2017
[15] Both studies at moderate risk of bias
[16] De 1999; Jutabha 2005; Lay 2006; Norberto 2007; Perez-Ayuso 2010; Singh 2022; Thuluvath 2005
[17] Kanwal 2022
[18] Khan 2017
[19] De 1999; Drastich 2005; Jutabha 2005; Lay 2006; Lui 2002; Norberto 2007; Perez-Ayuso 2010; Psilopoulos 2005; Sarin 1999; Schepke 2004; Shah 2014; Singh 2012; Thuluvath 2005; Tripathi 2009
[20] Sarin 1999; Singh 2022

[21] Abd El Rahim 2018; Singh 2022
[22] Downgraded twice for I2 > 66%
[23] Sarin 1999; Drastich 2005

1.1.6.2 Propranolol versus carvedilol for the primary prevention of variceal bleeding

Propranolol versus carvedilol for primary prevention of variceal bleeding in adults with medium or large oesophageal varices.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Interpretation of effect
				Risk with Control	Risk difference with Medium/large varices propranolol versus carvedilol (95% CI)	
Variceal bleeding	176 (1 study[1]) 12 months	⊕⊖⊖⊖ **VERY LOW**[2,3] due to risk of bias, imprecision	**RR 0.7** (0.33 to 1.52)	**155 per 1000**	**46 fewer per 1000** (from 104 fewer to 80 more)	**Could not differentiate**
Adverse events	176 (1 study[1]) 12 months	⊕⊕⊖⊖ **LOW**[2] due to risk of bias	**RR 2.43** (1.34 to 4.41)	**143 per 1000**	**204 more per 1000** (from 49 more to 487 more)	**Favours carvedilol**

*The basis for the **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Abd ElRahim (2018)
[2] Downgraded twice for single study at high risk of bias
[3] Downgraded twice for crossing 2 MIDs

See appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

A search was performed to identify published economic evaluations of relevance to this guideline update. This search retrieved 157 studies. Based on title and abstract screening, all of the studies were excluded for this question.

1.1.7.2 Excluded studies

No studies were examined at full text.

1.1.8 Summary of included economic evidence

No economic studies were included in this review.

1.1.9 Economic model

We developed a cost-utility model to compare the cost effectiveness of endoscopic variceal band ligation (EVL) with non-selective beta blockers (NSBBs). The ICER for EVL compared with NSBB was £511,614 per QALY gained. The findings from the economic model were summarised in the table below, with a full write up of the methods and results in Appendix I.

1.1.9.1 Health economic evidence profile: Endoscopic variceal band ligation (EVL) vs non-selective beta blockers (NSBBs)

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effect	Cost effectiveness	Uncertainty
Cost-utility analysis	Directly applicable	Potentially serious limitations	• Outcomes: incremental cost effectiveness ratio (ICER) • Population: People aged 16 years and older with cirrhosis, who have medium- sized or large oesophageal varices which have never bled • Comparators: EVL vs NSBBs • Time horizon: 1 year	£3,346	0.0065 QALYs	£511,614 per QALY gained	A number of deterministic scenarios were explored. Treatment effect had largest impact on the ICER. NSBBs remained cost effective for the majority of scenarios, except when the treatment effect for EVL was based on the lower limit of the 95% CIs for RRs (most favourable estimates)

1.1.10 Unit costs

The costs of the drugs included in recommendations for this review question are given below.

Resource	Daily dose	Unit costs	Source
Propranolol (tablets)	80–320 mg	£0.79 for 28 40mg tablets	BNF (accessed March 2023)
		£1.57 for 56 80mg tablets	
		£5.88 for 56 160mg tablets	
Propranolol (oral solution)	80–320 mg	£45.84 for 40mg	
		£50.45 for 50mg	
Carvedilol	6.25–12.5 mg	£0.88 for 28 6.25mg tablets	
		£1.25 for 28 12.5mg tablets	

1.1.11 The committee's discussion and interpretation of the evidence

1.1.11.1. The outcomes that matter most

The committee agreed that the primary outcomes of variceal bleeding, mortality and quality of life were the most important outcomes. The committee noted that the secondary outcomes of liver transplant, number of decompensation episodes, hospitalisation and other adverse events were also important outcomes. These outcomes were agreed and included in the review protocol (see appendix A) for this review. The committee acknowledged that the included studies did not provide evidence for all outcomes outlined in the review protocol.

1.1.11.2 The quality of the evidence

Overall, 4 new RCTs (Abd ElRahim, 2018; Kanwal, 2022; Khan, 2017; Singh, 2022) were identified for this update and considered alongside14 RCTs that were included in the previous version of this review (De, 1999, Drastich, 2011; Jutabha, 2005; Lay, 2006; Lui, 2002; Norberto, 2007; Perez-Ayuso, 2010; Psilopoulos, 2005; Sarin, 1999; Schepke, 2004; Shah, 2014; Singh, 2012; Thuluvath, 2005; Tripathi, 2009).

All 18 studies compared endoscopic band ligation (EVL) to non-selective beta-blockers (NSBB). The quality of the evidence assessed using GRADE was predominantly of very low quality with 3 outcomes (variceal bleeding by gender – male, variceal bleeding by age – 40-75 years, and hospitalisations) rated as being of low quality and 1 outcome (adverse events – lethargy) rated as being of moderate quality. The majority of downgrading was due serious or very serious risk of bias (due to lack of detail regarding randomisation or a lack of blinding which is not always possible given the interventions under investigation) or imprecision (due to wide 95% confidence intervals). 1 RCT (Abd ElRahim, 2018) provided data that allowed a comparison of two NSBBs - propranolol and carvedilol for 2 outcomes (variceal bleeding and adverse events) with the quality of the evidence assessed against GRADE as being of very low and low quality with downgrading due to very serious risk of bias or imprecision. The committee noted that in this sub-group analysis EVL demonstrated a statistically significant

effect compared with propranolol for the outcome of variceal bleeding. Two studies (Kanwal et al 2022; Khan et al 2017) provided data that allowed additional sub-group analysis by length of disease, age and gender for EVL compared to NSBBs for the outcome of variceal bleeding which indicated treatment equivalence. These sub-group analyses were considered in the committees' discussions alongside the committees' practice-based experience and the findings of the equality impact assessment when developing recommendations. None of the studies compared EVL plus an NSBB to either NSBB alone or EVL alone so the committee made a research recommendation about it to inform future versions of this guideline (see appendix K for full details).

The committee acknowledged that the included studies did not provide evidence for all outcomes outlined in the review protocol, for example quality of life. The committee discussed the equivalence of treatment effects across interventions for most outcomes including variceal bleeding (except in the case of a sub-group analysis for EVL compared with propranolol) and mortality. The committee noted the statistically significant effects for transplant free survival, adverse events and hospitalisations and discussed the value of both these outcomes in making recommendations on treatments.

The committee noted that EVL and NSBB are different treatment types (surgical and pharmacotherapy) and that the adverse events experienced need to be treated with some caution as they are not necessarily comparable. They noted that the adverse events reported for both NSBB and EVL were almost all transient and not life threatening. The committee also noted that the reasons for hospitalisation (which was one of the outcomes of interest) given in the included studies were not necessarily a consequence of treatment by NSBB or EVL but were more likely to be other consequences of living with decompensated cirrhosis and were treated with caution when informing recommendation development.

In developing recommendations, the committee noted the relatively low quality of the evidence but agreed they were able to make strong recommendation based on the health economic analysis combined with the committees' expertise, experience from practice, and issues identified in the equality impact assessment.

1.1.11.3 Benefits and harms

The committee discussed the inability of the studies to differentiate between EVL and NSBB in terms of treatment effects for primary outcomes, although the cost-effectiveness analysis showed that NSBB were more cost-effective than EVL (see 1.1.11.4 below). They highlighted that treatment decisions would depend on the individual patients needs and circumstances as well as the effectiveness and cost-effectiveness. This is because if a person is not compliant with any treatment it is not likely to be effective, and therefore cannot be cost-effective. They noted that many people with decompensated cirrhosis and medium/large varices were likely to live chaotic and complex lives where issues such as lifestyle, treatment adherence, and factors such as distance to travel to receive treatment were key factors in choosing which treatment would be best for them. The committee highlighted that having other treatment options available, provided the clinician with some flexibility and that the decision on whether to undertake further EVL or prescribe NSBB should be made in discussion with the patient bearing in mind the preference for NSBB.

The committee agreed that in practice an endoscopy would be undertaken in most cases to diagnose and assess varices and that whilst undertaking this procedure any identified varices could be banded. The rationale for this was that undertaking an endoscopy is an invasive process and from a practitioner's perspective it seemed more efficient and less detrimental to the person to band, if appropriate, during this initial procedure. They noted that

not all practitioners who undertake endoscopy are able to undertake EVL, and that the person would have to consent to banding prior to the endoscopy, so this was an opportunistic intervention rather than a universal one.

The committee discussed 1 RCT (Abd ElRahim, 2018) that provided data that facilitated a comparison of propranolol to carvedilol for the outcomes of variceal bleeding (RR 0.70 95% CI 0.33 to 1.52) and adverse events (RR 2.43 95% CI 1.34 to 1.52). The findings could not differentiate between the two treatments for preventing variceal bleeding but found a clinically significant effect favouring carvedilol for a lower number of adverse events. The committee were disappointed by the lack of RCT data comparing NSBB to each other for the prevention of variceal bleeding but agreed that guidelines from professional bodies and current practice favoured treatment with carvedilol. They noted that the use of carvedilol for this indication is off-label, whereas propranolol does have a licence for this indication.

The committee acknowledged that the SPC for carvedilol lists significant hepatic dysfunction as a contraindication. The basis of the contraindication relates to the fact that carvedilol is extensively metabolised by the liver and is also a heavily protein bound drug so impacted by hypoalbuminaemia (an abnormally low blood level of the protein albumin) arising from liver disease. They discussed this issue at length, noting that in spite of the contraindication, carvedilol is in common use for this indication, including in NIHR funded trials. They noted that the definition of significant hepatic impairment was open to some interpretation, and that different clinicians would interpret it differently. They agreed that in general, people with no history of decompensation do not have clinically significant hepatic impairment, therefore carvedilol could be used with some caution in these groups. The committee heard from the pharmacy and hepatology experts on the group that the reason for the contraindication to carvedilol is because the systemic availability of the drug is increased 80% in people with liver cirrhosis They agreed that, in spite of this, the mechanism of action, the side effect profile, better tolerability and better patient acceptability of carvedilol made it a good choice alongside propranolol for this indication. They also agreed that because of this contraindication, much more care needed to be taken with prescribing it, and so they supported the dosing schedule recommended by the British Society of Gastroenterology UK Guidelines for the Management of Variceal Haemorrhage in Cirrhotic Patients (Carvedilol: 6.25 mg once daily to increase to maintenance of 12.5 mg after a week if tolerated or once heart rate of <50–55 beats per minute (BPM) is reached (Tripathi et al 2022) which is half of the usual dose). They further agreed that for patients who were frail or who had low blood pressure, the dose might need to be reduced even further.

The committee noted the prescribing guidelines for NSBB should be observed, including monitoring heart rate and blood pressure to titrate the dose. It was noted that beta-blockers may increase risk of certain conditions during pregnancy and lactation.

1.1.11.4 Cost effectiveness and resource use

There was no relevant existing evidence identified that compared the band ligation (EVL) with beta-blockers (NSBBs) for the primary prevention of bleeding in people with medium to large varices. We developed a cost utility model with 1-year time horizon to evaluate the cost effectiveness of EVL versus NSBBs. We compared EVL to individual NSBBs (propranolol and carvedilol) in a scenario analysis. The treatment effects for EVL and NSBBs on variceal bleeding and all-cause mortality are based on the latest clinical evidence review (2023). The risk differences between these two interventions are not statistically or clinically significant, and the committee noted substantial uncertainties around the treatment effect. The total cost for each arm includes the cost of the interventions and management cost of variceal

bleeding. The cost of endoscopic surveillance was applied to people who had EVL for primary prevention of bleeding. QALY gains were from averted variceal bleeds and reduced all-cause mortality. In our base-case results, EVL compared with pooled NSBBs has an incremental cost of £3,346 (£3,888 vs £542) and an incremental QALY of 0.0065 (-0.468 vs -0.475) per person, yielding an ICER of £511,614 per QALY. There is little difference between EVL and NSBBs regarding the impact on quality of life, but EVL is estimated to be more expensive than NSBBs in our analysis. The majority of scenario analyses that we carried out provided similar conclusions, except when the treatment effect for EVL is at the most favourable bound of the 95% confidence interval, which did not reflect the clinical evidence or the committee's experience. Given the opportunity cost of £20,000 per QALY at NICE, the committee reflected that EVL does not represent value for money in the overall population in this review question.

There were some uncertainties associated with the model inputs that may have consequences for the interpretation of the results. Firstly, the number of EVL sessions required for the primary prevention was inconsistent between published clinical studies and the committee noted that protocols for giving band ligation vary across the country. However, varying the number of EVLs required between a minimum of 2.4 sessions and a maximum of 5, the scenario results found that EVL was not cost effective in either direction. The treatment effect on adverse events was based on low quality evidence, and the committee noted that it was difficult to compare the adverse events between EVL and NSBBs as they present differently after each intervention. In the case where the impact of lethargy, which affects people on NSBB more than on EVL, was included, EVL was still not considered cost effective compared to NSBBs.

One of limitations in the model was that the long-term impact of interventions was not considered. Because of the short follow-up times in the clinical studies, the long-term benefits associated with EVL and NSBBs remain unclear. The committee realised this and noted that many people who receive NSBBs may have adherence issues in the long run due to their associated side effects, which is further compounded by many people experiencing chaotic lifestyles.

While the economic analysis demonstrated that EVL is not cost effective compared with NSBB overall, the committee highlighted that there were some factors that meant that either EVL or NSBB would not be tolerable or acceptable for some people. When NSBBs are not acceptable, this would mean that these people would have poor adherence and would not experience the benefits demonstrated in the clinical trials, and so were not likely to be cost effective. The committee recognised that people with cirrhosis were more likely to come from vulnerable populations than those with other conditions. Many people are associated with factors such as poor socioeconomic status, alcohol misuse and chaotic lifestyles, which will affect their compliance to treatment. Additionally, there were some patient-level economic factors, for example hospital travel and prescription costs, that were not captured in the economic analysis, but the committee agreed that these factors were particularly important in this population and should be discussed with patients when making treatment decisions. The committee acknowledged that people receiving EVL would incur costs of travelling for procedures, and this might not be acceptable to those in rural areas or with chaotic lifestyles. Additionally, people who needed EVL procedures appeared to have a longer wait time for procedures during the COVID-19 pandemic. However, NSBBs could also put more pressure on low-income groups, arising from the extra prescription charges. Therefore, the committee agreed that the treatment decision should take into account factors such as post-pandemic healthcare constraints, accessibility to medical resources, physical health or pregnancy, as well as acceptability of treatment to decide whether EVL is a more suitable alternative to NSBB. Taking all of this into account, the committee made recommendations that for people

with cirrhosis with medium to large varices a discussion should be had explaining that carvedilol or propranolol are the preferred option to prevent variceal bleeding for people who can tolerate and take them regularly; but EVL may be the more appropriate option for others. The committee went on to recommend that these discussions should include information on benefits and harms and the requirements of both treatment options.

Taking into account the characteristics of EVL procedure, the committee recommended that EVL may be considered for people with medium to large varices when undergoing endoscopy assessment. The committee acknowledged that there was no clinical or economic evidence supporting this specific recommendation but agreed that the diagnostic endoscopy procedure presented a good opportunity to provide patients with the benefit of band ligation, and that the impact on resources would be minimal since these people were already in hospital, which is important given the current constraints on healthcare.

The treatment effect of carvedilol compared with propranolol was highly uncertain given that the clinical evidence was based on a single study. This uncertain clinical evidence would give rise to a high uncertainty in the economic evidence. As a result, the economic analysis did not compare individual NSBBs with each other.

The committee noted that prescribing NSBBs to people with medium to large varices has already been widely implemented in clinical practice. The committee indicated that the treatment decisions are being made on a case-by-case basis. People with large varices were more likely to be given EVL while those with smaller size were given NSBBs. Considering the constrained capacity of the NHS following the pandemic, a recommendation to provide NSBBs for those suitable rather than EVL can free up healthcare resources. There may also be additional benefits to hospitals by managing waiting lists for EVL procedures. However, to improve the compliance on NSBBs, community support and engagement was of vital importance.

1.1.11.5 Other factors the committee took into account

In making recommendations, the committee drew on their experience from practice, considered issues they had identified as a result of carrying out an equality impact assessment and reflected on recent changes in practice in this area.

The committee noted that both treatments may result in adverse effects, although they may be very different in nature and duration, with those associated with EVL occurring in the time after the procedure and those associated with NSBB occurring over the longer-term. Compliance with the treatment options was therefore an area which was discussed in detail by the committee, which noted that even though NSBB are the preferred treatment, there are various considerations that need to be taken into account. For this reason, the committee agreed that shared-decision making is key in deciding which treatment is the best option.

The committee noted that eradication of the oesophageal varices is usually achieved over several sessions and that regular follow up appointments are required for ongoing endoscopic surveillance. The committee noted that affordability and accessibility need to be considered. In particular, if the patient is not eligible for hospital transport, or if it is not available, or if they live in remote locations and have to travel some distance to attend. the appointments Likewise, for those who are not entitled to free prescriptions, the use of non-selective beta blockers over the long-term will entail an ongoing cost, as medication for liver diseases are not exempt from prescription charges.

As a result of their equality impact assessment, the committee identified particular groups for whom some treatment options may not be suitable. For example, the committee noted the need to avoid beta- blockade during pregnancy and lactation, but also noted that EVL may not be possible during pregnancy and that it may be necessary to discuss the balance of risks and benefits of delaying treatment during these periods.

The committee also noted that some people with learning disabilities may require general anaesthesia for band ligation, and they also may need support to comply with regularly taking NSBB over the long-term while living within the community. In addition, the committee noted that some people with learning disabilities may have difficulties in taking non-selective beta-blockers in tablet form. They noted that carvedilol is not available as a licensed liquid preparation (but is available as an unlicensed special order which is more expensive and takes longer to procure), however propranolol is, although it is more costly than propranolol tablets. The committee noted that this may help with compliance among those affected by this.

The committee also noted from experience, that a significant proportion of patients requiring treatment to prevent first variceal bleeding, may have chaotic lifestyles due to factors such as misuse of alcohol, homelessness and in some cases both. Concerns about attending follow-up appointments for EVL and compliance with obtaining and taking NSBB over the long term were raised by the committee and were influential in the committees' considerations in making their recommendations around taking the opportunity to band medium to large varices at the initial assessment endoscopy.

The committee were also aware from their experience in the field, that since the original guideline was published, other bodies have recommended that non-selective beta-blockers are used in preference to band ligation for the prevention of first variceal bleeding. Feedback from stakeholders regarding this change in practice is one of the factors that led to this review of the evidence and revisiting the NICE recommendations in this area. As practice has changed, the evidence of clinical effectiveness for the two interventions is equivocal, and there are several considerations relating to equity issues, the committee were keen to place shared decision making and where possible, patient choice at the centre of their recommendations.

1.1.12 Recommendations supported by this evidence review

This evidence review supports recommendations 1.2.9, 1.3.1 to 1.3.2, 1.3.4 to 1.3.5 and the research recommendation on NSBB + EVL compared to NSBB alone or EVL alone.

1.1.13 References – included studies

1.1.13.1 Effectiveness (new studies in BOLD)

Abd ElRahim, Ayman Yosry, Fouad, Rabab, Khairy, Marwa et al. (2018) Efficacy of carvedilol versus propranolol versus variceal band ligation for primary prevention of variceal bleeding. Hepatology international 12(1): 75-82

De, B K, Ghoshal, U C, Das, T et al. (1999) Endoscopic variceal ligation for primary prophylaxis of oesophageal variceal bleed: preliminary report of a randomized controlled trial. Journal of gastroenterology and hepatology 14(3): 220-4

Drastich, Pavel, Lata, Jan, Petrtyl, Jaromir et al. (2011) Endoscopic variceal band ligation compared with propranolol for prophylaxis of first variceal bleeding. Annals of hepatology 10(2): 142-9

Jutabha, Rome, Jensen, Dennis M, Martin, Paul et al. (2005) Randomized study comparing banding and propranolol to prevent initial variceal hemorrhage in cirrhotics with high-risk esophageal varices. Gastroenterology 128(4): 870-81

Kanwal, N., Sadaf, S., Butt, N.I. et al. (2022) Carvedilol vs endoscopic band ligation: primary prophylaxis of variceal bleed. Rawal Medical Journal 47(4): 850-853

Khan, M.S., Majeed, A., Ghauri, F. et al. (2017) Comparison of carvedilol and esophageal variceal band ligation for prevention of variceal bleed among cirrhotic patients. Pakistan Journal of Medical and Health Sciences 11(3): 1046-1048

Lay, Chii-Shyan, Tsai, Yang-Te, Lee, Fa-Yauh et al. (2006) Endoscopic variceal ligation versus propranolol in prophylaxis of first variceal bleeding in patients with cirrhosis. Journal of gastroenterology and hepatology 21(2): 413-9

Lui, Hock F, Stanley, Adrian J, Forrest, Ewan H et al. (2002) Primary prophylaxis of variceal hemorrhage: a randomized controlled trial comparing band ligation, propranolol, and isosorbide mononitrate. Gastroenterology 123(3): 735-44

Norberto, Lorenzo, Polese, Lino, Cillo, Umberto et al. (2007) A randomized study comparing ligation with propranolol for primary prophylaxis of variceal bleeding in candidates for liver transplantation. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 13(9): 1272-8

Perez-Ayuso, Rosa Maria, Valderrama, Sebastian, Espinoza, Manuel et al. (2010) Endoscopic band ligation versus propranolol for the primary prophylaxis of variceal bleeding in cirrhotic patients with high risk esophageal varices. Annals of hepatology 9(1): 15-22

Psilopoulos, Dimitrios, Galanis, Petros, Goulas, Spyros et al. (2005) Endoscopic variceal ligation vs. propranolol for prevention of first variceal bleeding: a randomized controlled trial. European journal of gastroenterology & hepatology 17(10): 1111-7

Sarin, S K, Lamba, G S, Kumar, M et al. (1999) Comparison of endoscopic ligation and propranolol for the primary prevention of variceal bleeding. The New England journal of medicine 340(13): 988-93

Schepke, Michael, Kleber, Gerhard, Nurnberg, Dieter et al. (2004) Ligation versus propranolol for the primary prophylaxis of variceal bleeding in cirrhosis. Hepatology (Baltimore, Md.) 40(1): 65-72

Shah, Hasnain Ali, Azam, Zahid, Rauf, Javeria et al. (2014) Carvedilol vs. esophageal variceal band ligation in the primary prophylaxis of variceal hemorrhage: a multicentre randomized controlled trial. Journal of hepatology 60(4): 757-64

Singh, B., Saxena, P.D., Rohtagi, V. et al. (2012) Comparison of endoscopic variceal ligation and propranolol for the primary prevention of variceal bleeding. Journal, Indian Academy of Clinical Medicine 13(3): 214-217

Singh, Virendra, Kumar, Pramod, Verma, Nipun et al. (2022) Propranolol vs. band ligation for primary prophylaxis of variceal hemorrhage in cirrhotic patients with ascites: a randomized controlled trial. Hepatology international 16(4): 944-953

Thuluvath, Paul J, Maheshwari, Anurag, Jagannath, Sanjay et al. (2005) A randomized controlled trial of beta-blockers versus endoscopic band ligation for primary prophylaxis: a large sample size is required to show a difference in bleeding rates. Digestive diseases and sciences 50(2): 407-10

Tripathi, Dhiraj, Ferguson, James W, Kochar, Narendra et al. (2009) Randomized controlled trial of carvedilol versus variceal band ligation for the prevention of the first variceal bleed. Hepatology (Baltimore, Md.) 50(3): 825-33

1.1.13.2 Economic

No economic studies were included in this review.

1.1.13.3 Other references

Mattock, Tripathi, O'Neill, Craig, Tanner, Patch et al. (2021) Economic evaluation of covered stents for transjugular intrahepatic portosystemic stent shunt in patients with variceal bleeding and refractory ascites secondary to cirrhosis. BMJ Open Gastroenterology 8(1): e000641

Schepke, M., Kleber, G., Nürnberg, D., Willert, J., Koch, L., Veltzke-Schlieker, W., Hellerbrand, C., Kuth, J., Schanz, S., Kahl, S., Fleig, W.E. and Sauerbruch, T. (2004), Ligation versus propranolol for the primary prophylaxis of variceal bleeding in cirrhosis. Hepatology, 40: 65-72.

Merkel, C., Marin, R., Sacerdoti, D., Donada, C., Cavallarin, G., Torboli, P., Amodio, P., Sebastianelli, G., Bolognesi, M., Felder, M., Mazzaro, C. and Gatta, A. (2000), Long-term results of a clinical trial of nadolol with or without isosorbide mononitrate for primary prophylaxis of variceal bleeding in cirrhosis. Hepatology, 31: 324-329.

Tripathi, D., Ferguson, J.W., Kochar, N., Leithead, J.A., Therapondos, G., Mcavoy, N.C., Stanley, A.J., Forrest, E.H., Hislop, W.S., Mills, P.R. and Hayes, P.C. (2009), Randomized controlled trial of carvedilol versus variceal band ligation for the prevention of the first variceal bleed. Hepatology, 50: 825-833.

British National Formulary (2023). Accessed at: https://bnf.nice.org.uk/

National Schedule of NHS Costs 2019/20. Accessed at: https://www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/

Unit Costs of Health and Social Care (PSSRU) 2020. Accessed at: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2020/

Appendices

Appendix A – Review protocol

Review protocol for primary prophylaxis of oesophageal variceal haemorrhage

ID	Field	Content
0.	PROSPERO registration number	CRD42023389605
1.	Review title	The clinical and cost-effectiveness of non-selective beta-blockers (NSBBs), endoscopic variceal band ligation (EVL) or NSBBs plus EVL compared to each other for the primary prevention of bleeding in people with medium to large oesophageal varices due to cirrhosis.
2.	Review question	What is the clinical and cost-effectiveness of non-selective beta-blockers (NSBBs), endoscopic variceal band ligation (EVL) or NSBBs plus EVL compared to each other for the primary prevention of bleeding in people with medium to large oesophageal varices due to cirrhosis?
3.	Objective	To determine the clinical and cost effectiveness of non-selective beta-blockers (NSBBs), endoscopic variceal band ligation (EVL) or NSBBs plus EVL and to determine their comparative clinical and cost effectiveness, for the primary prevention of bleeding in people with medium-sized or large oesophageal varices due to cirrhosis.
4.	Searches	**Databases** The principal search strategy will be developed in MEDLINE (Ovid interface) and then adapted, as appropriate, for use in the other sources listed, taking into account their size, search functionality and subject coverage. The following databases will be searched:

		• Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley • Cochrane Database of Systematic Reviews (CDSR) via Wiley • EconLit via Ovid • Epistemonikos • Embase via Ovid • International HTA Database via INAHTA • MEDLINE • MEDLINE in-process • MEDLINE Epub-Ahead-of-Print) via Ovid **Database search limits** Database functionality will be used, where available, to limit search results to the following: • Studies published on 24th October 2015 or after • English language studies • Studies that involve humans Filters to limit results to randomised controlled trials or systematic reviews will be used in relevant databases. Filters to identify economic evidence will also be used in relevant databases. **Other searches** A randomised controlled trial classifier may be used if appropriate The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion if more than 6 months passes from the original search date. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Primary prophylaxis of oesophageal variceal haemorrhage.
6.	Population	Inclusion: People aged 16 years and older with cirrhosis, who have medium- sized or large oesophageal varices which have never bled.

		Exclusion:
7.	Intervention/Exposure/Test	• Non-selective beta-blockers (NSBBs) - Nadolol, Timolol maleate, Sotalol, Carvedilol, Labetalol, Propranolol. • Endoscopic variceal band ligation (EVL) • NSBBs plus EVL
8.	Comparator/Reference standard/Confounding factors	• Each other (including intraclass for NSBBs)
9.	Types of study to be included	• Randomised controlled trials (RCTs)
10.	Other exclusion criteria	• Other non-comparative study types • Studies not published in English • Pre-prints • Dissertations
11.	Context	NICE guideline NG50 currently recommends endoscopic oesophageal variceal band ligation (also known as endoscopic variceal ligation [EVL] as primary prophylaxis for preventing bleeding from medium-sized or large oesophageal varices (see existing recommendation 1.3.1). Evidence identified through surveillance shows that non-selective beta-blockers (NSBBs) may be an effective alternative to EVL for reducing bleeding or mortality. Feedback from stakeholders suggests that healthcare professionals currently use NSBBs for this purpose. New published evidence may also change the guideline's current cost-effectiveness estimates for EVL, which could impact on the existing recommendations.
12.	Primary outcomes (critical outcomes)	• Primary variceal bleeding (at the longest and most frequently reported timepoints) • Mortality (including mortality caused by bleeding) (at the longest and most frequently reported timepoints) • Quality of life (using a validated scale) (at all reported timepoints)
13.	Secondary outcomes (important outcomes)	(All measured at the longest timepoint) • Liver transplant • Number of decompensation episodes • Hospitalisation (including length of hospital stay)

		• Other adverse events (for example, pain, low compliance/discontinuation with treatment due to side effects or for other reasons)
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias for RCTs will be assessed using Cochrane Risk of Bias v.2.0 as described in Developing NICE guidelines: the manual.
16.	Strategy for data synthesis	Pairwise meta-analyses will be performed in Cochrane Review Manager V5.3. A pooled relative risk will be calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event. A pooled mean difference will be calculated for continuous outcomes (using the inverse variance method) when the same scale will be used to measure an outcome across different studies. Where different studies presented continuous data measuring the same outcome but using different numerical scales these outcomes will be all converted to the same scale before meta-analysis is conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data will be analysed using standardised mean differences (SMDs, Hedges' g).

