H.6 Prophylaxis of variceal haemorrhage

Study	Andreani 1990[6]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=126)
Countries and setting	Conducted in France; setting: multicentre (2 centres)
Line of therapy	First line
Duration of study	Intervention + follow up: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Cirrhosis proven by histological examination (or if unavailable, on the basis of clinical or lab test results, regardless of origin)
Stratum	Size of varices (overall): Presence of oesophageal varices on endoscopy regardless of size
Subgroup analysis within study	Post-hoc subgroup analysis: Size of varices (grade I: non-confluent oesophageal varices flattened by insufflation; grade

Study	Andreani 1990[6]
	II: oesophageal varices separated by zones of normal oesophagus and not flattened by insufflation; grade III: confluent oesophageal varices not flattened by insufflation)
Inclusion criteria	All adult patients with 1) cirrhosis proven by histological examination (or if unavailable, on the basis of clinical or lab test results, regardless of origin); 2) presence of oesophageal varices on endoscopy regardless of size; 3) no history of gastrointestinal bleeding by rupture of oesophageal varices.
Exclusion criteria	1) HCC; 2) contraindication to the use of propranolol (cardiac insufficiency, asthma, disturbance of auriculoventricular conduction); 3) refusal or unfeasibility of treatment; 4) unfeasibility of regular surveillance; 5) serious associated illness reducing life expectancy to <1 year; 6) previous treatment with endoscopic sclerosis of oesophageal varices, propranolol or surgery for portal hypertension.
Recruitment/selection of patients	All eligible adult patients. November 1985 to February 1988.
Age, gender and ethnicity	Age – other: mean (SEM) propranolol: 55.0 (1.3), placebo: 55.6 (1.7). Gender (M:F): 50/34. Ethnicity: not reported.
Further population details	1. Age of patient: 65 years and under (propranolol: 55.0 [1.3], placebo: 55.6 [1.7]. Mean age in both arms <65 years). 2. Severity of underlying liver disease at the time of intervention (measured by MELD): Child-Pugh score B or C (Child-Pugh A: 23.8%; Child-Pugh B: 47.6%; Child-Pugh C: 27.4% [overall 75% Child-Pugh B and C]).
Extra comments	Size of varices (Grade I/II/III): propranolol 15/24/4; placebo 17/16/6. Child-Pugh class (A/B/C): propranolol 10/19/13; placebo 10/21/10. Ascites (absent/moderate/intractable): propranolol 17/20/6; placebo 18/16/7. Study has a third arm (sclerotherapy).
Indirectness of population	No indirectness
Interventions	(n=43) Intervention 1: Oral non-selective beta-blockers – propranolol. Propranolol twice daily. Dose titrated to achieve a 25% reduction in resting heart rate. Patients seen after 1 month and then at 3 month intervals. Duration 2 years. Concurrent medication/care: not reported. (n=41) Intervention 2: Placebo. Vitamin K (10 mg) twice daily as placebo. Patients seen after 1 month and then at 3 month intervals. Duration 2 years. Concurrent medication/care: other associated treatment authorised with the exception of beta-blockers.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PROPRANOLOL versus PLACEBO

Protocol outcome 1: survival (with or without transplant) at end of study
- Actual outcome for size of varices (overall): mortality at 2 years; Group 1: 13/37, Group 2: 18/39; risk of bias: high; indirectness of outcome: serious indirectness

Study	Andreani 1990[6]
Protocol outcome 2: primary variceal bleeding at end of study - Actual outcome for size of varices (small): variceal bleeding (active bleeding from the varices or the presence of a clot on a varix and no other detectable cause of haemorrhage) at 2 years; Group 1: 0/15, Group 2: 2/17; risk of bias: very high; indirectness of outcome: serious indirectness - Actual outcome for size of varices (medium/large): variceal bleeding (active bleeding from the varices or the presence of a clot on a varix and no other detectable cause of haemorrhage) at 2 years; Group 1: 2/28, Group 2: 8/22; risk of bias: very high; indirectness of outcome: serious indirectness Protocol outcome 3: primary upper gastrointestinal bleeding (irrespective of bleeding source) at end of study - Actual outcome for size of varices (small): gastrointestinal bleeding (variceal or other) at 2 years; Group 1: 0/15, Group 2: 3/17; risk of bias: very high; indirectness of outcome: no indirectness - Actual outcome for size of varices (medium/large): gastrointestinal bleeding (variceal or other) at 2 years; Group 1: 2/28, Group 2: 10/22; risk of bias: very high; indirectness of outcome: no indirectness Protocol outcome 4: bleeding related mortality at end of study - Actual outcome for size of varices (overall): variceal or gastrointestinal bleeding death at 2 years; Group 1: 1/37, Group 2: 4/39; risk of bias: very high; indirectness of outcome: serious indirectness	
Protocol outcomes not reported by the study	Health-related quality of life at end of study; hospital admission at end of study; hospital length of stay at end of study; adverse events: fatigue at end of study

Study (subsidiary papers)	Conn 1991[28] (Groszmann 1990[57])
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=102)
Countries and setting	Conducted in multiple countries, Spain, USA; setting: multicentre (3 centres)
Line of therapy	First line
Duration of study	Intervention + follow up: mean 16.3 months
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: well-established clinical diagnosis of cirrhosis (approximately 50% had histological confirmation)
Stratum	Size of varices (overall): endoscopically documented oesophageal varices
Subgroup analysis within study	Post-hoc subgroup analysis: size of varices (grade 1: 1–3 mm with Valsalva, grade 2: 1–3 mm without Valsalva, grade

Study (subsidiary papers)	Conn 1991[28] (Groszmann 1990[57])
	3: 3–3 mm; grade 4: >6 mm). Results reported separately for small varices (defined in study as grade 1 and 2) and large varices (defined in study as grade 3 and 4).
Inclusion criteria	Patients with a well-established clinical diagnosis of cirrhosis (approximately 50% had histological confirmation), endoscopically documented oesophageal varices and portal hypertension who had not previously bled from oesophageal varices or from an unknown upper gastrointestinal site.
Exclusion criteria	Known neoplasms or severe hepatic disease (for example hepatorenal syndrome) or non-hepatic disorders (for example cardiovascular, respiratory or renal failure) severe enough to interfere with participation.
Recruitment/selection of patients	Admitted to one of the participating hospitals between October 1982 and August 1986
Age, gender and ethnicity	Age – mean (SD): propranolol: 54 (9), placebo: 54 (11). Gender (M:F): 73/29. Ethnicity: not reported.
Further population details	1. Age of patient: 65 years and under (propranolol: 54 [9], placebo: 54 [11]. Mean age in both groups <65 years). 2. Severity of underlying liver disease at the time of intervention (measured by MELD): Child-Pugh score A (Child-Pugh A: 57.8%; Child-Pugh B & C: 42.2%).
Extra comments	Child-Pugh class (A/B/C): propranolol 35/11/5, placebo 24/24/3. Ascites: propranolol 22, placebo 31. Varices (small/large): propranolol 26/25, placebo 29/22.
Indirectness of population	No indirectness
Interventions	(n=51) Intervention 1: oral non-selective beta-blockers – propranolol. Dose for placebo/propranolol for the study determined prior to randomisation by the response of HVPG to increasing doses of propranolol during hepatic vein catheterisation (in order to keep the study blind by not adjusting dose according to resting heart rate). Dose not increased above the level determined during titration. Dose could be reduced because of bradycardia or hypotension. Seen as outpatients monthly for 3 months and then every 3 months thereafter. Duration mean 16.3 months. Concurrent medication/care: not reported. (n=51) Intervention 2: placebo. Dose for placebo/propranolol for the study determined prior to randomisation by the response of HVPG to increasing doses of propranolol during hepatic vein catheterisation (in order to keep the study blind by not adjusting dose according to resting heart rate). Dose not increased above the level determined during titration. Seen as outpatients monthly for 3 months and then every 3 months thereafter. Duration mean 16.3 months. Concurrent medication/care: not reported.
Funding	Study funded by industry (supported by Ayerst Laboratories, New York; Imperial Chemical Industries, Spain and the Veterans Administration Merit Review Program.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PROPRANOLOL versus PLACEBO	

