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Endoscopic therapy and beta-blockers for secondary prevention in adults with cirrhosis and oesophageal varices (Protocol)

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Endoscopic therapy and beta-blockers for secondary prevention in adults with cirrhosis and oesophageal varices

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A B S T R A C T

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To evaluate the beneficial and harmful effects of endoscopic therapy and beta-blockers used as a combination therapy versus monotherapy with either endoscopic therapy or beta-blockers for secondary prevention in people with cirrhosis and oesophageal varices.

B A C K G R O U N D

Description of the condition

People with cirrhosis develop oesophageal varices as a result of portal hypertension (Bosch 2003; Triantos 2007). About 30% of people with cirrhosis have oesophageal varices at the initial diagnosis (D'Amico 1995; D'Amico 1999; D'Amico 2007; De Lisi 2011). Five percent develop varices during the first year after the diagnosis, and 28% develop varices after three years (Merli 2003). The estimated two-year incidence of bleeding is approximately 24% (D'Amico 1995; D'Amico 1999), and 70% of these occur within two years of diagnosis. The inhospital mortality associated with variceal bleeding remains high. The overall risk ranges from 12% to 44%, depending on the proportion of high-risk patients. The risk of death within six weeks of the initial variceal haemorrhage is less than 10% in Child-Pugh Class A and more than 32% in those in Child-Pugh Class C (Carbonell 2004). The risk of rebleeding after the first episode of an acute variceal haemorrhage is about 63% within the first two years after the diagnosis and mortality is about 30% during the same period (D'Amico 1995; D'Amico 1999; D'Amico 2007).

Description of the intervention

Non-selective beta-blockers are recommended as secondary prevention of variceal bleeding (Garcia-Tsao 2007; Tripathi 2007; Garcia-Tsao 2008; Puente 2014). The drugs block the beta-1 and -2 receptors, which are found in several tissues including vascular smooth muscle and the heart. Beta-blockers used in clinical practice are propranolol, nadolol, and timolol, and, in recent years, carvedilol (Villanueva 2008). One meta-analysis with 20 randomised clinical trials found that beta-blockers reduced the risk of rebleeding (Cheng 2003). However, about 30% of trial participants did not respond to beta-blockers. The combination of beta-blockers and endoscopic therapy may be more effective than

beta-blockers alone (Gonzalez 2008; Shi 2013; Bai 2014; Puente 2014). The available endoscopic interventions include sclerotherapy and banding ligation. Variceal sclerotherapy, which involves injecting a strong and irritating sclerosant or glue, is associated with severe bleeding and oesophageal strictures (Schmitz 2001). Banding ligation may provide a safer option (Gluud 2007). Banding devices use a means of capturing the target tissue while a small-diameter circular band is deployed around the base of the tissue (ASGE 2008). The band may be rubber, latex, or similar materials. The ligation procedure results in a tight compression with vascular compromise leading to thrombosis, necrosis, and sloughing. Previous banding devices used an overtube for the repeated intubation, allowing placement of multiple bands (Collins 2001). The insertion of an overtube was associated with adverse events including perforation of the oesophagus (Wong 2000; Gluud 2007). Multi-band devices are now used, resulting in considerably fewer adverse events (ASGE 2008).

How the intervention might work

Non-selective beta-blockers have beta-1 receptor effects and beta-2 receptor effects. Beta-1 receptor blockade reduces cardiac output and portal venous inflow. Beta-2 receptor blockade leads to splanchnic vasoconstriction reducing the azygos blood flow and variceal pressure (D'Amico 1999; D'Amico 2007). Banding ligation works by capturing (ligating) a varix resulting in thrombosis. The tissue then necroses and sloughs off after two to seven days. The subsequent superficial mucosal ulceration heals within a few days.

Why it is important to do this review

Previous meta-analyses have found a potential benefit of the combination of beta-blockers and endoscopic therapy for prevention of variceal rebleeding (Gonzalez 2008; Funakoshi 2010; Shi 2013; Bai 2014; Puente 2014). However, the effect on mortality and risk of serious adverse events is unclear. The meta-analyses evaluated different combinations of beta-blockers (alone or with other drugs), banding ligation, and sclerotherapy. In addition, the analyses included participants with or without cirrhosis. Therefore, important differences may exist between subgroups and our Cochrane Review will aim to clarify this.

