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Selective versus non-selective shunts for the prevention of variceal rebleeding (Protocol)

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[Intervention Protocol]

Selective versus non-selective shunts for the prevention of variceal rebleeding

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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 assess the benefits and harms of any type of selective shunt versus any type of non-selective shunt for the prevention of oesophagogastric variceal rebleeding in people with portal hypertension.

B A C K G R O U N D

Description of the condition

Variceal bleeding is the most lethal complication of portal hypertension, occurring when the hepatic venous pressure gradient (HVPG) exceeds 12 mmHg (Sanyal 2008; Garcia-Tsao 2017). In people with decompensated cirrhosis, variceal bleeding is a major cause of mortality. Liver cirrhosis is the eleventh leading cause of adult death and accounts for 1.6% of global disability-adjusted life years (DALYs) (Mokdad 2014). The leading causes of liver cirrhosis vary depending on region, but they include alcohol, viral hepatitis, and non-alcoholic steatohepatitis. Half of people living with liver cirrhosis will develop varices, and bleeding from these varices occurs at a rate of 10% to 15% per year (Merli 2003; Kovalak 2007). In low-income countries, non-cirrhotic prehepatic portal hypertension accounts for the majority of variceal bleeding in children, while hepatosplenic schistosomiasis is common in the adult population (Poddar 2008). Irrespective of aetiology, varices occur commonly at the distal third of the oesophagus and proximal half of the stomach, where it is thought to be due to dilatation of natural portosystemic collateral veins. Recent evidence suggests that neo-angiogenesis accounts for the development of these collaterals (Fernandez 2004). The rupture of these varices occurs when intravariceal pressure exceeds the elastic limit of the variceal wall, as explained by the law of Laplace (Rigau 1989).

Portal hypertension develops through two mechanisms: 1) an increase in intrahepatic vascular resistance produced by changes in intrahepatic morphology, and vascular tones related to cirrhosis; and 2) an increased blood flow in splanchnic circulation produced by imbalance in vasoactive mediators and neo-angiogenesis. Both mechanisms are present in cirrhotic portal hypertension, but in non-cirrhotic prehepatic and presinusoidal portal hypertension, intrahepatic vascular resistance is normal. Evidence suggests that norepinephrine, angiotensin II, anti-diuretic hormone, endothelin, and nitric oxide are responsible for these changes in haemodynamics (Sharara 2001; Moore 2004).

An increased HVPG is a strong predictor of rebleeding and death in people with portal hypertension (Moitinho 1999; Ripoll 2005). However, in clinical practice, scoring models such as Child-Pugh score (Child 1964; Pugh 1973) and Model for End-Stage Liver Disease (MELD) (Kamath 2007) are used to predict risk of rebleeding and death. These scoring models of liver dysfunction have been shown to correlate well with HVPG measurements (Wadhawan 2006; Reverter 2014; Ramanathan 2016; Fortune 2017). Mortality approaches 25% during the first six weeks following an acute variceal bleed in people with cirrhotic portal hypertension, and the risk of rebleeding approaches 70% in two years, without secondary prophylaxis (D'Amico 2003; Fortune 2017). In non-cirrhotic portal hypertension, mortality from acute variceal bleeding approaches 10% after six weeks (Chofle 2014).

Although invasive oesophago-gastro-duodenoscopy remains the gold standard for the diagnosis and management of varices in the upper gastro-intestinal tract, recent evidence shows that a non-invasive test such as transient elastography can detect people with clinically significant portal hypertension (CSPH), who are at risk of bleeding (North Italian 1988; Foucher 2006; Stefanescu 2011; Shi 2013; Garcia-Tsao 2017).