Study (subsidiary papers)	Conn 1991[28] (Groszmann 1990[57])
Protocol outcome 1: survival (with or without transplant) at end of study - Actual outcome for size of varices (overall): death at mean 16.3 months; Group 1: 8/51, Group 2: 11/51; risk of bias: low; indirectness of outcome: serious indirectness Protocol outcome 2: primary variceal bleeding at end of study - Actual outcome for size of varices (small): endoscopic visualisation of an actively bleeding varix, a fresh clot or eschar on the surface of a varix or the absence of any other possible bleeding site in the upper gastrointestinal tract at mean 16.3 months; Group 1: 2/26, Group 2: 2/29; risk of bias: high; indirectness of outcome: serious indirectness - Actual outcome for size of varices (medium/large): endoscopic visualisation of an actively bleeding varix, a fresh clot or eschar on the surface of a varix or the absence of any other possible bleeding site in the upper gastrointestinal tract at mean 16.3 months; Group 1: 0/25, Group 2: 9/22; risk of bias: high; indirectness of outcome: serious indirectness Protocol outcome 3: primary upper gastrointestinal bleeding (irrespective of bleeding source) at end of study - Actual outcome for size of varices (overall): gastrointestinal haemorrhage at mean 16.3 months; Group 1: 4/51, Group 2: 14/51; risk of bias: low; indirectness of outcome: serious indirectness Protocol outcome 4: bleeding-related mortality at end of study - Actual outcome for size of varices (overall): death due to variceal haemorrhage at mean 16.3 months; Group 1: 2/51, Group 2: 3/51; risk of bias: low; indirectness of outcome: serious indirectness	
Protocol outcomes not reported by the study	Health-related quality of life at end of study; hospital admission at end of study; hospital length of stay at end of study; adverse events: fatigue at end of study

Study (subsidiary papers)	Gluud 2012[55] (Drastich 2011,[32] Gheorghe 2002,[52] Jutabha 2000,[65] Schcpka 2003,[124] Song 2000,[133] Chen 1998,[24] De 1999,[31] Sarin 1999,[121] De la Mora 2000,[29] Lui 2002,[82] Abulfutuh 2003,[4] Schepke 2004,[125] Jutabha 2005,[64] Thuluvath 2005,[148] Anon 2005,[1] Lay 2006,[75] Abdelfattah 2006,[2] Lo 2004,[79] Norberto 2007,[93] Perez-Ayuso 2010,[101] Psilopoulos 2005,[104] Sarin 1997,[123] Tripathi 2009[153])
Study type	Systematic review
Number of studies (number of participants)	19 studies (23 references) (n=total 1504. Mean [range] in individual studies 79 [24–152])
Countries and setting	Conducted in China, Czech Republic, Egypt, Germany, Greece, India, Italy, Mexico, Romania, South Korea, Taiwan, United Kingdom, USA; setting: 13 trials were single-centre trials. The remaining five trials included 2 to 13 clinical sites.

Study (subsidiary papers)	**Gluud 2012[55] (Drastich 2011,[32] Gheorghe 2002,[52] Jutabha 2000,[65] Schcpka 2003,[124] Song 2000,[133] Chen 1998,[24] De 1999,[31] Sarin 1999,[121] De la Mora 2000,[29] Lui 2002,[82] Abulfutuh 2003,[4] Schepke 2004,[125] Jutabha 2005,[64] Thuluvath 2005,[148] Anon 2005,[1] Lay 2006,[75] Abdelfattah 2006,[2] Lo 2004,[79] Norberto 2007,[93] Perez-Ayuso 2010,[101] Psilopoulos 2005,[104] Sarin 1997,[123] Tripathi 2009[153])**
Line of therapy	First line
Duration of study	Intervention + follow up: range of average follow-up times (10–55 months)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: included patients with cirrhosis diagnosed based on clinical, biochemical, or histological signs
Stratum	Size of varices (medium/large): included studies specified only patients with large or high-risk oesophageal varices were considered for inclusion. The criteria used for assessing the risk of bleeding were red colour signs, tortuous varices protruding as far as at least one third of the oesophageal lumen, or pseudotumourous varices (also known as F2 or F3 varices). Other trials classified as high risk if they had a diameter of at least 5 mm or at least 3 mm plus at least one red colour sign.
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult patients with endoscopically verified oesophageal varices that have never bled were included regardless of the underlying liver disease (cirrhosis or other cause).
Exclusion criteria	The reported exclusion criteria were contraindications to beta-blockers or severe concurrent illness, such as renal or malignant disease.
Recruitment/selection of patients	Systematic review – not reported
Age, gender and ethnicity	Age – mean (range): banding ligation: 53 (42–62), beta-blockers: 52 (39–59). Gender (M:F): 66%/34%. Ethnicity: systematic review – not reported.
Further population details	1. Age of patient: 65 years and under. 2. Severity of underlying liver disease at the time of intervention (measured by MELD): systematic review: mixed.
Extra comments	In 2 trials, all patients were eligible for liver transplantation (Gheorghe 2002, Norberto 2007). Mean number of patients with alcohol-related liver disease 22%. Seven trials published in abstract form.
Indirectness of population	Sarin 1999: cirrhosis not an inclusion criteria for study (7 patients had another underlying cause of portal hypertension); Chen 1998: risk or size of varices not stated.
Interventions	(n=731) Intervention 1: band ligation – multiband. Banding ligation performed with conventional or multiband ligators and was repeated at 3 to 4 week intervals until the varices were eradicated. On average, 2 to 3 sessions were necessary to achieve eradication. Patients were followed up at 3 to 6 month intervals and banding ligation repeated in the case of variceal recurrence. Duration range of average follow-up times (10–55 months). Concurrent medication/care: not stated.

Study (subsidiary papers)	**Gluud 2012[55] (Drastich 2011,[32] Gheorghe 2002,[52] Jutabha 2000,[65] Schcpka 2003,[124] Song 2000,[133] Chen 1998,[24] De 1999,[31] Sarin 1999,[121] De la Mora 2000,[29] Lui 2002,[82] Abulfutuh 2003,[4] Schepke 2004,[125] Jutabha 2005,[64] Thuluvath 2005,[148] Anon 2005,[1] Lay 2006,[75] Abdelfattah 2006,[2] Lo 2004,[79] Norberto 2007,[93] Perez-Ayuso 2010,[101] Psilopoulos 2005,[104] Sarin 1997,[123] Tripathi 2009[153])**
	(n=773) Intervention 2: oral non-selective beta-blockers – propranolol. One trial assessed nadolol (Lo 2004). The initial daily dose was 40 mg adjusted based on the heart rate (mean 60 mg). One trial assessed carvedilol (Tripathi 2009). The initial daily dose of carvedilol was 6.25 mg. The dose was increased to 12.5 mg if tolerated (the mean dose was not reported). The remaining trials assessed propranolol. The initial daily dose of propranolol ranged from 20 to 120 mg (mean 60 mg). The dose was adjusted to achieve a 20% to 25% reduction in heart rate, a resting heart rate of 55 beats per minute or less, or to a maximum dose of 160 or 320 mg. The mean dose administered in the trials was 70 mg/day (range 30 mg to 93 mg). Duration range of average follow-up times (10–55 months). Concurrent medication/care: not stated.
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BAND LIGATION versus NON-SELECTIVE BETA-BLOCKERS