OBJECTIVES

To evaluate the beneficial and harmful effects of endoscopic therapy and beta-blockers used as a combination therapy versus monotherapy with either endoscopic therapy or beta-blockers for secondary prevention in people with cirrhosis and oesophageal varices.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised clinical trials irrespective of publication type, publication status, and language.

We have chosen to include randomised clinical trials because they are more likely to provide unbiased information than other study designs about the differential effects of alternative forms of healthcare. If, during the selection of trials, we identify observational studies (i.e. quasi-randomised studies, cohort studies, or patient reports) that report adverse events caused by, or associated with, the interventions in our review, we will include these studies for a review of the adverse events. We will not specifically search for observational studies, which is a known limitation of our systematic review.

Types of participants

We will include adults (at least 18 years) with cirrhosis and endoscopically verified oesophageal varices that have bled.

Types of interventions

The intervention comparisons will include:
- banding ligation plus beta-blockers versus beta-blockers alone;
- banding ligation plus beta-blockers versus banding ligation alone;
- sclerotherapy plus beta-blockers versus beta-blockers alone;
- sclerotherapy plus beta-blockers versus sclerotherapy alone.

We will allow concurrent interventions such as isosorbide mononitrate or simvastatin to both intervention arms in our primary analyses, and we will evaluate the effect of concomitant interventions in subgroup analyses.

Types of outcome measures

We will assess all outcomes at the maximum duration of follow-up in our primary analyses.

Primary outcomes
- Mortality (all-cause).
- Serious adverse events defined as any untoward medical occurrence that does not necessarily have a causal relationship with the treatment (ICH-GCP 1997). We will define serious adverse events as those that led to death, were life-threatening, or

required hospitalisation or prolongation of hospitalisation (ICH-GCP 1997). We will analyse adverse events as a composite outcome (Gluud 2017).

Secondary outcomes

- Bleeding-related mortality.
- Health-related quality of life.
- Upper gastrointestinal bleeding.
- Variceal bleeding.
- Non-serious adverse events (all adverse events that did not fulfil the criteria for serious adverse events; ICH-GCP 1997).

Search methods for identification of studies

We will use a search strategy developed according to the Cochrane Hepato-Biliary Group recommendations.

Electronic searches

We will search The Cochrane Hepato-Biliary Group Controlled Trials Register (Gluud 2017), Cochrane Central Register of Controlled Trials (CENTRAL; latest issue) in the Cochrane Library, MEDLINE (1946 to the date of search; OvidSP), Embase (1974 to the date of search; OvidSP), and Science Citation Index Expanded (1900 to the date of search, Web of Science) (Royle 2003) using the preliminary strategies described in Appendix 1.

Searching other resources

We will scan the reference lists of relevant articles and proceedings from meetings of the British Society for Gastroenterology (BSG), the British Association for the Study of the Liver (BASL), the European Association for the Study of the Liver (EASL), the United European Gastroenterology Week (UEGW), the American Gastroenterological Association (AGA), and the American Association for the Study of Liver Diseases (AASLD). We will write to the principal authors of randomised clinical trials and pharmaceutical companies for additional information about completed randomised clinical trials and for information about any ongoing randomised clinical trials. We will also search online trial registries such as ClinicalTrial.gov (clinicaltrials.gov/), European Medicines Agency (EMA) (www.ema.europa.eu/ema/), World Health Organization (WHO) International Clinical Trial Registry Platform (www.who.int/ictrp), and the US Food and Drug Administration (FDA) (www.fda.gov) for ongoing or unpublished trials.

Data collection and analysis

The two review authors (LLG and MYM) will read the electronic searches, perform additional manual searches, and list potentially eligible randomised clinical trials; read the potentially eligible trial reports; and participate in the final selection of those to be included in the analyses. The review authors will reach the final selection through consensus. We will consult a Cochrane Hepato-Biliary Group review arbiter should we be unable to reach consensus. For randomised clinical trials reported in more than one publication, we will select the paper reporting the longest duration of follow-up as the primary reference.

Selection of studies

The two review authors (LLG and MYM) will participate in the searches for eligible trials and data extraction, and they will list the excluded trials with the reason for exclusion in the 'Characteristics of excluded studies' table. The review authors will resolve disagreements through discussion, before conducting the analyses. We will consult a Cochrane Hepato-Biliary Group review arbiter should we be unable to reach consensus. We will identify and exclude duplicates and collated multiple reports of the same study, so that each study, rather than each report, is the unit of interest in the review.