		Fixed effects models will be fitted unless there is significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$, or where significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis, when random effects models will be used instead. Where 10 or more studies are included as part of a single meta-analysis, a funnel plot will be produced to graphically assess the potential for publication bias. GRADE will be used to assess the quality of the outcomes. Outcomes using evidence from RCTs will be rated as high quality initially and downgraded from this point.		
17.	Analysis of sub-groups	Where disaggregation is possible: • Age of patient (65 years and under, over 65)? • Severity of underlying liver disease at the time of intervention (Child-Pugh score- Child-Pugh score A, Child Pugh score B or C)? • Size of varices (medium or large) • Underlying cause of liver disease		
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	Jan 2023		
22.	Anticipated completion date	Consultation on draft guideline (including publication of draft review): To be confirmed		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**

		Preliminary searches	☑ ☑	☑ ☑
		Piloting of the study selection process	☑ ☑	☑ ☑
		Formal screening of search results against eligibility criteria	☑ ☑	☑ ☑
		Data extraction	☑ ☑	☑ ☑
		Risk of bias (quality) assessment	☑ ☑	☑ ☑
		Data analysis	☑ ☑	☑ ☑
24.	Named contact	**5a. Named contact** NICE Guideline Development Team **5b Named contact e-mail** CirrhosisUpdate@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) Guideline Development Team B.		
25.	Review team members	From the NICE Guideline Development Team: • Mr Chris Carmona, Technical lead • Mr James Jagroo, Senior technical analyst • Ms Karen Peploe, Senior technical analyst • Ms Lindsay Claxton, Health economics adviser • Ms Yuanyuan Zhang, Technical analyst (economics) • Mr Wesley Hubbard, Information specialist		

		• Ms Nicola Cunliffe, Project manager
26.	Funding sources/sponsor	This systematic review is being completed by the NICE Guideline Development team which is an internal team at NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website. www.nice.org.uk.
29.	Other registration details	No other registrations of this protocol.
30.	Reference/URL for published protocol	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and

		publicising the guideline within NICE.
32.	Keywords	cirrhosis oesophageal varices beta blockers endoscopic variceal band ligation
33.	Details of existing review of same topic by same authors	Not applicable
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35.	Additional information	This review will be used to update the NICE guideline on Cirrhosis in over 16s: assessment and management
36.	Details of final publication	www.nice.org.uk

Appendix B – Literature search strategies

Background and development

Search design and peer review

A NICE information specialist conducted the literature searches for the evidence review. The searches were run on 20th December 2022. This search report is compliant with the requirements of the PRISMA Statement for Reporting Literature Searches in Systematic Reviews (for further details see: Rethlefsen M et al. PRISMA-S. *Systematic Reviews*, 10(1), 39).

The MEDLINE strategy below was quality assured (QA) by a trained NICE information specialist. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the Peer Review of Electronic Search Strategies Guideline Statement (for further details see: McGowan J et al. PRESS 2015 Guideline Statement. *Journal of Clinical Epidemiology*, 75, 40-46).

The principal search strategy was developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess 'low-probability' matches. All decisions made for the review can be accessed via the deduplication history.

Prior work

The literature search was based on the previous guideline search for "prophylaxis of variceal haemorrhage". Search terms were added or modified depending on requirements of the review protocol.

The strategy for the literature search is available here:

National Institute for Health and Care Excellence. (2016) *Cirrhosis in over 16s Assessment and management* [NICE guideline 50] Appendix 6.4.7 https://www.nice.org.uk/guidance/ng50/evidence/appendices-ah-pdf-2546538877

Limits and restrictions

English language limits were applied in adherence to standard NICE practice and the review protocol.

Limits to exclude conferences were applied in adherence to standard NICE practice and the review protocol.

The search was limited from October 2015 to December 2022 as defined in the review protocol.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from: Dickersin K, Scherer R & Lefebvre C. (1994) Systematic Reviews: Identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

Search filters and classifiers

Clinical searches

- RCT filters:
    - McMaster Therapy – Medline - “best balance of sensitivity and specificity” version.

Haynes RB et al. (2005) Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. *BMJ*, 330, 1179-1183.

    - McMaster Therapy – Embase “best balance of sensitivity and specificity” version.

Wong SSL et al. (2006) Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association, 94(1), 41-47.

- Systematic reviews filters:

Lee, E. et al. (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. *BMC Medical Research Methodology,* 12(1), 51.

In MEDLINE, the standard NICE modifications were used: pubmed.tw added; systematic review.pt added from MeSH update 2019.

In Embase, the standard NICE modifications were used: pubmed.tw added to line medline.tw.

Cost effectiveness searches

The following search filters were applied to the search strategies in MEDLINE and Embase to identify cost-effectiveness studies:

- Glanville J et al. (2009) Development and Testing of Search Filters to Identify Economic Evaluations in MEDLINE and EMBASE. Alberta: Canadian Agency for Drugs and Technologies in Health (CADTH)

Several modifications have been made to these filters over the years that are standard NICE practice.

Key decisions

The search strategy was based on the previous guideline strategy with additions to the population and intervention elements of the search when required. This was a result of requirements of the review protocol and additional synonyms and database subject terms identified as part of strategy development.

The search strategy was simplified for Epistemonikos to adapt to that databases functionality.

For INAHTA only the population element of the search strategy was used given the small number of results.

Clinical searches

Main search – Databases

Database	Date searched	Database platform	Database segment or version	No. of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	20/12/2022	Wiley	Cochrane Central Register of Controlled Trials Issue 11 of 12, November 2022	201
Cochrane Database of Systematic Reviews (CDSR)	20/12/2022	Wiley	Cochrane Database of Systematic Reviews Issue 12 of 12, December 2022	16
Embase	20/12/2022	Ovid	Embase 1974 to 2022 December 19	294
Epistemonikos	20/12/2022	Epistemonikos	-	224
MEDLINE	20/12/2022	Ovid	Ovid MEDLINE(R) 1946 to December 19, 2022	164
MEDLINE-in-Process	20/12/2022	Ovid	Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to December 19, 2022	0
MEDLINE Epub Ahead-of-Print	20/12/2022	Ovid	Ovid MEDLINE(R) Epub Ahead of Print December 19, 2022	1

Search strategy history
Database name: MEDLINE

1 "esophageal and gastric varices"/ (14314)
2 ((oesophag* or esophag* or gastroesophag* or gastrooesphag*) adj4 (varic* or varix*)).tw. (9948)
3 ((varix* or varic*) adj2 bleed*).tw. (6789)
4 Hypertension, Portal/ (17639)
5 (porta* adj2 (hypertens* or congest*)).tw. (18670)
6 Cruveilhier Baumgarten*.tw. (173)
7 or/1-6 (35253)
8 exp Adrenergic beta-Antagonists/ (86741)
9 ((beta* or b) adj4 (block* or antagonist* or sympatholy*)).tw. (78145)
10 Betasympatholy*.tw. (4)
11 Propranolol/ (32873)
12 (propranolol* or bedranol* or beta-prograne* or inderal* or syprol* or rexigen* or dexpropranolol* or dociton* or ob?idan* or anaprilin* or betadren* or arcablock* or authus* or avlocardyl* or beprane* or betadipresan* or betaryl* or cardinol* or ciplar* or corbeta* or deralin* or duranol* or efektolol* or elbrol* or frekven* or hemang?ol* or inderex* or innopran* or ipran* or prandol* or propabloc* or propercuten* or prophylux* or propranur* or sagittol*).tw. (33355)
13 Carvedilol/ (2851)
14 (carvedilol* or dilatrend* or querto* or eucardic* or kredex* or coropres* or coreg or cardiol or carvipress* or dilatrend* or dilibloc* or dimitone* or eucardic*).tw. (3759)
15 Nadolol/ (826)
16 (nadolol* or corgard* or solgol* or betadol*).tw. (1168)
17 Labetalol/ (1899)
18 (labetalol* or trandate* or albetol* or apolabetalol* or normodyne* or presolol* or dilevalol* or lamitol* or presdate*).tw. (2123)
19 exp Timolol/ (3844)
20 (timolol* or tiopex* or eysano* or timopt* or timacar* or blocadren* or optimol* or apotimolol* or timolo* or titol*).tw. (4311)
21 Sotalol/ (2123)
22 (sotalol* or sotacor* or darob* or betacardone* or betades* or betapace* or bonpro* or corsotalol* or gilucor* or rentibloc* or sorine* or sota saar* or sotabeta* or sotacor* or sotahexal* or sotalex* or sotapor* or sotastad* or sotylize* or tachytalol*).tw. (2760)
23 or/8-22 (138114)
24 Ligation/ (24489)
25 (ligat* or EBL or EVL or band* or multiband*).tw. (316530)
26 (endoscop* adj2 (therap* or treat* or surger* or operat* or procedure*)).tw. (40632)
27 endosurger*.tw. (245)
28 or/24-27 (362803)
29 23 or 28 (498916)
30 7 and 29 (5254)
31 limit 30 to english language (4367)
32 Animals/ not Humans/ (5040973)

33 31 not 32 (3579)
34 limit 33 to ed=20151001-20221219 (879)
35 randomized controlled trial.pt. (582652)
36 randomi?ed.mp. (942895)
37 placebo.mp. (221249)
38 or/35-37 (999534)
39 (MEDLINE or pubmed).tw. (245533)
40 systematic review.tw. (198599)
41 systematic review.pt. (208857)
42 meta-analysis.pt. (172461)
43 intervention$.ti. (161024)
44 or/39-43 (536885)
45 38 or 44 (1389264)
46 34 and 45 (164)

Database name: MEDLINE-in-Process

1 "esophageal and gastric varices"/ (0)
2 ((oesophag* or esophag* or gastroesophag* or gastrooesphag*) adj4 (varic* or varix*)).tw. (0)
3 ((varix* or varic*) adj2 bleed*).tw. (0)
4 Hypertension, Portal/ (0)
5 (porta* adj2 (hypertens* or congest*)).tw. (0)
6 Cruveilhier Baumgarten*.tw. (0)
7 or/1-6 (0)
8 exp Adrenergic beta-Antagonists/ (0)
9 ((beta* or b) adj4 (block* or antagonist* or sympatholy*)).tw. (10)
10 Betasympatholy*.tw. (0)
11 Propranolol/ (0)
12 (propranolol* or bedranol* or beta-prograne* or inderal* or syprol* or rexigen* or dexpropranolol* or dociton* or ob?idan* or anaprilin* or betadren* or arcablock* or authus* or avlocardyl* or beprane* or betadipresan* or betaryl* or cardinol* or ciplar* or corbeta* or deralin* or duranol* or efektolol* or elbrol* or frekven* or hemang?ol* or inderex* or innopran* or ipran* or prandol* or propabloc* or propercuten* or prophylux* or propranur* or sagittol*).tw. (0)
13 Carvedilol/ (0)
14 (carvedilol* or dilatrend* or querto* or eucardic* or kredex* or coropres* or coreg or cardiol or carvipress* or dilatrend* or dilibloc* or dimitone* or eucardic*).tw. (0)
15 Nadolol/ (0)
16 (nadolol* or corgard* or solgol* or betadol*).tw. (0)
17 Labetalol/ (0)
18 (labetalol* or trandate* or albetol* or apolabetalol* or normodyne* or presolol* or dilevalol* or lamitol* or presdate*).tw. (0)
19 exp Timolol/ (0)
20 (timolol* or tiopex* or eysano* or timopt* or timacar* or blocadren* or optimol* or apotimolol* or timolo* or titol*).tw. (0)
21 Sotalol/ (0)
22 (sotalol* or sotacor* or darob* or betacardone* or betades* or betapace* or bonpro* or corsotalol* or gilucor* or rentibloc* or sorine* or sota saar* or sotabeta* or

sotacor* or sotahexal* or sotalex* or sotapor* or sotastad* or sotylize* or tachytalol*).tw. (0)
23 or/8-22 (10)
24 Ligation/ (0)
25 (ligat* or EBL or EVL or band* or multiband*).tw. (76)
26 (endoscop* adj2 (therap* or treat* or surger* or operat* or procedure*)).tw. (11)
27 endosurger*.tw. (0)
28 or/24-27 (87)
29 23 or 28 (97)
30 7 and 29 (0)
31 limit 30 to english language (0)
32 Animals/ not Humans/ (0)
33 31 not 32 (0)
34 limit 33 to dt=20151001-20221219 (0)
35 randomized controlled trial.pt. (0)
36 randomi?ed.mp. (271)
37 placebo.mp. (42)
38 or/35-37 (279)
39 (MEDLINE or pubmed).tw. (233)
40 systematic review.tw. (198)
41 systematic review.pt. (3)
42 meta-analysis.pt. (0)
43 intervention$.ti. (104)
44 or/39-43 (386)
45 38 or 44 (588)
46 34 and 45 (0)

Database name: MEDLINE Epub Ahead-of-Print
1 "esophageal and gastric varices"/ (0)
2 ((oesophag* or esophag* or gastroesophag* or gastrooesphag*) adj4 (varic* or varix*)).tw. (68)
3 ((varix* or varic*) adj2 bleed*).tw. (63)
4 Hypertension, Portal/ (0)
5 (porta* adj2 (hypertens* or congest*)).tw. (171)
6 Cruveilhier Baumgarten*.tw. (0)
7 or/1-6 (241)
8 exp Adrenergic beta-Antagonists/ (0)
9 ((beta* or b) adj4 (block* or antagonist* or sympatholy*)).tw. (521)
10 Betasympatholy*.tw. (0)
11 Propranolol/ (0)
12 (propranolol* or bedranol* or beta-prograne* or inderal* or syprol* or rexigen* or dexpropranolol* or dociton* or ob?idan* or anaprilin* or betadren* or arcablock* or authus* or avlocardyl* or beprane* or betadipresan* or betaryl* or cardinol* or ciplar* or corbeta* or deralin* or duranol* or efektolol* or elbrol* or frekven* or hemang?ol* or inderex* or innopran* or ipran* or prandol* or propabloc* or propercuten* or prophylux* or propranur* or sagittol*).tw. (115)
13 Carvedilol/ (0)

14 (carvedilol* or dilatrend* or querto* or eucardic* or kredex* or coropres* or coreg or cardiol or carvipress* or dilatrend* or dilibloc* or dimitone* or eucardic*).tw. (49)
15 Nadolol/ (0)
16 (nadolol* or corgard* or solgol* or betadol*).tw. (7)
17 Labetalol/ (0)
18 (labetalol* or trandate* or albetol* or apolabetalol* or normodyne* or presolol* or dilevalol* or lamitol* or presdate*).tw. (14)
19 exp Timolol/ (0)
20 (timolol* or tiopex* or eysano* or timopt* or timacar* or blocadren* or optimol* or apotimolol* or timolo* or titol*).tw. (38)
21 Sotalol/ (0)
22 (sotalol* or sotacor* or darob* or betacardone* or betades* or betapace* or bonpro* or corsotalol* or gilucor* or rentibloc* or sorine* or sota saar* or sotabeta* or sotacor* or sotahexal* or sotalex* or sotapor* or sotastad* or sotylize* or tachytalol*).tw. (28)
23 or/8-22 (695)
24 Ligation/ (0)
25 (ligat* or EBL or EVL or band* or multiband*).tw. (4045)
26 (endoscop* adj2 (therap* or treat* or surger* or operat* or procedure*)).tw. (744)
27 endosurger*.tw. (2)
28 or/24-27 (4776)
29 23 or 28 (5465)
30 7 and 29 (38)
31 limit 30 to english language (34)
32 Animals/ not Humans/ (0)
33 31 not 32 (34)
34 randomized controlled trial.pt. (1)
35 randomi?ed.mp. (12070)
36 placebo.mp. (2394)
37 or/34-36 (12831)
38 (MEDLINE or pubmed).tw. (8473)
39 systematic review.tw. (8632)
40 systematic review.pt. (177)
41 meta-analysis.pt. (83)
42 intervention$.ti. (3497)
43 or/38-42 (15067)
44 37 or 43 (24420)
45 33 and 44 (1)

Database name: Embase

1 exp esophagus varices/ (21723)
2 ((oesophag* or esophag* or gastroesophag* or gastrooesphag*) adj4 (varic* or varix*)).tw. (17045)
3 ((varix* or varic*) adj2 bleed*).tw. (13223)
4 exp portal hypertension/ (36133)
5 (porta* adj2 (hypertens* or congest*)).tw. (29909)

6 Cruveilhier Baumgarten*.tw. (67)
7 or/1-6 (60451)
8 exp beta adrenergic receptor blocking agent/ (323600)
9 ((beta* or b) adj4 (block* or antagonist* or sympatholy*)).tw. (113134)
10 Betasympatholy*.tw. (0)
11 propranolol/ (94173)
12 (propranolol* or bedranol* or beta-prograne* or inderal* or syprol* or rexigen* or dexpropranolol* or dociton* or ob?idan* or anaprilin* or betadren* or arcablock* or authus* or avlocardyl* or beprane* or betadipresan* or betaryl* or cardinol* or ciplar* or corbeta* or deralin* or duranol* or efektolol* or elbrol* or frekven* or hemang?ol* or inderex* or innopran* or ipran* or prandol* or propabloc* or propercuten* or prophylux* or propranur* or sagittol*).tw. (45425)
13 carvedilol/ (17474)
14 (carvedilol* or dilatrend* or querto* or eucardic* or kredex* or coropres* or coreg or cardiol or carvipress* or dilatrend* or dilibloc* or dimitone* or eucardic*).tw. (8887)
15 nadolol/ (5937)
16 (nadolol* or corgard* or solgol* or betadol*).tw. (2135)
17 labetalol/ (11781)
18 (labetalol* or trandate* or albetol* or apolabetalol* or normodyne* or presolol* or dilevalol* or lamitol* or presdate*).tw. (4038)
19 timolol/ (12255)
20 (timolol* or tiopex* or eysano* or timopt* or timacar* or blocadren* or optimol* or apotimolol* or timolo* or titol*).tw. (6776)
21 sotalol/ (14050)
22 (sotalol* or sotacor* or darob* or betacardone* or betades* or betapace* or bonpro* or corsotalol* or gilucor* or rentibloc* or sorine* or sota saar* or sotabeta* or sotacor* or sotahexal* or sotalex* or sotapor* or sotastad* or sotylize* or tachytalol*).tw. (4707)
23 or/8-22 (367716)
24 ligation/ or endoscopic variceal ligation/ (31060)
25 (ligat* or EBL or EVL or band* or multiband*).tw. (484569)
26 (endoscop* adj2 (therap* or treat* or surger* or operat* or procedure*)).tw. (76246)
27 endosurger*.tw. (886)
28 or/24-27 (565905)
29 23 or 28 (929567)
30 7 and 29 (11658)
31 limit 30 to english language (10208)
32 nonhuman/ not human/ (5112309)
33 31 not 32 (9300)
34 limit 33 to (conference abstract or conference paper or "conference review") (3343)
35 33 not 34 (5957)
36 limit 35 to dc=20151001-20221219 (1864)
37 random:.tw. (1868056)
38 placebo:.mp. (506655)
39 double-blind:.tw. (236417)

40 or/37-39 (2139983)
41 (MEDLINE or pubmed).tw. (372659)
42 exp systematic review/ or systematic review.tw. (458759)
43 meta-analysis/ (265182)
44 intervention$.ti. (249639)
45 or/41-44 (892420)
46 40 or 45 (2755412)
47 36 and 46 (293)

Database name: Cochrane Library

#1 MeSH descriptor: [Esophageal and Gastric Varices] this term only 920
#2 ((oesophag* or esophag* or gastroesophag* or gastrooesphag*) NEAR/4 (varic* or varix*)):ti,ab,kw 2198
#3 ((varix* or varic*) NEAR/2 (bleed*)):ti,ab,kw 1721
#4 MeSH descriptor: [Hypertension, Portal] this term only 493
#5 ((porta*) NEAR/2 (hypertens* or congest*)):ti,ab,kw 1607
#6 (Cruveilhier Baumgarten*):ti,ab,kw 1
#7 {or #1-#6} 3606
#8 MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees 4649
#9 ((beta* or b) NEAR/4 (block* or antagonist* or sympatholy*)):ti,ab,kw 15846
#10 (Betasympatholy*):ti,ab,kw 3
#11 MeSH descriptor: [Propranolol] this term only 2920
#12 (propranolol* or bedranol* or beta-prograne* or inderal* or syprol* or rexigen* or dexpropranolol* or dociton* or obsidan* or obzidan* or anaprilin* or betadren* or arcablock* or authus* or avlocardyl* or beprane* or betadipresan* or betaryl* or cardinol* or ciplar* or corbeta* or deralin* or duranol* or efektolol* or elbrol* or frekven* or hemangeol* or hemangiol* or inderex* or innopran* or ipran* or prandol* or propabloc* or propercuten* or prophylux* or propranur* or sagittol*):ti,ab,kw 5351
#13 MeSH descriptor: [Carvedilol] this term only 689
#14 (carvedilol* or dilatrend* or querto* or eucardic* or kredex* or coropres* or coreg or cardiol or carvipress* or dilatrend* or dilibloc* or dimitone* or eucardic*):ti,ab,kw 1555
#15 MeSH descriptor: [Nadolol] this term only 187
#16 (nadolol* or corgard* or solgol* or betadol*):ti,ab,kw 389
#17 MeSH descriptor: [Labetalol] this term only 430
#18 (labetalol* or trandate* or albetol* or apolabetalol* or normodyne* or presolol* or dilevalol* or lamitol* or presdate*):ti,ab,kw 895
#19 MeSH descriptor: [Timolol] explode all trees 1235
#20 (timolol* or tiopex* or eysano* or timopt* or timacar* or blocadren* or optimol* or apotimolol* or timolo* or titol*):ti,ab,kw 2402
#21 MeSH descriptor: [Sotalol] this term only 306
#22 (sotalol* or sotacor* or darob* or betacardone* or betades* or betapace* or bonpro* or corsotalol* or gilucor* or rentibloc* or sorine* or sota saar* or sotabeta* or sotacor* or sotahexal* or sotalex* or sotapor* or sotastad* or sotylize* or tachytalol*):ti,ab,kw 629
#23 {or #8-#22} 22335

#24 MeSH descriptor: [Ligation] this term only 668
#25 (ligat* or EBL or EVL or band* or multiband*):ti,ab,kw 17428
#26 ((endoscop*) NEAR/2 (therap* or treat* or surger* or operat* or procedure*)):ti,ab,kw 8043
#27 (endosurger*):ti,ab,kw 94
#28 {OR #24-#27} 25094
#29 #23 OR #28 47030
#30 #7 AND #29 1411
#31 "conference":pt or (clinicaltrials or trialsearch):so 656457
#32 #30 NOT #31 with Cochrane Library publication date Between Oct 2015 and Dec 2022 226

Database name: Epistemonikos

(advanced_title_en:((advanced_title_en:(oesophag* OR esophag* OR gastroesophag* OR gastrooesphag*) OR advanced_abstract_en:(oesophag* OR esophag* OR gastroesophag* OR gastrooesphag*)) AND (advanced_title_en:(varic* OR varix*) OR advanced_abstract_en:(varic* OR varix*)) OR (advanced_title_en:(varix* OR varic*) OR advanced_abstract_en:(varix* OR varic*)) AND (advanced_title_en:(bleed*) OR advanced_abstract_en:(bleed*)) OR (advanced_title_en:(porta*) OR advanced_abstract_en:(porta*)) AND (advanced_title_en:(hypertens* OR congest*) OR advanced_abstract_en:(hypertens* OR congest*))) OR advanced_abstract_en:((advanced_title_en:(oesophag* OR esophag* OR gastroesophag* OR gastrooesphag*) OR advanced_abstract_en:(oesophag* OR esophag* OR gastroesophag* OR gastrooesphag*)) AND (advanced_title_en:(varic* OR varix*) OR advanced_abstract_en:(varic* OR varix*)) OR (advanced_title_en:(varix* OR varic*) OR advanced_abstract_en:(varix* OR varic*)) AND (advanced_title_en:(bleed*) OR advanced_abstract_en:(bleed*)) OR (advanced_title_en:(porta*) OR advanced_abstract_en:(porta*)) AND (advanced_title_en:(hypertens* OR congest*) OR advanced_abstract_en:(hypertens* OR congest*)))) AND (advanced_title_en:((advanced_title_en:(beta* OR b) OR advanced_abstract_en:(beta* OR b)) AND (advanced_title_en:(block* OR antagonist* OR sympatholy*) OR advanced_abstract_en:(block* OR antagonist* OR sympatholy*)) OR (advanced_title_en:(propranolol* OR carvedilol* OR nadolol* OR labetalol* OR timolol* OR sotalol*) OR advanced_abstract_en:(propranolol* OR carvedilol* OR nadolol* OR labetalol* OR timolol* OR sotalol*))) OR advanced_abstract_en:((advanced_title_en:(beta* OR b) OR advanced_abstract_en:(beta* OR b)) AND (advanced_title_en:(block* OR antagonist* OR sympatholy*) OR advanced_abstract_en:(block* OR antagonist* OR sympatholy*)) OR (advanced_title_en:(propranolol* OR carvedilol* OR nadolol* OR labetalol* OR timolol* OR sotalol*) OR advanced_abstract_en:(propranolol* OR carvedilol* OR nadolol* OR labetalol* OR timolol* OR sotalol*)))) OR (advanced_title_en:((advanced_title_en:(ligat* OR EBL OR EVL OR band* OR multiband*) OR advanced_abstract_en:(ligat* OR EBL OR EVL OR band* OR multiband*)) OR (advanced_title_en:(endoscop*) OR advanced_abstract_en:(endoscop*)) AND (advanced_title_en:(therap* OR treat* OR surger* OR operat* OR procedure*) OR advanced_abstract_en:(therap* OR treat* OR surger* OR operat* OR procedure*))) OR

advanced_abstract_en:((advanced_title_en:(ligat* OR EBL OR EVL OR band* OR multiband*) OR advanced_abstract_en:(ligat* OR EBL OR EVL OR band* OR multiband*)) OR (advanced_title_en:(endoscop*) OR advanced_abstract_en:(endoscop*)) AND (advanced_title_en:(therap* OR treat* OR surger* OR operat* OR procedure*) OR advanced_abstract_en:(therap* OR treat* OR surger* OR operat* OR procedure*)))) [Filters: protocol=no, min_year=2015, max_year=2022]

Cost-effectiveness searches

Main search – Databases

Database	Date searched	Database Platform	Database segment or version	No. of results downloaded
EconLit	21/12/2022	OVID	Econlit 1886 to December 15, 2022	0
Embase	21/12/2022	Ovid	Embase 1974 to 2022 December 20	148
INAHTA	21/12/2022	INAHTA		2
MEDLINE	21/12/2022	Ovid	Ovid MEDLINE(R) 1946 to December 19, 2022	49
MEDLINE-in-Process	21/12/2022	Ovid	Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to December 19, 2022	0
MEDLINE Epub Ahead-of-Print	21/12/2022	Ovid	Ovid MEDLINE(R) Epub Ahead of Print December 19, 2022	3

Search strategy history

Database name: MEDLINE

1 "esophageal and gastric varices"/ (14315)
2 ((oesophag* or esophag* or gastroesophag* or gastrooesphag*) adj4 (varic* or varix*)).tw. (9948)
3 ((varix* or varic*) adj2 bleed*).tw. (6789)
4 Hypertension, Portal/ (17639)
5 (porta* adj2 (hypertens* or congest*)).tw. (18670)
6 Cruveilhier Baumgarten*.tw. (173)
7 or/1-6 (35254)
8 exp Adrenergic beta-Antagonists/ (86744)
9 ((beta* or b) adj4 (block* or antagonist* or sympatholy*)).tw. (78151)
10 Betasympatholy*.tw. (4)
11 Propranolol/ (32873)
12 (propranolol* or bedranol* or beta-prograne* or inderal* or syprol* or rexigen* or dexpropranolol* or dociton* or ob?idan* or anaprilin* or betadren* or arcablock* or authus* or avlocardyl* or beprane* or betadipresan* or betaryl* or cardinol* or ciplar* or corbeta* or deralin* or duranol* or efektolol* or elbrol* or frekven* or hemang?ol* or inderex* or innopran* or ipran* or prandol* or propabloc* or propercuten* or prophylux* or propranur* or sagittol*).tw. (33355)
13 Carvedilol/ (2851)
14 (carvedilol* or dilatrend* or querto* or eucardic* or kredex* or coropres* or coreg or cardiol or carvipress* or dilatrend* or dilibloc* or dimitone* or eucardic*).tw. (3759)

15 Nadolol/ (826)
16 (nadolol* or corgard* or solgol* or betadol*).tw. (1168)
17 Labetalol/ (1899)
18 (labetalol* or trandate* or albetol* or apolabetalol* or normodyne* or presolol* or dilevalol* or lamitol* or presdate*).tw. (2123)
19 exp Timolol/ (3844)
20 (timolol* or tiopex* or eysano* or timopt* or timacar* or blocadren* or optimol* or apotimolol* or timolo* or titol*).tw. (4311)
21 Sotalol/ (2123)
22 (sotalol* or sotacor* or darob* or betacardone* or betades* or betapace* or bonpro* or corsotalol* or gilucor* or rentibloc* or sorine* or sota saar* or sotabeta* or sotacor* or sotahexal* or sotalex* or sotapor* or sotastad* or sotylize* or tachytalol*).tw. (2760)
23 or/8-22 (138120)
24 Ligation/ (24492)
25 (ligat* or EBL or EVL or band* or multiband*).tw. (316560)
26 (endoscop* adj2 (therap* or treat* or surger* or operat* or procedure*)).tw. (40639)
27 endosurger*.tw. (245)
28 or/24-27 (362840)
29 23 or 28 (498959)
30 7 and 29 (5254)
31 limit 30 to english language (4367)
32 Animals/ not Humans/ (5041578)
33 31 not 32 (3579)
34 limit 33 to ed=20151001-20221219 (879)
35 Economics/ (27483)
36 exp "Costs and Cost Analysis"/ (261725)
37 Economics, Dental/ (1920)
38 exp Economics, Hospital/ (25658)
39 exp Economics, Medical/ (14373)
40 Economics, Nursing/ (4013)
41 Economics, Pharmaceutical/ (3091)
42 Budgets/ (11662)
43 exp Models, Economic/ (16166)
44 Markov Chains/ (15873)
45 Monte Carlo Method/ (31798)
46 Decision Trees/ (12041)
47 econom$.tw. (305982)
48 cba.tw. (10420)
49 cea.tw. (23228)
50 cua.tw. (1134)
51 markov$.tw. (22315)
52 (monte adj carlo).tw. (35329)
53 (decision adj3 (tree$ or analys$)).tw. (19830)
54 (cost or costs or costing$ or costly or costed).tw. (565730)
55 (price$ or pricing$).tw. (40875)
56 budget$.tw. (27759)

57 expenditure$.tw. (58519)
58 (value adj3 (money or monetary)).tw. (2625)
59 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (3843)
60 or/35-59 (1116943)
61 "Quality of Life"/ (255967)
62 quality of life.tw. (296943)
63 "Value of Life"/ (5795)
64 Quality-Adjusted Life Years/ (15283)
65 quality adjusted life.tw. (14327)
66 (qaly$ or qald$ or qale$ or qtime$).tw. (11754)
67 disability adjusted life.tw. (4093)
68 daly$.tw. (3633)
69 Health Status Indicators/ (24074)
70 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (26250)
71 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1552)
72 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (6313)
73 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (33)
74 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (412)
75 (euroqol or euro qol or eq5d or eq 5d).tw. (13041)
76 (qol or hql or hqol or hrqol).tw. (58331)
77 (hye or hyes).tw. (63)
78 health$ year$ equivalent$.tw. (38)
79 utilit$.tw. (213424)
80 (hui or hui1 or hui2 or hui3).tw. (1573)
81 disutili$.tw. (503)
82 rosser.tw. (100)
83 quality of wellbeing.tw. (27)
84 quality of well-being.tw. (428)
85 qwb.tw. (201)
86 willingness to pay.tw. (6576)
87 standard gamble$.tw. (832)
88 time trade off.tw. (1186)
89 time tradeoff.tw. (249)
90 tto.tw. (1110)
91 or/61-90 (612046)
92 Cost-Benefit Analysis/ (91319)
93 Quality-Adjusted Life Years/ (15283)
94 Markov Chains/ (15873)
95 exp Models, Economic/ (16166)
96 cost*.ti. (121170)
97 (cost* adj2 utilit*).tw. (6181)