Protocol outcome 1: survival (with or without transplant) at end of study
- Actual outcome for size of varices (medium/large): mortality at range of average follow-up times (10–55 months); Group 1: 176/731, Group 2: 178/773; risk of bias: high; indirectness of outcome: serious indirectness
- Actual outcome for Drastich 2011[32] and size of varices (medium/large): overall survival at median 11 months; HR 0.81 (95% CI 0.11 to 5.77) calculated – from logrank P-value; indirectness of outcome: no indirectness
- Actual outcome for Lo 2004[79] and size of varices (medium/large): overall survival at median 21.8 months; HR 0.81 (95% CI 0.36 to 1.84) calculated – from logrank P-value; indirectness of outcome: no indirectness
- Actual outcome for Perez-ayuso 2010[101] and size of varices (medium/large): overall survival at median 55 months; HR 1.48 (95% CI 0.74 to 2.96) calculated – from logrank P-value; indirectness of outcome: no indirectness
- Actual outcome for Lui 2002[82] and size of varices (medium/large): overall survival at mean 19.7 months; HR 1.09 (95% CI 0.5 to 2.36) calculated – from curve and numbers at risk; indirectness of outcome: no indirectness
- Actual outcome for Psilopoulos 2005[104] and size of varices (medium/large): overall survival (censored when have variceal bleeding event) at mean 27.5 months; HR 0.79 (95% CI 0.34 to 1.84) calculated – from logrank P-value; indirectness of outcome: no indirectness
- Actual outcome for Schepke 2004[125] and size of varices (medium/large): overall survival at mean 34.3 months; HR 1.24 (95% CI 0.77 to 2.01) calculated – from logrank P-value; indirectness of outcome: no indirectness
- Actual outcome for Tripathi 2009[153] and size of varices (medium/large): overall survival at mean 25.5 months; HR 0.9 (95% CI 0.53 to 1.55) calculated – from logrank P-value; indirectness of outcome: no indirectness

Study (subsidiary papers)	Gluud 2012[55] (Drastich 2011,[32] Gheorghe 2002,[52] Jutabha 2000,[65] Schcpka 2003,[124] Song 2000,[133] Chen 1998,[24] De 1999,[31] Sarin 1999,[121] De la Mora 2000,[29] Lui 2002,[82] Abulfutuh 2003,[4] Schepke 2004,[125] Jutabha 2005,[64] Thuluvath 2005,[148] Anon 2005,[1] Lay 2006,[75] Abdelfattah 2006,[2] Lo 2004,[79] Norberto 2007,[93] Perez-Ayuso 2010,[101] Psilopoulos 2005,[104] Sarin 1997,[123] Tripathi 2009[153])
	Protocol outcome 2: primary variceal bleeding at end of study - Actual outcome for size of varices (medium/large): variceal bleeding at range of average follow-up times (10–55 months); Group 1: 75/590, Group 2: 112/611; risk of bias: high; indirectness of outcome: serious indirectness - Actual outcome for Drastich 2011[32] and size of varices (medium/large): without variceal bleeding at median 11 months; HR 0.64 (95% CI 0.09 to 4.6) calculated – from logrank P-value; indirectness of outcome: no indirectness - Actual outcome for Lo 2004[79] and size of varices (medium/large): free from first bleeding of oesophageal varices at median 21.8 months; HR 0.57 (95% CI 0.19 to 1.69) reported; indirectness of outcome: no indirectness - Actual outcome for Lui 2002[82] and size of varices (medium/large): free from variceal bleeding at mean 19.7 months; HR 0.46 (95% CI 0.15 to 1.47) calculated – from logrank P-value; indirectness of outcome: no indirectness - Actual outcome for Psilopoulos 2005[104] and size of varices (medium/large): free from variceal bleeding at mean 27.5 months; HR 0.21 (95% CI 0.04 to 0.95) calculated – from logrank P-value; indirectness of outcome: no indirectness - Actual outcome for Sarin 1997[123] and size of varices (medium/large): free from variceal bleeding at mean 13 months; HR 0.33 (95% CI 0.11 to 0.77) reported; indirectness of outcome: no indirectness - Actual outcome for Schepke 2004[125] and size of varices (medium/large): without first variceal bleed at mean 34.3 months; HR 1.05 (95% CI 0.57 to 1.94) calculated – from logrank P-value; indirectness of outcome: no indirectness - Actual outcome for Tripathi 2009[153] and size of varices (medium/large): free from variceal bleeding at mean 25.5 months; HR 2.4 (95% CI 1.03 to 5.55) reported; indirectness of outcome: no indirectness Protocol outcome 3: hospital admission at end of study - Actual outcome for Sarin 1997[123] and size of varices (medium/large): hospitalisations at mean 13 months; Group 1: 5/45, Group 2: 12/44; indirectness of outcome: no indirectness Protocol outcome 4: primary upper gastrointestinal bleeding (irrespective of bleeding source) at end of study - Actual outcome for size of varices (medium/large): upper gastrointestinal bleeding at range of average follow-up times (10–55 months); Group 1: 103/731, Group 2: 157/773; risk of bias: high; indirectness of outcome: no indirectness Protocol outcome 5: bleeding related mortality at end of study - Actual outcome for size of varices (medium/large): bleeding related mortality at range of average follow-up times (10–55 months); Group 1: 29/567, Group 2: 37/585; risk of bias: high; indirectness of outcome: no indirectness Protocol outcome 6: adverse events: fatigue at end of study

Study (subsidiary papers)	Gluud 2012[55] (Drastich 2011,[32] Gheorghe 2002,[52] Jutabha 2000,[65] Schcpka 2003,[124] Song 2000,[133] Chen 1998,[24] De 1999,[31] Sarin 1999,[121] De la Mora 2000,[29] Lui 2002,[82] Abulfutuh 2003,[4] Schepke 2004,[125] Jutabha 2005,[64] Thuluvath 2005,[148] Anon 2005,[1] Lay 2006,[75] Abdelfattah 2006,[2] Lo 2004,[79] Norberto 2007,[93] Perez-Ayuso 2010,[101] Psilopoulos 2005,[104] Sarin 1997,[123] Tripathi 2009[153])
- Actual outcome for size of varices (medium/large): lethargy at range of average follow-up times (10–55 months); Group 1: 0/86, Group 2: 22/77; risk of bias: high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Health-related quality of life at end of study; hospital length of stay at end of study

Study	Lay 1997[76]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=126)
Countries and setting	Conducted in China; setting: general hospital
Line of therapy	First line
Duration of study	Intervention + follow up: mean (SD) months: EVL: 13 (11), control: 14 (10)
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: cirrhosis with no other disease (for example cancer) reducing the life expectancy
Stratum	Size of varices (medium/large): all patients had oesophageal varices at high risk of bleeding of F2 or F3 size
Subgroup analysis within study	Unclear: Child-Pugh classification (subgroup analysis for first oesophageal bleeding episode but data inconsistent with total number reported in the text and at an unknown timepoint)
Inclusion criteria	1) No known previous bleeding from the upper gastrointestinal tract; 2) Oesophageal varices at high risk of bleeding, as defined below; and 3) Cirrhosis with no other disease (for example cancer) reducing the life expectancy. Oesophageal varices at high risk of bleeding (score <-0.38 resulting from the total sum of the category scores (fundamental colour, red colour sign, form, and oesophagitis). Therefore, all patients had blue varices of F2 or F3 size with at least one of the following: red wale markings (++, +++), cherry-red spots (++, +++), or hematocystic spots (+).
Exclusion criteria	Presence of gastric or ectopic varices were excluded
Recruitment/selection of patients	January 1993 to December 1995
Age, gender and ethnicity	Age – mean (SD): endoscopic variceal ligation (EVL): 56 (11); control: 55 (10). Gender (M:F): 101/25. Ethnicity: not reported.
Further population details	1. Age of patient: 65 years and under (mean for each arm <65 years. EVL: 56 [11]; control: 55 [10]). 2. Severity of

Study	Lay 1997[76]
	underlying liver disease at the time of intervention (measured by MELD): Child-Pugh score B or C (Child-Pugh A: 26.2%; Child-Pugh B: 35.7%; Child-Pugh C: 38.1%% [Overall 73.8% Child Pugh B or C]).
Extra comments	Aetiology (alcohol/hepatitis/other): EVL: 12/47/3; control: 11/49/4. Child-Pugh classification (A/B/C): EVL: 17/22/23; control: 16/23/25. Ascites: EVL: 33; control: 32.
Indirectness of population	No indirectness
Interventions	(n=62) Intervention 1: band ligation – conventional. Each varix was ligated with 1 to 3 rubber bands (adapted endoscopic ligating device, Bard Interventional Products, Billerica, MA). Ligation was performed by 2 experienced endoscopists who had performed more than 10 sessions. 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. Endoscopic treatment was performed weekly for the first 3 weeks, when possible, unless extensive oesophageal ulcers occurred or delays resulted from complications; then, treatment was performed every 2 weeks until the oesophageal varices were eradicated. Duration: mean 13 months. Concurrent medication/care: follow-up endoscopic examination was performed later on a 3-month basis. Patients were instructed to identify any symptoms or signs suggestive of complications and bleeding, and to visit the hospital immediately. (n=64) Intervention 2: no intervention. No details reported. Duration: mean 14 months. Concurrent medication/care: no details reported.
Funding	Academic or government funding (supported by grant NSC 83-0412-B-075A-011 from the National Science Council)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CONVENTIONAL versus NO INTERVENTION