We will complete a PRISMA flow chart.

Data extraction and management

Two review authors (LLG and MYM) will independently collect data and resolve contrary opinions through discussion. We will use pilot tested data extraction sheets (developed, based on pilot testing of four studies). We will consult a Cochrane Hepato-Biliary Group review arbiter should we be unable to reach consensus. The collected data will include information on:

- randomised clinical trials: design (cross-over or parallel), settings (number of clinical sites; inclusion period), country of origin;
- participants: size of varices, proportion of participants with high-risk varices (based on the primary author's definition), mean age, proportion of men, aetiology of cirrhosis, proportion of participants with Child-Pugh Class A/B/C;
- interventions: number of banding sessions, number of bands used per session.

We will gather the primary and secondary outcome data, including the criteria used in the definition of high- or low-risk varices, methods, and definitions used to assess bleeding and bias control. If we cannot find the relevant data in the published trial reports, we will write to the primary investigators to ask for additional information.

We will present the data in a 'Characteristics of included studies' table.

Assessment of risk of bias in included studies

We will assess bias control using the domains described in the Cochrane Hepato-Biliary Group Module (Higgins 2011; Gluud 2017).

Allocation sequence generation

- Low risk of bias: the study authors performed sequence generation using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were adequate if an independent person not otherwise involved in the study performed them.
- Unclear risk of bias: not specified.
- High risk of bias: the sequence generation was not random. We plan to include such studies for assessment of harms.

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. Allocation was controlled by a central and independent randomisation unit. The allocation sequence was unknown to the investigators (e.g. if the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Unclear risk of bias: the method used to conceal the allocation was not described so that intervention allocations may have been foreseen in advance of, or during, enrolment.
- High risk of bias: the allocation sequence was likely to be known to the investigators who assigned the participants.

Blinding of participants and personnel

- Low risk of bias: the outcome was mortality, which, according to previous empirical evidence, is not likely to be influenced by lack of blinding (Hróbjartsson 2001; Savović 2012); or blinding of participants and key study personnel was ensured, and it was unlikely that the blinding could have been broken.
- Unclear risk of bias: insufficient information to permit judgement of 'low risk' or 'high risk.'
- High risk of bias: no blinding or incomplete blinding, and the outcome was likely to have been influenced by lack of blinding (non-mortality outcomes).

Blinding of outcome assessors

- Low risk of bias: the outcome was mortality, which, according to previous empirical evidence, is not likely to be influenced by lack of blinding (Hróbjartsson 2001; Savović 2012); or blinding of outcome assessment was ensured, and it was unlikely that the blinding could have been broken.
- Unclear risk of bias: insufficient information to permit judgement of 'low risk' or 'high risk.'

- High risk of bias: no blinding or inadequate blinding (e.g. intravenous versus orally administered drugs) and the outcome was likely to have been influenced by lack of blinding (non-mortality outcomes).

Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. The investigators used sufficient methods, such as intention-to-treat analyses with multiple imputations or carry-forward analyses to handle missing data.
- Unclear risk of bias: there was insufficient information to assess whether missing data in combination with the method used to handle missing data induced bias on the results.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk of bias: the trial reported clinically relevant outcomes (mortality, hepatic encephalopathy, and serious adverse events). If we had access to the original trial protocol, the outcomes should be those called for in that protocol. If we obtained information from a trial registry (such as www.clinicaltrials.gov), we only used the information if the investigators registered the trial before inclusion of the first participant.
- Unclear risk of bias: predefined outcomes were not reported fully.
- High risk of bias: one or more predefined outcomes were not reported.

For-profit bias

- Low risk of bias: the trial appeared to be free of industry sponsorship or other type of for-profit support.
- Unclear risk of bias: no information on clinical trial support or sponsorship was available.
- High risk of bias: the trial was sponsored by industry, received support in the form of terlipressin or placebo, or received any other type of support.

Other bias

- Low risk of bias: the trial appeared to be free of other biases including: medicinal dosing problems or follow-up (as defined under 'High risk of bias' below).
- Unclear risk of bias: the trial may or may not have been free of other domains that could put it at risk of bias.
- High risk of bias: there were other factors in the trial that could put it at risk of bias such as the administration of inappropriate treatments being given to the controls (e.g. an

inappropriate dose) or follow-up (e.g. the trial included different follow-up schedules for participants in the allocation groups), or premature discontinuation of the trial.