98 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (214242)
99 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. (36791)
100 (qualit* adj2 adjust* adj2 life*).tw. (14632)
101 QALY*.tw. (11627)
102 (incremental* adj2 cost*).tw. (14219)
103 ICER.tw. (4643)
104 utilities.tw. (7362)
105 markov*.tw. (22315)
106 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (45081)
107 ((utility or effective*) adj2 analys*).tw. (20021)
108 (willing* adj2 pay*).tw. (7512)
109 (EQ5D* or EQ-5D*).tw. (10260)
110 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. (2758)
111 (european* adj2 quality adj3 ("5" or five)).tw. (520)
112 or/92-111 (399280)
113 60 or 91 or 112 (1671570)
114 34 and 113 (49)

Database name: MEDLINE-in-Process
1 "esophageal and gastric varices"/ (0)
2 ((oesophag* or esophag* or gastroesophag* or gastrooesphag*) adj4 (varic* or varix*)).tw. (0)
3 ((varix* or varic*) adj2 bleed*).tw. (0)
4 Hypertension, Portal/ (0)
5 (porta* adj2 (hypertens* or congest*)).tw. (0)
6 Cruveilhier Baumgarten*.tw. (0)
7 or/1-6 (0)
8 exp Adrenergic beta-Antagonists/ (0)
9 ((beta* or b) adj4 (block* or antagonist* or sympatholy*)).tw. (7)
10 Betasympatholy*.tw. (0)
11 Propranolol/ (0)
12 (propranolol* or bedranol* or beta-prograne* or inderal* or syprol* or rexigen* or dexpropranolol* or dociton* or ob?idan* or anaprilin* or betadren* or arcablock* or authus* or avlocardyl* or beprane* or betadipresan* or betaryl* or cardinol* or ciplar* or corbeta* or deralin* or duranol* or efektolol* or elbrol* or frekven* or hemang?ol* or inderex* or innopran* or ipran* or prandol* or propabloc* or propercuten* or prophylux* or propranur* or sagittol*).tw. (3)
13 Carvedilol/ (0)
14 (carvedilol* or dilatrend* or querto* or eucardic* or kredex* or coropres* or coreg or cardiol or carvipress* or dilatrend* or dilibloc* or dimitone* or eucardic*).tw. (0)
15 Nadolol/ (0)
16 (nadolol* or corgard* or solgol* or betadol*).tw. (0)
17 Labetalol/ (0)

18 (labetalol* or trandate* or albetol* or apolabetalol* or normodyne* or presolol* or dilevalol* or lamitol* or presdate*).tw. (1)
19 exp Timolol/ (0)
20 (timolol* or tiopex* or eysano* or timopt* or timacar* or blocadren* or optimol* or apotimolol* or timolo* or titol*).tw. (1)
21 Sotalol/ (0)
22 (sotalol* or sotacor* or darob* or betacardone* or betades* or betapace* or bonpro* or corsotalol* or gilucor* or rentibloc* or sorine* or sota saar* or sotabeta* or sotacor* or sotahexal* or sotalex* or sotapor* or sotastad* or sotylize* or tachytalol*).tw. (0)
23 or/8-22 (11)
24 Ligation/ (0)
25 (ligat* or EBL or EVL or band* or multiband*).tw. (95)
26 (endoscop* adj2 (therap* or treat* or surger* or operat* or procedure*)).tw. (18)
27 endosurger*.tw. (0)
28 or/24-27 (113)
29 23 or 28 (124)
30 7 and 29 (0)
31 limit 30 to english language (0)
32 Animals/ not Humans/ (0)
33 31 not 32 (0)
34 limit 33 to dt=20151001-20221219 (0)
35 Economics/ (0)
36 exp "Costs and Cost Analysis"/ (0)
37 Economics, Dental/ (0)
38 exp Economics, Hospital/ (0)
39 exp Economics, Medical/ (0)
40 Economics, Nursing/ (0)
41 Economics, Pharmaceutical/ (0)
42 Budgets/ (0)
43 exp Models, Economic/ (0)
44 Markov Chains/ (0)
45 Monte Carlo Method/ (0)
46 Decision Trees/ (0)
47 econom$.tw. (191)
48 cba.tw. (1)
49 cea.tw. (8)
50 cua.tw. (0)
51 markov$.tw. (7)
52 (monte adj carlo).tw. (14)
53 (decision adj3 (tree$ or analys$)).tw. (24)
54 (cost or costs or costing$ or costly or costed).tw. (332)
55 (price$ or pricing$).tw. (27)
56 budget$.tw. (10)
57 expenditure$.tw. (25)
58 (value adj3 (money or monetary)).tw. (2)
59 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (4)
60 or/35-59 (547)

61 "Quality of Life"/ (0)
62 quality of life.tw. (231)
63 "Value of Life"/ (0)
64 Quality-Adjusted Life Years/ (0)
65 quality adjusted life.tw. (11)
66 (qaly$ or qald$ or qale$ or qtime$).tw. (9)
67 disability adjusted life.tw. (2)
68 daly$.tw. (1)
69 Health Status Indicators/ (0)
70 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (12)
71 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (0)
72 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (3)
73 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (0)
74 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (0)
75 (euroqol or euro qol or eq5d or eq 5d).tw. (24)
76 (qol or hql or hqol or hrqol).tw. (51)
77 (hye or hyes).tw. (0)
78 health$ year$ equivalent$.tw. (0)
79 utilit$.tw. (116)
80 (hui or hui1 or hui2 or hui3).tw. (1)
81 disutili$.tw. (1)
82 rosser.tw. (0)
83 quality of wellbeing.tw. (0)
84 quality of well-being.tw. (0)
85 qwb.tw. (0)
86 willingness to pay.tw. (6)
87 standard gamble$.tw. (0)
88 time trade off.tw. (7)
89 time tradeoff.tw. (0)
90 tto.tw. (2)
91 or/61-90 (359)
92 Cost-Benefit Analysis/ (0)
93 Quality-Adjusted Life Years/ (0)
94 Markov Chains/ (0)
95 exp Models, Economic/ (0)
96 cost*.ti. (47)
97 (cost* adj2 utilit*).tw. (3)
98 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (124)
99 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. (29)
100 (qualit* adj2 adjust* adj2 life*).tw. (11)

101 QALY*.tw. (9)
102 (incremental* adj2 cost*).tw. (8)
103 ICER.tw. (3)
104 utilities.tw. (5)
105 markov*.tw. (7)
106 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (26)
107 ((utility or effective*) adj2 analys*).tw. (8)
108 (willing* adj2 pay*).tw. (6)
109 (EQ5D* or EQ-5D*).tw. (20)
110 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. (6)
111 (european* adj2 quality adj3 ("5" or five)).tw. (2)
112 or/92-111 (217)
113 60 or 91 or 112 (883)
114 34 and 113 (0)

Database name: MEDLINE Epub Ahead-of-Print

1 "esophageal and gastric varices"/ (0)
2 ((oesophag* or esophag* or gastroesophag* or gastrooesphag*) adj4 (varic* or varix*)).tw. (70)
3 ((varix* or varic*) adj2 bleed*).tw. (64)
4 Hypertension, Portal/ (0)
5 (porta* adj2 (hypertens* or congest*)).tw. (175)
6 Cruveilhier Baumgarten*.tw. (0)
7 or/1-6 (245)
8 exp Adrenergic beta-Antagonists/ (0)
9 ((beta* or b) adj4 (block* or antagonist* or sympatholy*)).tw. (527)
10 Betasympatholy*.tw. (0)
11 Propranolol/ (0)
12 (propranolol* or bedranol* or beta-prograne* or inderal* or syprol* or rexigen* or dexpropranolol* or dociton* or ob?idan* or anaprilin* or betadren* or arcablock* or authus* or avlocardyl* or beprane* or betadipresan* or betaryl* or cardinol* or ciplar* or corbeta* or deralin* or duranol* or efektolol* or elbrol* or frekven* or hemang?ol* or inderex* or innopran* or ipran* or prandol* or propabloc* or propercuten* or prophylux* or propranur* or sagittol*).tw. (114)
13 Carvedilol/ (0)
14 (carvedilol* or dilatrend* or querto* or eucardic* or kredex* or coropres* or coreg or cardiol or carvipress* or dilatrend* or dilibloc* or dimitone* or eucardic*).tw. (50)
15 Nadolol/ (0)
16 (nadolol* or corgard* or solgol* or betadol*).tw. (7)
17 Labetalol/ (0)
18 (labetalol* or trandate* or albetol* or apolabetalol* or normodyne* or presolol* or dilevalol* or lamitol* or presdate*).tw. (13)
19 exp Timolol/ (0)
20 (timolol* or tiopex* or eysano* or timopt* or timacar* or blocadren* or optimol* or apotimolol* or timolo* or titol*).tw. (37)

21 Sotalol/ (0)
22 (sotalol* or sotacor* or darob* or betacardone* or betades* or betapace* or bonpro* or corsotalol* or gilucor* or rentibloc* or sorine* or sota saar* or sotabeta* or sotacor* or sotahexal* or sotalex* or sotapor* or sotastad* or sotylize* or tachytalol*).tw. (28)
23 or/8-22 (698)
24 Ligation/ (0)
25 (ligat* or EBL or EVL or band* or multiband*).tw. (4084)
26 (endoscop* adj2 (therap* or treat* or surger* or operat* or procedure*)).tw. (743)
27 endosurger*.tw. (2)
28 or/24-27 (4813)
29 23 or 28 (5505)
30 7 and 29 (39)
31 limit 30 to english language (35)
32 Animals/ not Humans/ (0)
33 31 not 32 (35)
34 Economics/ (0)
35 exp "Costs and Cost Analysis"/ (0)
36 Economics, Dental/ (0)
37 exp Economics, Hospital/ (0)
38 exp Economics, Medical/ (0)
39 Economics, Nursing/ (0)
40 Economics, Pharmaceutical/ (0)
41 Budgets/ (0)
42 exp Models, Economic/ (0)
43 Markov Chains/ (0)
44 Monte Carlo Method/ (0)
45 Decision Trees/ (0)
46 econom$.tw. (7395)
47 cba.tw. (55)
48 cea.tw. (246)
49 cua.tw. (16)
50 markov$.tw. (559)
51 (monte adj carlo).tw. (882)
52 (decision adj3 (tree$ or analys$)).tw. (643)
53 (cost or costs or costing$ or costly or costed).tw. (12409)
54 (price$ or pricing$).tw. (1011)
55 budget$.tw. (526)
56 expenditure$.tw. (1021)
57 (value adj3 (money or monetary)).tw. (82)
58 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (44)
59 or/34-58 (21275)
60 "Quality of Life"/ (0)
61 quality of life.tw. (7203)
62 "Value of Life"/ (0)
63 Quality-Adjusted Life Years/ (0)
64 quality adjusted life.tw. (405)

65 (qaly$ or qald$ or qale$ or qtime$).tw. (337)
66 disability adjusted life.tw. (115)
67 daly$.tw. (102)
68 Health Status Indicators/ (0)
69 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (379)
70 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (40)
71 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (134)
72 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (0)
73 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (4)
74 (euroqol or euro qol or eq5d or eq 5d).tw. (468)
75 (qol or hql or hqol or hrqol).tw. (1419)
76 (hye or hyes).tw. (1)
77 health$ year$ equivalent$.tw. (0)
78 utilit$.tw. (4196)
79 (hui or hui1 or hui2 or hui3).tw. (27)
80 disutili$.tw. (15)
81 rosser.tw. (0)
82 quality of wellbeing.tw. (2)
83 quality of well-being.tw. (8)
84 qwb.tw. (2)
85 willingness to pay.tw. (197)
86 standard gamble$.tw. (6)
87 time trade off.tw. (28)
88 time tradeoff.tw. (0)
89 tto.tw. (29)
90 or/60-89 (11716)
91 Cost-Benefit Analysis/ (0)
92 Quality-Adjusted Life Years/ (0)
93 Markov Chains/ (0)
94 exp Models, Economic/ (0)
95 cost*.ti. (1710)
96 (cost* adj2 utilit*).tw. (215)
97 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (4956)
98 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. (979)
99 (qualit* adj2 adjust* adj2 life*).tw. (410)
100 QALY*.tw. (337)
101 (incremental* adj2 cost*).tw. (346)
102 ICER.tw. (155)
103 utilities.tw. (171)
104 markov*.tw. (559)

105 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (791)
106 ((utility or effective*) adj2 analys*).tw. (533)
107 (willing* adj2 pay*).tw. (213)
108 (EQ5D* or EQ-5D*).tw. (394)
109 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. (107)
110 (european* adj2 quality adj3 ("5" or five)).tw. (24)
111 or/91-110 (7795)
112 59 or 90 or 111 (31549)
113 33 and 112 (3)

Database name: Embase
1 exp esophagus varices/ (21725)
2 ((oesophag* or esophag* or gastroesophag* or gastrooesphag*) adj4 (varic* or varix*)).tw. (17052)
3 ((varix* or varic*) adj2 bleed*).tw. (13230)
4 exp portal hypertension/ (36141)
5 (porta* adj2 (hypertens* or congest*)).tw. (29914)
6 Cruveilhier Baumgarten*.tw. (67)
7 or/1-6 (60465)
8 exp beta adrenergic receptor blocking agent/ (323648)
9 ((beta* or b) adj4 (block* or antagonist* or sympatholy*)).tw. (113155)
10 Betasympatholy*.tw. (0)
11 propranolol/ (94183)
12 (propranolol* or bedranol* or beta-prograne* or inderal* or syprol* or rexigen* or dexpropranolol* or dociton* or ob?idan* or anaprilin* or betadren* or arcablock* or authus* or avlocardyl* or beprane* or betadipresan* or betaryl* or cardinol* or ciplar* or corbeta* or deralin* or duranol* or efektolol* or elbrol* or frekven* or hemang?ol* or inderex* or innopran* or ipran* or prandol* or propabloc* or propercuten* or prophylux* or propranur* or sagittol*).tw. (45433)
13 carvedilol/ (17480)
14 (carvedilol* or dilatrend* or querto* or eucardic* or kredex* or coropres* or coreg or cardiol or carvipress* or dilatrend* or dilibloc* or dimitone* or eucardic*).tw. (8895)
15 nadolol/ (5937)
16 (nadolol* or corgard* or solgol* or betadol*).tw. (2135)
17 labetalol/ (11782)
18 (labetalol* or trandate* or albetol* or apolabetalol* or normodyne* or presolol* or dilevalol* or lamitol* or presdate*).tw. (4039)
19 timolol/ (12256)
20 (timolol* or tiopex* or eysano* or timopt* or timacar* or blocadren* or optimol* or apotimolol* or timolo* or titol*).tw. (6777)
21 sotalol/ (14050)
22 (sotalol* or sotacor* or darob* or betacardone* or betades* or betapace* or bonpro* or corsotalol* or gilucor* or rentibloc* or sorine* or sota saar* or sotabeta* or sotacor* or sotahexal* or sotalex* or sotapor* or sotastad* or sotylize* or tachytalol*).tw. (4707)

23 or/8-22 (367775)
24 ligation/ or endoscopic variceal ligation/ (31062)
25 (ligat* or EBL or EVL or band* or multiband*).tw. (484724)
26 (endoscop* adj2 (therap* or treat* or surger* or operat* or procedure*)).tw. (76278)
27 endosurger*.tw. (886)
28 or/24-27 (566088)
29 23 or 28 (929807)
30 7 and 29 (11663)
31 limit 30 to english language (10213)
32 nonhuman/ not human/ (5114015)
33 31 not 32 (9305)
34 limit 33 to (conference abstract or conference paper or "conference review") (3343)
35 33 not 34 (5962)
36 limit 35 to dc=20151001-20221219 (1866)
37 exp Health Economics/ (988911)
38 exp "Health Care Cost"/ (328218)
39 exp Pharmacoeconomics/ (224339)
40 Monte Carlo Method/ (48194)
41 Decision Tree/ (19332)
42 econom$.tw. (464408)
43 cba.tw. (13805)
44 cea.tw. (39801)
45 cua.tw. (1762)
46 markov$.tw. (37455)
47 (monte adj carlo).tw. (58115)
48 (decision adj3 (tree$ or analys$)).tw. (34083)
49 (cost or costs or costing$ or costly or costed).tw. (938548)
50 (price$ or pricing$).tw. (68913)
51 budget$.tw. (45101)
52 expenditure$.tw. (86894)
53 (value adj3 (money or monetary)).tw. (4099)
54 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (9414)
55 or/37-54 (2131015)
56 "Quality of Life"/ (584327)
57 Quality Adjusted Life Year/ (33017)
58 Quality of Life Index/ (3098)
59 Short Form 36/ (36889)
60 Health Status/ (145870)
61 quality of life.tw. (552717)
62 quality adjusted life.tw. (24729)
63 (qaly$ or qald$ or qale$ or qtime$).tw. (25064)
64 disability adjusted life.tw. (5767)
65 daly$.tw. (5537)
66 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (47977)

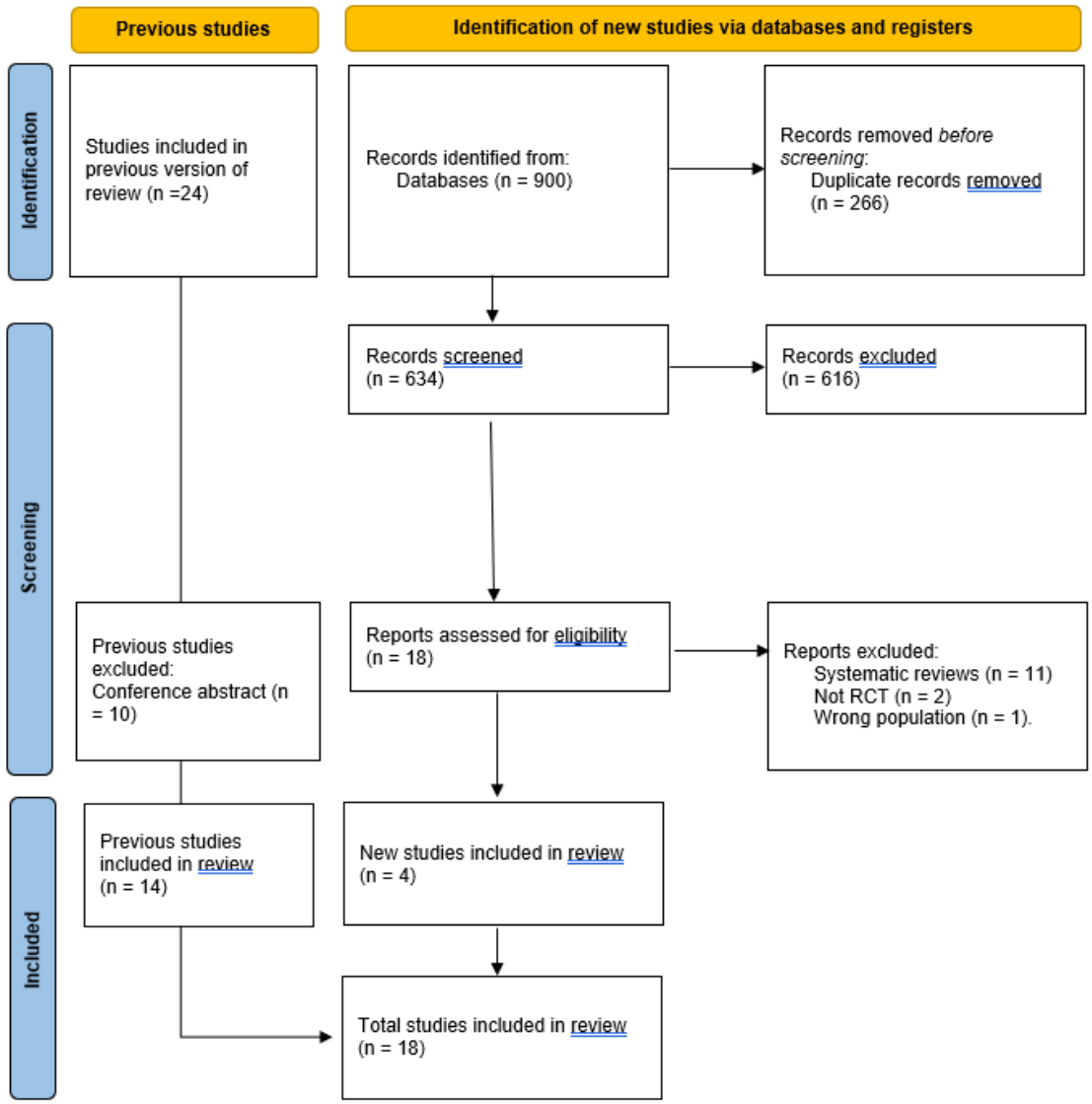
67 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (2817)
68 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (11612)
69 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (68)
70 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (506)
71 (euroqol or euro qol or eq5d or eq 5d).tw. (27925)
72 (qol or hql or hqol or hrqol).tw. (122848)
73 (hye or hyes).tw. (158)
74 health$ year$ equivalent$.tw. (41)
75 utilit$.tw. (354676)
76 (hui or hui1 or hui2 or hui3).tw. (2917)
77 disutili$.tw. (1149)
78 rosser.tw. (138)
79 quality of wellbeing.tw. (69)
80 quality of well-being.tw. (551)
81 qwb.tw. (266)
82 willingness to pay.tw. (11885)
83 standard gamble$.tw. (1175)
84 time trade off.tw. (1968)
85 time tradeoff.tw. (310)
86 tto.tw. (2090)
87 or/56-86 (1219016)
88 cost utility analysis/ (11557)
89 quality adjusted life year/ (33017)
90 cost*.ti. (185603)
91 (cost* adj2 utilit*).tw. (11824)
92 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (360562)
93 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. (61685)
94 (qualit* adj2 adjust* adj2 life*).tw. (25332)
95 QALY*.tw. (24810)
96 (incremental* adj2 cost*).tw. (26660)
97 ICER.tw. (11926)
98 utilities.tw. (14149)
99 markov*.tw. (37455)
100 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (68017)
101 ((utility or effective*) adj2 analys*).tw. (35127)
102 (willing* adj2 pay*).tw. (13432)
103 (EQ5D* or EQ-5D*).tw. (23649)
104 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. (4694)
105 (european* adj2 quality adj3 ("5" or five)).tw. (877)
106 or/88-105 (594803)

107 55 or 87 or 106 (3197735)
108 36 and 107 (148)

Database name: EconLit
1 ((oesophag* or esophag* or gastroesophag* or gastrooesphag*) adj4 (varic* or varix*)).tw. (0)
2 ((varix* or varic*) adj2 bleed*).tw. (0)
3 (porta* adj2 (hypertens* or congest*)).tw. (0)
4 Cruveilhier Baumgarten*.tw. (0)
5 or/1-4 (0)
6 ((beta* or b) adj4 (block* or antagonist* or sympatholy*)).tw. (40)
7 (propranolol* or bedranol* or beta-prograne* or inderal* or syprol* or rexigen* or dexpropranolol* or dociton* or ob?idan* or anaprilin* or betadren* or arcablock* or authus* or avlocardyl* or beprane* or betadipresan* or betaryl* or cardinol* or ciplar* or corbeta* or deralin* or duranol* or efektolol* or elbrol* or frekven* or hemang?ol* or inderex* or innopran* or ipran* or prandol* or propabloc* or propercuten* or prophylux* or propranur* or sagittol*).tw. (8)
8 (carvedilol* or dilatrend* or querto* or eucardic* or kredex* or coropres* or coreg or cardiol or carvipress* or dilatrend* or dilibloc* or dimitone* or eucardic*).tw. (0)
9 (nadolol* or corgard* or solgol* or betadol*).tw. (0)
10 (labetalol* or trandate* or albetol* or apolabetalol* or normodyne* or presolol* or dilevalol* or lamitol* or presdate*).tw. (0)
11 (timolol* or tiopex* or eysano* or timopt* or timacar* or blocadren* or optimol* or apotimolol* or timolo* or titol*).tw. (43)
12 (sotalol* or sotacor* or darob* or betacardone* or betades* or betapace* or bonpro* or corsotalol* or gilucor* or rentibloc* or sorine* or sota saar* or sotabeta* or sotacor* or sotahexal* or sotalex* or sotapor* or sotastad* or sotylize* or tachytalol*).tw. (1)
13 or/6-12 (92)
14 (ligat* or EBL or EVL or band* or multiband*).tw. (3948)
15 (endoscop* adj2 (therap* or treat* or surger* or operat* or procedure*)).tw. (5)
16 endosurger*.tw. (0)
17 or/14-16 (3953)
18 13 or 17 (4045)
19 5 and 18 (0)

Database name: INAHTA
(Cruveilhier Baumgarten*) OR (((porta*) AND (hypertens* or congest*))) OR ("Hypertension, Portal"[mh]) OR (((varix* or varic*) AND (bleed*))) OR (((oesophag* or esophag* or gastroesophag* or gastrooesphag*) AND (varic* or varix*))) OR ("Esophageal and Gastric Varices"[mh])

Appendix C – Effectiveness evidence study selection



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Appendix D – Effectiveness evidence

Abd ElRahim, 2018

Bibliographic Reference	Abd ElRahim, Ayman Yosry; Fouad, Rabab; Khairy, Marwa; Elsharkawy, Aisha; Fathalah, Waleed; Khatamish, Haytham; Khorshid, Omayma; Moussa, Mona; Seyam, Moataz; Efficacy of carvedilol versus propranolol versus variceal band ligation for primary prevention of variceal bleeding.; Hepatology international; 2018; vol. 12 (no. 1); 75-82

Study details

Study type	Randomised controlled trial (RCT) Outlined in the study as a "cross-sectional randomised controlled trial"
Study location	Egypt
Study setting	Hepatology and Gastroenterology Department — Endoscopy Unit— Theodor Bilharz Research Institute, a specialised centre for management of patients with chronic liver diseases
Study dates	May 2015 until June 2016
Inclusion criteria	• No history of bleeding • Variceal bleeding was evaluated by history of melena, frank haematemesis and endoscopic evaluation in case of emergency or follow-up endoscopy • No prior endoscopic, radiological or surgical treatment of varices or ascites • No prior pharmacological treatment for primary variceal prophylaxis regimens
Exclusion criteria	• Non-cirrhotic cause of portal hypertension • <18 or >75 years of age • Pregnant, lactating, or of childbearing age without use of contraception • Obstructive airways disease • Portal vein thrombosis • Visualisation of thrombus by imaging techniques and absence of Doppler flow • Heart block • Atrioventricular block of grade II and III • Congestive cardiac failure • Chronic renal insufficiency with plasma creatinine ≥ 150 µmol/l • Chronic renal insufficiency (plasma creatinine >/=1.5 mg/dl) • History of variceal bleeding • Hepatocellular carcinoma • Diagnosed by two imaging techniques (one of them showing the characteristic contrast uptake and washout pattern for hepatocellular carcinoma)

	• Previous primary or secondary prevention of varices • Sick sinus syndrome • Bradycardia under 60 beats/min • Asthma • Uncontrolled diabetes mellitus • Drugs affecting portal pressure (betablockers, vasopressors, nitrates, and vasodilators) • Active schistosomiasis • Chronic alcoholism
Intervention(s)	Group 1: Band ligation group received band ligation every 2 weeks using a multiband ligation device (sixshooter, Wilson-Cook Inc) up to six bands were placed per session from the distal oesophagus just above the gastroesophageal junction until oesophageal varices were eradicated.
Comparator	Group 2: Carvedilol group after assessment of baseline heart rate and blood pressure measurements, received a starting dosage of 6.25 mg daily, titrated up every 4 days to reach up to 12.5–50 mg, to achieve reduction of baseline heart rate by 25%, but not below 55 beats/min. Group 3: Propranolol group after assessment of baseline heart rate and blood pressure, received a starting dosage of 40 mg daily, adjusted in 20–40 mg increments at 2-weekly intervals, to achieve reduction of baseline heart rate by 25%, but not below 55 beats/min.
Outcome measures	• Variceal haemorrhage • Treatment related complications
Number of participants	330
Duration of follow-up	At 1 year for primary prophylaxis regimens on disease progression through follow-up based on Child score. At 1 year for portal hypertensive gastropathy by upper endoscopy and history and histopathological examination. The study does not state the specific follow-up for efficacy, side-effects, and outcome of band ligation, propranolol, and carvedilol for primary prophylaxis of variceal bleeding but given the study duration (13 months) it is assumed to be 1 year.
Loss to follow-up	66 (20%)
Methods of analysis	Data were collected and statistically analysed using SPSS version 11 statistical package. Comparison of qualitative data was performed with chi-squared test. p-Value<0.05 was considered significant. Kruskal–Wallis test followed by post hoc comparison by adjusting the probability was used for comparison between nonparametric quantitative data between the three groups. Follow-up data (trend data) were compared by applying repeated-measures analysis.

Study arms

- Variceal band ligation - VBL (N = 110)

- Propranolol (N = 110)
- Carvedilol (N = 110)

Characteristics
Arm-level characteristics

Characteristic	Variceal band ligation - VBL (N = 110)	Propranolol (N = 110)	Carvedilol (N = 110)
% Female	62	56	66
Mean age (SD)	50.6 (5.9)	51.8 (5.9)	51.2 (11)
% Chronic HCV	80	76	70
% Chronic HBV	14	14	16
Child score (%)			
Score A	20	18	30
Score B	24	30	28
Score C	56	52	42
Varices (%)			
% Medium	58	64	68
% Large	42	36	32

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(The study does not blind investigators which is a potential source of bias. Post randomisation there was a greater percentage of large varices in group 3 vs group 1 (10% difference) and greater percentage of severe portal hypertensive gastropathy in group 3 vs group 1 (>20%) and vs 2 (18%) indicating a potential issue with the randomisation. There was no assessment for differences across study arms to*

Section	Question	Answer
		address the observed differences post-randomisation. There was a 20% drop-out at follow-up and no reference to an analysis to consider the effect of allocation to intervention (ITT) or outcomes).
Overall bias and Directness	Overall Directness	Directly applicable

De, 1999

Bibliographic Reference	De, B K; Ghoshal, U C; Das, T; Santra, A; Biswas, P K; Endoscopic variceal ligation for primary prophylaxis of oesophageal variceal bleed: preliminary report of a randomized controlled trial.; Journal of gastroenterology and hepatology; 1999; vol. 14 (no. 3); 220-4

Study details

Study type	Randomised controlled trial (RCT)
Study location	India
Study setting	Hospital
Study dates	August 1994 to September 1996
Sources of funding	Not stated
Inclusion criteria	• No history of bleeding • Grade III to IV oesophageal varices • Hepatic venous pressure gradient =/<12 mmHg
Exclusion criteria	• Heart block • Congestive cardiac failure • History of bronchial asthma
Intervention(s)	Endoscopic variceal ligation (EVL) was done by a standard technique using a forward viewing fibrescope (XP 20) and endoscopic ligation device weekly to fortnightly until variceal obliteration. During EVL an overtube was not used as it has been associated with complications with this procedure and the patients tolerated the procedure quite well without an overtube. The varices were ligated individually with O rings starting at or just above gastro-oesophageal junction and then every 5–7 cm proximally. A maximum of five bands were used during each session. After the varices were obliterated, the patients were put on surveillance endoscopy every 6 weeks for 3 months and then 3 monthly during the period of follow up.
Comparator	Propranolol 40 mg thrice daily. The dose was titrated to achieve the target pulse rate (a 25% reduction from the baseline pulse rate) during the hospital stay. After hospital discharge patients were asked to attend the clinic at an interval of 2 weeks initially and then every 4–6 weeks. Patients

	were monitored for side effects of therapy (e.g. bradycardia, heart failure and bronchospasm). The patients were asked to maintain a diary and to bring the empty medicine strips during their follow-up visits to check for compliance.
Outcome measures	Variceal haemorrhage
Number of participants	30
Duration of follow-up	17.6 ± 4.7 months EVL - after the varices were obliterated, the patients were put on surveillance endoscopy every 6 weeks for 3 months and then 3 monthly during the period of follow up. Propranolol - after discharge from the hospital the patients were asked to attend the clinic at an interval of 2 weeks initially and then every 4–6 weeks
Loss to follow-up	0
Methods of analysis	The differences between parametric data were analysed by the Students t-test. For non-parametric data, the Chi-squared test with Yates' correction was used when applicable.