Description of the intervention

Acute variceal bleeding is treated with a combination of pharmacological therapy (vasoactive drugs and antibiotics) and endoscopy. Endoscopic methods include rubber-band ligation and sclerotherapy of bleeding varices. Novel endoscopic modalities have emerged, including use of self-expandable metallic stents (SEMS), haemostatic powders, and endoscopic ultrasound-guided injection of varices. Pharmacological and endoscopic treatment strategies are effective in 80% of patients, but for those who continue to bleed or rebleed, decompressive shunts should be considered (de Franchis 2015; Garcia-Tsao 2017; Tripathi 2015; Thabut 2018). Shunt interventions involve connecting the hypertensive portal venous system into a normotensive systemic vein, so as to reduce elevated portal pressure. Shunts are classified as surgical (invasive) and radiologic (non-invasive) (transjugular intrahepatic portosystemic shunt (TIPS)). Shunts are further classified by their effect on portal haemodynamics, into selective shunts (which divert a portion of portal blood flow into the systemic circulation) and non-selective shunts (which divert all portal blood flow into systemic circulation). Examples of selective shunts include distal splenorenal shunts that connect the distal splenic vein to the left renal vein and H-graft polytetrafluorethylene reinforced grafts measuring 8 millimetres (mm) in internal diameter, that connect superior mesenteric vein or portal vein to the inferior vena cava. Finally, there are small-diameter TIPS constructed with stents measuring 8 mm or less in internal diameter. Non-selective shunts are portocaval shunts that connect portal vein directly to the inferior vena cava, mesocaval shunts that connect superior mesenteric vein to the inferior vena cava, and proximal splenorenal shunts that connect the proximal splenic vein to the left renal vein. Other types of non-selective shunt interventions include H-graft polytetrafluorethylene reinforced grafts, measuring 16 mm or more in internal diameter, and TIPS constructed with stents, measuring 10 mm or more in internal diameter. The technique of shunt interventions have been described in previous reviews (Brand 2018; Ede 2018). Although non-selective surgical shunts (such as the portocaval shunt) appear easier to create compared to the selective distal splenorenal shunt, their effect or portal haemodynamics can be profound. The incidence of encephalopathy with non-selective surgical shunts ranges from 40% to 80%, in contrast to 10% to 20% with selective surgical shunts (Warren 1974; McInnes 1985; Raia 1994). When large-diameter TIPS was compared to small-diameter TIPS, the rate of encephalopathy with 10 mm TIPS was approximately 40% (Escorsell 2002; Wang 2017) versus 18% to 27% with 8 mm TIPS (Sauerbruch 2015; Wang 2017). Rebleeding after TIPS intervention was 13% to 17% with 10 mm TIPS (Escorsell 2002; Wang 2017) compared to 7% to 16% with 8 mm TIPS (Sauerbruch 2015; Wang 2017). However, small-diameter TIPS was associated with the need for more re-interventions (Rabei 2018). Whether shunts selectively allow nutrient hepatic flow will depend on the diameter of the shunt and their anatomical location.

How the intervention might work

Portosystemic shunts divert portal venous blood into systemic venous circulation, so as to reduce portal pressure. Evidence suggests that maintaining HVPG below 12 mmHg, or achieving a decrease in HVPG greater than 20% from baseline, has the potential to prevent variceal bleeding in people with portal hypertension (Bosch 2003; D'Amico 2006; Li 2015).

Why it is important to do this review

A decompressive shunt is advocated as an effective modality to prevent variceal rebleeding in people with portal hypertension complicated by variceal bleeding, who have received first-line treatment in the form of pharmacological and endoscopic therapy (de Franchis 2015; Tripathi 2015; Garcia-Tsao 2017; Thabut 2018). Hence, an evidence-based approach should be developed to guide the use of decompressive shunts in preventing potentially life-threatening variceal rebleeding in people with portal hypertension.

In a meta-analysis that compared non-selective shunts with distal splenorenal shunts (DSRS) in people with variceal rebleeding, D'Amico and colleagues included only six trials with 336 participants who received either a portocaval shunt, mesocaval shunt, central splenorenal shunt, or large-diameter H-graft shunt in the experimental arm, and DSRS in the control arm (D'Amico 1995). The authors concluded there was no difference between the two types of intervention in terms of variceal rebleeding, encephalopathy, and all-cause mortality in people with cirrhosis. This meta-analysis has not been updated since its first publication. The authors did not assess the risk of bias in the included trials, or the certainty of the evidence. In a subgroup analysis of selective surgical shunts versus non-selective surgical shunts, Yin and colleagues concluded that there was no difference between the interventions regarding variceal rebleeding, encephalopathy, and all-cause mortality (Yin 2013). Although the study by Yin and colleagues is more recent, it was designed to compare surgical shunts to devascularisation, so the study authors may have overlooked trials relevant to this planned Cochrane Review. In addition, the authors included quasi-randomised studies; this casts doubt on the conclusions that can be made from the results, because of risk of bias in such studies. Therefore, we will use Cochrane methodology to investigate the type of decompressive shunt that may have the best overall benefit in preventing variceal rebleeding in people with portal hypertension, irrespective of aetiology.