Overall bias assessment

- Low risk of bias: all domains were classified as low risk of bias using the definitions described above.
- High risk of bias: one or more of the bias domains were classified as unclear or high risk of bias.

Measures of treatment effect

We will use risk ratios (RR) for dichotomous outcomes and mean differences (MD) for continuous outcomes, both with 95% confidence intervals (CI). For statistically significant outcomes that do not overlap the 95% CI, we will calculate the number needed to treat for an additional beneficial outcome (NNTB) as 1/risk difference (RD).

Unit of analysis issues

We do not expect to identify cross-over randomised clinical trials. However, if we identify randomised clinical trials using a cross-over design, we will include only the precross-over period in our analyses.

Dealing with missing data

We will extract data on all randomised participants to allow intention-to-treat analyses. To evaluate the importance of missing data, we will conduct a worst-case scenario analysis with inclusion of missing outcomes as treatment failures. In addition, we will conduct an 'extreme' worst-case scenario analysis in which we include missing outcome data as treatment failures (intervention group) or successes (control group).

Assessment of heterogeneity

We will express heterogeneity as I^2 values using the following thresholds: 0% to 40% (unimportant), 40% to 60% (moderate), 60% to 80% (substantial), and greater than 80% (considerable). We will include this information in 'Summary of findings' tables (GRADEpro).

Assessment of reporting biases

For meta-analyses with at least 10 randomised clinical trials, we will assess reporting biases through regression analyses and funnel plots.

Data synthesis

We will perform the analyses in Review Manager 5 (RevMan 2014), STATA (Stata), and Trial Sequential Analysis (TSA 2011).

Meta-analysis

We will prepare separate meta-analyses of randomised clinical trials evaluating the different intervention comparisons (i.e. we do not plan to combine randomised clinical trials evaluating banding ligation and randomised clinical trials evaluating sclerotherapy). We will undertake both fixed-effect and random-effects meta-analyses. The fixed-effect meta-analysis generates an estimate of a 'typical intervention effect' from included randomised clinical trials and calculates CIs with the assumption that the true intervention effect is the same value in every randomised clinical trial. We will report fixed-effect model meta-analyses if we find evidence that the observed differences among randomised clinical trials are due to the play of chance. If we find 'unexplained' heterogeneity, we will incorporate heterogeneity into a random-effects model assuming that the estimated effects are not identical, but follow a distribution. If we suspect that there may be an influence of small-study effects on the results of our meta-analysis (e.g. heterogeneity, I^2 greater than 0), we will compare the fixed-effect and random-effects estimates of the intervention effect. If the estimates are similar, then we will assume that small-study effects have little effect on the intervention effect estimate. If the two models are similar, we will report the result with the widest CIs. If the random-effects estimate is more beneficial, we will consider whether it is reasonable to conclude that the intervention is more effective in the smaller randomised clinical trials or there is bias. If the larger randomised clinical trials are conducted with a lower risk of bias (or under more 'typical' circumstances), then we will consider reporting the results of meta-analyses restricted to the larger, more rigorous studies.

Trial Sequential Analysis

We will perform Trial Sequential Analyses (TSA 2011) and define the required information size (also known as the diversity-adjusted required information size) as the number of participants needed to detect or reject an intervention effect based on the relative risk reduction (RRR) and control group risk. The analyses will show firm evidence if the Z-curves cross the monitoring boundaries (also known as the trial sequential monitoring boundaries) before reaching the required information sizes (TSA 2011). We will construct futility boundaries to evaluate the uncertainty of obtaining a chance negative finding and perform the analyses with alpha set to 2.5%, beta 10%, and model-based diversity. Based on previous evidence (Gluud 2007), we will set the RRR to the upper limit of the 95% CI and use the control group event rate observed in the meta-analysis. We will conduct the meta-analyses including only randomised clinical trials with low risk of bias and including all randomised clinical trials.