Protocol outcome 1: survival (with or without transplant) at end of study
- Actual outcome for size of varices (medium/large): overall survival at up to 2 years (mean 13 months); HR 0.41 (95%CI 0.24 to 0.7) calculated – from logrank P-value; risk of bias: high; indirectness of outcome: no indirectness

Protocol outcome 2: primary variceal bleeding at end of study
- Actual outcome for size of varices (medium/large): active variceal bleeding was diagnosed when blood was seen directly by endoscopy to issue from a varix, or when fresh blood was seen in the oesophagus of patients with cherry-red spots on large varices and no other potential site of bleeding was discovered. Clinical signs were defined as new onset of haematemesis, coffee ground vomitus, hematochezia, or melena with increasing pulse rate over 110 beats per minute and decreasing blood pressure below 90 mm Hg at up to 2 years (mean 13 months); HR 0.33 (95%CI 0.19 to 0.58) calculated – from logrank P-value; risk of bias: high; indirectness of outcome: no indirectness

Study	Lay 1997[76]
Protocol outcome 3: primary upper gastrointestinal bleeding (irrespective of bleeding source) at end of study - Actual outcome for size of varices (medium/large): variceal bleeding at up to 2 years (mean 13 months); Group 1: 12/62, Group 2: 38/64; risk of bias: high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Health-related quality of life at end of study; hospital admission at end of study; hospital length of stay at end of study; bleeding-related mortality at end of study; adverse events: fatigue at end of study

Study	Lo 1999[80]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=133)
Countries and setting	Conducted in Taiwan; setting: general hospital
Line of therapy	First line
Duration of study	Intervention + follow up: median 29 months
Method of assessment of guideline condition	Method of assessment/diagnosis not stated: cause of portal hypertension was cirrhosis
Stratum	Size of varices (medium/large): endoscopically assessed high risk oesophageal varices (F2 or F3 , associated with a moderate degree of red colour signs)
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	January 1992 to March 1995
Age, gender and ethnicity	Age – mean (SD): endoscopic variceal ligation (EVL): 55 (12); control: 57 (11). Gender (M:F): not reported. Ethnicity: not reported.
Further population details	1. Age of patient: 65 years and under (range for study 20–70 years. Mean for each arm <65 years). 2. Severity of underlying liver disease at the time of intervention (measured by MELD): Child-Pugh score B or C (Child-Pugh A: 28.3%; Child-Pugh B: 43.3%; Child-Pugh C: 28.3% [Overall 71.7% Child Pugh B or C]).
Extra comments	Aetiology of cirrhosis (alcohol/hepatitis B/hepatitis C/ cryptogenic) EVL: 18/23/19/4; control: 20/18/22/3. Ascites EVL: 21; control: 22. Child-Pugh class (A/B/C) EVL: 16/30/18; control: 20/25/17. Variceal size (F2/F3): EVL: 27/37; control: 30/33. Red colour signs (moderate/severe): EVL: 33/31; control: 36/27.

Study	Lo 1999[80]
Indirectness of population	No indirectness
Interventions	(n=66) Intervention 1: band ligation – conventional. Performed under premeditation with 20 mg of buscopan intramuscularly. Performed by 2 experienced endoscopists. Each varix ligated with 1 to 2 rubber bands (Bard Interventional Products, Billerica, MA, USA). Performed at intervals of 3 weeks until all varices were obliterated or too small to be ligated. Duration: median 28 months. Concurrent medication/care: sucralfate granules 1 g four times per day were administered to patients during the course of EVL treatment. After obliteration, patients in the treatment group underwent follow-up endoscopy every 3 months. Repeat EVL was performed in case of variceal recurrence. Patients in both groups were advised to receive follow-up consisting of abdominal sonogram, serum alpha-fetoprotein and biochemistry at 3-month intervals. Patients in both groups were advised to abstain from alcohol. (n=67) Intervention 2: no intervention. Control group, no intervention. Duration: median 30 months. Concurrent medication/care: in the control group, endoscopy was carried out every 6 months. Patients in both groups were advised to receive follow-up consisting of abdominal sonogram, serum alpha-fetoprotein and biochemistry at 3-month intervals. Patients in both groups were advised to abstain from alcohol.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CONVENTIONAL BAND LIGATION versus NO INTERVENTION

Protocol outcome 1: survival (with or without transplant) at end of study
- Actual outcome for size of varices (medium/large): survival at mean 29 months; HR 0.66 (95% CI 0.35 to 1.23) calculated – from MH P-value; risk of bias: high; indirectness of outcome: no indirectness

Protocol outcome 2: primary variceal bleeding at end of study
- Actual outcome for size of varices (medium/large): oesophageal variceal bleeding (appearance of haematemesis or melena, together with a decrease of haemoglobin and a requirement for blood transfusion of 2 or more units, and the bleeding source proven by emergency endoscopy) at mean 29 months; HR 0.59 (95% CI 0.26 to 1.37) calculated – from MH P-value; risk of bias: high; indirectness of outcome: no indirectness

Protocol outcome 3: primary upper gastrointestinal bleeding (irrespective of bleeding source) at end of study
- Actual outcome for size of varices (medium/large): upper gastrointestinal haemorrhage at mean 29 months; Group 1: 14/64, Group 2: 22/63; risk of bias: high; indirectness of outcome: serious indirectness

Protocol outcome 4: bleeding-related mortality at end of study
- Actual outcome for size of varices (medium/large): death due to variceal bleeding or ulcer bleeding at mean 29 months; Group 1: 4/64, Group 2: 9/63; risk of bias:

Study	Lo 1999[80]
very high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Health-related quality of life at end of study; hospital admission at end of study; hospital length of stay at end of study; adverse events: fatigue at end of study

Study (subsidiary papers)	Pagliaro 1989[94] (Pagliaro 1988,[95] Pagliaro 1989[96])
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=174)
Countries and setting	Conducted in Italy; setting: multicentre (4 hospitals)
Line of therapy	First line
Duration of study	Intervention + follow up: 2 years
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: cirrhosis biopsy proven in 43%
Stratum	Size of varices (medium/large): large oesophageal varices endoscopically assessed (F3 according to the Japanese Research Society for Portal Hypertension, that is, varices occupying more than one-third of the oesophageal lumen)
Subgroup analysis within study	Post-hoc subgroup analysis: Child-Pugh classification
Inclusion criteria	All patients with liver cirrhosis and 1) Large oesophageal varices (F3 according to the Japanese Research Society for Portal Hypertension, that is, varices occupying more than one third of the oesophageal lumen); 2) No previous upper gastrointestinal bleeding.
Exclusion criteria	1) Hepatocellular carcinoma; 2) Tense ascites, resistant to in-hospital diuretic treatment, or chronic or recurrent (>3 episodes per year) encephalopathy; 3) Bilirubin >3mg/dl; 4) Heart failure or obstructive lung disease.
Recruitment/selection of patients	Consecutive patients from July 1982 to Jan 1984
Age, gender and ethnicity	Age – mean (SD): propranolol: 55 (11), placebo: 53 (11). Gender (M:F): 122/52. Ethnicity: not reported.
Further population details	1. Age of patient: 65 years and under (propranolol: 55 [11], placebo: 53 [11]. Mean age in both arms <65 years). 2. Severity of underlying liver disease at the time of intervention (measured by MELD): Child-Pugh score A (Child-Pugh A: 59.2%, Child-Pugh B: 34.5%, Child-Pugh C: 6.3%. Overall Child-Pugh A 59.2%).
Extra comments	Child-Pugh classification (A/B/C): propranolol 47/32/6, placebo 56/28/5. Ascites: propranolol 39, placebo 38.
Indirectness of population	No indirectness
Interventions	(n=85) Intervention 1: oral non-selective beta-blockers – propranolol. Oral propranolol twice daily at a dose reducing