Study arms

- EVL (N = 15)
- Propranolol (N = 15)

Characteristics
Arm-level characteristics

Characteristic	EVL (N = 15)	Propranolol (N = 15)
% Female	33	20
Mean age (SD) (years)	41.6 (12.5)	39.2 (16.6)
Aetiology of cirrhosis		
% Alcoholic	13	20
Size of varices		
% Grade 3	13	27

Characteristic	EVL (N = 15)	Propranolol (N = 15)
% Grade 4	87	73
Child-Pugh score		
% Score A	33	40
% Score B	53	47
% Score C	14	13

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(Method for randomisation unclear. No blinding. Study states that there were no significant differences between study arms but there is no reference to how this was established).*
Overall bias and Directness	Overall Directness	Directly applicable *(Participants and interventions are in scope and satisfy research protocol criteria.)*

Drastich, 2011

Bibliographic Reference	Drastich, Pavel; Lata, Jan; Petrtyl, Jaromir; Bruha, Radan; Prochazka, Vlastimil; Vanasek, Tomas; Zdenek, Petr; Skibova, Jelena; Hucl, Tomas; Spicak, Julius; Endoscopic variceal band ligation compared with propranolol for prophylaxis of first variceal bleeding.; Annals of hepatology; 2011; vol. 10 (no. 2); 142-9

Study details

Trial registration number and/or trial name	Not reported
Study type	Randomised controlled trial (RCT)
Study location	Czech Republic
Study setting	Six participating university hospitals
Study dates	Not stated

Sources of funding	Not stated
Inclusion criteria	• Portal hypertension due to cirrhosis • Large oesophageal varices
Exclusion criteria	• Non-cirrhotic cause of portal hypertension. • History of gastrointestinal bleeding • Pregnant, lactating, or of childbearing age without use of contraception • Malignancy that significantly affects survival • Obstructive airways disease • Heart block • Congestive cardiac failure • History of bronchial asthma • History of sclerotherapy, EVBL or portosystemic shunt • Gastric or duodenal ulcer • Chronic renal insufficiency with plasma creatinine ≥ 150 µmol/l • Treatment with β-blockers, nitrates, ACE inhibitors or verapamil within 2 months before randomization • Concomitant antiviral therapy • Hypersensitivity to propranolol • Decompensated diabetes mellitus
Intervention(s)	Patients assigned to the EVL group underwent ligation after an initial screening gastroscopy that was performed to assess the size and appearance of oesophageal and gastric varices and portal hypertensive gastropathy (PHG) and to exclude other lesions such as ulcers and tumours. EVL was performed within 1 week of randomisation using a multiband ligation device (Six-shooter, Wilson-Cook Inc., Winston-Salem, NC) and up to 6 bands were placed per session beginning in the distal oesophagus just above the gastroesophageal junction. Procedures were performed at 2 week intervals until oesophageal varices were eradicated (defined as a complete disappearance of varices or the presence of a varix being too small to be ligated). The interval between sessions was prolonged by 1 week if post-ligation ulcers were present. EVBL was performed by 1 or 2 experienced endoscopists. All side effects were carefully recorded. Patients were administered 1g of sucralfat emulsion 4 times per day on an individual basis until oesophageal varices were eradicated. EVL was continued in patients with recurrence, defined as the presence of a varix larger than 5 mm in diameter after initial eradication.
Comparator	Patients were started on propranolol therapy within one week of randomisation and the initial evaluation gastroscopy. During the initial visit, patients underwent baseline heart rate and blood pressure measurements and electrocardiography after 15 minutes of rest in a horizontal position. The starting dose for all patients was 20 mg twice daily. Patients were advised to take the evening dose before bedtime. The dose of propranolol was adjusted in 20-40 mg increments at weekly intervals, to achieve a reduction of the baseline heart rate by 25%, however not to decrease below 55 beats/min. All measurements were done under the same conditions. In case of side effects, heart rate <55 beats/min or systolic

	blood pressure < 80 mmHg, propranolol dosage was reduced by 20 to 40 mg/day. Compliance was carefully assessed by a pill count and by pulse rate measurements.
Outcome measures	• Variceal haemorrhage • Death • Death due to variceal bleeding
Number of participants	73
Duration of follow-up	All patients were seen in clinic every 3 months for clinical and biochemical examinations and an upper GI endoscopy was performed at 6 month intervals over a follow-up time of up to 18 months.
Loss to follow-up	Two patients were lost to follow-up (one from each group) and one patient underwent a liver transplantation 14 months after randomisation.
Methods of analysis	Intention to treat analysis. Variables between the two arms were compared using the non-paired t-test, Chi-square test, Fisher's exact test or approximation based on arcsine transformation for comparison of the two relative frequencies (when appropriate). The actuarial probabilities of variceal bleeding and death were calculated by the Kaplan-Meier method and a comparison made using the long-rank test.
Additional comments	

Study arms

- EVL (N = 40)
- Propranolol (N = 33)

Characteristics
Arm-level characteristics

Characteristic	EVL (N = 40)	Propranolol (N = 33)
% Female	40 (n = 16)	18 (n = 6)
Mean age (SD)	57 (9)	56 (10)
Aetiology of liver cirrhosis		
- **Alcoholic (use of ETOH)** (n)	6	2
- **Alcoholic (without use of ETOH)** (n)	20	18
- **Autoimmune** (n)	1	1

Characteristic	EVL (N = 40)	Propranolol (N = 33)
- **Viral** (n)	4	5
- **Cholestatic** (n)	6	4
- **Others** (n)	3	3
Variceal red signs		
- **No signs** (n)	23	19
- **Cherry red spots** (n)	13	13
- **Red wale markings** (n)	2	0
- **Haemocystic spots** (n)	5	5
% Gastric varices before treatment	n = 11 % = 28	n = 7 % = 21
Child-Pugh's score		
% Score A	n = 18 % = 45	n = 20 % = 61
% Score B	n = 20 % = 50	n = 10 % = 30
% Score C	n = 2 % = 5	n = 3 % = 9
Ascites %	33	21

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(Randomisation method outlined. Study refers to variables between the two arms being compared using the non-paired t-test, Chi-square test, Fisher's exact test or approximation based on arcsine transformation for comparison of the two relative frequencies (when appropriate) but does not confirm if there was a difference or not between study arms after randomisation. Blinding of participants is difficult given the*

Section	Question	Answer
		interventions under investigation. No personnel blinding which is a potential source of bias. Personnel were not blinded which is a potential source of bias. There were deviations and adaptions in each arm as a consequence of adverse effects during the follow-up period which are outlined in the results section. All data reported for all outcomes outlined in study methodology. Objective measures were used to measure outcomes. All patients were seen in clinic every 3 months for clinical and biochemical examinations and an upper GI endoscopy was performed at 6 month intervals over a follow up time of up to 18 months).
Overall bias and Directness	Overall Directness	Directly applicable *(Study meets research protocol).*

Jutabha, 2005

Bibliographic Reference	Jutabha, Rome; Jensen, Dennis M; Martin, Paul; Savides, Thomas; Han, Steven-Huy; Gornbein, Jeffrey; Randomized study comparing banding and propranolol to prevent initial variceal hemorrhage in cirrhotics with high-risk esophageal varices.; Gastroenterology; 2005; vol. 128 (no. 4); 870-81

Study details

Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	3 tertiary care referral medical centres where orthotopic liver transplantation (OLT) is available
Study dates	Study subjects were selected from a pool of patients referred for OLT evaluation from July 1996 to June 2001. All patients randomised were followed up until an interim analysis and then a final analysis was performed (June 2001).
Sources of funding	The study and investigators were supported in part by 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-RR008658-25.
Inclusion criteria	• Large oesophageal varices • No history of bleeding • Age >18 years • Age <75 years • High risk varices (medium sized with red colour) • No prior endoscopic, radiological or surgical treatment of varices or ascites

	• No current beta-blocker therapy (unless it can be discontinued or replaced with another medication) • Life expectancy of at least 24 months without OLT
Exclusion criteria	• Serious systemic illness (cardiorespiratory, sepsis) • Portal vein thrombosis • Gastric or duodenal ulcer • Moderate or large ulcers • Uncooperative, no written consent, could not return for follow-up • Contraindicated to beta-blockers • Severe coagulopathy unresponsive to blood product transfusions • Severe thrombocytopenia • Increased alpha-fetoprotein level • Positive beta-human chorionic gonadotropin (women only) • Documented hepatoma • Hepatic vein thrombosis • Large-volume or tense ascites that could not be controlled with diuretics and sodium restriction and required repeated therapeutic paracentesis • Contraindication to therapeutic endoscopy • Severe erosive oesophagitis, oesophageal stricture requiring dilation, active duodenal or gastric ulceration, or UGI tumour • Severe UGI angioma syndrome • Severe portal hypertensive gastropathy with spontaneous or contact bleeding • Severe recurrent UGI bleeding • Severe anaemia with hemoccult-positive stools thought to be secondary to the UGI angioma syndrome or portal hypertensive gastropathy because of an otherwise negative gastrointestinal evaluation that excluded another source of gastrointestinal haemorrhage
Intervention(s)	Initial screening undertaken to assess size, number of columns, presence of red colour and location of varices. Band placement performed with multi-shot ligating device (six-shooter) and banding was started at the gastroesophageal junction (GEJ), targeting the largest varices. Bands were then sequentially placed, progressing proximally every 1–2 cm targeting the largest varices at each level. All endoscopic treatments were focused on the distal 5–7 cm of the oesophagus on each variceal column. Subsequent bands were spaced at least 1 cm apart and not directly adjacent to previous bands or at the same level of the oesophagus. Patients were prescribed proton pump inhibitors (once a day) until oesophageal varices were obliterated. Follow-up banding procedures were performed after 4–5 weeks to allow complete healing of post-banding ulcers. Follow-up endoscopic procedures were repeated at pre-set intervals (1, 2, 3, 6, 12, 24, 36, 48, and 60 months after randomisation). Banding was performed for all oesophageal variceal columns up to 5–7 cm above the GEJ until complete obliteration or a reduction to small size whereby variceal ligation was no longer possible. Recurrent oesophageal varices seen at surveillance endoscopies were also banded in the distal 5–7 cm of the GEJ.

Comparator	Long-acting propranolol starting dose of 80 mg once daily (Inderal LA). Patients were seen weekly in the clinic to adjust the dose by 80-mg increments (maximum dose, 400 mg) to reduce the baseline heart rate by 25% while maintaining a minimum heart rate of >50 beats/min and a systolic blood pressure of >90 mm Hg. All patients were switched to the equivalent doses of propranolol taken twice daily during year 3 due to drug supply issues. In the latter patients starting on propranolol, the initial dose was 40 mg twice daily, and this was increased every 2 weeks by 40–80 mg/day as tolerated. Patients experiencing side effects from the higher doses had the daily doses reduced by increments of 40 mg (regular propranolol) or 80 mg (for Inderal LA). Patients who had severe side effects of propranolol, such as hypotension, dizziness, or fainting, were instructed to report to study investigators, their primary care physician, or an emergency room for examination. Pulse rate and blood pressure were measured during each clinic follow-up visit every 1–2 weeks for the first 3 months (or until the pulse was reduced by >/= 25% from baseline) and then every 3 months when a stable dose of propranolol and pulse reduction were achieved.
Outcome measures	• Death from oesophageal variceal bleeding • Variceal haemorrhage • Death
Number of participants	62
Duration of follow-up	Up to 60 months post randomisation
Loss to follow-up	0 - No patients were lost to follow-up
Methods of analysis	Discrete time-to-event outcomes (time to failure, haemorrhage, and death) were compared in the 2 groups by the log-rank test. Post-randomisation transfusions (units of red blood cells, platelets, and fresh frozen plasma), hospital days, intensive care unit days, and direct costs were summarised an compared over time by using repeated-measures analysis of variance methods or the nonparametric equivalent. Findings at baseline by treatment were compared: Discrete outcomes at baseline were compared by Chi-2 tests. Comparison of continuous outcomes at baseline was made by t tests or the nonparametric rank-based analog (Wilcoxon signed rank test), if a Gaussian model was not appropriate for the continuous data in any scale. P values and 95% CIs for discrete outcomes such as differences in proportions were computed by using exact binomial methods where appropriate (StatXact, version 5; Cytel Software Corp., Cambridge, MA).
Additional comments	

Study arms

- Endoscopic variceal ligation (N = 31)
- Propranolol (N = 31)

Characteristics
Arm-level characteristics

Characteristic	Endoscopic variceal ligation (N = 31)	Propranolol (N = 31)
% Female (%)	32	26
Mean age (SE) (years)	54.3 (1.7)	54.9 (2.2)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No blinding. The study identified significant a difference in participant characteristics post randomisation (at interim analysis) that led to study recruitment being stopped before all recruitment had been completed. The results of this study represent the findings of the interim analysis. Further there were some issues with the supply of propranolol at year 3 leading to participants being moved onto a different treatment regimen - this deviation may have had some impact but did not need to be balanced across both arms as interventions were different. Both these factors introduce bias and findings should be treated with some caution.)*
Overall bias and Directness	Overall Directness	Directly applicable

Kanwal, 2022

Bibliographic Reference	Kanwal, N.; Sadaf, S.; Butt, N.I.; Awan, H.A.; Ashfaq, F.; Zia, N.; Carvedilol vs endoscopic band ligation: primary prophylaxis of variceal bleed; Rawal Medical Journal; 2022; vol. 47 (no. 4); 850-853

Study details

Trial registration number and/or trial name	Not reported
Study type	Randomised controlled trial (RCT)
Study location	Rawalpindi, Pakistan
Study setting	Department of Medicine, District Head Quarter Hospital
Study dates	September 1st 2016 to February 28th 2017

Sources of funding	Not reported
Inclusion criteria	Oesophageal varices
Exclusion criteria	• Allergy to carvedilol • Existing use of beta blockers • Obstructive airways disease • History of sclerotherapy, EVBL or portosystemic shunt • History of variceal bleeding
Intervention(s)	Carvedilol group were started on dose of once daily 6.25mg initially for 1 week and subsequently titrated to twice daily 6.25mg
Comparator	EBL group, Saeed Six Shooter Multi-Band Ligator connected to a video endoscope (Olympus, Tokyo, Japan) was used and the procedure was done every 3 weeks until achievement of variceal obliteration.
Outcome measures	Bleeding
Number of participants	254
Duration of follow-up	Patients in both groups were followed up for up to duration of three months or first variceal bleed, whichever was earlier.
Loss to follow-up	0
Methods of analysis	Data were analysed using SPSS version 20. Effect modifiers and confounders such as age, gender, duration of disease were controlled through stratification and Chi-Square test applied by taking p-value ≤ 0.05 significant.
Additional comments	Rationale and further details regarding methodology and analysis were limited.

Study arms

- Carvedilol (N = 127)
- Endoscopic band ligation (N = 127)

Characteristics

Arm-level characteristics

Characteristic	Carvedilol (N = 127)	Endoscopic band ligation (N = 127)
% Female (%)	n = 35 % = 27.5	n = 31 % = 24.4
Age		
18 - 40 years	n = 9 % = 7	n = 9 % = 7

Characteristic	Carvedilol (N = 127)	Endoscopic band ligation (N = 127)
40 - 75 years	n = 118 % = 92.9	n = 118 % = 92.9

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(The study does not appear to reference blinding protocol which is a source of potential bias. The study lacked information with which to confirm methodological approaches for example the impact of randomisation of allocation to trial arms or ITT to account for allocation to interventions both potential sources of bias. The briefness of the narrative made it difficult to discern the rationale for approaches undertaken.)*
Overall bias and Directness	Overall Directness	Partially applicable *(The inclusion criteria states varices as an inclusion criteria but it's unclear what size or grade these were. The inclusion criteria for this review is specific regarding varices.)*

Khan, 2017

Bibliographic Reference	Khan, M.S.; Majeed, A.; Ghauri, F.; Asghar, U.; Waheed, I.; Comparison of carvedilol and esophageal variceal band ligation for prevention of variceal bleed among cirrhotic patients; Pakistan Journal of Medical and Health Sciences; 2017; vol. 11 (no. 3); 1046-1048

Study details

Study type	Randomised controlled trial (RCT)
Study location	Pakistan
Study setting	Department of Medicine, Mayo Hospital, Lahore
Study dates	Not reported. Sample collected over 6 months.
Sources of funding	Not reported
Inclusion criteria	• Diagnosis of cirrhosis • Aged 30 to 80 years • Increased bilirubin (at least 30 mmol/L) • Enlarged or shrunken liver on USG • Ascites and oedema with oesophageal varices on endoscopy (grade I & II)
Exclusion criteria	• History of gastrointestinal bleeding • Pregnant, lactating, or of childbearing age without use of contraception • Allergy to carvedilol

	• Existing use of beta blockers • Serious systemic illness (cardiorespiratory, sepsis) • Mean arterial pressure <55 mm Hg or pulse <50 beats per minute at baseline • Portal vein thrombosis • Severe comorbidity substantially reducing life expectancy (advanced cancer including hepatocellular carcinoma, renal failure, advanced HIV infection) • Diabetes mellitus • SBR>200mg/dl
Intervention(s)	Carvedilol 12.5mg daily
Comparator	EVBL was performed using a multibander device. All EVBL was done by a single consultant gastroenterologist. Then patients were shifted to the ward after EVBL by researcher.
Outcome measures	Bleeding
Number of participants	250
Duration of follow-up	6-months
Methods of analysis	SPSS version 21.0 was used to analyses the data. Chi-squared test was applied to compare VB in both groups. P-value<0.05 was taken as significant
Additional comments	This study does not provide enough detail regarding methodological process and the rationale underpinning its approach.

Study arms

- Carvedilol (N = 125)
- Oesophageal variceal band ligation (N = 125)

Characteristics

Arm-level characteristics

Characteristic	Carvedilol (N = 125)	Oesophageal variceal band ligation (N = 125)
% Female	38.4 (n = 48)	44 (n = 55)
Mean age (SD)	52.06 (14.71)	54.07 (14.27)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(The study does not refer to blinding protocol and the primary investigator appears to have been the individual who looked after participants post EVL. There was a lack of information for a number of the RoB criteria which raised some concerns. There is no reference to analysis to assess the impact of randomisation and differences in participant characteristics across trial arms.)*
Overall bias and Directness	Overall Directness	Partially applicable *(It's unclear from the study if participants had a previous bleed. This is not outlined as an exclusion criteria.)*

Lay, 2006

Bibliographic Reference	Lay, Chii-Shyan; Tsai, Yang-Te; Lee, Fa-Yauh; Lai, Yi-Liang; Yu, Cheng-Ju; Chen, Chih-Bin; Peng, Cheng-Yuan; Endoscopic variceal ligation versus propranolol in prophylaxis of first variceal bleeding in patients with cirrhosis.; Journal of gastroenterology and hepatology; 2006; vol. 21 (no. 2); 413-9

Study details

Trial registration number and/or trial name	Not reported
Study type	Randomised controlled trial (RCT)
Study location	Taiwan
Study setting	Hospital
Study dates	January 1998 and December 2002
Inclusion criteria	• No history of bleeding • Diagnosis of cirrhosis • High risk varices (medium-sized with red colour) - As defined by the Japanese Research Society for Portal Hypertension. • No other disease (e.g. cancer) reducing the life expectancy
Intervention(s)	Endoscopic variceal ligation technique: Endoscopic ligating device was adapted. A 25-cm overtube was backloaded over the shaft of the endoscope. Ligation was performed by two experienced 'endoscopists'. Ligation was performed at 1–5 cm above the gastroesophageal junction. Each varix was ligated with one to three rubber bands. After completion of ligation, water instillation and suction were applied above the ligation sites to check bleeding. During elective sessions, individual ligation sites were

	gradually reduced until the varices were too small to ligate. The total did not exceed 10 rubber bands per treatment session
Comparator	Propranolol 40 mg twice daily. Dosage was increased by 10 mg twice daily either until a reduction of the resting heart rate of 20% compared to the pre-treatment heart rate was achieved, or up to the maximal dose without side-effects. In case of side-effects already induced by the initial daily dose of 80 mg, propranolol dosage was reduced by 10 mg twice daily, and the maximum tolerated dosage was given
Outcome measures	• Bleeding • Death from oesophageal variceal bleeding • Death
Number of participants	100
Duration of follow-up	24 months
Loss to follow-up	Unclear. The study outlines that n=2 patients in the EVL arm and n=3 patients in the propranolol arm were lost to follow-up. The study also outlines that n=10 in the propranolol arm had to withdraw from the study due to side-effects (symptomatic hypotension, n = 8; dizziness, n = 2). It is unclear how this is accounted for in the analysis.
Methods of analysis	The variables of interest were compared by either the $\chi 2$ test or Student's t-test for independent samples, with values expressed as means ± SD.
Additional comments	28% (14/50) in the EVL group and 24% (12/50) in the propranolol group of patients died up to 2 years after inclusion. It is unclear from the study how these individuals are accounted for in the analysis.

Study arms

- EVL (N = 50)
- Propranolol (N = 50)

Characteristics
Arm-level characteristics

Characteristic	EVL (N = 50)	Propranolol (N = 50)
% Female	24 (n = 12)	20 (n=10)
Mean age (SD)	56 (10)	55 (11)
Child-Pugh class		
Class A	n = 22 % = 44	n = 23 % = 46
Class B	n = 21 % = 42	n = 18 % = 36

Characteristic	EVL (N = 50)	Propranolol (N = 50)
Class C	n = 7 % = 14	n = 9 % = 18
Ascites present (%)	n = 8 % = 16	n = 9 % = 18

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(No blinding. Some concerns due to lack of consideration of participant withdrawals from study and mortality in the analysis and conclusion sections. It is unclear in the paper how the participant withdrawals were considered.)*
Overall bias and Directness	Overall Directness	Directly applicable

Lui, 2002

Bibliographic Reference	Lui, Hock F; Stanley, Adrian J; Forrest, Ewan H; Jalan, Rajiv; Hislop, W Stuart; Mills, Peter R; Finlayson, Niall D C; Macgilchrist, Alastair J; Hayes, Peter C; Primary prophylaxis of variceal hemorrhage: a randomized controlled trial comparing band ligation, propranolol, and isosorbide mononitrate.; Gastroenterology; 2002; vol. 123 (no. 3); 735-44

Study details

Study type	Randomised controlled trial (RCT) This was a 3-armed trial but one of the treatments is outside the scope of this guideline.
Study location	2 centres in Scotland - Royal Infirmary of Edinburgh and Royal Alexandra Hospital, Paisley.
Study setting	Hospital
Study dates	The first patient was randomised on March 1, 1993, and the last patient was randomised on February 28, 1999
Sources of funding	Not reported
Inclusion criteria	• Diagnosis of cirrhosis • Grade II and III varices
Exclusion criteria	• Non-cirrhotic cause of portal hypertension • <18 or >75 years of age • Serious systemic illness (cardiorespiratory, sepsis)

	• Mean arterial pressure <55 mm Hg or pulse <50 beats per minute at baseline • Unable to give informed consent (e.g. learning disability, psychiatric illness) • Contraindicated to beta-blockers • Currently using vasoactive agents • Systolic blood pressure <100 mm Hg or diastolic blood pressure <50 mm Hg before commencing medication
Intervention(s)	Variceal Band Ligation: eradication programme of 2 weekly endoscopies and band ligations until eradication of varices was achieved. Each session was performed on an in-patient basis and conducted by an endoscopist experienced in VBL. Patients were sedated by using Midazolam but concurrent pharyngeal anaesthesia was not used. One band was applied to each column of varices in the distal 5 cm of the oesophagus. Initially the single band device (Bard Interventional Products, Tewksbury, MA) was used, with or without the aid of the overtube. The 2-week interval was set to allow complete healing of banding ulcers. Acid suppression therapy was not routinely used. Surveillance endoscopy was performed at the 1st, 4th, and 11th month after eradication followed by annual surveillance endoscopy. On the diagnosis of variceal recurrence to grade II or more, the patient was re-entered into the variceal banding programme.
Comparator	Propranolol: Incremental dosing to achieve the target dose of 160 mg/day starting at a dose of 40 mg twice daily and increased to 80 mg twice daily after 3 days if the medication was well tolerated, the systolic blood pressure was >100 mm Hg, and the pulse rate was >50/min. On the occurrence of intolerable side effects, systolic blood pressure <100 mm Hg or pulse rate <50 mm Hg, the dose of medication was decreased step wise and eventually stopped if these adverse events persisted. Reintroduction of the medication was attempted if cessation of the medication did not result in improvement of the reported side effect.
Outcome measures	• Death from oesophageal variceal bleeding • Variceal haemorrhage • Death
Number of participants	110
Duration of follow-up	Follow-up at 3 month intervals until either primary or secondary end points or until June 1st 1999 (date of first randomisation was March 1st 1993).
Loss to follow-up	EVL: 2 patients lost to follow-up Propranolol: 5 patients lost to follow-up
Methods of analysis	Outcomes were analysed on the intention-to-treat principle and a further analysis was performed on the as-treated basis. Results were expressed as mean +/- SD unless otherwise stated. Comparisons of baseline characteristics among the 3 groups were performed by using analysis of variance for parametric variables, the Kruskal–Wallis test for nonparametric variables, and the Chi-2 test for dichotomous variables. Variceal bleeding

	and survival estimates were described by the Kaplan–Meier curves. Univariate analyses of baseline variables for bleeding and mortality were performed by using the log rank test. When continuous variables were encountered (e.g., albumin), they would be categorized into 2 groups separated at the mean (e.g., albumin >35 mmol/L and >36 mmol/L) to facilitate log rank testing. Variables that were statistically significant on univariate analyses were then included in the Cox proportional hazard regression model for multivariate analysis to identify independent prognostic factors. The level of statistical significance was taken at P<0.05.
Additional comments	This was a three-armed trial that included a treatment outside of the review protocol. Only the relevant 2 arms were extracted.

Study arms

- Variceal band ligation - VBL (N = 44)
- Propranolol (N = 66)

Characteristics
Arm-level characteristics

Characteristic	Variceal band ligation - VBL (N = 44)	Propranolol (N = 66)
% Female (%)	38.6 (n = 17)	46.9 (n = 31)
Mean age (SD)	53.6 (10.2)	55.2 (10.5)
Cause of cirrhosis		
- **Alcohol-induced**	n = 31 % = 70.5	n = 41 % = 62.1
- **Non–alcohol-induced**	n = 13 % = 29.5	n = 25 % = 37.9
Child-Pugh class		
Class A	n = 13 % = 30.8	n = 18 % = 26.7
Class B	n = 16 % = 35.9	n = 25 % = 38.3
Class C	n = 15 % = 33.3	n = 23 % = 35
Ascites (n)	20	26
Oesophageal varices		

Characteristic	Variceal band ligation - VBL (N = 44)	Propranolol (N = 66)
Grade II	n = 40 % = 90.9	n = 54 % = 81.8
Grade III	n = 4 % = 9.1	n = 12 % = 18.2
Red markings	n = 0 % = 0	n = 4 % = 6.4

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(Study was randomised using envelopes kept in a central coordinating centre and managed by a trial coordinator. The process of randomisation and its impact on participant allocation was assessed via analysis of variance for parametric variables, the Kruskal–Wallis test for nonparametric variables, and the Chi-2 test for dichotomous variables with deviations from allocated interventions not identified. There was no evidence of investigator blinding which potentially introduces bias. Patient outcomes considered with dropouts accounted for via ITT. Outcomes were measured via objective measures.)*
Overall bias and Directness	Overall Directness	Directly applicable

Norberto, 2007

Bibliographic Reference	Norberto, Lorenzo; Polese, Lino; Cillo, Umberto; Grigoletto, Francesco; Burroughs, Andrew K; Neri, Daniele; Zanus, Giacomo; Boccagni, Patrizia; Burra, Patrizia; D'Amico, Davide F; A randomized study comparing ligation with propranolol for primary prophylaxis of variceal bleeding in candidates for liver transplantation.; Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society; 2007; vol. 13 (no. 9); 1272-8

Study details

Study type	Randomised controlled trial (RCT)
Study location	Italy
Study setting	Department of Surgical and Gastroenterological Sciences of Padova University (University hospital)
Study dates	September 2001 and December 2005
Inclusion criteria	• No history of bleeding • Diagnosis of cirrhosis

	• Child-Turcotte-Pugh >/= B7 • Studied for liver transplantation • Age between 18 and 65 years • Informed consent • Oesophageal varices F3 or F2 blue with red signs
Exclusion criteria	• Pregnant, lactating, or of childbearing age without use of contraception • Serious systemic illness (cardiorespiratory, sepsis) • Severe heart, respiratory, or renal failure • Portal vein thrombosis • Contraindicated to beta-blockers • Severe chronic obstructive pulmonary disease, severe asthma, severe insulin-dependent diabetes mellitus, bradyarrhythmia • Oesophageal varices less than F3 or F2 blue with red signs • Presence of gastric varices • Previous endoscopic, radiological, or surgical treatment of oesophageal varices • Hepatocarcinoma • Treatment with nitrates, calcium antagonists, or other antiarrhythmic drugs, including betablockers, that cannot be suspended • Neoplasias • An uncooperative attitude or the suspicion that the candidate could or would not return for routine follow-up examinations
Intervention(s)	EVL: diagnostic esophagogastroduodenoscopy without the ligation device was performed before banding to confirm the presence of high-risk oesophageal varices and the absence of gastric varices. Banding placement was then performed using a multiband ligator with 6 or 7 bands (Six-shooter). The endoscopist entered the oesophagus only once and banded the varices starting from the cardias and progressing proximally every 1 cm, in an upward spiral fashion. Patients were treated during a 1-day hospital stay, followed by a liquid diet for 24-hours and semiliquid diet for 1 week. Subsequent sessions were performed every 2 weeks until the varices were completely eradicated, avoiding placing the bands near to the scars left by the previous treatment. During the period of eradication patients were also prescribed proton-pump inhibitors. Recurrent varices detected during the follow-up esophagogastroduodenoscopy were banded again using the same method as above
Comparator	Propranolol: started with a low dosage of 10 mg/twice a day and increasing by 20 mg/day until a 25% reduction of the baseline heart rate was obtained. The amount of 160 mg twice daily was considered the maximal dosage. Study investigator decided if the propranolol dosage needed to be modified based on systolic and diastolic blood pressure and pulse rate after the first week. Treatment was interrupted when the systolic blood pressure fell to below 90 mmHg, or the heart rate was under 50 beats/minute, or when patients developed severe disabling side effects
Outcome measures	• Bleeding (confirmed by an esophagogastroduodenoscopy) • Death from oesophageal variceal bleeding

	• Death
Number of participants	62
Duration of follow-up	After starting treatment all patients had an esophagogastroduodenoscopy and a clinical examination every 6 months and were provided with the emergency numbers of investigators so that they could report all new events about treatment complications or bleeding. Mean (SD) follow-up period across the sample was 14.6 months (+/- 10.3 months) with mean follow-up for EVL 16.8 months (+/- 11 months) and for Propranolol 12.29 months (+/- 9 months).
Loss to follow-up	EVL: 2 patients; Propranolol: 2 patients
Methods of analysis	For continuous variables, comparison of the baseline characteristics of the 2 groups of patients was made using a t-test or the Mann Whitney test if a Gaussian model was not appropriate. When the variables were categorical, the chi-squared or the Fisher's exact test. Was used Discrete time-to-event outcomes (time to haemorrhage and death) were compared in the 2 groups by the Kaplan Meier method and significance testing by log-rank test. Statistical difference was set at P<0.05. Statistical calculations were made by using SAS software for Windows (SAS Institute, Cary, NC).
Additional comments	

Study arms

- Endoscopic variceal ligation (EVL) (N = 31)
- Propranolol (N = 31)

Characteristics
Arm-level characteristics

Characteristic	Endoscopic variceal ligation (EVL) (N = 31)	Propranolol (N = 31)
Mean age (SD)	52.6 (7.1)	52.5 (6.1)
Aetiology		
Hepatitis C virus (n)	17	15
Others Not defined (n)	14	16
Varices (Total numbers)		
F2	27	26

Characteristic	Endoscopic variceal ligation (EVL) (N = 31)	Propranolol (N = 31)
F3	4	5
Mean length varices (cm) Mean (SD)	12.8 (3.42)	13.2 (3.63)
Child-Turcotte-Pugh score Mean (SD)	8.51 (1.95)	8.29 (1.44)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(The study outlines methods for randomisation and assessment of baseline characteristics in each arm of the study post randomisation. There was no blinding protocol which is a potential source of bias. There was no indication of deviations from allocated interventions. There were dropouts from the trial but these were small (n=4) and balanced across study arms and were not seen to introduce bias. The trial was ended early due to recorded deaths. ITT was undertaken. No indication that outcomes reported were selected.)*
Overall bias and Directness	Overall Directness	Directly applicable

Perez-Ayuso, 2010

Bibliographic Reference	Perez-Ayuso, Rosa Maria; Valderrama, Sebastian; Espinoza, Manuel; Rollan, Antonio; Sanchez, Rene; Otarola, Francisco; Medina, Brenda; Riquelme, Arnoldo; Endoscopic band ligation versus propranolol for the primary prophylaxis of variceal bleeding in cirrhotic patients with high risk esophageal varices.; Annals of hepatology; 2010; vol. 9 (no. 1); 15-22

Study details

Study type	Randomised controlled trial (RCT)
Study location	Chile
Study setting	2 tertiary care referral medical centres
Study dates	April 1998 to June 2007. Patients were followed up for a median of 55 months +/- 36.5 months. The mean time period between randomisation and the end of the study was 67 +/- 34.7 months.