Subgroup analysis and investigation of heterogeneity

We will conduct subgroup analyses to evaluate:

- randomised clinical trials using isosorbide mononitrate as a concomitant intervention and randomised clinical trials not using isosorbide mononitrate;
- people with high- or low-risk varices (using the original investigators' definitions);
- Child-Pugh Class A/B/C cirrhosis;
- randomised clinical trials with a 'low risk' compared with 'high risk' of bias in the overall assessment.

Sensitivity analysis

We will conduct a worst-case scenario analysis, and an 'extreme' worst-case scenario analysis as described in Dealing with missing data.

'Summary of findings' tables

We will use the GRADE system to evaluate the quality of the evidence for outcomes reported in the review (mortality, serious adverse events, health-related quality of life, upper gastrointestinal bleeding, variceal bleeding, non-serious adverse events) considering the within-study risk of bias (methodological quality), indirectness of evidence (population, intervention, control, outcomes), unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses); imprecision of effect estimate (wide CIs and as evaluated with our Trial Sequential Analyses), and risk of publication bias (GRADEpro). We will define the certainty of the evidence as 'high', 'moderate', 'low,' or 'very low.' These grades are defined as follows.

- High certainty: this research provides a very good indication of the likely effect; the likelihood that the effect will be substantially different is low.
- Moderate certainty: this research provides a good indication of the likely effect; the likelihood that the effect will be substantially different is moderate.
- Low certainty: this research provides some indication of the likely effect; however, the likelihood that it will be substantially different is high.
- Very low certainty: this research does not provide a reliable indication of the likely effect; the likelihood that the effect will be substantially different is very high.

REFERENCES

Additional references

ASGE 2008
ASGE Technology Committee, Liu J, Petersen BT, Tierney WM, Chuttani R, Disario JA, Coffie JM, et al. Endoscopic banding devices. *Gastrointestinal Endoscopy* 2008;**68**: 217–21.

Bai 2014
Bai M, Qi X, Yang M, Han G, Fan D. Combined therapies versus monotherapies for the first variceal bleeding in patients with high-risk varices: a meta-analysis of randomized controlled trials. *Journal of Gastroenterology and Hepatology* 2014;**29**(3):442–52. [PUBMED: 24118091]

Bosch 2003
Bosch J, Garcia-Pagan JC. Prevention of variceal rebleeding. *Lancet* 2003;**361**:952–54.

Carbonell 2004
Carbonell N, Pauwels A, Serfaty L, Fourdan O, Lévy VG, Poupon R. Improved survival after variceal bleeding in patients with cirrhosis over the past two decades. *Hepatology* 2004;**40**:652–9.

Cheng 2003
Cheng JW, Zhu L, Gu MJ, Song ZM. Meta analysis of propranolol effects on gastrointestinal hemorrhage in cirrhotic patients. *World Journal of Gastroenterology* 2003;**9** (8):1836–9. [PUBMED: 12918133]

Collins 2001
Collins D, Worthley LI. Acute gastrointestinal bleeding: part II. *Critical Care and Resuscitation* 2001;**3**:117–24.

D'Amico 1995
D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: a meta-analytic review. *Hepatology*

(Baltimore, Md.) 1995;**22**:332–54.

D'Amico 1999
D'Amico G, Pagliaro L, Bosch J. Pharmacological treatment of portal hypertension: an evidence-based approach. *Seminars in Liver Disease* 1999;**19**:475–505.

D'Amico 2007
D'Amico G, Garcia-Pagan JC, Luca A, Bosch J. Hepatic vein pressure gradient reduction and prevention of variceal bleeding in cirrhosis: a systematic review. *Gastroenterology* 2007;**131**:1611–24.

De Lisi 2011
De Lisi S, Peralta S, Arini A, Simone F, Craxì A. Oesophagogastroduodenoscopy in patients with cirrhosis: extending the range of detection beyond portal hypertension. Digestive and Liver Disease 2011; Vol. 43, issue 1:48–53.

Funakoshi 2010
Funakoshi N, Segalas-Largey F, Duny Y, Oberti F, Valats JC, Bismuth M, et al. Benefit of combination beta-blocker and endoscopic treatment to prevent variceal rebleeding: a meta-analysis. *World Journal of Gastroenterology* 2010;**16** (47):5982–92. [PUBMED: 21157975]

Garcia-Tsao 2007
Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W, Practice Guidelines Committee of the American Association for the Study of Liver Diseases. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology (Baltimore, Md.)* 2007;**46**:922–38.