O B J E C T I V E S

To assess the benefits and harms of any type of selective shunt versus any type of non-selective shunt for the prevention of oesophagogastric variceal rebleeding in people with portal hypertension.

M E T H O D S

Criteria for considering studies for this review

Types of studies

We will include randomised clinical trials that compared any type of selective shunt versus any type of non-selective shunt for the prevention of variceal rebleeding in people with portal hypertension. We will not place limitations on publication type, publication status, or language.

Types of participants

We will include participants diagnosed with oesophagogastric variceal bleeding, who have received primary treatment (endoscopic, pharmacological, balloon tamponade, or stent) and are subsequently scheduled for a shunt intervention. We will include participants irrespective of age, sex, or the aetiology of the portal hypertension.

Types of interventions

We will consider as experimental intervention the following types of selective shunts:

- Distal splenorenal shunt. This shunt intervention connects the distal splenic vein to the left renal vein, with or without spleno-pancreatic and -gastric connection.
- Small-diameter H-graft shunt. This shunt is constructed with polytetrafluoroethylene reinforced grafts that measure 8 mm in internal diameter and connects the superior mesenteric vein or portal vein to inferior vena cava.
- Small-diameter TIPS. This is TIPS constructed with stents measuring 8 mm or less in internal diameter, or primarily constrained to reduce the internal diameter. The stent may or may not be covered with polytetrafluoroethylene.

We will consider as control intervention the following types of non-selective shunts:

- Portocaval shunt. This shunt is constructed to connect the portal vein to the inferior vena cava directly.
- Mesocaval shunt. This shunt is constructed to connect the superior mesenteric vein to the inferior vena cava directly.
- Central (proximal) splenorenal shunt. This shunt is constructed to connect the proximal splenic vein to the left renal vein, with or without spleno-pancreatic and -gastric connection or splenectomy.
- Large-diameter H-graft shunt. This shunt is constructed with polytetrafluoroethylene reinforced grafts that measure 16 mm or greater in internal diameter and connects superior mesenteric vein or portal vein to the inferior vena cava.
- Large-diameter TIPS. This is TIPS constructed with stents, measuring 10 mm or more in internal diameter. The stent may or may not be covered with polytetrafluoroethylene.

Our main comparison will be a meta-analysis of all types of selective shunts versus non-selective shunts. We will compare surgical and radiologic shunts in a subgroup analysis.

Types of outcome measures

We will include studies irrespective of the type of outcome measures reported.

Primary outcomes

- All-cause mortality up to 30 days, 90 days, and 5 years following intervention. Our primary time point will be mortality up to 5 years.
- Variceal rebleeding up to 30 days. We will assess the number of participants who developed haematemesis or melaena up to 30 days of the intervention, and bleeding assessed at gastrointestinal endoscopy to originate from oesophagogastric varices.
- Health-related quality of life (HRQOL): we will measure HRQOL with the scale defined in the trials, but only if it is a validated one.

Secondary outcomes

- Post-shunt encephalopathy. We will assess the number of participants who developed new encephalopathy, or worsening of pre-existing encephalopathy, up to 30 days and 1 year following intervention. Our primary time point will be encephalopathy up to 1 year. We will define encephalopathy based on the presence

of clinical signs, result of psychometric testing, and electroen-cephalogram (Ferenci 2002; Vilstrup 2014; Allampati 2015).

- Post-shunt ascites. We will assess the number of participants who developed ascites detected through imaging up to 30 days and 1 year following intervention. Our primary time point will be ascites up to 1 year.
- Irreversible shunt occlusion. We will assess the number of participants with non-functioning shunts despite re-interventions up to 5 years following the index intervention.
- Proportion of trial participants with one or more adverse events considered to be serious. We will assess serious adverse events judged to be related to the intervention, that occurred in hospital, up to 30 days, or up to 90 days of the intervention. We will report procedure-related mortality up to 30 days as our primary time point. We will use standard definitions for adverse events (see: prsinfo.clinicaltrials.gov/results_definitions.html#AdverseEventsDefinition).