Study (subsidiary papers)	Pagliaro 1989[94] (Pagliaro 1988,[95] Pagliaro 1989[96])
	the resting heart rate by 25%. Dose ranged from 10–480 mg. Follow-up every 3 months. Duration: 2 years. Concurrent medication/care: same treatment protocol in patients who bled. (n=89) Intervention 2: placebo. Oral vitamin K tablets (10 mg) twice daily (not identical to propranolol but stated that patients did not know what treatment they were receiving in unlabelled bottles). Follow-up every 3 months. Duration: 2 years. Concurrent medication/care: same treatment protocol in patients who bled.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PROPRANOLOL versus PLACEBO Protocol outcome 1: survival (with or without transplant) at end of study - Actual outcome for size of varices (medium/large): survival at 2 years (mean 28 months); HR 1.49 (95%CI 0.91 to 2.42) calculated – from logrank P-value; risk of bias: low; indirectness of outcome: no indirectness Protocol outcome 2: primary variceal bleeding at end of study - Actual outcome for size of varices (medium/large): bleeding cause varices (haematemesis and/or fresh melena) at 2 years (mean 28 months); Group 1: 13/83, Group 2: 18/88; risk of bias: low; indirectness of outcome: serious indirectness Protocol outcome 3: primary upper gastrointestinal bleeding (irrespective of bleeding source) at end of study - Actual outcome for size of varices (medium/large): patients who bled (varices, erosions or undetermined). Haematemesis and/or fresh melena at 2 years (mean 28 months); Group 1: 18/83, Group 2: 31/88; risk of bias: low; indirectness of outcome: no indirectness - Actual outcome for size of varices (medium/large): Child-Pugh A. Patients who bled (varices, erosions or undetermined). Haematemesis and/or fresh melena at 2 years (mean 28 months); Group 1: 6/47, Group 2: 18/56; risk of bias: high; indirectness of outcome: no indirectness - Actual outcome for size of varices (medium/large): Child-Pugh B&C. Patients who bled (varices, erosions or undetermined). Haematemesis and/or fresh melena at 2 years (mean 28 months); Group 1: 12/38, Group 2: 13/33; risk of bias: high; indirectness of outcome: no indirectness Protocol outcome 4: bleeding related mortality at end of study - Actual outcome for size of varices (medium/large): death due to bleeding at 2 years (mean 28 months); Group 1: 10/83, Group 2: 12/88; risk of bias: low; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Health-related quality of life at end of study; hospital admission at end of study; hospital length of stay at end of study; adverse events: fatigue at end of study

Study (subsidiary papers)	Pascal 1989[99] (Pascal 1987[98])
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=230)
Countries and setting	Conducted in France; setting: multicentre
Line of therapy	First line
Duration of study	Intervention + follow up: mean 1.2 years
Method of assessment of guideline condition	Method of assessment/diagnosis not stated: cirrhosis confirmed by liver biopsy or biochemical and clinical data
Stratum	Size of varices (medium/large): grade II or II (medium or large) oesophageal varices at endoscopy (Italian Liver Cirrhosis Project, Witzel et al 1987). Grade II: not flattened by insufflation and separated by areas of normal mucosa; grade III: confluent and not flattened by insufflation.
Subgroup analysis within study	Stratified then randomised: stratified by Child-Pugh score <9 and 9–13
Inclusion criteria	Aged under 75 years; cirrhosis and Child-Pugh score <14; grade II or II (medium or large) oesophageal varices at endoscopy (Italian Liver Cirrhosis Project, Witzel et al 1987)
Exclusion criteria	Contraindication to beta-blockers; a past history of upper gastrointestinal bleeding; evidence of gastroduodenal ulcer or hepatic carcinoma, receiving treatment that altered portal haemodynamics
Recruitment/selection of patients	Every patient with cirrhosis and no history of bleeding and none of the exclusion criteria had an endoscopy
Age, gender and ethnicity	Age – range of means: 51.5–55.5 years. Gender (M:F): not reported. Ethnicity: not reported.
Further population details	1. Age of patient: 65 years and under (mean age in both arms <65 years). 2. Severity of underlying liver disease at the time of intervention (measured by MELD): Child-Pugh score B or C (Overall Child-Pugh classification % A/B/C: 17%/37%/46%).
Extra comments	Overall Child-Pugh classification % A/B/C: 17%/37%/46%; varices (grade II/III): propranolol 86/27, placebo 85/25. Violations of inclusion: patients with non-cirrhotic liver: propranolol 0, placebo 1; previous haemorrhage: propranolol 3, placebo 2; small varices: propranolol 2, placebo 2; aged >75: propranolol 0, placebo 2; hepatic carcinoma: propranolol 2, placebo 0.
Indirectness of population	No indirectness
Interventions	(n=118) Intervention 1: oral non-selective beta-blockers – propranolol. Starting dose 20 mg of conventional formulation twice daily. Titrated up to 160 mg or 320 mg of long-acting once daily to achieve a 20–25% reduction in resting heart rate or until maximum dose permitted (320 mg of long acting once daily). Patients evaluated every 2 months. Duration: mean 1.2 years. Concurrent medication/care: not reported.

Study (subsidiary papers)	Pascal 1989[99] (Pascal 1987[98])
	(n=112) Intervention 2: placebo. Identical placebo tablet once daily. Duration: mean 1.2 years. Concurrent medication/care: not reported.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PROPRANOLOL versus PLACEBO Protocol outcome 1: survival (with or without transplant) at end of study - Actual outcome for size of varices (medium/large): survival at mean 1.2 years; HR 0.96 (95% CI 0.59 to 1.56) calculated – from Cox SE/variance; risk of bias: low; indirectness of outcome: no indirectness Protocol outcome 2: primary upper gastrointestinal bleeding (irrespective of bleeding source) at end of study - Actual outcome for size of varices (medium/large): upper gastrointestinal bleeding at mean 1.2 years; Group 1: 20/116, Group 2: 30/111; risk of bias: low; indirectness of outcome: serious indirectness Protocol outcome 3: bleeding-related mortality at end of study - Actual outcome for size of varices (medium/large): cause of death bleeding at mean 1.2 years; Group 1: 10/116, Group 2: 18/111; risk of bias: low; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Health-related quality of life at end of study; primary variceal bleeding at end of study; hospital admission at end of study; hospital length of stay at end of study; adverse events: fatigue at end of study

Study	Sarin 1996[120]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=68)
Countries and setting	Conducted in India; setting: hospital based
Line of therapy	First line
Duration of study	Intervention + follow up: mean 14 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: all patients had portal hypertension, 6/68 had causes other than cirrhosis