Inclusion criteria	• No history of bleeding • Diagnosis of cirrhosis • High risk varices (medium-sized with red colour) • No current beta-blocker therapy (unless it can be discontinued or replaced with another medication)
Exclusion criteria	• Contraindicated to beta-blockers • For example chronic obstructive pulmonary disease, type 1 diabetes mellitus, congestive heart failure, asthma, complete atrioventricular block • Previous endoscopic, radiological, or surgical treatment of oesophageal varices • An uncooperative attitude or the suspicion that the candidate could or would not return for routine follow-up examinations • Large gastric varices • Hepatocellular carcinoma • <18 or >70 years of age • Portal thrombosis • Trans-jugular intrahepatic portosystemic shunt • Surgical shunt • Renal failure (creatinine >2.0 mg/dL)
Intervention(s)	Endoscopic band ligation: Variceal ligations were performed at 3 weeks intervals until eradication (defined as the absence of ligable oesophageal varices). During each session, up to 6 bands were placed beginning in the distal oesophagus using a multiband ligation device (Sixshooter or Speedband). Overtube or other band ligation devices were not used. After variceal eradication, endoscopic control was scheduled every 3 months. Religation was performed when at least 1 varix with a diameter greater than 5 mm reoccurred and repeated every 3-4 weeks until reobliteration.
Comparator	Propranolol. Started at a dose of 20 mg twice daily. Dosage was increased every 3 days until a reduction of 25% of the pre-treatment resting heart rate was achieved, the heart rate was 55 beats per minute or systolic blood pressure was <90 mm Hg. The maximum dose accepted was 320 mg/day. Afterwards, the dosage was adjusted in each clinical control according to the resting heart rate.
Outcome measures	• Bleeding • Death • Bleeding related mortality (within 6 weeks of index bleed) • Adverse events
Number of participants	75
Duration of follow-up	Patients were followed for a median of 55 ± 36.5 months (range 0.7 to 119 months).
Loss to follow-up	11 patients. 7 patients propranolol (2 patients did not tolerate propranolol) and 4 EVL (no reasons outlined)

Methods of analysis	Data were analysed on an intention-to-treat basis and were expressed as mean (±SD). Differences between groups were analysed by chi-square test, Fisher exact test, and the unpaired Student t test. The actuarial probabilities of bleeding and death were calculated by using the Kaplan-Meier method, and comparisons were made using the long-rank test. Bleeding episodes prevalence was further compared by chi-square test. A two-tailed p-value of less than 0.05 was considered of statistical significance. Data analysis was performed using STATA 10.
Additional comments	

Study arms

- Endoscopic band ligation (N = 39)
- Propranolol (N = 36)

Characteristics
Arm-level characteristics

Characteristic	Endoscopic band ligation (N = 39)	Propranolol (N = 36)
% Female	n = 20 % = 52	n = 18 % = 50
Mean age (SD)	60 (7)	58 (9)
Aetiology of cirrhosis		
- **Alcoholic**	n = 8 % = 20.5	n = 10 % = 27.8
- **Hepatitis C virus**	n = 5 % = 12.8	n = 4 % = 11.1
- **Others - Not specified**	n = 26 % = 66.7	n = 22 % = 61.1
Child-Pugh class		
Class A	n = 23 % = 59	n = 17 % = 47.2
Class B	n = 14 % = 35.9	n = 15 % = 41.7
Class C	n = 2 % = 5.1	n = 4 % = 11.1
Model for End-stage liver disease (MELD score) Mean (SD)	10.9 (3.6)	11.5 (3.2)

Characteristic	Endoscopic band ligation (N = 39)	Propranolol (N = 36)
Ascites (%)	n = 11 % = 28.2	n = 14 % = 38.9

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(There were deviations from intended intervention post randomisation with 2 patients in the propranolol arm suffering adverse events and being crossed over to the EVL arm of the study. This deviation does not appear to have been balanced across the study (or is not documented) and the analysis of findings does not appear to account for this crossover. There was approximately 15% loss to follow-up with no reference to an analysis to consider the impact of a lack of adherence to the interventions under study. These factors introduce bias that has not been accounted for in the analysis or discussion.)*
Overall bias and Directness	Overall Directness	Directly applicable

Psilopoulos, 2005

Bibliographic Reference	Psilopoulos, Dimitrios; Galanis, Petros; Goulas, Spyros; Papanikolaou, Ioannis S; Elefsiniotis, Ioannis; Liatsos, Christos; Sparos, Loukas; Mavrogiannis, Christos; Endoscopic variceal ligation vs. propranolol for prevention of first variceal bleeding: a randomized controlled trial.; European journal of gastroenterology & hepatology; 2005; vol. 17 (no. 10); 1111-7

Study details

Study type	Randomised controlled trial (RCT)
Study location	Greece
Study setting	Hospital
Study dates	November 1999 to July 2004
Sources of funding	The study was partially funded by a grant of the Hellenic Society of Gastroenterology.
Inclusion criteria	• Portal hypertension due to cirrhosis • No history of bleeding • No current beta-blocker therapy (unless it can be discontinued or replaced with another medication) • Grade II and III varices • F2, F3 according to Beppu classification

	• Informed consent • Oesophageal varices F3 or F2 blue with red signs
Exclusion criteria	• History of sclerotherapy, EVBL or portosystemic shunt • Surgical portacaval shunt • Contraindicated to beta-blockers • Presence of gastric varices • Severe comorbidity substantially reducing life expectancy (advanced cancer including hepatocellular carcinoma, renal failure, advanced HIV infection) • Heart failure, obstructive airway disease, hypotension (systolic pressure less than 90 mmHg), bradycardia (pulse rate <60/min), diabetes mellitus, severe peripheral vascular disease. • <20 and >70 years of age • Ectopic varices • Refractory ascites, hepatic encephalopathy or marked jaundice
Intervention(s)	EVL ligation at the first endoscopy session. Midazolam 1–2.5mg and pethidine 25 mg were given intravenously as premedication. EVL was carried out using a multiband ligation device (Speedband or Six-shooter). The varices were ligated starting at or just above the gastroesophageal junction and then up to 5 cm proximally. One to two bands were applied to each varix, depending on their size, and up to six bands per session. Ligation procedures were performed by three experienced endoscopists. Sessions were repeated every 2–3 weeks until variceal eradication was achieved or until residual varices were too small to be ligated. All ligated patients were continuously treated with proton pump inhibitors, starting immediately after the first session, until variceal eradication.
Comparator	Propranolol treatment: 40 mg PPL orally the dosage was adjusted to achieve a 25% maximal reduction of the pre-treatment pulse rate. In patients presenting side effects with a 25% reduction of the pulse rate, the PPL dosage was reduced to achieve a 20% reduction of the pre-treatment pulse rate. On the occurrence of serious side effects, such as pulse rate <55/min or systolic blood pressure <90mmHg, treatment was stopped.
Outcome measures	• Death from oesophageal variceal bleeding • Variceal haemorrhage • Death
Number of participants	60
Duration of follow-up	1 year after recruitment of the last patient (June 2003) or whenever one of the end points of the study was reached. The mean follow-up for patients in the EVL arm was 27.2 ±15.1 months (range, 0.5–52 months) and the mean follow-up for patients in the PPL arm was 27.9 ±14.4 months (range, 2–49 months).
Loss to follow-up	0

Methods of analysis	Data were analysed according to an intention-to-treat strategy. Quantitative data were expressed as means (±SD), and an appropriate non-parametric test was used to compare values in the two groups. Qualitative data were analysed by the chi-square test or Fisher's exact test. Comparisons between the two groups were made with the use of the incidence rate difference of first variceal bleeding and the mortality rate difference. The actuarial probabilities of variceal bleeding and death from any cause were calculated for all patients by the Kaplan–Meier method and comparisons were made with the use of the log-rank test. In the analysis of variceal bleeding, patients were censored at death or at the end of follow-up. In the analysis of survival, patients were censored at variceal bleeding or at the end of follow-up. Logistic regression was carried out to assess the effect of confounding variables. A two-tailed P value less than 0.05 was considered to demonstrate statistical significance.
Additional comments	

Study arms

- Endoscopic variceal ligation (EVL) (N = 30)
- Propranolol (N = 30)

Characteristics
Arm-level characteristics

Characteristic	Endoscopic variceal ligation (EVL) (N = 30)	Propranolol (N = 30)
% Female	n = 8 % = 26.7	n = 10 % = 33.3
Mean age (SD)	61.5 (8.25)	59.3 (9.48)
Aetiology of cirrhosis		
Hepatitis B virus	n = 12 % = 40	n = 12 % = 40
Hepatitis C virus	n = 4 % = 13.3	n = 5 % = 16.6
Hepatitis B virus + hepatitis C virus	n = 1 % = 3.3	n = 2 % = 3.3
Cryptogenic	n = 3 % = 10	n = 2 % = 6.7
Alcohol	n = 8 % = 26.7	n = 7 % = 23.3

Characteristic	Endoscopic variceal ligation (EVL) (N = 30)	Propranolol (N = 30)
Primary biliary cirrhosis	n = 1 % = 3.3	n = 1 % = 3.3
Autoimmune	n = 1 % = 3.3	n = 1 % = 3.3
Child–Pugh classification		
Class A	n = 13 % = 43.3	n = 15 % = 50
Class B	n = 12 % = 40	n = 12 % = 40
Class C	n = 5 % = 16.7	n = 3 % = 10
Grade of varices		
Grade II	n = 23 % = 76.7	n = 23 % = 76.7
Grade III	n = 7 % = 23.3	n = 7 % = 23.3

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(There was no evidence of investigator blinding which is a potential source of bias. During the study 2 participants in the EVL arm developed variceal bleeding post first and second EVL session and were treated with endoscopic sclerotherapy which was outlined as an exclusion criteria. In the PPL arm treatment was discontinued for 4 participants. It is unclear how the analysis accounted for these deviations from the study protocol. 10% of those randomised did not adhere to their allocated intervention due to adverse outcomes and it's unclear how the analysis accounted for this outside of the ITT undertaken.)*
Overall bias and Directness	Overall Directness	Partially applicable *(The study includes participants who received an intervention (endoscopic sclerotherapy) as a consequence of adverse effects from the allocated intervention, that is an exclude in the NICE review protocol.)*

Sarin, 1999

Bibliographic Reference	Sarin, S K; Lamba, G S; Kumar, M; Misra, A; Murthy, N S; Comparison of endoscopic ligation and propranolol for the primary prevention of variceal bleeding.; The New England journal of medicine; 1999; vol. 340 (no. 13); 988-93

Study details

Trial registration number and/or trial name	Not reported
Study type	Randomised controlled trial (RCT)
Study location	New Delhi, India
Study setting	Department of Gastroenterology, G.B. Pant Hospital
Study dates	September 1994 to July 1997
Sources of funding	Not reported
Inclusion criteria	• Large oesophageal varices • Grade III to IV oesophageal varices
Exclusion criteria	• An uncooperative attitude or the suspicion that the candidate could or would not return for routine follow-up examinations • Medical contraindications or intolerance to beta blockers • Hepatic or other malignancy which could impair longevity of life
Intervention(s)	Patients assigned to the ligation group underwent ligation at the first endoscopy session or within the next 24 hours. After local application of lidocaine, an endoscope (model GIF X-Q 20 or CV-1, Olympus Optical, Tokyo) was introduced, and the ligation was carried out by placing a single rubber band (Bard Interventional Products, Tewksbury, Mass.) over a varix each time the endoscope was inserted. As many bands as possible (average, three to nine bands, with fewer in later sessions) were placed in the lower 5 to 7 cm of all variceal columns (vertical veins). Each residual varix was ligated distally and proximally to accelerate obliteration. Endoscopic ligation was performed every week until the varices were obliterated or were reduced to a size of grade 1. In the latter instance, it was not possible to apply any more bands because of the small size of the varices.
Comparator	Patients assigned to receive propranolol underwent base-line electrocardiography and cardiac evaluation after 15 minutes of rest. Treatment then began with the oral administration of 40 mg of propranolol. The heart rate and blood pressure were checked after 12 and 24 hours. Instead of adjusting the dose by monitoring the hepatic venous pressure gradient, the dose was increased in increments of 20 to 40 mg per day until a 25 percent decrease in the base-line heart rate was achieved. Treatment

	was stopped if any of the following occurred: systolic blood pressure less than 80 mm Hg, heart rate less than 55 beats per minute, or other serious side effects.
Outcome measures	• Death from oesophageal variceal bleeding • Variceal haemorrhage • Death • Adverse events • Hospital admissions
Number of participants	90
Duration of follow-up	EVL - 13 months (SD: 10) Propranolol - 14 months (SD: 9)
Loss to follow-up	One patient assigned to the ligation group failed to appear the next day and hence was excluded
Methods of analysis	Data were analysed according to an intention-to-treat strategy. Quantitative data were expressed as means (±SD) or as medians. Student's two-tailed t-test or an appropriate nonparametric test was used to compare values in the two groups. Qualitative data were analysed by the chi-square test or Fisher's exact test.
Additional comments	

Study arms

- EVL (N = 46)
- NSBB (Propranolol) (N = 44)

Characteristics
Arm-level characteristics

Characteristic	EVL (N = 46)	NSBB (Propranolol) (N = 44)
Age Mean (SD)	44 (12)	39 (17)
% Female	n = 12 % = 27	n = 12 % = 27
Cause of varices		
- **Cirrhosis**	n = 41 % = 91	n = 41 % = 93
Alcoholic	n = 11	n = 9
Hepatitis B	n =16	n =15
Hepatitis C	n = 5	n = 2

Characteristic	EVL (N = 46)	NSBB (Propranolol) (N = 44)
Hepatitis B and C	n = 0	n = 1
Autoimmune	n = 2	n = 2
Cryptogenic	n = 7	n = 12
- **Extrahepatic portal-vein obstruction**	n = 3 % = 7	n = 3 % = 7
- **Noncirrhotic portal fibrosis**	n = 1 % = 2	n = 0 % = 0
Grade of varices		
Grade 3	n = 32 % = 71	n = 34 % = 77
Grade 4	n = 13 % = 29	n = 10 % = 23
Child classification		
Class A	n = 7 % = 16	n = 9 % = 20
Class B	n = 23 % = 51	n = 22 % = 50
Class C	n = 15 % = 33	n = 13 % = 30
Ascites	n = 31 % = 69	n = 27 % = 61
Encephalopathy	n = 7 % = 16	n = 6 % = 14

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(Some concerns due to the inability to blind participants, clinicians and relatives and carers to allocation.)*
Overall bias and Directness	Overall Directness	Directly applicable *(A small number of patients (7 out of 90) did not have cirrhosis and therefore not applicable to the inclusion criteria for this review. Since this was a small proportion (<10%) the results can be considered directly applicable.)*

Schepke, 2004

Bibliographic Reference	Schepke, Michael; Kleber, Gerhard; Nurnberg, Dieter; Willert, Jorg; Koch, Lydia; Veltzke-Schlieker, Wilfried; Hellerbrand, Claus; Kuth, Johannes; Schanz, Stefan; Kahl, Stefan; Fleig, Wolfgang E; Sauerbruch, Tilman; German Study Group for the Primary Prophylaxis of Variceal, Bleeding; Ligation versus propranolol for the primary prophylaxis of variceal bleeding in cirrhosis.; Hepatology (Baltimore, Md.); 2004; vol. 40 (no. 1); 65-72

Study details

Trial registration number and/or trial name	Not reported
Study type	Randomised controlled trial (RCT)
Study location	Germany
Study setting	27 hospitals
Study dates	1st October 1996 to 31st March 2003 (randomisation ceased 31st March 2001).
Sources of funding	Supported by the German Association for the Study of the Liver (GASL) and the Ernst und Berta Grimmke Stiftung, Dusseldorf, Germany.
Inclusion criteria	• Diagnosis of cirrhosis • Age >18 years • Age <75 years • Informed consent • 2 or more oesophageal varices with diameter >5mm
Exclusion criteria	• Trans-jugular intrahepatic portosystemic shunt • Previous variceal bleeding or any other reported episode of haematemesis or melena unless clearly proven to be independent from portal hypertension • Prehepatic portal hypertension • brady-cardia < 64 per minute • Systolic blood pressure <100mm Hg • Contraindications to propranolol (obstructive airway disease, congestive heart failure, severe peripheral vascular disease, diabetes mellitus type 1) • Severe comorbidity substantially reducing life expectancy (advanced cancer including hepatocellular carcinoma, renal failure, advanced HIV infection) • Listed for liver transplantation • Long-term anticoagulant treatment • Inability to give informed consent • Treatment with beta-blockers or nitrates within 30 days before randomisation

	• Assumed incompliance with the study protocol.
Intervention(s)	In the EVL arm, ligations were carried at weekly intervals under mild sedation using midazolam. Up to 10 bands were placed in each session, beginning in the distal oesophagus, using a multiband ligation device (Sixshooter; Wilson Cook Inc., Winston-Salem, NC or Speedband; Boston Scientific, Inc., Natick, MA) until eradication of varices was achieved. Re-ligation was carried out when at least 1 varix with a diameter greater than 5 mm reoccurred.
Comparator	In the propranolol arm, treatment was started at a dosage of 40mg twice daily. This dosage was increased by 10 mg twice daily either until a reduction in the resting heart rate of 20% compared to the pre-treatment heart rate, was achieved, or up to the maximum dose without side effects. In case of side effects already induced by the initial daily dose of 80 mg, dosage was reduced by 10 mg twice daily, and the maximum tolerated dosage was given.
Outcome measures	• Death • Bleeding related mortality (within 6 weeks of index bleed) • Adverse events
Number of participants	152 participants were randomised to EVL (n=75) or to receive propranolol (n=77).
Duration of follow-up	After dose-finding for propranolol or successful band ligation, clinic follow-up visits, including surveillance endoscopies, were carried out at 6-month intervals in both groups. In the EVL group, 1 additional endoscopy was carried out 3 months after randomisation. Each participant was followed until death or for at least 2 years (the minimum follow-up period defined by the study protocol. Patients were followed for 34.4 +/- 18.9 months (range, 0.1-73.2). The mean time period between randomisation and termination of the study was 51.8+/-15.0 months.
Loss to follow-up	No patient was lost to follow-up during the first 2 years after randomisation with the exception of 5 patients who were censored due to liver transplant. During the entire follow-up period, a total of 10 patients were censored due to liver transplantation (EVL n=6, Propranolol n =4). 25% (n=19) patients in the propranolol arm withdrew from treatment, 12 due to side effects that were unresolved after a reduction in dose and a further 7 due to incompliance despite having no side effects.
Methods of analysis	ITT analyses were carried out. Differences between groups were analysed by Chi-square test, Fisher exact test, and the unpaired Student t test. The actuarial probabilities of bleeding or death were calculated by the Kaplan-Meier method and comparisons were made using the log-rank test. Observed bleeding episodes within 2 years were further compared by chi-square test. A two-tailed P value of less than .05 was considered to demonstrate statistical significance.
Additional comments	Authors report that the study committee agreed the trial should be designed to show a 10% difference in bleeding rates in favour of EVL. Due to uncertainty at the time of the effect of EVL on the primary prevention of variceal bleeding, the protocol included an interim analysis carried out 6

	months after the inclusion of 100 patients. It had been calculated that 200 participants in each arm would be required. However, at the interim analysis, virtually no difference was seen between the 2 arms and it was clear that 200 participants in each arm would be insufficient to detect a difference in bleeding rates between the two groups. After seeking external advice from 2 advisories, the committee decided to cease randomisation at the end of March 2001.

Study arms

- EVL (N = 75)
- Propranolol (N = 77)

Characteristics

Arm-level characteristics

Characteristic	EVL (N = 75)	Propranolol (N = 77)
Age Mean (SD)	54.3 (10.5)	57.3 (9.7)
% Female	n = 25 % = 33.3	n = 23 % = 29.9
Aetiology of cirrhosis		
- **Alcoholic**	n = 40 % = 53.3	n = 38 % = 49.4
- **Viral**	n = 22 % = 29.3	n = 25 % = 32.5
- **Other**	n = 13 % = 17.3	n = 14 % = 18.2
Child-Pugh score Mean (SD)	7.3 (1.8)	7 (1.9)
Child-Pugh class		
Class A	n = 34 % = 45.3	n = 37 % = 48.1
Class B	n = 31 % = 41.3	n = 31 % = 40.3
Class C	n = 10 % = 13.3	n = 9 % = 11.7
Ascites	n = 32 % = 42.7	n = 29 % = 37.7
Endoscopic findings		

Characteristic	EVL (N = 75)	Propranolol (N = 77)
Grade II oesophageal varices	n = 32 % = 42.7	n = 35 % = 45.5
Grade III oesophageal varices	n = 43 % = 57.3	n = 42 % = 54.5
Red markings	n = 29 % = 38.7	n = 30 % = 39

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Some concerns regarding adherence to intervention. In the EVL group this relates to failure of treatment due to bleeding from ligation ulcers which occurred in 6.7% patients (n =5). The paper states this was unexpectedly serious in 3 patients and resulted in death in 2 patients and life- threatening bleeding in another. In the propranolol group, 25% (n=19) participants withdrew from the treatment, 12 due to side effects which did not resolve with dose reduction and a further 7 due to incompliance despite no side effects. In addition, the authors note that the study committee agreed the trial should be designed to show a 10% difference in bleeding rates in favour of EVL. Due to uncertainty at the time of the effect of EVL on the primary prevention of variceal bleeding, the protocol included an interim analysis carried out 6 months after the inclusion of 100 patients. It had been calculated that 200 participants in each arm would be required. However, at the interim analysis, virtually no difference was seen between the 2 arms and it was clear that 200 participants in each arm would be insufficient to detect a difference in bleeding rates between the two groups and the trial was closed early.)*
Overall bias and Directness	Overall Directness	Directly applicable *(Participants in the study meet the inclusion criteria for this review.)*

Shah, 2014

Bibliographic Reference	Shah, Hasnain Ali; Azam, Zahid; Rauf, Javeria; Abid, Shahab; Hamid, Saeed; Jafri, Wasim; Khalid, Abdullah; Ismail, Faisal Wasim; Parkash, Om; Subhan, Amna; Munir, Syed Mohammad; Carvedilol vs. esophageal variceal band ligation in the primary prophylaxis of variceal hemorrhage: a multicentre randomized controlled trial.; Journal of hepatology; 2014; vol. 60 (no. 4); 757-64

Study details

Trial registration number and/or trial name	NCT 01070641
Study type	Randomised controlled trial (RCT)
Study location	Pakistan
Study setting	Three tertiary care hospitals in Karachi
Study dates	May 2007 to September 2011
Sources of funding	Study funded by industry (Ferozsons Laboratories (BF Biosciences), Pakistan (drug costs, clinical research associate honorarium and pharmacy charges – no role in study design, collection or analysis of data).
Inclusion criteria	• No history of bleeding • Grade III to IV oesophageal varices • Diagnosis of cirrhosis • Age >18 years • Age <75 years
Exclusion criteria	• Allergy to carvedilol • Existing use of beta blockers • Unable to give informed consent (e.g. learning disability, psychiatric illness) • Pregnant or lactating • Reactive airway disease • Hepatic or other malignancy which could impair longevity of life • Severe systemic illness which could impair ability to participate • Gastric varices alone
Intervention(s)	Participants randomised to the Carvedilol arm were given Carvedilol (Carvida, Ferozsons Laboratories, Pakistan) in an initial dose of 6.25 mg once a day which was increased to twice a day after a period of 1 week.
Comparator	Participants assigned to EVL underwent the procedure within 48 hours of randomisation. EVL was performed using Saeed Six Shooter Multiband ligator (Wilson Cook Medical, USA). Performed by gastroenterologists with at least 5 years' experience. Repeated every 3 weeks until obliteration of varices was achieved (no varices or only small varices which were flattened on air insufflations). Endoscopy was performed every 6 months and the procedure was repeated if varices recurred.
Outcome measures	• Variceal haemorrhage • Death • Bleeding related mortality (within 6 weeks of index bleed)
Number of participants	168 participants randomised to Carvedilol (n= 82) and EVL (n= 86).

Duration of follow-up	In the Carvedilol arm, participants were followed up at 2 weeks, at 6 weeks and then at 3 monthly intervals. The mean duration was 13.2 months. In the EVL arm, follow-up took place at 3 monthly intervals. The mean duration was 13.4 months.
Loss to follow-up	All participants randomised to EVL (n= 86) received the allocated intervention and none were excluded from the ITT analysis. 2 of the participants randomised to Carvedilol (n= 82) were unable to tolerate the treatment. No participants were excluded from the ITT analysis.
Methods of analysis	77 patients in total were required in each trial arm to achieve 80% power at 5% level of significance. It was assumed that carvedilol would be more effective than EVL with a bleeding rate of 5% in the carvedilol group and 20% in the EVL group at 24 months. The figure for EVL arm was derived from a published study [Sarin et al 1999]. Sample size was inflated by 10% for dropout (lost to follow up) or withdrawal of consent. No interim analysis was planned or performed. Mean ± Standard Deviation for age, Child's score and laboratory characteristics was used for the two study groups and any differences in the groups were analysed using an unpaired Student's t test. Frequencies (%) for gender, ultrasound characteristics and aetiology of cirrhosis were presented. Non-parametric data were analysed using the Chi square test. Cumulative bleeding and survival were expressed using the Kaplan-Meier method and the differences assessed using the log-rank test. Cox proportional hazard ratio was used to assess variables predicting end points. Intention to analysis was used. Variables with p <0.05 following univariate analysis were entered into multivariate analysis. SPSS (version 19, Chicago, IL) statistical package was used for analysis.
Additional comments	More patients randomised to the EVL arm had large oesophageal varices compared to the Carvedilol arm, however this difference was not statistically different.