Exploratory Outcomes

- Post-shunt hepatic venous pressure gradients
- Proportion of trial participants with one or more adverse events that are considered to be non-serious

Search methods for identification of studies

Electronic searches

We will perform electronic searches in the Cochrane Hepato-Biliary Group (CHBG) Controlled Trials Register (maintained and searched internally by the CHBG Information Specialist via the Cochrane Register of Studies Web), Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE Ovid, Embase Ovid, LILACS (Latin American and Caribbean Health Sciences Literature; Bireme), Science Citation Index Expanded (Web of Science), and Conference Proceedings Citation Index- Science (Web of Science) (Royle 2003). We will not apply any language restrictions to our searches. Our preliminary search strategies and time spans of the searches are listed in Appendix 1.

Searching other resources

We will search online trial registries such as ClinicalTrials.gov (clinicaltrials.gov/), the European Medicines Agency (EMA) (www.ema.europa.eu/ema/), WHO International Clinical Trials Registry Platform (www.who.int/ictrp), and the Food and Drug Administration (FDA) (www.fda.gov). We will also search pharmaceutical company sources, reference lists of potentially eligible studies and relevant reviews for ongoing or unpublished trials. We will search for grey literature in the System for Information on Grey Literature in Europe "OpenGrey" (www.opengrey.eu/).

Data collection and analysis

Selection of studies

Two review authors (CJE and RE) will independently screen the lists of titles and abstracts retrieved by our searches in order to identify studies fulfilling the inclusion criteria as outlined in our review protocol. We will consider observational studies (i.e. quasi-randomised studies, cohort studies, case-control studies, case reports, case series, or letters to the editors) for their report on harms, if they are retrieved during our searches for randomised clinical trials. We will include these studies only for a separate analysis of harms of interventions, and we will present the data in a narrative way. By

choosing this strategy we are aware that we will put more focus on potential benefits and may overlook late-occurring or rare harms, which are often missed in meta-analysis of randomised clinical trials (Storebø 2018). If we demonstrate clear benefits of one type of intervention, then a systematic review of harms in observational studies ought to be undertaken. CJE and RE will contact study authors to seek clarity where selected trials do not provide clear and sufficient information. We will resolve all disagreements between CJE and RE by discussion with MB.

Data extraction and management

Two review authors (CJE and RE) will independently extract data from included trials using a piloted, standardised data extraction form. We will extract information in sufficient detail to populate tables detailing the characteristics of included and excluded studies. The extracted information will include the following.

- General information: name of first author, title, journal, year of publication, country of trial, publication status, trial design
- Sample size: number of participants screened, number of participants included, number of participants excluded, dropouts (with reasons)
- Inclusion and exclusion criteria of the trial
- Participant information: age, sex, race, Child-Pugh score, MELD score
- Method of diagnosis of disease, aetiology of portal hypertension
- Risks of bias
- Outcomes: proportion of participants with events for categorical outcomes, and mean events with standard deviation or standardised mean difference for continuous outcomes
- Duration of follow-up
- Numerical data to facilitate our planned analyses

Assessment of risk of bias in included studies

Two review authors (CJE and RE) will independently assess the risk of bias of each included trial using the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019) and methodological studies (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Hrobjartsson 2012; Savović 2012a; Savović 2012b; Hrobjartsson 2013; Hrobjartsson 2014a; Hrobjartsson 2014b; Savović 2018). We will use the Revised Cochrane risk-of-bias tool for randomised trials (RoB 2) (Sterne 2019), to assess risk of bias based on the following five domains.

- Bias arising from the randomisation process
- Bias due to deviations from intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

We will assess bias due to deviation from intended interventions produced by development of encephalopathy and non-adherence by trial participants to their assigned intervention.

Overall risk of bias

Based on the response to signalling questions, we will make a judgement about the risk of bias in each domain (low risk of bias, some concerns, or high risk of bias). We will also make a judgement

about the overall risk of bias in each trial, based on the following criteria.

- Low risk of bias: the study is judged to be at low risk of bias for all domains for the result
- Some concerns: the study is judged to raise some concerns in at least one domain for the result, but is not judged to be at high risk of bias for any domain
- High risk of bias: the study is judged to be at high risk of bias in at least one domain for the result, or the study is judged to raise some concerns for multiple domains in a way that substantially lowers confidence in the result

Following our definitions, we will not include studies with high risk of bias arising from the randomisation process when assessing the benefit of interventions. Such studies will be considered only to assess harms of the interventions in a narrative way.