Garcia-Tsao 2008
Garcia-Tsao G, Bosch J, Groszmann RJ. Portal hypertension and variceal bleeding - unresolved issues. Summary of an American Association for the Study of Liver Diseases and European Association for the Study of the Liver single-topic conference. *Hepatology (Baltimore, Md.)* 2008;**47**:1764–72.

Gluud 2007
Gluud LL, Klingenberg S, Nikolova D, Gluud C. Banding ligation versus beta-blockers as primary prophylaxis in esophageal varices: systematic review of randomized trials. *American Journal of Gastroenterology* 2007;**102**:2842–8.

Gluud 2017
Gluud C, Nikolova D, Klingenberg SL. Cochrane Hepato-Biliary Group. About Cochrane (Cochrane Review Groups (CRGs)) 2017, Issue 10. Art. No.: LIVER.

Gonzalez 2008
Gonzalez R, Zamora J, Gomez-Camarero J, Molinero LM, Banares R, Albillos A. Meta-analysis: combination endoscopic and drug therapy to prevent variceal rebleeding in cirrhosis. *Annals of Internal Medicine* 2008;**149**(2): 109–22. [PUBMED: 18626050]

GRADEpro [Computer program]
Brozek J, Oxman A, Schünemann H. GRADEpro. Version 3.2 for Windows. Grade Working Group 2004–2007, 2008.

Higgins 2011
Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hróbjartsson 2001
Hróbjartsson A, Gøtzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *New England Journal of Medicine* 2001;**344**: 1594–602.

ICH-GCP 1997
International Conference on Harmonisation Expert Working Group. *International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. ICH harmonised tripartite guideline. Guideline for good clinical practice CFR & ICH Guidelines*. Vol. **1**, Philadelphia (PA): Barnett International/PAREXEL, 1997.

Merli 2003
Merli M, Nicolini G, Angeloni S, Rinaldi V, De Santis A, Merkel C, et al. Incidence and natural history of small esophageal varices in cirrhotic patients. *Journal of Hepatology* 2003;**38**:266–72.

Puente 2014
Puente A, Hernandez-Gea V, Graupera I, Roque M, Colomo A, Poca M, et al. Drugs plus ligation to prevent rebleeding in cirrhosis: an updated systematic review. *Liver International* 2014;**34**(6):823–33. [PUBMED: 24373180]

RevMan 2014 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Royle 2003
Royle P, Milne R. Literature searching for randomized controlled trials used in Cochrane Reviews: rapid versus exhaustive searches. *International Journal of Technology Assessment in Health Care* 2003;**19**(4):591–603.

Savović 2012
Savović J, Jones H, Altman D, Harris R, Jni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomised controlled trials: combined analysis of meta-epidemiological studies. *Health Technology Assessment* 2012;**16**:1–82.

Schmitz 2001
Schmitz RJ, Sharma P, Badr AS, Qamar MT, Weston AP. Incidence and management of esophageal stricture formation, ulcer bleeding, perforation, and massive hematoma formation from sclerotherapy versus band ligation. *American Journal of Gastroenterology* 2001;**96**(2): 437–41. [PUBMED: 11232687]

Shi 2013
Shi KQ, Liu WY, Pan ZZ, Ling XF, Chen SL, Chen YP, et al. Secondary prophylaxis of variceal bleeding for cirrhotic patients: a multiple-treatments meta-analysis. *European*

Journal of Clinical Investigation 2013;**43**(8):844–54. [PUBMED: 23725530]

Stata [Computer program]

Stata Corp. Stata 13. College Station (TX): Stata Corp, 2007.

Triantos 2007

Triantos CK, Burroughs AK. Prevention of the development of varices and first portal hypertensive bleeding episode. *Best Practice & Research. Clinical Gastroenterology* 2007;**21**: 31–42.

Tripathi 2007

Tripathi D, Graham C, Hayes PC. Variceal band ligation versus beta-blockers for primary prevention of variceal bleeding: a meta-analysis. *European Journal of Gastroenterology & Hepatology* 2007;**19**(10):835–45. [PUBMED: 17873606]

TSA 2011 [Computer program]

Copenhagen Trial Unit. TSA - Trial Sequential Analysis. Version 0.9 Beta. Copenhagen (Denmark): Copenhagen Trial Unit, 2011.