Study arms

- Carvedilol (N = 82)
- EVL (N = 86)

Characteristics
Arm-level characteristics

Characteristic	Carvedilol (N = 82)	EVL (N = 86)
Age Mean (SD)	48.3 (11.3)	47.2 (13.2)
% Female	n = 23 % = 28	n = 23 % = 26.7
Ascites	n = 33 % = 40.7	n = 32 % = 37.6
Size of varices		

Characteristic	Carvedilol (N = 82)	EVL (N = 86)
Medium	n = 49 % = 59.8	n = 42 % = 48.8
Large	n = 33 % = 40.2	n = 44 % = 51.2
Child-Pugh score Mean (SD)	7.4 (1.6)	7.2 (1.5)
Child Pugh Class		
Class A	n = 37 % = 45.1	n = 37 % = 43
Class B	n = 35 % = 42.7	n = 37 ; % = 43
Class C	n = 10 % = 12.2	n = 12 % = 14
Aetiology of cirrhosis		
- **Viral**	n = 74 % = 90.2	n = 77 % = 89.5
- **Alcohol-related**	n = 0 % = 0	n = 3 % = 3.5
- **Other (cryptogenic and autoimmune)**	n = 8 % = 9.8	n = 6 % = 7

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(No blinding. One patient in the EVL group bled from an oesophageal ulcer caused by the banding procedure. However, this was considered treatment failure on ITT and classed as a serious adverse event and so appears to have been accounted for in the analysis of the outcomes. 2/ 82 patients in the carvedilol arm could not tolerate the treatment but were included in the ITT analyses.)*
Overall bias and Directness	Overall Directness	Directly applicable *(Patients included in the study met the inclusion criteria for this review.)*

Singh, 2012

Bibliographic Reference	Singh, B.; Saxena, P.D.; Rohtagi, V.; Kumar, V.; Comparison of endoscopic variceal ligation and propranolol for the primary prevention of variceal bleeding; Journal, Indian Academy of Clinical Medicine; 2012; vol. 13 (no. 3); 214-217

Study details

Study type	Randomised controlled trial (RCT)
Study location	India
Study setting	Not reported
Study dates	Not reported
Sources of funding	Not reported
Inclusion criteria	• No history of bleeding • Diagnosis of cirrhosis • Large Grade 3 or 4 varices (graded according to criteria published by Conn et al 1972) and independently evaluated by two endoscopists
Exclusion criteria	• History of bronchial asthma • Concomitant antiviral therapy • Concomitant hepatoma or other tumour • Severe cardiopulmonary or renal disease • Bradycardia (basal heart rate <55 beat per minute) • Heart failure • Diabetes mellitus • Peripheral vascular disease • Psychiatric disorder • Glaucoma • Prostatic hypertrophy
Intervention(s)	Patients assigned to the EVL group underwent ligation at the first endoscopy session or within the next 24 hours. An endoscope (model PENTAX EX-2000) was introduced and the ligation was carried-out by placing multiple rubber bands (PentaGun Multi Band Ligator, Hospiline Medi Devices, India). As many bands as possible (three to six bands, with fewer in later sessions) were placed in the lower 5 to 7 cm of all variceal columns (vertical veins). Each residual varix was ligated distally and proximally to accelerate obliteration. EVL was carried out every week until the varices were obliterated or were reduced to a size of grade 1, in which case it was not possible to apply any more bands because of their small size. Patients were asked to record all symptoms including chest pain, fever, and dysphagia. The presence of ulcers or strictures was noted on endoscopy. After the varices had been obliterated or reduced in size to grade 1, patients underwent endoscopy each month for the first three months and then once every three months

	until the end of follow-up. If varices recurred and became grade 2 in size or larger, ligation was repeated to obliterate them.
Comparator	Patients in the propranolol arm underwent base-line electrocardiography and cardiac evaluation after 15 minutes of rest. Treatment commenced with 40 mg of oral propranolol. Heart rate and blood pressure were checked after 12 and 24 hours. The dose was increased in increments of 20 to 40 mg per day until a 25 percent decrease in the base-line heart rate was achieved. Treatment was stopped if systolic blood pressure was less than 90 mm Hg, heart rate was less than 55 beats per minute, or if there were other serious side effects. Patients were monitored daily until beta-blockade was adequate, then monthly for the first three months and every three months thereafter. Drug compliance was ascertained by interviewing the patient and by measuring the heart rate. Patients were advised to refrain from consuming alcohol and from taking nonsteroidal anti-inflammatory drugs, histamine H2 blockers, or proton-pump inhibitors.
Outcome measures	• Death • Death due to variceal bleeding
Number of participants	38 participants were randomised to EVL (n=18) or propranolol (n=20).
Duration of follow-up	12 months
Loss to follow-up	In the propranolol group treatment was stopped due to side effects in 2 / 20 participants. An ITT analysis was carried out.
Methods of analysis	Data were analysed according to an intention-to-treat strategy. Quantitative data were expressed as means (± SD) or as medians. Student's two-tailed t-test or an appropriate nonparametric test was used to compare values in the two groups. Qualitative data were analysed by the chi-square test or Fisher's exact test. Agreement between observers with regard to the red signs on endoscopy was measured by the kappa statistic. Cox proportional-hazards regression analysis was carried-out to assess the effect of confounding variables.

Study arms

- EVL (N = 18)
- Propranolol (N = 20)

Characteristics

Arm-level characteristics

Characteristic	EVL (N = 18)	Propranolol (N = 20)
Age (years)	NR	NR

Characteristic	EVL (N = 18)	Propranolol (N = 20)
% Female	NR	NR
Aetiology of cirrhosis		
- **Alcoholic**	n = 8 % = 44.4	n = 11 % = 55
- **Hepatitis B**	n = 5 % = 27.5	n = 6 % = 30
- **Hepatitis C**	n = 2 % = 11.1	n = 2 % = 10
- **Autoimmune**	n = 1 % = 5.5	n = 0 % = 0
- **Other**	n = 2 % = 11.1	n = 1 % = 5
Ascites	n = 11 % = 61.1	n = 12 % = 60

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No information is provided on whether allocation was concealed until participants enrolled and assigned to intervention. No blinding. Few details on patient characteristics are given. There are also some concerns that not all outcomes listed as end points appear to be reported.)*
Overall bias and Directness	Overall Directness	Partially applicable *(Age of participants is not reported and some patients in the study appeared to have gastric varices possibly in addition to oesophageal varices.)*

Singh, 2022

Bibliographic Reference	Singh, Virendra; Kumar, Pramod; Verma, Nipun; Vijayvergiya, Rajesh; Singh, Akash; Bhalla, Ashish; Propranolol vs. band ligation for primary prophylaxis of variceal hemorrhage in cirrhotic patients with ascites: a randomized controlled trial.; Hepatology international; 2022; vol. 16 (no. 4); 944-953

Study details

Trial registration number	NCT02649335

and/or trial name	
Study type	Randomised controlled trial (RCT)
Study location	India
Study setting	Tertiary care centre
Study dates	July 2015 and December 2016
Sources of funding	Partially funded by Society for the Study of Liver Diseases (SSLD)
Inclusion criteria	• Diagnosis of cirrhosis • Child-Turcotte-Pugh, CTP-B or C • Age >18 years • Age <75 years • ≥ grade2 ascites with oesophageal varices
Exclusion criteria	• Existing use of beta blockers • Portal vein thrombosis • Unable to give informed consent (e.g. learning disability, psychiatric illness) • History of variceal bleeding • Previous banding or sclerotherapy • Hepatocellular carcinoma • Contraindications to propranolol (obstructive airway disease, congestive heart failure, severe peripheral vascular disease, diabetes mellitus type 1) • Asthma • Chronic alcoholism • Diabetes mellitus • Active/recent infection within 2 weeks • Hepatic encephalopathy (HE) • Renal dysfunction • Refractory ascites
Intervention(s)	Propranolol +standard treatment: Long-acting PPL orally at 40 mg/day, with weekly dose titration with a target heart rate of 55–60 beats/min or 20–25% reduction or maximum tolerated dose. The dose was reduced by half in case of side effects with the initial dose. Temporary stoppage or down-titration of PPL was allowed in situations such as hypotension (Systolic blood pressure, SyBP<90 mmHg), hyponatremia, SBP, renal dysfunction (creatinine > 1.5 mg/dL), and acute V.H. Compliance with PPL was assessed by monthly pill counts and/or self-reporting. Standard treatment was low sodium diet (2 g/day) and a combination of furosemide (20–160 mg/day) and spironolactone (50–400 mg/day) with dose escalation by one step at a time. The dose of diuretics was escalated when there was lack of mobilization defined as < 0.8 kg of weight loss over

	4 days. Large-volume paracentesis (LVP) was done for symptomatic tense ascites with intravenous albumin (8 g/L ascites removed). Patients who developed R.A. on follow-up were treated with a low sodium diet, diuretics, albumin, and repeated LVP.
Comparator	EVL (+standard treatment) -group underwent regular sessions of EVL using a multi-band ligation device (six shooter) till variceal eradication every 4 weeks followed by 3 monthly for the initial 6 months and 6 monthly thereafter. Variceal eradication was defined by the absence of varices. Recurrent oesophageal varices were banded till eradication. Gastric varices were planned to be treated with cyanoacrylate glue injections only if they bled. Standard treatment was low sodium diet (2 g/day) and a combination of furosemide (20–160 mg/day) and spironolactone (50–400 mg/day) with dose escalation by one step at a time. The dose of diuretics was escalated when there was lack of mobilization defined as < 0.8 kg of weight loss over 4 days. Large-volume paracentesis (LVP) was done for symptomatic tense ascites with intravenous albumin (8 g/L ascites removed). Patients who developed R.A. on follow-up were treated with a low sodium diet, diuretics, albumin, and repeated LVP.
Outcome measures	• Variceal haemorrhage • Adverse events • Transplant-free-survival • Hospital admissions
Number of participants	160 (ITT) 138 (Per Protocol)
Duration of follow-up	12 months
Loss to follow-up	PPL n=10; EVL n=12 The patients lost to follow-up and withdrawn from the study were censored in the per protocol analysis.
Methods of analysis	Data were analysed using SPSS according to the intention-to-treat (ITT) principle unless otherwise stated. As appropriate, categorical data were represented as a number (percentage) and quantitative data as mean ± standard deviation or median (interquartile range). Kolmogorov–Smirnov test was used for data distribution. Student t test and Mann–Whitney U-test were applied to compare between two groups, as appropriate. Proportions were compared using Chi-square or Fisher's exact test. Survival analysis was done by the Kaplan–Meier method, and groups were compared by Log-Rank test. Cox-Proportional regression analysis was done to find independent predictors of survival, where variables in univariable analysis with $p \leq 0.10$ were entered into the stepwise forward multivariable model. All tests were two-sided at a significance level of $p < 0.05$ and adjusted for subgroup comparisons.
Additional comments	Patients developing acute variceal haemorrhage on follow-up in either group were hospitalised and treated with EVL within 12 h, intravenous terlipressin 2 mg 4 hourly, oral lactulose, and intravenous ceftriaxone 1gm

	once daily for 3–5 days. These patients were continued in the allocated group with close monitoring after discharge.

Study arms

- Propranolol (N = 80)
- Endoscopic variceal ligation (N = 80)

Characteristics
Arm-level characteristics

Characteristic	Propranolol (N = 80)	Endoscopic variceal ligation (N = 80)
% Female	n = 18 % = 22.5	n = 19 % = 23.75
Mean age (SD)	50.8 (10)	48.2 (11.3)
Aetiology of cirrhosis		
- **Alcohol**	n = 38 % = 47.5	n = 43 % = 53.7
- **Non-alcoholic steatohepatitis**	n = 11 % = 13.7	n = 7 % = 8.7
- **Hepatitis C virus**	n = 11 % = 13.7	n = 8 % = 10
- **Hepatitis B virus**	n = 5 % = 6.2	n = 7 % = 8.7
- **Hepatitis C virus + alcohol**	n = 4 % = 5	n = 6 % = 7.5
- **Hepatitis B virus + alcohol**	n = 2 % = 2.5	n = 2 % = 2.5
- **Cryptogenic**	n = 5 % = 6.2	n = 4 % = 5
Grade 2 ascites	n = 62 % = 77.5	n = 63 % = 78.7
Grade 3 ascites	n = 18 % = 22.5	n = 17 % = 21.3
Child-Turcotte-Pugh score Mean (SD)	8.9 (1.6)	8.9 (1.5)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(No blinding.)*
Overall bias and Directness	Overall Directness	Directly applicable

Thuluvath, 2005

Bibliographic Reference	Thuluvath, Paul J; Maheshwari, Anurag; Jagannath, Sanjay; Arepally, Aravind; A randomized controlled trial of beta-blockers versus endoscopic band ligation for primary prophylaxis: a large sample size is required to show a difference in bleeding rates.; Digestive diseases and sciences; 2005; vol. 50 (no. 2); 407-10

Study details

Trial registration number and/or trial name	Not reported
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Not specified
Study dates	March 2000 to March 2002
Sources of funding	Not reported
Inclusion criteria	• Large oesophageal varices • Diagnosis of cirrhosis • Hepatic vein wedge pressure gradient HVWPG =/>12mm Hg
Exclusion criteria	• Large gastric varices • History of variceal bleeding • Previous banding or sclerotherapy • Pregnancy • Hepatocellular carcinoma • Life expectancy < 6 months • Medical contraindications or intolerance to beta blockers • Hepatic vein wedge pressure gradient HVWPG <12mm Hg
Intervention(s)	Patients randomised to the EVL arm underwent serial band ligation (every 2–3 weeks) using a Wilson Cook multiple band ligator, until all oesophageal varices were obliterated.

Comparator	Patients in the Propranolol arm were started on propranolol and the dose was titrated to achieve a resting heart rate of <60 bpm, or a 25% reduction from baseline, or until the maximum tolerated dose was achieved. Patients were maintained on long-acting propranolol to improve compliance.
Outcome measures	• Variceal haemorrhage • Death • Bleeding related mortality (within 6 weeks of index bleed)
Number of participants	31 participants were enrolled in the trial. 16 were randomised to the EVL arm and 15 to the propranolol arm.
Duration of follow-up	All participants were followed in the outpatient clinics at 3-month intervals. The mean follow-up period was 27.4 ± 12.9 months.
Loss to follow-up	All participants completed the study.
Methods of analysis	It was assumed that the patient population selected on the basis of elevated HVWPG would have a higher bleeding rate than previously reported by the meta-analyses. With an expected bleeding rate of 35% in the β-blocker therapy group and 15% in the band ligation group, it was estimated that 90 patients would be required in each arm, with an early dropout of about 10%, to achieve 80% power at the 5% (α) level of significance. Categorical variables were analysed using the two-tailed Fisher's exact test and continuous variables were compared by t-test; a P value of 0.05 or less was considered statistically significant. All data were analysed using SPSS version 11.0 (Chicago, IL).
Additional comments	The study was terminated prematurely when it was realised that the sample size was grossly underestimated based on the observed bleeding rate of 9.6% (expected~25%). It was realised that a sample size of 90 patients in either arm would not be sufficient to show a difference if it existed and that approximately 420 participants would be needed in each arm to show a difference in bleeding rates.

Study arms

- EVL (N = 16)
- Propranolol (N = 15)

Characteristics
Arm-level characteristics

Characteristic	EVL (N = 16)	Beta blockers - Propranolol (N = 15)
Age Mean (SD)	50 (10)	53.5 (10.5)
% Female	n = 6 % = 38	n = 8 % = 53

Characteristic	EVL (N = 16)	Beta blockers - Propranolol (N = 15)
Ethnicity		
Caucasian	n = 12 % = 75	n = 14 % = 93
African American	n = 4 % = 25	n = 1 % = 7
Hepatic venous wedge pressure gradient (HVWPG) (mmHg) Mean (SD)	17.7 (7)	20.5 (11)
Aetiology of liver disease		
- **Alcohol**	n = 5 % = 31	n = 1 % = 7
- **Hepatitis C virus**	n = 5 % = 31	n = 7 % = 46
- **Hepatitis B virus**	n = 0 % = 0	n = 1 % = 7
- **Primary Biliary Cirrhosis**	n = 2 % = 13	n = 1 % = 7
- **Primary Sclerosing Cholangitis**	n = 1 % = 6	n = 1 % = 7
- **Autoimmune hepatitis**	n = 1 % = 6	n = 2 % = 13
- **Other**	n = 2 % = 13	n = 2 % = 13
Model for End Stage Liver Disease Score (MELD score} Mean (SD)	11.7 (4)	14.4 (4.3)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(No blinding. Compliance was self-reported by patients rather than by a validated measure. The study was terminated early due to realisation that the required sample size to show a difference between the trial arms had been grossly underestimated.)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable *(Study participants met the inclusion criteria for the protocol for this review.)*

Tripathi, 2009

Bibliographic Reference	Tripathi, Dhiraj; Ferguson, James W; Kochar, Narendra; Leithead, Joanna A; Therapondos, George; McAvoy, Norma C; Stanley, Adrian J; Forrest, Ewan H; Hislop, William S; Mills, Peter R; Hayes, Peter C; Randomized controlled trial of carvedilol versus variceal band ligation for the prevention of the first variceal bleed.; Hepatology (Baltimore, Md.); 2009; vol. 50 (no. 3); 825-33

Study details

Trial registration number and/or trial name	ISRCTN26269039.
Study type	Randomised controlled trial (RCT)
Study location	Scotland
Study setting	5 Scottish hospitals (1 in Edinburgh, 3 in Glasgow and 1 in Paisley)
Study dates	April 30th 2000 to May 24th 2006
Sources of funding	Supported by the University of Edinburgh
Inclusion criteria	• No history of bleeding • Diagnosis of cirrhosis • Grade II or larger oesophageal varices
Exclusion criteria	• <18 or >75 years of age • Pregnant, lactating, or of childbearing age without use of contraception • Allergy to carvedilol • Existing use of beta blockers • Existing use of nitrates • Malignancy that significantly affects survival • Serious systemic illness (cardiorespiratory, sepsis) • Obstructive airways disease • mean arterial pressure <55 mm Hg or pulse <50 beats per minute at baseline • Portal vein thrombosis • Unable to give informed consent (e.g. learning disability, psychiatric illness)

Intervention(s)	Carvedilol was administered orally at a starting dose of 6.25 mg per day at 9am. After 1 week, this was increased to a target dose of 12.5 mg per day if systolic blood pressure did not fall below 90mm Hg.
Comparator	Endoscopic variceal band ligation (EVL) was carried out using multibander devices (Speedbander, Boston Scientific, Herts, UK; 6-Shooter Saeed Multi-Band Ligator, Cook, Ireland; or Speedband Superview Super 7,Boston Scientific, Natick, MA) by senior fully trained endoscopists or under their direct supervision. Varices were banded starting at the gastroesophageal junction and approximately 5 cm proximally. Following randomisation, patients underwent EVL every 2 weeks until eradication. EVL was carried out as soon as possible following randomisation, excluding the day of randomisation. Eradication was defined as the absence of varices or presence of grade I oesophageal varices. Following eradication, the interval for the next endoscopy was 3 months, and every 6 months thereafter if varices did not recur. Recurrent oesophageal varices were banded and repeat EVL was performed every 2 weeks until eradication and followed up after eradication as above. There was no routine use of acid suppression or muco-protectants. Secondary gastric varices were treated endoscopically only if they bled.
Outcome measures	• Death from oesophageal variceal bleeding • Variceal haemorrhage • Death
Number of participants	152 patients in total were randomised for entry into the trial, 77 in the carvedilol arm and 75 in the EVL arm.
Duration of follow-up	An initial clinic visit took place 1 week after introduction of carvedilol and then at 6 weeks in both trial arms. Successive follow-up intervals ranged between 3-6 months. Full biochemical and haematological profile was obtained at each consultation. Clinical examination was carried out and patients underwent 6 monthly ultrasound examinations as part of hepatoma surveillance. Compliance with carvedilol was assessed through direct questioning and collateral history from relatives and/or the patient's general practitioner. Where appropriate, continued alcohol consumption was assessed by direct questioning and by random serum ethanol levels. Patients were censored if they were lost to follow-up, had a liver transplantation, or underwent a transjugular intrahepatic portosystemic shunt (TIPS). Follow-up was continued in both trial arms for 6 months after recruitment of the last patient.
Loss to follow-up	In the carvedilol arm, 2 of the 77 patients originally randomised to this treatment were lost to follow up. A further 23 discontinued the intervention (12 due to intolerance to the therapy, 7 due to non-compliance, 2 due to varices being inadvertently banded and 2 due to patient choice). In the EVL arm, none of the 75 patients originally randomised to this treatment were lost to follow up. However, 23 discontinued the intervention (9 due to intolerance to the therapy, 13 due to non-compliance and 1 due to patient choice).
Methods of analysis	All data was primarily analysed using an intention-to-treat (ITT) model, which was supplemented by per-protocol analysis in order to control for

	patients who may not comply fully with the treatments. In this analysis, time zero was defined as the start of treatment following randomisation. Subsequently, follow-up was only valid if the patients remained on the treatments to which they were randomised. Patients were followed up until they reached the end points (primary end point - first variceal bleed, secondary end-points - overall mortality and bleeding-related mortality defined as death within 6 weeks of the index variceal bleed), had a liver transplant or transjugular intrahepatic portosystemic shunt (TIPS), or were lost to follow-up. Baseline parametric data were expressed as the mean +/- standard deviation, and any differences in the groups were analysed using an unpaired Student t-test. Differences in parametric data over time were analysed using the paired sample t-test. Nonparametric data were analysed using the chi-squared test. Cumulative bleeding and survival were expressed using the Kaplan-Meier method, and differences were assessed using the log-rank test. Cox proportional regression analysis was used to assess variables predicting the end points. Variables with P <0.1 following univariate analysis were entered into multivariate analysis. SPSS (version 15, Chicago, IL), and Excel (Excel XP Version, 2002) statistical packages were used.
Additional comments	Patients who were intolerant of EVL were offered propranolol and not carvedilol, because the efficacy of carvedilol in primary prophylaxis was unknown at the time of study design. Those who were intolerant of carvedilol were entered into the banding arm because EVL was a proven alternative to beta-blockers for primary prophylaxis at the time of study design. The primary end point was the first variceal bleed, defined as haematemesis and/or melena with endoscopic evidence of variceal bleeding or stigmata of recent haemorrhage and at least a 2 g/dL reduction in haemoglobin within 24 hours of admission. The definition also included bleeding from banding ulceration. Authors note as a limitation that the difference in favour of carvedilol in the ITT analysis has to be interpreted with caution in view of the difficulties in adherence to the banding protocol.

Study arms

- Carvedilol (N = 77)
- EVL (N = 75)

Characteristics
Arm-level characteristics

Characteristic	Carvedilol (N = 77)	EVL (N = 75)
Age (years) Mean (SD)	54.2 (9.4)	54.5 (11.1)
% Female	n = 23 % = 29.8	n = 20 % = 26.7

Characteristic	Carvedilol (N = 77)	EVL (N = 75)
Pugh score Median (range)	8 (5 to 13)	8 (5 to 14)
Child Grade		
Child score A	n = 29 % = 38	n = 26 % = 35
Child score B	n = 19 % = 24	n = 19 % = 25
Child score C	n = 29 % = 38	n = 30 % = 40
Varices		
Grade III varices	n = 6 % = 8	n = 7 % = 11
Red signs	n = 5 % = 6	n = 2 % = 3
Ascites	n = 38 % = 49	n = 40 % = 53
Alcohol liver disease	n = 57 % = 74	n = 54 % = 72
Alcohol liver disease - abstained	n = 17 % = 30	n = 12 % = 16

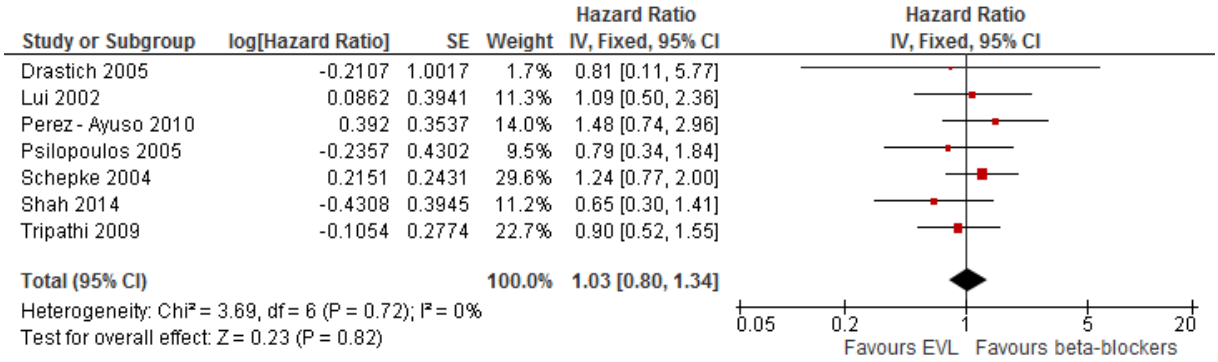
Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Loss of approximately 1/3 participants in each arm. Some concerns about lack of blinding for participants, relatives and clinicians. People in EVL arm given NSBB if unable to tolerate EVL.)*
Overall bias and Directness	Overall Directness	Directly applicable

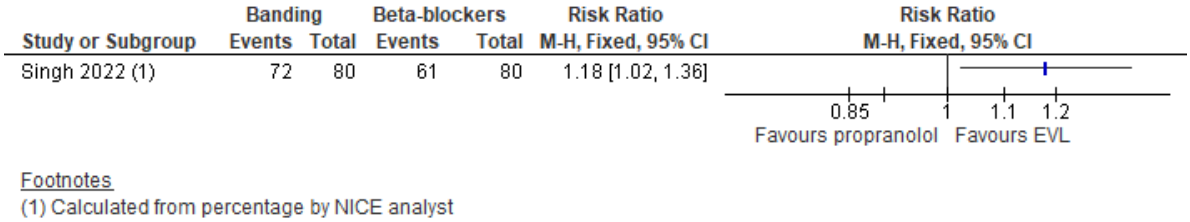
Appendix E – Forest plots

E1 Banding ligation versus non-selective beta-blockers for medium to large varices.

E1.1 Survival.

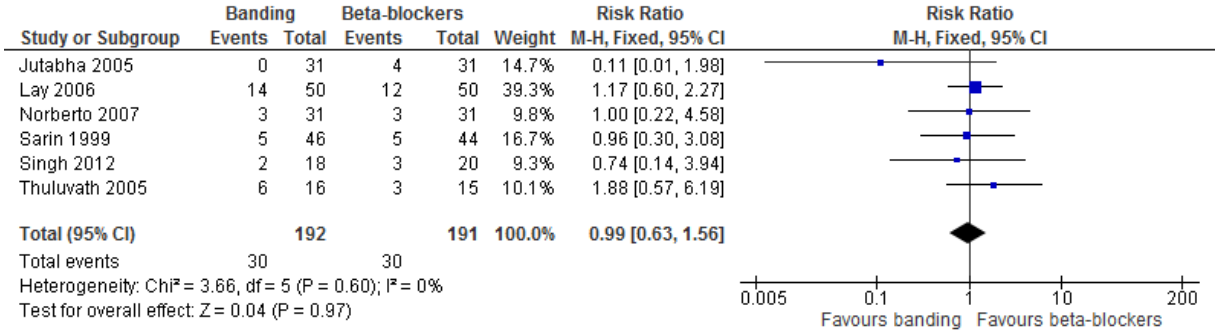


E1.2 Transplant free survival.

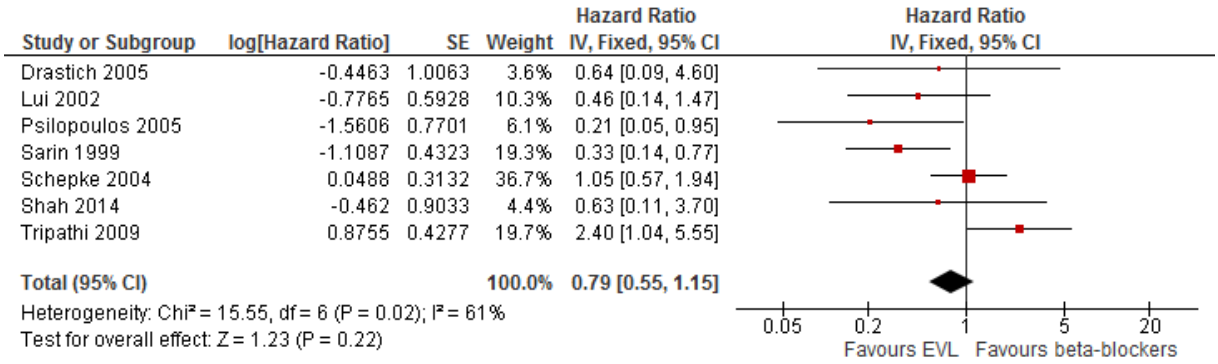


Footnotes
(1) Calculated from percentage by NICE analyst

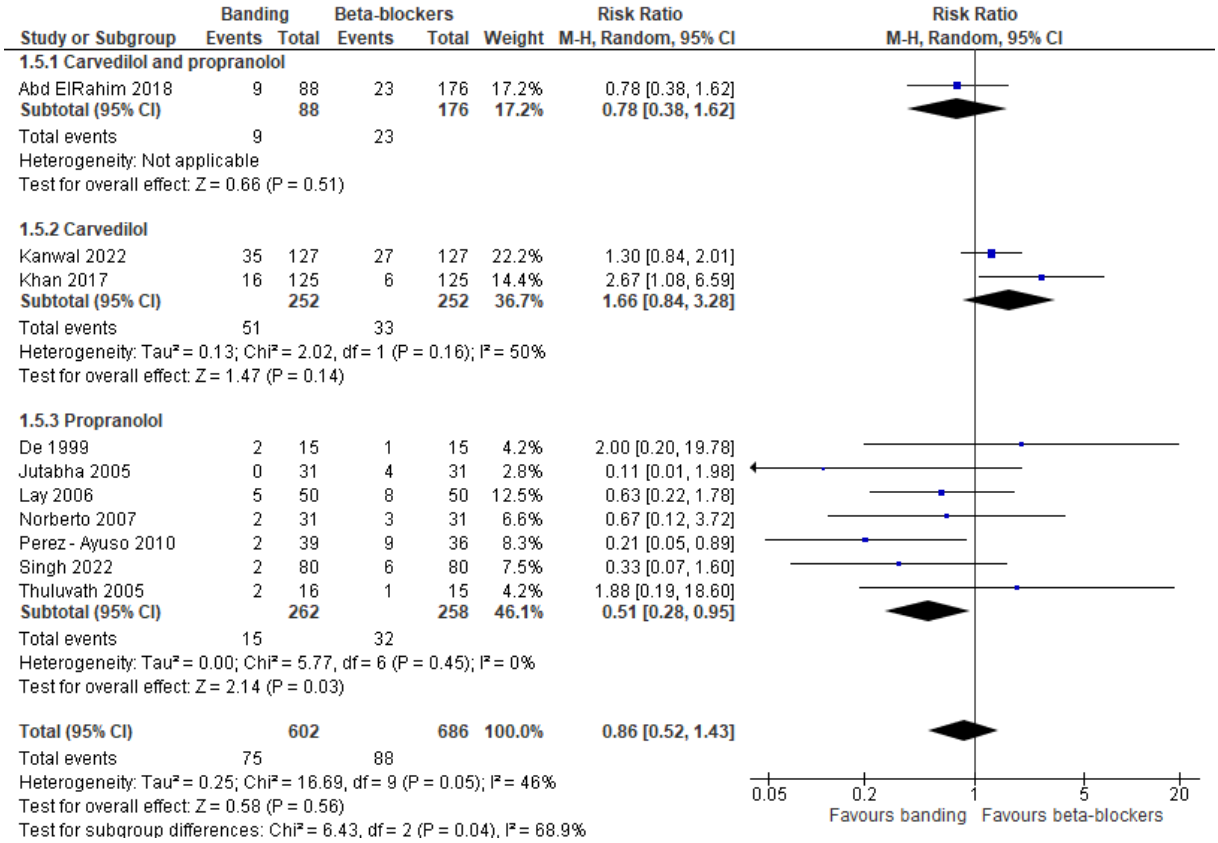
E1.3 Mortality.