Study	Sarin 1996[120]
Stratum	Size of varices (medium/large): patients had blue varices of F2 or F3 size with at least one of the red colour signs
Subgroup analysis within study	Not applicable
Inclusion criteria	1) Portal hypertension; 2) Without previous history of upper or lower gastrointestinal bleeding (including bleeding from portal hypertensive gastropathy or ulcer); 3) High risk varices (see below); 4) Presence of one or more red colour signs on the varices; no previous sclerotherapy or banding; available for informed consent. High risk varices assessed endoscopically: patients with large varices >5 mm assessed for risk of bleeding according to Beppu (score <0 defined high risk). This included blue varices of F2 or F3 size with at least one of the red colour signs.
Exclusion criteria	Hepatorenal syndrome or hepatic encephalopathy
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age – mean (SD): endoscopic variceal ligation (EVL): 41.8 (13.7), control: 39.3 (11.9). Gender (M:F): 54/14. Ethnicity: not reported.
Further population details	1. Age of patient: 65 years and under (EVL: 41.8 [13.7], control: 39.3 [11.9]. Mean age in both arms <65 years). 2. Severity of underlying liver disease at the time of intervention (measured by MELD): Child-Pugh score B or C (Child-Pugh A: 27.9%; Child-Pugh B: 27.9%; Child-Pugh C: 30.9%%. Overall Child-Pugh B and C 58.8%).
Extra comments	Aetiology (alcohol-related cirrhosis/non-alcohol related cirrhosis/non-cirrhotic portal fibrosis/extrahepatic portal vein obstruction): EVL 14/18/1/2, control 11/19/2/1. Ascites: EVL 30, control 26. Child-Pugh classification (A/B/C): EVL 9/16/11, control 10/13/10.
Indirectness of population	Serious indirectness: portal hypertension was due to cirrhosis in 62 of the patients and non-cirrhotic portal hypertension in 6 patients
Interventions	(n=35) Intervention 1: band ligation – conventional. Varices ligated about 1–2 cm above the gastro-oesophageal junction. One or two bands applied at each variceal column between the lower 4–5 cm of the oesophagus. EVL done at regular 7–10 day intervals until total variceal obliteration achieved (no variceal column visible) or it was not possible to suck in a varix for band ligation (grade 1 varices). Endoscopy performed every 3 months after the eradication of varices. Duration: mean 14 months. Concurrent medication/care: asked to refrain from the use of alcohol and NSAIDs. (n=33) Intervention 2: no intervention. Carefully followed up clinically every 4 weeks. Duration: mean 14 months. Concurrent medication/care: asked to refrain from the use of alcohol and NSAIDs.
Funding	Funding not stated

Study	Sarin 1996[120]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CONVENTIONAL BAND LIGATION versus NO INTERVENTION Protocol outcome 1: survival (with or without transplant) at end of study - Actual outcome for size of varices (medium/large): mortality at mean 14 months; Group 1: 4/35, Group 2: 8/33; risk of bias: very high; indirectness of outcome: serious indirectness Protocol outcome 2: primary variceal bleeding at end of study - Actual outcome for size of varices (medium/large): variceal bleeding defined as active bleeding identified from the varix, or if a clot was seen adherent to a varix and no other cause of bleeding from the gastrointestinal tract was evident at mean 14 months; Group 1: 3/35, Group 2: 13/33; risk of bias: very high; indirectness of outcome: serious indirectness Protocol outcome 3: primary upper gastrointestinal bleeding (irrespective of bleeding source) at end of study - Actual outcome for size of varices (medium/large): variceal bleeding at mean 14 months; Group 1: 3/35, Group 2: 13/33; risk of bias: very high; indirectness of outcome: no indirectness Protocol outcome 4: bleeding-related mortality at end of study - Actual outcome for size of varices (medium/large): death due to variceal bleeding at mean 14 months; Group 1: 1/35, Group 2: 5/33; risk of bias: very high; indirectness of outcome: serious indirectness	
Protocol outcomes not reported by the study	Health-related quality of life at end of study; hospital admission at end of study; hospital length of stay at end of study; adverse events: fatigue at end of study

Study	Sarin 2013[122]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=150)
Countries and setting	Conducted in India; setting: single-centre, hospital liver clinic
Line of therapy	First line
Duration of study	Intervention + follow up: mean 25 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: clinical, radiological or histological diagnosis of cirrhosis
Stratum	Size of varices (small): small (grade 1 or 2 by Conn's classification or small as per Baveno).

Study	Sarin 2013[122]
Subgroup analysis within study	Not applicable
Inclusion criteria	1) Clinical, radiological or histological diagnosis of cirrhosis; 2) Aged between 18 and 70 years; 3) Oesophageal varices were small (grade 1 or 2 by Conn's classification or small as per Baveno); 4) No history of variceal bleeding.
Exclusion criteria	Previous medical, surgical or endoscopic treatment of portal hypertension; a Child-Pugh score >13; neoplastic disease of any site; splenic or portal vein thrombosis; concurrent illnesses expected to decrease life expectancy to less than 1 year; pregnancy; contraindication to beta-blockers (second or higher degree of atrio-ventricular block, sinus bradycardia with a heart rate <50 BPM, atrial hypotension with a systolic BP <90 mmHg, heart failure, peripheral arterial disease, diabetes needing insulin treatment or bronchial asthma); concurrent antiviral treatment during the study period; concurrent treatment with any drug having an effect on portal hypertension; inability to comply with follow-up protocol; failure to give consent.
Recruitment/selection of patients	Consecutive patients (October 2004–June 2007)
Age, gender and ethnicity	Age – mean (SD): propranolol: 42 (13); placebo: 44 (13). Gender (M:F): 120/30. Ethnicity: not reported.
Further population details	1. Age of patient: 65 years and under (propranolol: 42 [13]; placebo: 44 [13]. Age in both arms <65 years). 2. Severity of underlying liver disease at the time of intervention (measured by MELD): not applicable/not stated/ unclear.
Extra comments	Aetiology (viral/alcoholic/other): propranolol 42/27/8; placebo 38/26/9. Ascites: propranolol 33; placebo 35. Child-Pugh score: propranolol 7.4 (1.9); placebo 7.7 (2.3). Gastric varices: propranolol 5; placebo 6.
Indirectness of population	No indirectness
Interventions	(n=77) Intervention 1: oral non-selective beta-blockers – propranolol. Starting dose 20 mg twice daily. Incremental dosing used to achieve target heart rate (dose increased every alternate day to achieve a target heart rate of 55/minute or to the maximum dose of 360 mg/day if the medication was well tolerated and the systolic BP remained above 90 mmHg). Dose decreased stepwise on occurrence of intolerable adverse effects, systolic BP <90 mmHg or pulse rate <55/minute). Patients seen in the liver clinic every alternate day for dose titration and follow-up at the clinic at a 1-month interval for 3 months, then every 6 months. Biochemical assessment and endoscopy done every 3–6 months. Patients further randomised to undergo no HVPG measurements, HVPG measurements at baseline or serial HVPG measurements. Duration: mean 25 months. Concurrent medication/care: patients developing large varices were treated with either propranolol or EVL according to the clinical decisions of the attending physician. (n=73) Intervention 2: placebo. No details of placebo given. Unclear if patients seen in the liver clinic every alternate day (as with intervention arm). Follow-up at the clinic at a 1-month interval for 3 months then every 6 months. Biochemical assessment and endoscopy done every 3–6 months. Patients further randomised to undergo no HVPG measurements, HVPG measurements at baseline or serial HVPG measurements. Duration: mean 25 months. Concurrent medication/care: patients developing large varices were treated with either propranolol or EVL according

Study	Sarin 2013[122]
	to the clinical decisions of the attending physician.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PROPRANOLOL versus PLACEBO Protocol outcome 1: survival (with or without transplant) at end of study - Actual outcome for size of varices (small): mortality at mean 25 months; Group 1: 3/77, Group 2: 2/73; risk of bias: high; indirectness of outcome: serious indirectness Protocol outcome 2: primary variceal bleeding at end of study - Actual outcome for size of varices (small): variceal bleeding defined as any haematemesis or melena and endoscopy showed active bleeding from varices, varices with an adherent clot or no other sources of bleeding at mean 25 months; Group 1: 4/77, Group 2: 1/73; risk of bias: high; indirectness of outcome: serious indirectness Protocol outcome 3: primary upper gastrointestinal bleeding (irrespective of bleeding source) at end of study - Actual outcome for size of varices (small): upper gastrointestinal bleeding at mean 25 months; Group 1: 4/77, Group 2: 1/73; risk of bias: high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Health-related quality of life at end of study; hospital admission at end of study; hospital length of stay at end of study; bleeding-related mortality at end of study; adverse events: fatigue at end of study

Study	Shah 2014[127]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=168)
Countries and setting	Conducted in Pakistan; setting: multicentre (3 tertiary care hospitals)
Line of therapy	First line
Duration of study	Intervention + follow up: mean 13.2 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: diagnosis of cirrhosis made on the basis of clinical, radiological, biochemical features and liver histology where available
Stratum	Size of varices (medium/large): medium or large sized oesophageal varices (grade II-IV)
Subgroup analysis within study	Not applicable