Villanueva 2008

Villanueva C, Balanzó J. Variceal bleeding: pharmacological treatment and prophylactic strategies. *Drugs* 2008;**68**(16): 2303–24. [DOI: 10.2165/0003495-200868160-00004]

Wong 2000

Wong T, Pereira SP, McNair A, Harrison PM. A prospective, randomized comparison of the ease and safety of variceal ligation using a multiband vs. a conventional ligation device. *Endoscopy* 2000;**32**:931–4.

* Indicates the major publication for the study

APPENDICES

Appendix 1. Search strategies

Database	Time span	Search terms
The Cochrane Hepato-Biliary Group Controlled Trials Register	Date will be given at review stage.	(beta-blocker* OR 'adrenergic beta antagonist*' OR propranolol OR atenolol OR nadolol OR metoprolol OR bisoprolol OR carvedilol OR tertatolol OR nipradilol OR penbutolol OR timolol OR mepindolol) AND '*esophageal varic*'
Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (Wiley)	Latest issue.	#1 MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees #2 MeSH descriptor: [Propranolol] explode all trees #3 MeSH descriptor: [Atenolol] explode all trees #4 MeSH descriptor: [Nadolol] explode all trees #5 MeSH descriptor: [Metoprolol] explode all trees #6 MeSH descriptor: [Bisoprolol] explode all trees #7 MeSH descriptor: [Penbutolol] explode all trees #8 MeSH descriptor: [Timolol] explode all trees #9 beta-blocker* or 'adrenergic beta antagonist*' or propranolol or atenolol or nadolol or metoprolol or bisoprolol or carvedilol or tertatolol or nipradilol or penbutolol or timolol or mepindolol #10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9

		#11 MeSH descriptor: [Esophageal and Gastric Varices] explode all trees #12 *esophageal varic* #13 #11 or #12 #14 #10 and #13
MEDLINE (OvidSP)	1946 to date of search.	1. exp Adrenergic beta-Antagonists/ 2. exp Propranolol/ 3. exp Atenolol/ 4. exp Nadolol/ 5. exp Metoprolol/ 6. exp Bisoprolol/ 7. exp Penbutolol/ 8. exp Timolol/ 9. (beta-blocker* or adrenergic beta antagonist* or propranolol or atenolol or nadolol or metoprolol or bisoprolol or carvedilol or tertatolol or nipradilol or penbutolol or timolol or mepindolol).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 11. exp "Esophageal and Gastric Varices"/ 12. ((oesophageal or esophageal) and varic*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 13. 11 or 12 14. 10 and 13 15. (random* or blind* or placebo* or meta-analysis).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 16. 14 and 15
Embase (OvidSP)	1974 to date of search.	1. exp beta adrenergic receptor blocking agent/ 2. exp PROPRANOLOL/ 3. exp ATENOLOL/ 4. exp NADOLOL/ 5. exp METOPROLOL/ 6. exp BISOPROLOL/ 7. exp CARVEDILOL/ 8. exp TERTATOLOL/ 9. exp NIPRADILOL/ 10. exp PENBUTOLOL/ 11. exp TIMOLOL/ 12. exp MEPINDOLOL/ 13. (beta-blocker* or adrenergic beta antagonist* or propranolol or atenolol or nadolol or metoprolol or bisoprolol or carvedilol or tertatolol or nipradilol or penbutolol or timolol or mepindolol)

(Continued)

		.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer] 14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 15. exp esophagus varices/ 16. ((oesophageal or esophageal) and varic*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer] 17. 15 or 16 18. 14 and 17 19. (random* or blind* or placebo* or meta-analysis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer] 20. 18 and 19
Science Citation Index Expanded (Web of Science)	1900 to date of search.	# 4 #3 AND #2 AND #1 # 3 TS=(random* or blind* or placebo* or meta-analysis) # 2 TS=((oesophageal or esophageal) and varic*) # 1 TS=(beta-blocker* or adrenergic beta antagonist* or propranolol or atenolol or nadolol or metoprolol or bisoprolol or carvedilol or tertatolol or nipradilol or penbutolol or timolol or mepindolol)

CONTRIBUTIONS OF AUTHORS

LLG: drafted and revised the protocol and approved the final version.

MYM revised the protocol and approved the final version.

DECLARATIONS OF INTEREST

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MYM: no conflicts of interest.

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