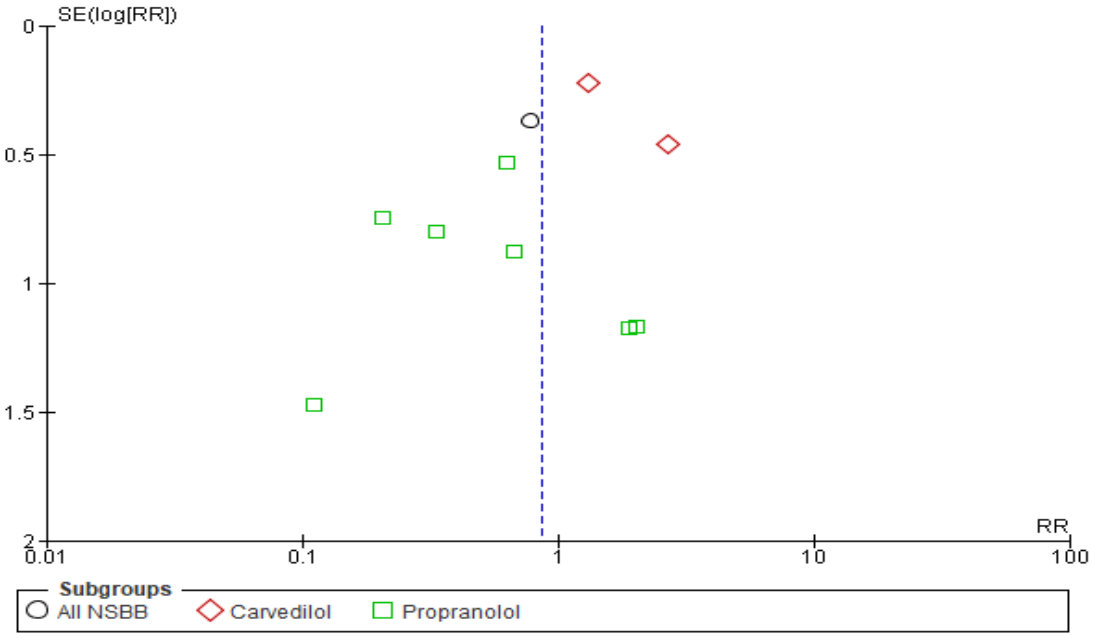
E1.4 Free from variceal bleeding.



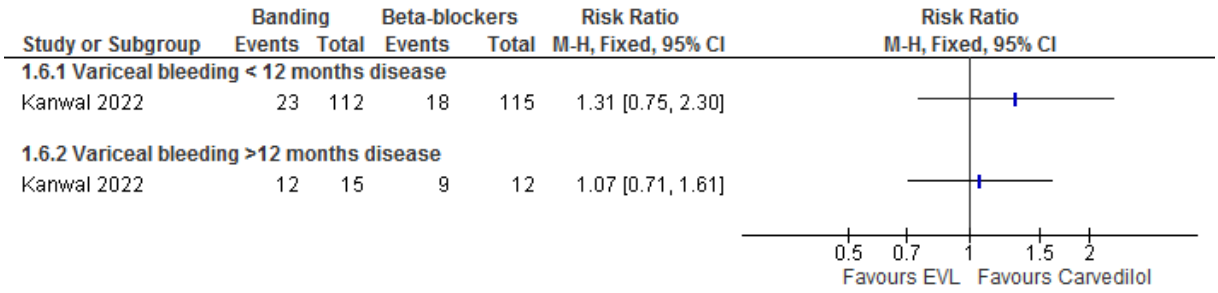
E1.5 Variceal bleeding



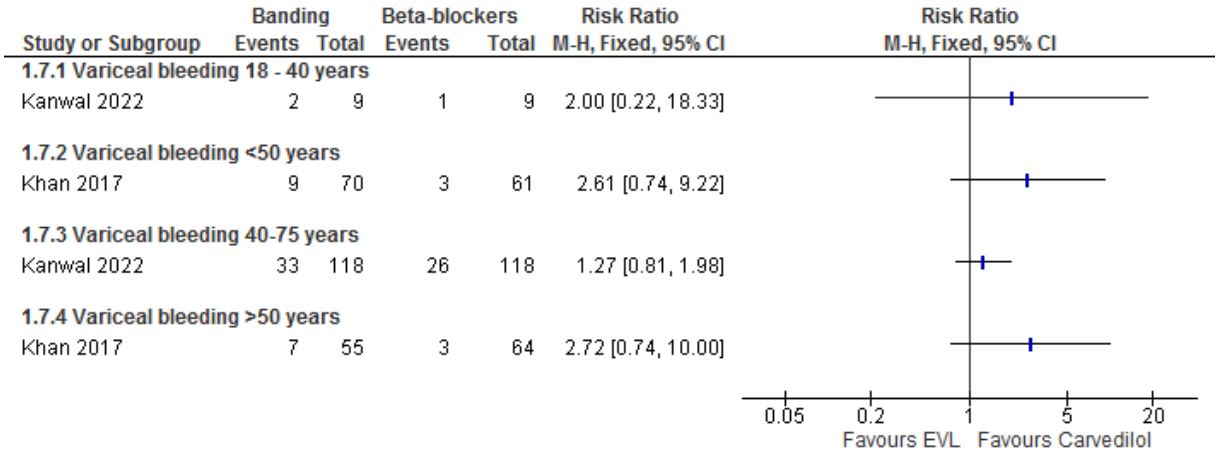
E1.5a Variceal bleeding – funnel plot



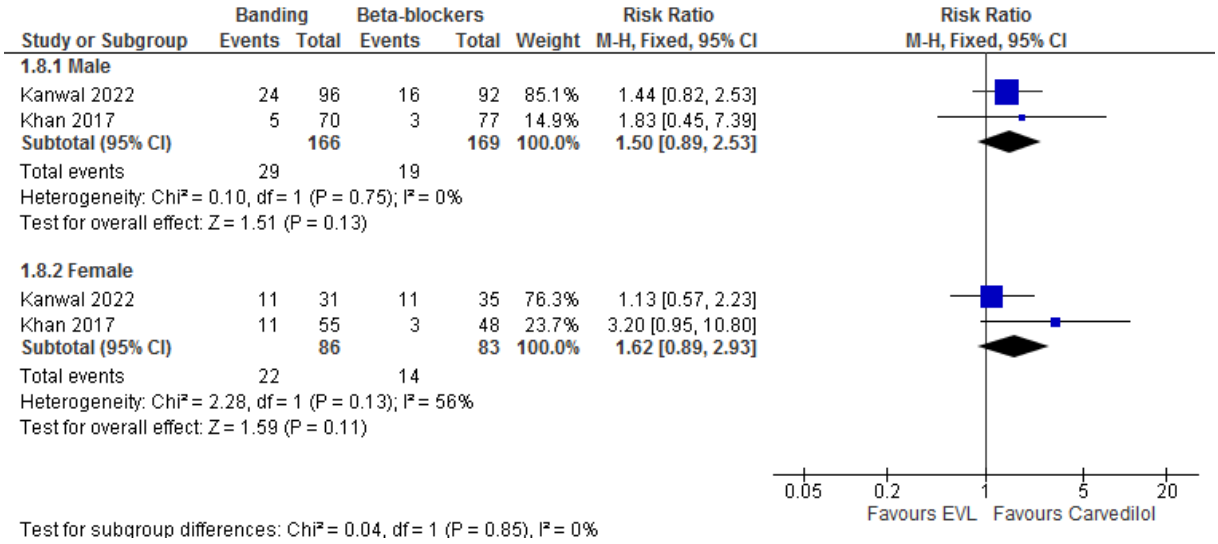
E1.6 Variceal bleeding by length of disease



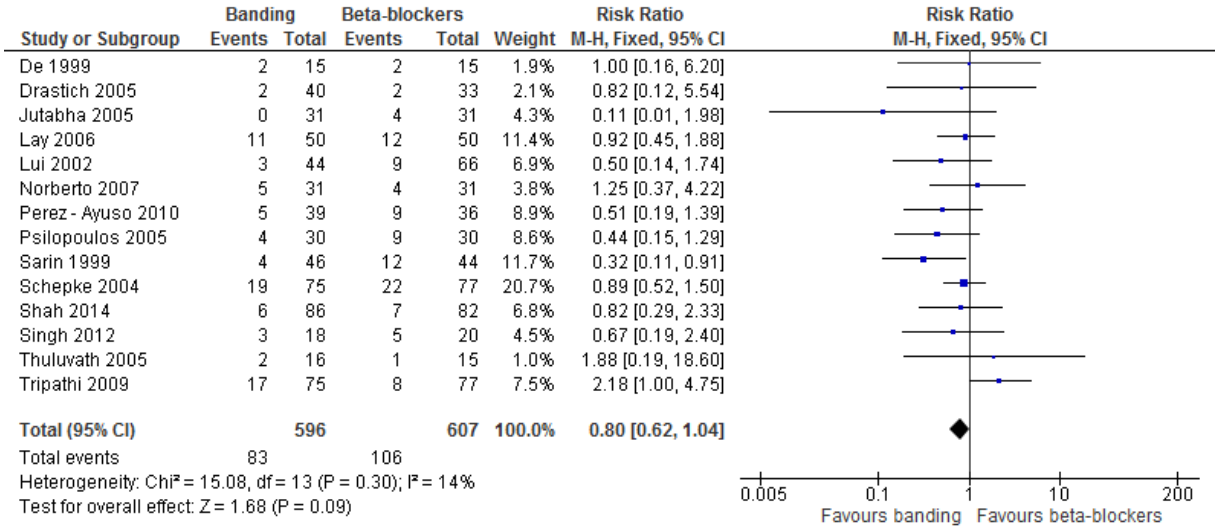
E1.7 Variceal bleeding by age



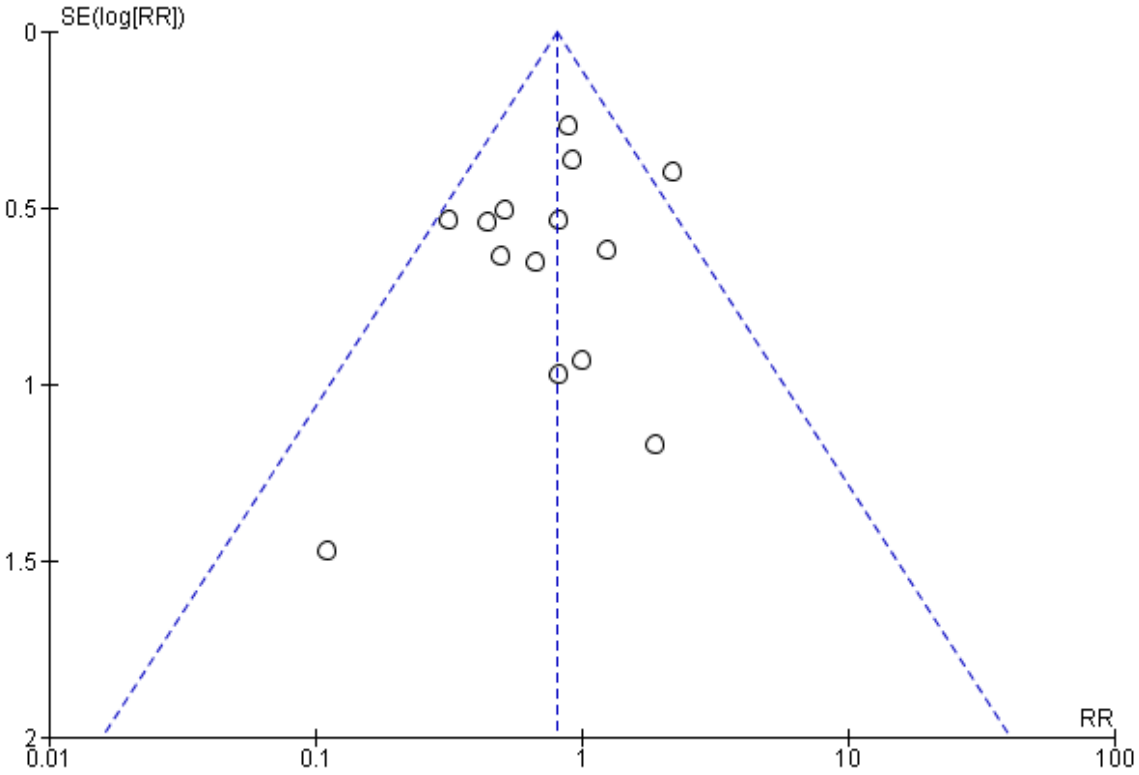
E1.8 Variceal bleeding by gender



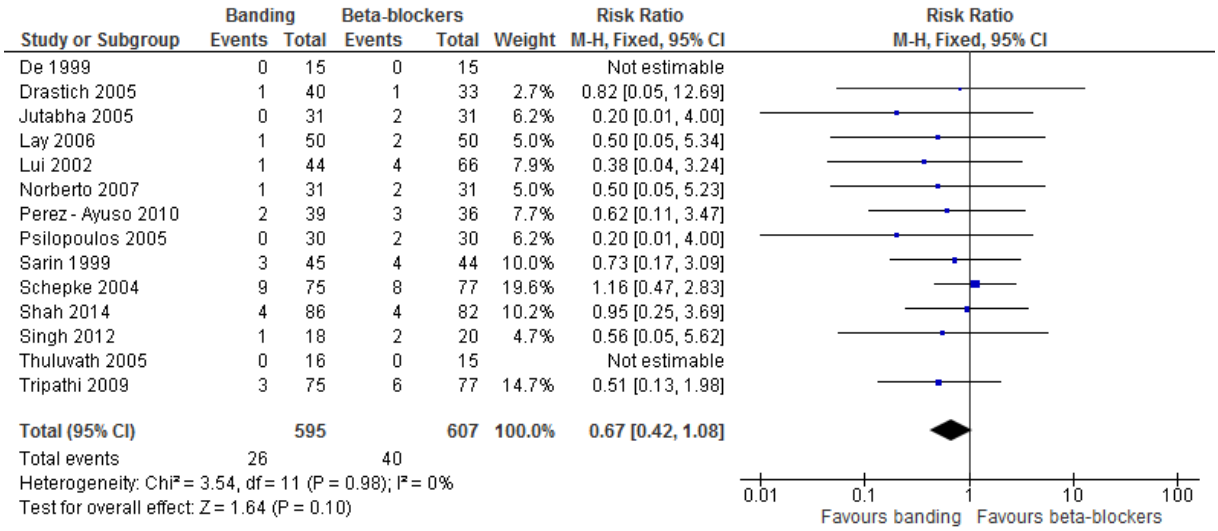
E1.9 Upper gastrointestinal bleeding



E1.9a Upper gastrointestinal bleeding funnel plot



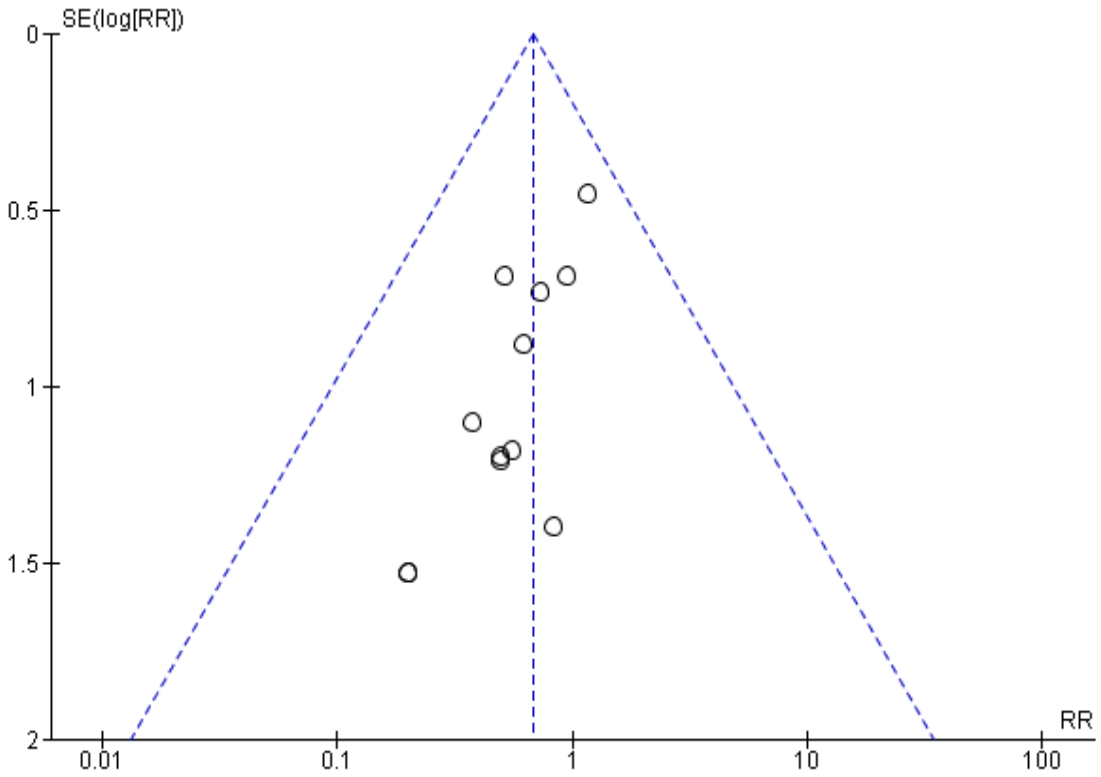
E1.10 Bleeding-related mortality



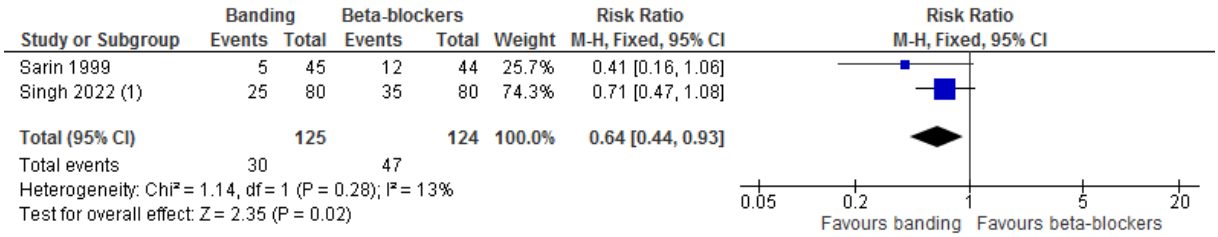
Study or Subgroup	Banding Events	Banding Total	Beta-blockers Events	Beta-blockers Total	Weight	Risk Ratio M-H, Fixed, 95% CI
De 1999	0	15	0	15		Not estimable
Drastich 2005	1	40	1	33	2.7%	0.82 [0.05, 12.69]
Jutabha 2005	0	31	2	31	6.2%	0.20 [0.01, 4.00]
Lay 2006	1	50	2	50	5.0%	0.50 [0.05, 5.34]
Lui 2002	1	44	4	66	7.9%	0.38 [0.04, 3.24]
Norberto 2007	1	31	2	31	5.0%	0.50 [0.05, 5.23]
Perez - Ayuso 2010	2	39	3	36	7.7%	0.62 [0.11, 3.47]
Psilopoulos 2005	0	30	2	30	6.2%	0.20 [0.01, 4.00]
Sarin 1999	3	45	4	44	10.0%	0.73 [0.17, 3.09]
Schepke 2004	9	75	8	77	19.6%	1.16 [0.47, 2.83]
Shah 2014	4	86	4	82	10.2%	0.95 [0.25, 3.69]
Singh 2012	1	18	2	20	4.7%	0.56 [0.05, 5.62]
Thuluvath 2005	0	16	0	15		Not estimable
Tripathi 2009	3	75	6	77	14.7%	0.51 [0.13, 1.98]
Total (95% CI)		**595**		**607**	**100.0%**	**0.67 [0.42, 1.08]**
Total events	26		40			

Heterogeneity: Chi² = 3.54, df = 11 (P = 0.98); I² = 0%
Test for overall effect: Z = 1.64 (P = 0.10)

E1.10a Bleeding-related mortality funnel plot

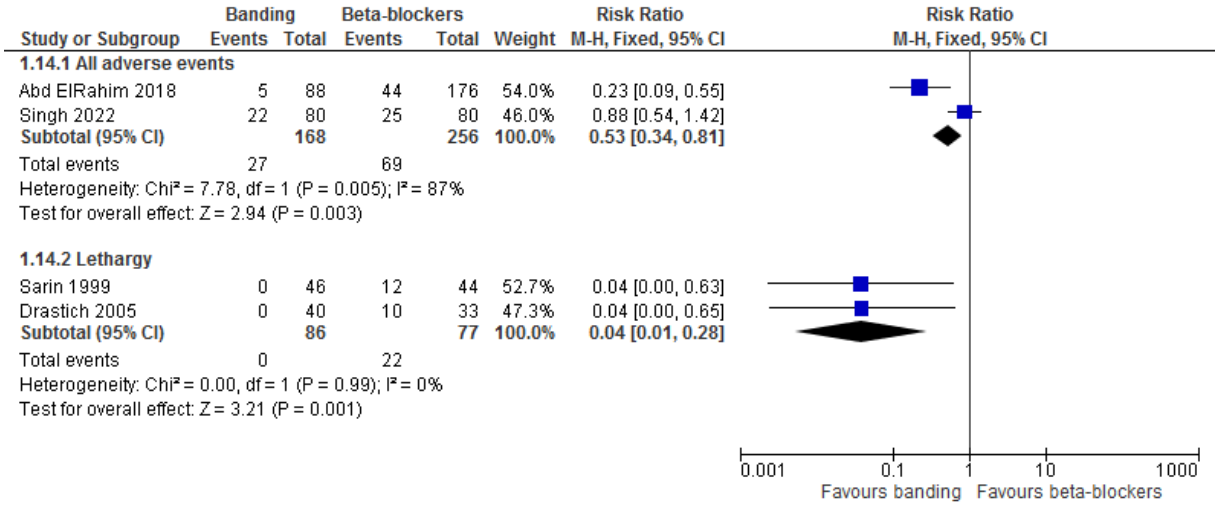


E1.11 Hospitalisation



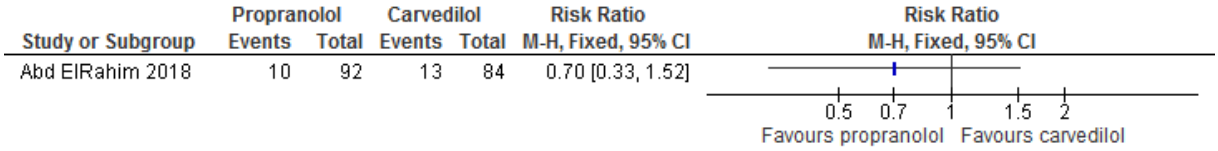
Footnotes
(1) Calculated from percentage figures by NICE

E1.12 Adverse events

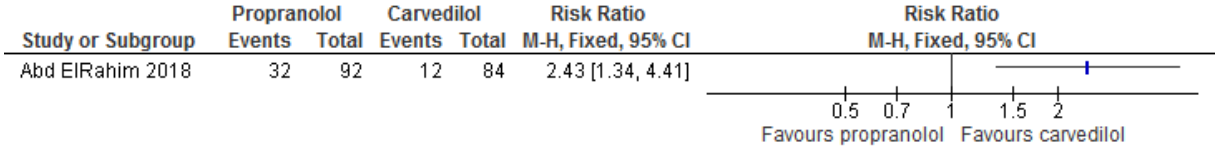


E2 Propranolol versus carvedilol for medium to large varices

E2.1 Variceal bleeding



E2.2 Adverse events



Appendix F – GRADE tables

F.1 Banding ligation versus non-selective beta-blockers for medium to large varices

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Banding ligation	Non-selective beta-blockers	Relative (95% CI)	Absolute	
Survival (all follow up times) [>1 favours NSBB]											
7[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	-	33.3%[4]	HR 1.03 (0.8 to 1.34)	8 more per 1000 (from 56 fewer to 86 more)	⊕OOO VERY LOW
Transplant free survival (follow-up 12 months) [>1 favours EVL]											
1[5]	randomised trials	serious[6]	NA[7]	no serious indirectness	serious[8]	none	72/80 (90%)	61/80 (76.3%)	RR 1.18 (1.02 to 1.36)	137 more per 1000 (from 15 more to 275 more)	⊕⊕OO LOW
Mortality (all follow up times) [>1 favours NSBB]											
6[9]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[10]	none	30/192 (15.6%)	30/191 (15.7%)	RR 0.99 (0.63 to 1.56)	2 fewer per 1000 (from 58 fewer to 88 more)	⊕OOO VERY LOW
Free from variceal bleeding (all follow up times) [>1 favours NSBB]											
7[11]	randomised trials	very serious[2]	serious[12]	no serious indirectness	very serious[3]	none	-	27.3%[4]	HR 0.79 (0.55 to 1.15)	50 fewer per 1000 (from 112 fewer to 34 more)	⊕OOO VERY LOW
Variceal bleeding (all follow up times) [>1 favours NSBB]											
10[13]	randomised trials	very serious[2]	serious[12]	no serious indirectness	very serious[3]	none	75/602 (12.5%)	88/686 (12.8%)	RR 0.86 (0.52 to 1.43)	18 fewer per 1000 (from 62 fewer to 55 more)	⊕OOO VERY LOW
Variceal bleeding - All NSBB (follow-up 12 months) [>1 favours NSBB]											
1[14]	randomised trials	very serious[10]	NA[7]	no serious indirectness	very serious[3]	none	9/88 (10.2%)	23/176 (13.1%)	RR 0.78 (0.38 to 1.62)	29 fewer per 1000 (from 81 fewer to 81 more)	⊕OOO VERY LOW
Variceal bleeding - Carvedilol (follow-up 3-6 months) [>1 favours NSBB]											

2[15]	randomised trials	serious[16]	very serious[12]	no serious indirectness	serious[8]	none	51/252 (20.2%)	33/252 (13.1%)	RR 1.66 (0.84 to 3.28)	86 more per 1000 (from 21 fewer to 299 more)	⊕OOO VERY LOW
Variceal bleeding – Propranolol (all follow up times) [>1 favours NSBB]											
7[17]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[8]	none	15/262 (5.7%)	32/258 (12.4%)	RR 0.51 (0.28 to 0.95)	61 fewer per 1000 (from 6 fewer to 89 fewer)	⊕OOO VERY LOW
Variceal bleeding by length of disease - Variceal bleeding < 12 months disease (follow-up 3 months) [>1 favours NSBB]											
1[18]	randomised trials	serious[6]	NA[7]	no serious indirectness	very serious[3]	none	23/112 (20.5%)	18/115 (15.7%)	RR 1.31 (0.75 to 2.3)	49 more per 1000 (from 39 fewer to 203 more)	⊕OOO VERY LOW
Variceal bleeding by length of disease - Variceal bleeding >12 months disease (follow-up 3 months) [>1 favours NSBB]											
1[18]	randomised trials	serious[6]	NA[7]	no serious indirectness	very serious[3]	none	12/15 (80%)	9/12 (75%)	RR 1.07 (0.71 to 1.61)	53 more per 1000 (from 218 fewer to 458 more)	⊕OOO VERY LOW
Variceal bleeding by age - Variceal bleeding 18 - 40 years (follow-up 3 months) [>1 favours NSBB]											
1[18]	randomised trials	serious[6]	NA[7]	no serious indirectness	very serious[3]	none	2/9 (22.2%)	1/9 (11.1%)	RR 2 (0.22 to 18.33)	111 more per 1000 (from 87 fewer to 1000 more)	⊕OOO VERY LOW
Variceal bleeding by age - Variceal bleeding <50 years (follow-up 6 months) [>1 favours NSBB]											
1[19]	randomised trials	serious[6]	NA[7]	no serious indirectness	very serious[3]	none	9/70 (12.9%)	3/61 (4.9%)	RR 2.61 (0.74 to 9.22)	79 more per 1000 (from 13 fewer to 404 more)	⊕OOO VERY LOW
Variceal bleeding by age - Variceal bleeding 40-75 years (follow-up 3 months) [>1 favours NSBB]											
1[18]	randomised trials	serious[6]	NA[7]	no serious indirectness	serious[8]	none	33/118 (28%)	26/118 (22%)	RR 1.27 (0.81 to 1.98)	59 more per 1000 (from 42 fewer to 216 more)	⊕⊕OO LOW
Variceal bleeding by age - Variceal bleeding >50 years (follow-up 6 months) [>1 favours NSBB]											
1[19]	randomised trials	serious[6]	NA[7]	no serious indirectness	very serious[3]	none	7/55 (12.7%)	3/64 (4.7%)	RR 2.72 (0.74 to 10)	81 more per 1000 (from 12 fewer to 422 more)	⊕OOO VERY LOW
Variceal bleeding by gender - Male (follow-up 3-6 months) [>1 favours NSBB]											
2[15]	randomised trials	serious[16]	no serious inconsistency	no serious indirectness	serious[8]	none	29/166 (17.5%)	19/169 (11.2%)	RR 1.5 (0.89 to 2.53)	56 more per 1000 (from 12 fewer to 172 more)	⊕⊕OO LOW
Variceal bleeding by gender - Female (follow-up 3-6 months) [>1 favours NSBB]											

2[15]	randomised trials	serious[16]	serious[12]	no serious indirectness	serious[8]	none	22/86 (25.6%)	14/83 (16.9%)	RR 1.62 (0.89 to 2.93)	105 more per 1000 (from 19 fewer to 326 more)	⊕OOO VERY LOW
Upper gastrointestinal bleeding (all follow up times) [>1 favours NSBB]											
14[20]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[8]	none	83/596 (13.9%)	106/607 (17.5%)	RR 0.8 (0.62 to 1.04)	35 fewer per 1000 (from 66 fewer to 7 more)	⊕OOO VERY LOW
Bleeding-related mortality (all follow up times) [>1 favours NSBB]											
14[20]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[8]	none	26/595 (4.4%)	40/607 (6.6%)	RR 0.67 (0.42 to 1.08)	22 fewer per 1000 (from 38 fewer to 5 more)	⊕OOO VERY LOW
Hospitalisation (all follow up times) [>1 favours NSBB]											
2[21]	randomised trials	serious[16]	no serious inconsistency	no serious indirectness	serious[8]	none	30/125 (24%)	47/124 (37.9%)	RR 0.64 (0.44 to 0.93)	136 fewer per 1000 (from 27 fewer to 212 fewer)	⊕⊕OO LOW
Adverse events - All adverse events (follow-up 12 months) [>1 favours NSBB]											
2[22]	randomised trials	very serious[2]	very serious[23]	no serious indirectness	serious[8]	none	27/168 (16.1%)	69/256 (27%)	RR 0.53 (0.34 to 0.81)	127 fewer per 1000 (from 51 fewer to 178 fewer)	⊕OOO VERY LOW
Adverse events – Lethargy (all follow up times) [>1 favours NSBB]											
2[24]	randomised trials	serious[16]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/86 (0%)	22/77 (28.6%)	RR 0.04 (0.01 to 0.28)	274 fewer per 1000 (from 206 fewer to 283 fewer)	⊕⊕⊕O MODERATE

[1] Drastlich 2005; Lui 2002; Perez-Ayuso 2010; Psilopoulos 2005; Schepke 2004; Shah 2014; Tripathi 2009
[2] Downgraded twice because greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias
[3] Downgraded twice for crossing both MIDs
[4] Calculated from the median control group rate at the end of the study
[5] Singh 2022
[6] Single study at moderate risk of bias
[7] Not applicable. Single study
[8] Downgraded once for crossing 1 MID
[9] Jutabha 2005; Lay 2006; Norbeto 2007; Sarin 1999; Singh 2012; Thuluvath 2005
[10] Single study at high risk of bias
[11] Drastich 2005; Lui 2002; Psilopoulos 2005; Sarin 1999; Schepke 2004; Shah 2014; Tripathi 2009
[12] Downgraded once because I2 >33% and less than 66%
[13] Abd El Rahim 2018; Kanwal 2022; Khan 2017; De 1999; Jutabha 2005; Lay 2006; Norberto 2007; Perez-Ayuso 2010; Singh 2022; Thuluvath 2005
[14] Abd El Rahim 2018
[15] Kanwal 2022; Khan 2017

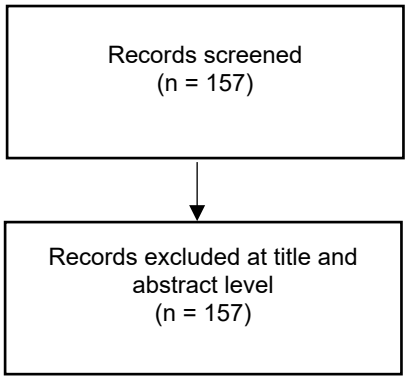
[16] Both studies at moderate risk of bias
[17] De 1999; Jutabha 2005; Lay 2006; Norberto 2007; Perez-Ayuso 2010; Singh 2022; Thuluvath 2005
[18] Kanwal 2022
[19] Khan 2017
[20] De 1999; Drastich 2005; Jutabha 2005; Lay 2006; Lui 2002; Norberto 2007; Perez-Ayuso 2010; Psilopoulos 2005; Sarin 1999; Schepke 2004; Shah 2014; Singh 2012; Thuluvath 2005; Tripathi 2009
[21] Sarin 1999; Singh 2022
[22] Abd El Rahim 2018; Singh 2022
[23] Downgraded twice for I^2 > 66%
[24] Sarin 1999; Drastich 2005

F.2 Propranolol versus carvedilol for medium to large varices

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Propranolol	Carvedilol	Relative (95% CI)	Absolute	
Variceal bleeding (follow-up 12 months)											
1[1]	randomised trials	very serious[2]	NA[3]	no serious indirectness	very serious[4]	none	10/92 (10.9%)	13/84 (15.5%)	RR 0.7 (0.33 to 1.52)	46 fewer per 1000 (from 104 fewer to 80 more)	⊕OOO VERY LOW
Adverse events (follow-up 12 months)											
1[1]	randomised trials	very serious[2]	NA[3]	no serious indirectness	no serious imprecision	none	32/92 (34.8%)	12/84 (14.3%)	RR 2.43 (1.34 to 4.41)	204 more per 1000 (from 49 more to 487 more)	⊕⊕OO LOW

1 Abd El Rahim (2018)
2 Downgraded twice for single study at high risk of bias
3 Not applicable. Single study
4 Downgraded twice for crossing 2 MIDs

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

No economic studies were included in this review.