Study	Shah 2014[127]
Inclusion criteria	Cirrhosis (made on the basis of clinical, radiological, biochemical features and liver histology where available); without history of variceal bleed; male and female between 18 and 75 years; medium or large sized oesophageal varices (grade II-IV).
Exclusion criteria	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 of life or presence of severe systemic illness which could impair the subject's ability to participate in the trial; psychiatric or mentally handicapped people; gastric varices alone.
Recruitment/selection of patients	May 2007 to September 2011
Age, gender and ethnicity	Age – mean (SD): EVL: 47.2 (13.2); carvedilol 48.3 (11.3). Gender (M:F): not reported. Ethnicity: not reported.
Further population details	1. Age of patient: 65 years and under (EVL: 47.2 [13.2]; carvedilol 48.3 [11.3]. Mean age in both arms <65 years). 2. Severity of underlying liver disease at the time of intervention (measured by MELD): Child-Pugh score B or C (Child-Pugh A 44.0%, Child-Pugh B & C 56.0%).
Extra comments	Aetiology (viral/alcohol related/other): EVL 77/3/6, carvedilol 74/0/8 Child-Pugh (A/B/C): EVL 37/37/12, carvedilol 37/35/10. Varices size (medium/large): EVL 42/44, carvedilol 49/33. Ascites: EVL 32, carvedilol 33.
Indirectness of population	No indirectness
Interventions	(n=86) Intervention 1: band ligation – multiband. EVL 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 achieved (no varices or only small varices which were flattened on air insufflations). Endoscopy performed every 6 months and procedure repeated if varices recurred. Follow-up at 3 monthly intervals. Duration: mean 13.4 months. Concurrent medication/care: not reported. (n=82) Intervention 2: oral non-selective beta-blockers – Carvedilol. Carvedilol (Carvida, Ferozsons Laboratories, Pakistan) initial dose 6.25 mg once a day increased to twice a day after a period of 1 week. Follow-up at 2 weeks, 6 weeks and then 3-monthly intervals. Duration: mean 13.2 months. Concurrent medication/care: not reported.
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).

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MULTIBAND LIGATION versus CARVEDILOL

Protocol outcome 1: survival (with or without transplant) at end of study
- Actual outcome for size of varices (medium/large): survival at 2 years; HR 0.65 (95% CI 0.3 to 1.41) reported; risk of bias: low; indirectness of outcome: no indirectness

Study	Shah 2014[127]
Protocol outcome 2: primary variceal bleeding at end of study - Actual outcome for size of varices (medium/large): free of variceal bleeding (overt haematemesis and/or melena with endoscopic evidence of variceal bleeding or signs of recent bleed and at least 2 g/dl drop in haemoglobin within 24 hours of admission) at 2 years; HR 0.63 (95%CI 0.1 to 3.7) reported; risk of bias: low; indirectness of outcome: no indirectness Protocol outcome 3: primary upper gastrointestinal bleeding (irrespective of bleeding source) at end of study - Actual outcome for size of varices (medium/large): upper gastrointestinal bleeding at 2 years; Group 1: 6/86, Group 2: 7/82; risk of bias: low; indirectness of outcome: no indirectness Protocol outcome 4: bleeding-related mortality at end of study - Actual outcome for size of varices (medium/large): death due to variceal bleeding (overt haematemesis and/or melena with endoscopic evidence of variceal bleeding or signs of recent bleed and at least 2 g/dl drop in haemoglobin within 24 hours of admission) at 2 years; Group 1: 4/86, Group 2: 4/82; risk of bias: low; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Health-related quality of life at end of study; hospital admission at end of study; hospital length of stay at end of study; adverse events: fatigue at end of study

Study	Singh 2012[131]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=38)
Countries and setting	Conducted in India
Line of therapy	First line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: eligibility criteria does not specify cirrhosis but results report all patients had cirrhosis and cirrhosis was diagnosed on the basis of clinical biochemical, histologic, or ultrasonographic evidence.
Stratum	Size of varices (medium/large): large, grade 3 or 4 varices at high risk (Conn's criteria: grade 3, varices of 3 to 6 mm; grade 4, varices of >6 mm).
Subgroup analysis within study	Not applicable
Inclusion criteria	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 to 6 mm; grade 4, varices of >6

Study	Singh 2012[131]
	mm). The risk of bleeding in large varices (>5 mm) was assessed by looking for the presence of at least one "red sign," such as a cherry-red spot, a red wale, or a haematocystic spot.
Exclusion criteria	Receiving antiviral therapy or if they had concomitant hepatoma or another tumour, severe cardio-pulmonary or renal disease, bradycardia (basal heart rate <55 beats per minute), bronchial asthma, diabetes mellitus, heart failure, peripheral vascular disease, a psychiatric disorder, glaucoma, or prostatic hypertrophy.
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age – other: not reported. Gender (M:F): not reported. Ethnicity: not reported.
Further population details	1. Age of patient: not applicable/not stated/unclear. 2. Severity of underlying liver disease at the time of intervention (measured by MELD): not applicable/not stated/unclear.
Extra comments	Aetiology (alcohol-related/hepatitis B/hepatitis C/autoimmune/other): EVL 8/5/2/1/2, propranolol 11/6/2/0/1. Ascites: EVL 11, propranolol 12.
Indirectness of population	No indirectness
Interventions	(n=18) Intervention 1: band ligation – multiband. Ligation carried out by placing multiple rubber bands (PentaGun Multiband Ligator, Hospiline Medi-Devices, India) – as many bands as possible, 3–6 bands (with fewer in later sessions) were placed in the lower 5–7 cm of all variceal columns. Performed weekly until varices obliterated or reduced to size grade 1 and it was not possible to apply any more bands because of the small size of the varices. If varices recurred or became grade 2 or larger in size, ligation was repeated to obliterate them. Duration: 12 months. Concurrent medication/care: underwent endoscopy for monthly for the first 3 months and then once every 3 months. (n=20) Intervention 2: oral non-selective beta-blockers – propranolol. Treatment started with 40 mg oral propranolol. Dose increased by increments of 20–40 mg/day until a 25% decrease in the resting heart rate was achieved. Treatment stopped if systolic BP below 90 mmHg, HR less than 55 bpm or serious side effects. Duration: 12 months. Concurrent medication/care: underwent endoscopy for monthly for the first 3 months and then once every 3 months.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MULTIBAND LIGATION versus PROPRANOLOL

Protocol outcome 1: survival (with or without transplant) at end of study
- Actual outcome for size of varices (medium/large): mortality at 12 months; Group 1: 2/18, Group 2: 3/20; indirectness of outcome: serious indirectness

Protocol outcome 2: primary upper gastrointestinal bleeding (irrespective of bleeding source) at end of study

Study	Singh 2012[131]
- Actual outcome for size of varices (medium/large): upper gastrointestinal bleeding at 12 months; Group 1: 3/18, Group 2: 5/20; indirectness of outcome: no indirectness Protocol outcome 3: bleeding-related mortality at end of study - Actual outcome for size of varices (medium/large): death due to bleeding at 12 months; Group 1: 1/18, Group 2: 2/20; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Health-related quality of life at end of study; primary variceal bleeding at end of study; hospital admission at end of study; hospital length of stay at end of study; adverse events: fatigue at end of study

Study	Svoboda 1999[144]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=186)
Countries and setting	Conducted in Czech Republic; setting: referral from district gastroenterologists
Line of therapy	First line
Duration of study	Intervention + follow up: mean 25 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: liver cirrhosis with no other serious disease
Stratum	Size of varices (medium/large): oesophageal varices of grades III and IV; oesophageal varices of grade II with signs of high risk (Paquet's classification)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 15-70 who had no previous history of upper gastrointestinal bleeding, oesophargeal varices of grade III and IV; oesophageal varices of grade II with signs of high risk; no previous endoscopic treatment of oesophageal varices; liver cirrhosis with no other serious disease; fully informed consent.
Exclusion criteria	Not reported
Recruitment/selection of patients	Referral of all suitable patients between August 1994 and September 1994
Age, gender and ethnicity	Age – mean (SD): intervention: 48 (12); control: 47 (11). Gender (M:F): not reported. Ethnicity: not reported.
Further population details	1. Age of patient: 65 years and under (intervention: 48 (12); control: 47 (11). Mean for both arms <65 years). 2. Severity of underlying liver disease at the time of intervention (measured by MELD): Child-Pugh score A (Child-Pugh A: 58.8%; Child-Pugh B: 29.4%; Child-Pugh C: 11.8% [overall: 58.8% Child-Pugh A]).