Appendix I – Health economic model

Model overview

The objective of this model was to evaluate the cost effectiveness of endoscopic band ligation (EVL) with non-selective beta blockers (NSBB) for the primary prevention of bleeding in people with medium to large oesophageal varices due to cirrhosis. We developed a cost-utility model from the perspective of NHS and personal and social services in England.

Population

People aged 16 years and older with cirrhosis, who have medium- sized or large oesophageal varices which have never bled.

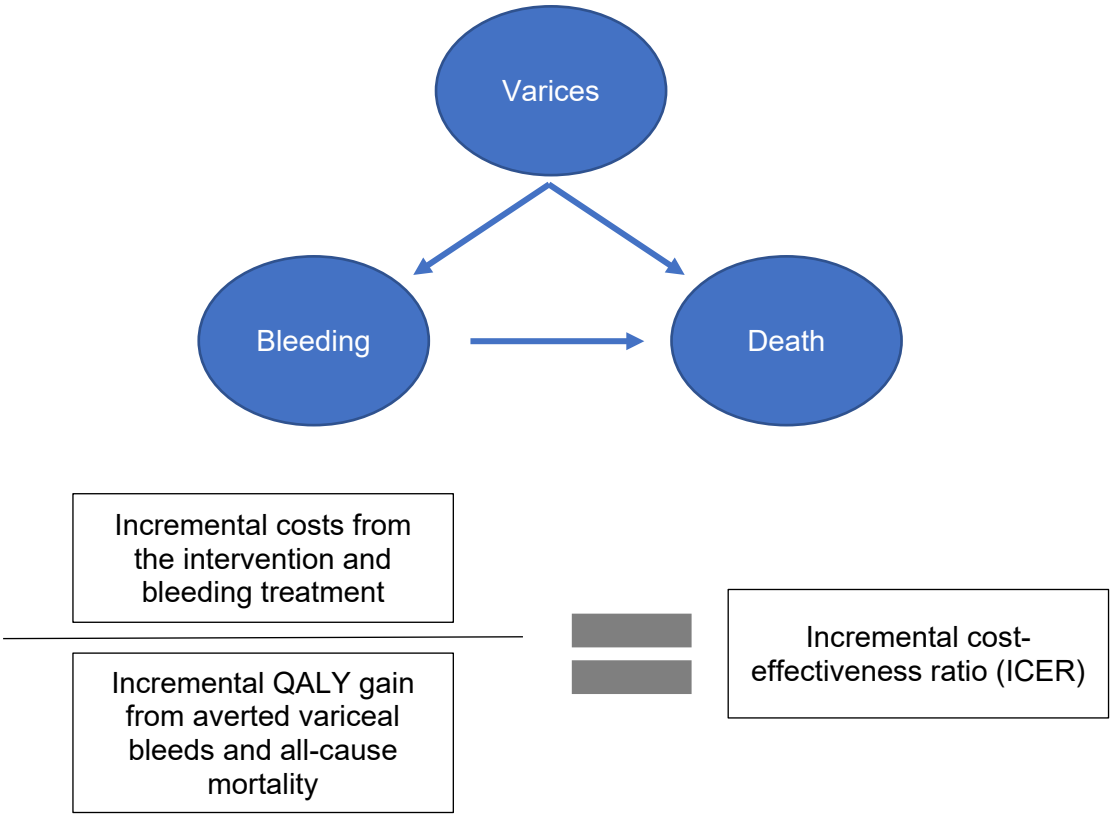
Comparators

Two interventions were included in the model: endoscopic variceal band ligation (EVL) and non-selective beta-blockers (NSBBs). Modelled NSBBs included propranolol and carvedilol, the NSBBs included in the studies in the clinical review, and nadolol which is also used in clinical practice.

Model structure

We developed a cost-utility model with 1-year time horizon (Figure 1). The health effect in the model was measured by quality-adjusted life years (QALYs) from averted variceal bleeds and all-cause mortality. The cost outcome was measured by costs associated with the interventions and variceal bleeding treatment. In the base case, EVL was compared with pooled NSBBs. Comparisons between EVL and individual NSBBs including propranolol and carvedilol were also conducted separately in the scenario analysis. The results were represented by incremental cost-effectiveness ratios (ICERs), which represents the extra cost per extra unit of QALY gain by using EVL for the primary prevention of bleeding compared to NSBBs.

Figure 1 Model diagram



Model inputs

Treatment effect

The risks of bleeding and all-cause mortality at baseline as well as the risk difference between NSBBs and EVL (Table 3) were obtained from the latest clinical review (2023) conducted by the NICE development team. There were high uncertainties around the clinical data. The risk difference between pooled NSBBs and EVL was not statistically significant.

Table 3 Treatment effect of EVL and NSBBs

	Baseline rate (NSBB)	Risk difference (NSBB vs EVL)
Variceal bleeding		

NSBB vs EVL	128 per 1000	18 more per 1000 (from 55 fewer to 62 more)
Propranolol vs EVL	124 per 1000	61 more per 1000 (from 6 more to 89 more)
Carvedilol vs EVL	131 per 1000	86 fewer per 1000 (from 299 fewer to 21 more)
Mortality		
NSBB vs EVL	157 per 1000	2 more per 1000 (from 88 fewer to 58 more)

Quality of life

Quality of life is generally represented by utility values, which is scored on a 0 to 1 scale where 0 is equal to death and 1 is equivalent to perfect health. NICE's preferred measure of health outcomes is the QALY, which combines both life expectancy and utilities into a single measure index.

In this analysis, the utility values were not available from the literature review. Instead, the same assumption from the previous guideline update (2017) was applied here. In the previous guideline, the QALY loss from death appeared to have been based on the utility value for compensated health state (between 0.5 and 0.6, depending on the underlying aetiology of cirrhosis) and remaining life expectancy when varices have developed (approximately 5 years). To fully capture the QALY impact of averted deaths, we extended the one-year time horizon to the whole remaining lifetime to derive the value. The QALY loss from a bleed was based on the difference between the utility values for the compensated cirrhosis and the decompensated health states (0.06) and a duration of 6 months for the impact of the bleed on quality of life.

The QALY loss from bleed and death have been given below:

- QALY loss from bleed: 0.03
- QALY loss from death: 3

Costs and healthcare resources

Cost inputs and resource utilisation were identified from published economic studies. Assumptions based on clinical guidelines and expert opinion of the guideline committee were applied wherever the data were not available. All costs were inflated to 2019/20 price level using the NHS cost inflation index.

Management costs of adverse events were not included in the model, due to a lack of suitable data on their event rate identified in the systematic review.

The following costs were included in the analysis:

- Cost of NSBBs,
- Cost of EVL delivered as primary prophylaxis for bleeding,
- Cost of endoscopic surveillance for people with EVL as primary prophylaxis,
- Cost of variceal bleeding treatment.

Cost of NSBBs

The unit costs of individual NSBBs were derived from the BNF (accessed March 2023). Due to the issue around data availability, the proportion of drug usage was assumed to be 75% for propranolol, 12.5% for carvedilol and 12.5% for nadolol, based on committee opinion and that propranolol is often recommended as the first-line NSBB in other guidelines. The daily dosage of each drug was obtained from the published clinical studies in the review, and was 77.3mg for propranolol, 12.5mg for carvedilol and 68mg for nadolol. The weighted cost of pooled NSBBs was computed according to the proportion of drug usage, mean daily dosage and unit costs of each individual NSBBs, which was estimated to be £25.27 per year.

NSBB	Proportion	Daily dosage	Unit price per mg	BNF (package size/drug tariff)
Propranolol	75%	77.3mg	£0.0007	40mg*28 tablets/£0.81

Carvedilol	12.5%	12.5mg	£0.0028	12.5mg*28 tablets/£0.99
Nadolol	12.5%	68mg	£0.0027	80mg*28 tablets/£6

Cost of EVL for bleeding prevention

The cost of EVL for the bleeding prevention over 1-year time period was estimated to be £2,243, calculated by multiplying the number of EVL sessions by the unit cost of EVL. Because of the inconsistently reported number across published clinical trials and clinical centres, the mean number of EVL sessions required for the bleeding prevention was assumed to be 4 to reflect the experience of the guideline committee. The uncertainty associated with the number of EVL sessions was explored in the scenario analyses using the value reported in clinical studies, where the number of EVL session required was supposed to vary between 2.4 and 5. In the past analysis, the unit cost of EVL was from an NHS hospital trust where a committee member worked in. Since no published NHS cost data were available for the EVL, this analysis inflated that 2016 cost to the 2019/20 price level, which was equal to £561.

Cost of endoscopic surveillance

It was understood that people on EVL for the primary prevention of bleeding required endoscopic surveillance. Following variceal eradication, people who received EVL underwent endoscopy at 3 months, and then 6 monthly thereafter. As a result, for people who had EVL, the cost of endoscopic surveillance was taken into account. The weighted cost of endoscopy per visit was about £481, which was computed according to the percentage of endoscopy that was performed in a day case setting versus an outpatient setting. It was worth noting that the proportion of procedures was estimated based on the number of procedures across all departments. The number of procedures and unit cost in each clinical setting were derived from the national schedule of NHS costs 2019/20 (Table 4). Given that there was little difference in the unit cost between the day case and outpatient setting, the potentially overstated proportions had little impact on the weighted cost per visit. The total cost of endoscopic surveillance over the time period was computed by multiplying the weighted cost per visit by the frequency of endoscopy.

The cost of endoscopic surveillance was not included in the previous development, therefore, the impact of this cost on the cost effectiveness was assessed in the scenario analysis.

Table 4 Costs of endoscopic surveillance

FE22Z Diagnostic Endoscopic Upper Gastrointestinal Tract Procedures, 19 years and over	Number of procedures	Proportion	Unit cost
Day case	165,997	96.68%	£482.23
Outpatient procedure for gastroenterology	5,709	3.32%	£430.93

Cost of treating a variceal bleeding

The treatment cost of variceal bleeding was derived from a cost-effectiveness study on treatments for patients with variceal bleeding and refractory ascites secondary to cirrhosis, Mattock et al (2021). The treatment strategy for variceal bleeding in the Mattock study was NSBBs (i.e., carvedilol, propranolol and nadolol) in combination with outpatient EVL over 24-month survival period, which costed about £3,862 using 2017/18 price. Uprating this cost to the 2019/20 price level, the mean cost of bleeding treatment was estimated to be £4,039.

According to the clinical evidence, hospitalisation showed a significant effect favouring EVL. To explore the impact of hospitalisation on the cost effectiveness result, the cost of hospitalisation for managing a bleed was included in the scenario analyses. The total hospitalisation cost in the Mattock study was about £6,454 (2017/18 price), assuming that 25% of people required an ICU and there were 7.97 non-elective bed days. This gave rise to a total hospitalisation cost of £6,749 in 2019/20 price.

Scenario analyses

A variety of scenario analyses were carried out to evaluate the impact of uncertainties in our sources of data and modelling assumptions. A brief description of each scenario was summarised in the table below.

Table 5 Description of scenario analyses in the economic model

Scenario	Description of scenario
NSBBs: lower limits of 95% CI of risk difference for bleed (-0.055) and mortality (-0.088) simultaneously	Compared with EVL, NSBB had 55 fewer bleeds and 88 fewer deaths per thousand.
NSBBs: upper limits of 95% CI of risk difference for bleed (0.062) and mortality (0.058) simultaneously	Compared with EVL, NSBB had 62 more bleeds and 58 more deaths per thousand.
NSBBs including propranolol and carvedilol only	Regarding NSBBs, nadolol was not used in the UK. The proportion of drug usage for propranolol and carvedilol was assumed to be 75% and 25%, respectively in this scenario.
NSBB cost based on the unit costs of propranolol 40mg package and carvedilol 6.25mg package	The mean daily dosage for each three NSBBs was same with the base case. The unit costs of propranolol and carvedilol were replaced with the costs of minimum package size on the BNF list.
NSBB cost based on the upper limit for doses (i.e., propranolol 160mg twice daily/carvedilol 12.5mg daily/nadolol 240mg daily)	People on NSBBs were given maximum dosage. The unit costs for individual NSBBs were also updated accordingly using the price of maximum package size on the BNF list.
Exclusion of the endoscopic surveillance cost from EVL	To assess the consistency with the previous analysis, the endoscopic surveillance cost was excluded for people who received EVL.

EVL vs carvedilol	A comparison between EVL and carvedilol alone.
EVL vs propranolol	A comparison between EVL and propranolol alone.
Number of EVL sessions for primary prevention: min 2.4	Assumption that the minimum number of EVL session required for the bleeding prevention was 2.4
Number of EVL sessions for primary prevention: max 5	Assumption that the maximum number of EVL session required for the bleeding prevention was 5
Cost of variceal bleeding treatment: lower bound value £2,309	Lower limit of the treatment cost of bleeding
Cost of variceal bleeding treatment (including hospitalisation): upper bound value £6,749	Taking into account the cost of hospitalisation for the bleeding management.
QALY loss from bleed: 0.015	Half the value in the base case
QALY loss from bleed: 0.06	Double the value in the base case
Adverse event for lethargy: risk with NSBBs 0.286, risk difference for EVL -0.274, disutility 0.1	Assuming an ongoing disutility was 0.1, no additional management cost for lethargy,
24-month time horizon	To explore the uncertainty in the time frame, 24-month time horizon was based on the average follow-up time reported in clinical studies for propranolol.

Results

Base-case results

In the base case, EVL had an additional cost of £3,346 and an incremental QALY of 0.0065 compared with NSBBs, giving an ICER of £511,614 per QALY. The impact on the quality of life was pretty much close between EVL and NSBBs. The total annual cost for the pooled NSBBs was only about £542 per person while the total cost for EVL a year was approximately £3,888. The huge cost in the EVL arm was partially arising from the high cost of EVL procedure itself and endoscopic surveillance. As the ICER was above the opportunity cost threshold of £20,000 at NICE, EVL was not cost effective for the primary prevention of bleeding.

Scenario analysis results

A number of scenarios were conducted to explore the impact of uncertainties on the cost effectiveness. The table below summarised the outcomes for each scenario. The main driver of the cost effectiveness was treatment effect for variceal bleeding and mortality. These clinical data were based on low quality evidence with high uncertainties. When the pooled NSBBs had 62 more bleeds and 58 more deaths than EVL per thousand people, the ICER was equivalent to £18,016 which indicated that EVL was cost effective. EVL was dominated by the pooled NSBBs in the scenario where NSBBs had 55 fewer bleeds and 88 fewer deaths per thousand (ICER was -£13,705). EVL remained not cost effective in all the rest of scenarios with an ICER above NICE's £20,000 threshold.

Table 1 Scenario analyses

Scenarios	Cost (EVL)	QALY loss (EVL)	Cost (NSBBs)	QALY loss (NSBBs)	ICER
Base case	£3,888	-0.468	£542	-0.475	£511,614
NSBBs: lower limits of 95% CI of risk difference for bleed (-0.055) and mortality (-0.088) simultaneously	£4,183	-0.740	£542	-0.475	-£13,705

NSBBs: upper limits of 95% CI of risk difference for bleed (0.062) and mortality (0.058) simultaneously	£3,711	-0.299	£542	-0.475	£18,016
NSBBs including propranolol and carvedilol only	£3,888	-0.468	£536	-0.475	£512,574
NSBB cost based on the unit costs of propranolol 40mg package and carvedilol 6.25mg package	£3,888	-0.468	£543	-0.475	£511,487
NSBB cost based on the upper limit for doses (i.e., propranolol 160mg twice daily/carvedilol 12.5mg daily/nadolol 240mg daily)	£3,888	-0.468	£606	-0.475	£501,892
Exclusion of the endoscopic surveillance cost from EVL	£2,687	-0.468	£542	-0.475	£327,928
EVL vs carvedilol	£4,320	-0.472	£545	-0.475	£1,103,799
EVL vs propranolol	£3,698	-0.467	£521	-0.475	£405,831
Number of EVL sessions for primary prevention: min 2.4	£2,991	-0.468	£542	-0.475	£374,451
Number of EVL sessions for primary prevention: max 5	£4,449	-0.468	£542	-0.475	£597,342
Cost of variceal bleeding treatment: lower bound value £2,309	£3,698	-0.468	£321	-0.475	£516,377
Cost of variceal bleeding treatment (including hospitalisation): upper bound value £6,749	£4,186	-0.468	£889	-0.475	£504,156
QALY loss from bleed: 0.015	£3,888	-0.467	£542	-0.473	£533,646
QALY loss from bleed: 0.06	£3,888	-0.472	£542	-0.479	£472,593

Adverse event for lethargy: risk with NSBBs 0.286, risk difference for EVL -0.274, disutility 0.1	£3,888	-0.470	£542	-0.503	£98,585
24-month time horizon	£4,849	-0.468	£568	-0.475	£654,699

Discussions

Principal findings

NSBBs seem to be a more cost-effective option compared with EVL for the primary prevention of variceal bleeding.

A number of scenarios are performed to investigate the uncertainty associated with model assumptions and parameters. In general, the outcomes are consistent and robust that NSBBs and EVL have a similar impact on the quality of life while EVL is much more expensive than NSBBs. EVL only appears to be cost effective in the case where pooled NSBBs had 62 more bleeds and 58 more deaths than EVL per thousand people, which represents the most favourable bound of the 95% confidence interval for the EVL treatment effect. Thus, the treatment effects, namely, the risk reductions in bleed and mortality are the key drivers of this analysis.

Strengths of the analysis

One of the strengths of this model is that the outcomes are robust to a majority of assumptions or parameters explored. Only the risk differences in bleed and mortality between these two interventions affect the conclusion.

This analysis was conducted using the latest and best available evidence. We updated the value in the previous guideline from the updated NHS collection cost or derived the inputs from a UK-based economic study (Mattock 2021). We also used the clinical data from the latest clinical review undertaken by the NICE development team. All parameters and assumptions have been validated by the NICE committee of clinical experts. This indicates that our analysis is representative of clinical practice in the UK.

Weakness of the analysis

One of weaknesses is that this simplified model structure only incorporates the outcomes of variceal bleeding and all-cause mortality. According to the latest clinical review, hospitalisation seems have a significant effect favouring EVL, therefore only the cost of hospitalisation for managing a bleed is explored in this analysis. Management costs of adverse events were not included in the model given that these events associated with NSBBs were less likely to incur high costs. Nevertheless, we assess the impact of lethargy on the quality of life given that the significant treatment effect of lethargy between EVL and NSBBs indicated by the clinical evidence.

Furthermore, there are substantial uncertainties around the treatment effect between EVL and NSBBs. Overall, the treatment effect of bleeding between NSBBs and EVL is not statistically significant. Compared with EVL, carvedilol reduces the risk of bleeding, which shows an opposite effect to propranolol. However, this clinical evidence is based solely on two studies, therefore it is not conclusive and less robust. Regarding the risk difference in mortality, NSBBs show a smaller treatment effect in this updated clinical review than the previous analysis.

Another weakness is the uncertainty around the time frame over the clinical benefits. The difference in follow-up time across clinical studies gives rise to some uncertainties when trying to pool them together. Hence, we assume 1-year time horizon to evaluate the benefits. Because the mean follow-up time over a number of trials comparing propranolol against EVL was approximately 24 months, we also explored the benefits over 2-year time horizon.

In addition, there is an issue around the data availability, such as the number of EVL sessions, cost of EVL and average daily dosage of NSBBs. Although the committee members have provided some information based on their own experience and validated our assumptions, further data collection in future would support us to update our results and eliminate the uncertainties.

Conclusions

EVL is less likely to be cost effective compared to NSBBs for the primary prevention of bleeding in people with medium to large oesophageal varices due to cirrhosis.

NSBBs cost much less than EVL while the impact of these two interventions on the quality of life is essentially similar. High-quality data collection in future can enhance the certainty of this analysis.

Appendix J – Excluded studies

J1 Effectiveness evidence

Study	Reason for exclusion
(2005) 202 Endoscopic variceal band ligation in comparison with propranolol in prophylaxis of first variceal bleeding in patients with liver cirrhosis. Journal of Hepatology 42: 79	- Conference abstract
Abdelfattah, M.H., Rashed, M.A., Elfakhry, A.A. et al. (2006) 201 Endoscopic variceal ligation versus pharmacologic treatment for primary prophylaxis of variceal bleeding: a randomised study. Journal of Hepatology 44: 83	- Conference abstract
Abulfutuh, Ashraf R., Morsy, Mohammed, Solyman, Abd El Ghany et al. (2003) Study of variceal band ligation, propranolol and isosorbide mononitrate in the prevention of the first variceal bleeding. Gastroenterology 124(4): a780	- Conference abstract
Anonymous. (2019) Erratum: beta blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised, double-blind, placebo-controlled, multicentre trial (The Lancet (2019) 393(10181) (1597-1608), (S0140673618318750), (10.1016/S0140-6736(18)31875-0)). The Lancet 393(10190): 2492	- Not a relevant study design *Erratum for excluded paper.*
Chen, CY; Sheu, MZ; Su, SY (1998) Prophylactic endoscopic variceal ligation (EVL) with multiple band ligator for esophageal varices. Gastroenterology 114: a1224	- Conference abstract
Chirapongsathorn, Sakkarin, Valentin, Nelson, Alahdab, Fares et al. (2016) Nonselective beta-Blockers and Survival in Patients With Cirrhosis and Ascites: A Systematic Review and Meta-analysis. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association 14(8): 1096-1104e9	- Systematic review used as source of primary studies

Study	Reason for exclusion
de la Mora, Jose G., Farca-Belsaguy, Alberto A., Uribe, Misael et al. (2000) Ligation VS propranolol for primary prophilaxis of variceal bleeding using a multiple band liga-tor and objective measurements of treatment adequacy: Preliminary results. Gastroenterology 118(4): a1434-a1435	- Conference abstract
Dwinata, M, Putera, DD, Adda'i, MF et al. (2019) Carvedilol vs endoscopic variceal ligation for primary and secondary prevention of variceal bleeding: Systematic review and meta-analysis. World journal of hepatology 11(5): 464-476	- Systematic review used as source of primary studies
Funakoshi, N., Duny, Y., Valats, J.-C. et al. (2012) Meta-analysis: beta-blockers versus banding ligation for primary prophylaxis of esophageal variceal bleeding. Annals of Hepatology 11(3): 369-383	- Systematic review used as source of primary studies
Gheorghe, Cristian, Gheorghe, Liana, Vadan, Roxana et al. (2002) Prophylactic banding ligation of high risk esophageal varices inpatients on the waiting list for liver transplantation: an interim report. Journal of Hepatology 36: 38	- Conference abstract
Jutabha, Rome, Jensen, Dennis M., Martin, Paul et al. (2000) Initial report of a randomized, prospective study of prophylactic propranolol compared to rubber band ligation for prevention of first variceal hemorrhage in cirrhotics with large esophageal varices. Gastroenterology 118(4): a212-a213	- Conference abstract
Li, Tong, Ke, Wenbo, Sun, Ping et al. (2016) Carvedilol for portal hypertension in cirrhosis: systematic review with meta-analysis. BMJ open 6(5): e010902	- Systematic review used as source of primary studies
Malandris, K., Paschos, P., Katsoula, A. et al. (2019) Carvedilol for prevention of variceal bleeding: A systematic review and meta-analysis. Annals of Gastroenterology 32(3): 287-297	- Systematic review used as source of primary studies
McDowell, Hannah R, Chuah, Cher Shiong, Tripathi, Dhiraj et al. (2021) Carvedilol is associated with improved survival in	- Not a relevant study design *Post-hoc cohort study of an included RCT.*

Study	Reason for exclusion
patients with cirrhosis: a long-term follow-up study. Alimentary pharmacology & therapeutics 53(4): 531-539	
Roccarina, Davide, Best, Lawrence Mj, Freeman, Suzanne C et al. (2021) Primary prevention of variceal bleeding in people with oesophageal varices due to liver cirrhosis: a network meta-analysis. The Cochrane database of systematic reviews 4: cd013121	- Systematic review used as source of primary studies
Sarin SK, Lamba GS, Kumar M et al. (1997) Randomized trial of propranolol vs endoscopic variceal ligation in the primary prophylaxis of bleeding from high risk varices in cirrhosis: an interim analysis. 26(4 (pt2)): 360A	- Conference abstract
Schepke M, Goebel C, Nuernberg D et al. (2003) Endoscopic banding ligation versus propranolol for the primary prevention of variceal bleeding in cirrhosis: a randomized controlled multicenter trial [Abstract]. 38: 218	- Conference abstract
Sharma, Mayank, Singh, Siddharth, Desai, Vivek et al. (2019) Comparison of Therapies for Primary Prevention of Esophageal Variceal Bleeding: A Systematic Review and Network Meta-analysis. Hepatology (Baltimore, Md.) 69(4): 1657-1675	- Systematic review used as source of primary studies
Song, I.H., Shin, J.W., Kim, I.H. et al. (2000) A prospective randomized trial between the prophylactic endoscopicvariceal ligation and propranolol administration for prevention offirst bleeding in cirrhotic patients with high-risk esophageal varices. Journal of Hepatology 32: 41	- Conference abstract
Tian, S., Li, R., Guo, Y. et al. (2019) Carvedilol vs endoscopic band ligation for the prevention of variceal bleeding: A meta-analysis. Therapeutics and Clinical Risk Management 15: 191-200	- Systematic review used as source of primary studies
Villanueva, Candid, Albillos, Agustin, Genesca, Joan et al. (2019) beta blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised,	- Does not contain a population of people with cirrhosis and varices

Study	Reason for exclusion
double-blind, placebo-controlled, multicentre trial. Lancet (London, England) 393(10181): 1597-1608	
Villanueva, Candid, Torres, Ferran, Sarin, Shiv Kumar et al. (2022) Carvedilol reduces the risk of decompensation and mortality in patients with compensated cirrhosis in a competing-risk meta-analysis. Journal of hepatology 77(4): 1014-1025	- Systematic review used as source of primary studies
Wei, Z.-G., Wei, F.-X., Shao, Z.-W. et al. (2019) Lowering hepatic venous pressure agent carvedilol versus variceal banding ligation for clinical outcomes of cirrhotic portal hypertension. Therapeutics and Clinical Risk Management 15: 45-57	- Systematic review used as source of primary studies
Zacharias, Antony P, Jeyaraj, Rebecca, Hobolth, Lise et al. (2018) Carvedilol versus traditional, non-selective beta-blockers for adults with cirrhosis and gastroesophageal varices. The Cochrane database of systematic reviews 10: cd011510	- Systematic review used as source of primary studies

Appendix K– Research recommendations – full details

K1.1 Research recommendation

What is the effectiveness and cost-effectiveness of endoscopic variceal band ligation (EVL) plus a non-selective beta-blocker (NSBB) compared to either EVL or NSBB alone for the primary prevention of variceal bleeding in adults with cirrhosis and medium or large oesophageal varices?

K1.1.1 Why this is important

Both NSBB and EVL show similar effectiveness at preventing bleeding, but none of the studies found for this evidence review used them in combination. There may be added benefit in combining the treatments.

K1.1.2 Rationale for research recommendation

Importance to 'patients' or the population	Bleeding from varices is a significant and life-threatening event for people living with cirrhosis. Preventing bleeding has an impact on their quality and length of life.
Relevance to NICE guidance	The evidence for EVL versus NSBB was not strong and no included studies compared EVL or NSBB with both together. This is relevant for future updates of this guideline
Relevance to the NHS	The outcome would affect the types of treatment provided by the NHS and may also predict future healthcare needs for people with oesophageal varices
National priorities	Medium
Current evidence base	Evidence on EVL alone and NSBB alone, but no evidence in combination.
Equality considerations	People with cirrhosis are disproportionately from excluded groups such as people who are homeless or misuse alcohol.

K1.1.3 Modified PICO table

Population	People aged 16 years and older with cirrhosis, who have medium- sized or large oesophageal varices which have never bled.
Intervention	Non-selective beta-blockers (NSBBs) (Nadolol, Timolol maleate, Sotalol, Carvedilol, Labetalol, Propranolol) plus endoscopic variceal band ligation (EVL).
Comparator	• EVL alone. • NSBB alone
Outcome	• Primary variceal bleeding • Mortality (including mortality caused by bleeding)

	• Quality of life (using a validated scale) • Liver transplant • Number of decompensation episodes • Hospitalisation (including length of hospital stay) • Other adverse events (for example, pain, low compliance/discontinuation with treatment due to side effects or for other reasons)
Study design	RCT
Timeframe	Medium term
Additional information	None