Study	Svoboda 1999[144]
Extra comments	Aetiology (alcohol/infection): intervention 35/17; control 34/16. Child-Pugh (A/B/C): intervention 32/14/6; control 28/16/6. Varices (II/III/IV): intervention: 2/36/14; control: 1/38/11. Study is a 3-arm trial including n=55 patients receiving sclerotherapy intervention.
Indirectness of population	No indirectness
Interventions	(n=52) Intervention 1: band ligation – multiband. Three sessions at 2-week intervals, and then every month until the varices were too small to treat. Repeated if recurrence of varices occurred. Ligation performed using an endoscopic ligation device (suction oesophageal varices ligator, Pauldrach Medical, Germany). Later multiband ligators were also used (Wilson-Cook medical, USA or Microvasive, USA). Endoscopies performed by 2 experienced endoscopists who had performed >300 EIL or EVS procedures. In each session the largest number possible (up to 6) of elastic bands were positioned in the distal oesophagus. Duration: mean 25 months. Concurrent medication/care: all patients given ACE inhibitor enalapril (later quinapril) 2x 5–10mg orally to decrease portal pressure. Regular endoscopy every 3 months. Comments: 29 lost to follow-up, trial arm not specified. (n=50) Intervention 2: no intervention. Duration: mean 26 months. Concurrent medication/care: all patients given ACE inhibitor enalapril (later quinapril) 2x 5–10mg orally to decrease portal pressure. Regular clinical examination and endoscopy every 3 months. Comments: 29 lost to follow-up, trial arm not specified.
Funding	Academic or government funding (supported by grant IGA MZ CR 5187 of Internal Grant Agency of Ministry of Health of the Czech Republic)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MULTIBAND OR CONVENTIONAL BAND LIGATION (LI) versus NO INTERVENTION

Protocol outcome 1: survival (with or without transplant) at end of study
- Actual outcome for size of varices (medium/large): mortality at mean 25 months; Group 1: 12/52, Group 2: 19/50; risk of bias: high; indirectness of outcome: serious indirectness

Protocol outcome 2: primary variceal bleeding at end of study
- Actual outcome for size of varices (medium/large): variceal bleeding at mean 25 months; Group 1: 15/52, Group 2: 27/50; risk of bias: high; indirectness of outcome: serious indirectness

Protocol outcome 3: primary upper gastrointestinal bleeding (irrespective of bleeding source) at end of study
- Actual outcome for size of varices (medium/large): variceal bleeding at mean 25 months; Group 1: 15/52, Group 2: 27/50; risk of bias: high; indirectness of outcome:

Study	Svoboda 1999[144]
no indirectness Protocol outcome 4: bleeding related mortality at end of study - Actual outcome for size of varices (medium/large): death due to bleeding from oesophageal varices at mean 25 months; Group 1: 5/52, Group 2: 13/50; risk of bias: very high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Health-related quality of life at end of study; hospital admission at end of study; hospital length of stay at end of study; adverse events: fatigue at end of study

Study	Triantos 2005[151]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=52)
Countries and setting	Conducted in Greece; setting: multicentre: 1 tertiary referral centre for liver diseases and 1 general hospital
Line of therapy	First line
Duration of study	Intervention + follow up: mean 20.6 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: patients with cirrhosis
Stratum	Size of varices (overall): small varices: <5 mm diameter (patients with large and small varices reported separately in study)
Subgroup analysis within study	Post-hoc subgroup analysis: small and large varices
Inclusion criteria	Age >18 and <76 years; varices of any size (assessed endoscopically by 2 independent observers; large varices: diameter of large varix >5 mm – measured with open forceps and not disappearing on oesophageal insufflation; small varices: <5 mm diameter); contraindication or intolerance to beta-blocker therapy; no prior bleeding from portal hypertensive sources; no previous prophylactic sclerotherapy or banding; absence of terminal disease (likelihood of dying within 6 months); ability to give consent; no contraindication to banding.
Exclusion criteria	Not reported
Recruitment/selection of patients	December 1999 to November 2003
Age, gender and ethnicity	Age – mean (SD): endoscopic banding ligation (EBL): 60 (9.4), control: 63 (10.3). Gender (M:F): 38/14. Ethnicity: not reported.
Further population details	1. Age of patient: 65 years and under (EBL: 60 [9.4], control: 63 [10.3]. Mean age in both arms <65 years). 2. Severity of

Study	Triantos 2005[151]
	underlying liver disease at the time of intervention (measured by MELD): Child-Pugh score B or C (Child-Pugh A: 32.7%; Child-Pugh B: 25%; Child-Pugh C: 42.3%. Overall Child-Pugh B and C 67.3%).
Extra comments	Aetiology (alcohol/viral/other): EBL 9/11/5, control: 9/7/11; Child-Pugh (A/B/C): EBL 9/6/10, control: 8/7/12; Ascites: EBL 11, control: 19; Varices size (small/large): EBL 14/11, control 17/10. Trial stopped early due to interim analysis and twice as much bleeding than expected in the EBL group.
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: band ligation – multiband. Bands were placed starting at the gastro-oesophageal junction and then proximally in a helical fashion for approximately 5 cm, putting at least 1 band on each varix (Multiband ligator 6 shooter, Wilson-Cook, Ireland). Subsequent sessions at 14-day intervals until the varices were too small to ligate (no effect of suction). Banding performed by 4 experienced endoscopists. Duration: mean 20.6 months. Concurrent medication/care: not reported. (n=27) Intervention 2: no intervention. Yearly endoscopy and staging of liver disease. Duration: mean 18.3 months. Concurrent medication/care: not reported.
Funding	Other (principle author funded by the Hellenic Association for the Study of the Liver)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MULTIBAND BAND LIGATION versus NO INTERVENTION

Protocol outcome 1: survival (with or without transplant) at end of study
- Actual outcome for size of varices (overall): survival at mean 18.3–20.6 months; HR 0.72 (95% CI 0.29 to 1.82) calculated – from logrank P-value; risk of bias: high; indirectness of outcome: serious indirectness

Protocol outcome 2: primary variceal bleeding at end of study
- Actual outcome for size of varices (overall): bleeding from varix at mean 18.3–20.6 months; Group 1: 3/25, Group 2: 2/27; risk of bias: high; indirectness of outcome: serious indirectness

Protocol outcome 3: primary upper gastrointestinal bleeding (irrespective of bleeding source) at end of study
- Actual outcome for size of varices (small): portal hypertensive bleeding (haematemesis or melaena, either from a bleeding varix or a clot adherent to a varix, a variceal ulceration, portal hypertensive gastropathy, or presumed to be from these sources when there were no other visible lesions at endoscopy) at mean 18.3–20.6 months; Group 1: 1/14, Group 2: 0/17; risk of bias: high; indirectness of outcome: no indirectness
- Actual outcome for size of varices (medium/large): portal hypertensive bleeding (haematemesis or melaena, either from a bleeding varix or a clot adherent to a varix, a variceal ulceration, portal hypertensive gastropathy, or presumed to be from these sources when there were no other visible lesions at endoscopy) at mean 18.3–20.6

Study	Triantos 2005[151]
months; Group 1: 4/11, Group 2: 2/10; risk of bias: high; indirectness of outcome: no indirectness Protocol outcome 4: bleeding related mortality at end of study - Actual outcome for size of varices (overall): cause of death variceal bleeding at mean 18.3–20.6 months; Group 1: 3/25, Group 2: 0/27; risk of bias: high; indirectness of outcome: serious indirectness	
Protocol outcomes not reported by the study	Health-related quality of life at end of study; hospital admission at end of study; hospital length of stay at end of study; adverse events: fatigue at end of study