Measures of treatment effect

We will compute intervention effects for dichotomous outcomes as risk ratios (RRs) with 95% confidence intervals (CIs). For continuous outcomes we will calculate the mean difference (MD) if all studies reported the outcome using the same scale, and the standardised mean difference (SMD) with 95% CIs if the studies used different scales. We will re-express the calculated SMD using the rule of thumb (Cohen 1988), where Cohen's d = 0.2 will be considered a 'small' effect size, 0.5 a 'medium' effect size, and 0.8 a 'large' effect size. For time-to-event data, we will calculate hazard ratio (HR) with 95% CIs.

Unit of analysis issues

The unit of analysis will be trial participants as randomised to intervention groups. If we identify trials with more than two intervention groups, we will only extract data from the trial groups that correspond to the interventions being considered for this review. For cross-over trials, we will only include participants from the first treatment period, using the analytical methods described by Elbourne and colleagues (Elbourne 2002). For cluster-randomised trials, we will consider the individual clusters as the unit of analysis. However, we do not expect to find cross-over or cluster-randomised trials.

Dealing with missing data

We will seek to perform an intention-to-treat analysis. We will deal with missing or unclear data in the published report by writing to the study authors to ask for additional information. In our analysis of health-related quality of life, should missing standard deviations not be obtained through contacting study authors, we will estimate the standard deviation using statistical methods described in section 6.5.2 of the *Cochrane Handbook* (Higgins 2019). Where this is not possible, we will impute the standard deviations from other studies included in our meta-analysis.

We will include missing data by considering trial participants as either treatment failures or treatment successes in sensitivity analyses using the following scenarios.

- Extreme case analysis that favours the experimental intervention ('best-worst' case scenario): none of the dropouts or participants lost from the experimental group, but all of the dropouts or participants lost from the control group are assumed to

have experienced the outcome, including all randomised participants in the denominator.

- Extreme case analysis that favours the control ('worst-best' case scenario): all dropouts or participants lost from the experimental group, but none from the control group, are assumed to have experienced the outcome, including all randomised participants in the denominator.

Assessment of heterogeneity

We will investigate the presence and extent of both clinical and methodological diversity across studies. We will assess statistical heterogeneity that is a consequence of clinical or methodological diversity, or both, using the Ch^2 test and I^2 statistic (Higgins 2002). We will interpret an I^2 value of 50% or more as indicating a substantial level of heterogeneity (Higgins 2003; Sterne 2011). We will further explore the possible causes of substantial heterogeneity in a subgroup analyses or meta-regression, if we find sufficient studies. This will help to reduce the uncertainty that occurs when the Chi^2 test and I^2 statistic are used to investigate heterogeneity in meta-analyses where there are few studies with a small sample size.

Assessment of reporting biases

We will assess reporting biases by visual assessment of funnel plots of all primary and secondary outcomes, providing we identify at least ten trials for the meta-analysis. We will use two statistical tests to assess funnel plot asymmetry: the adjusted rank correlation test (Begg 1994) and regression asymmetry test (Egger 1997).

Data synthesis

We will conduct the systematic review according to the recommendations in the *Cochrane Handbook* (Higgins 2019). We will use the statistical software package Review Manager 5.3, provided by Cochrane (Review Manager 2014). We will meta-analyse data using a random-effects model (DerSimonian 1986) and a fixed-effects model (DeMets 1987), following the recommendations in section 10.10.4 of the *Cochrane Handbook* (Higgins 2019). Where there are discrepancies in the estimates of both models, which suggests the presence of heterogeneity among the studies, we will investigate the cause of heterogeneity by funnel plot analyses if we identify enough studies. We plan to present the result of the random-effects model if there is no indication of funnel plot asymmetry. On the other hand, the presence of funnel plot asymmetry will push the result of the random-effects analysis towards the findings in the smaller studies, hence we plan to perform a sensitivity analysis by excluding small studies and present the results from the larger studies. If we are not able to find enough studies to test for funnel plot asymmetry, we will report the result of both models. Where data are only available from one trial, we will use Fisher's test for dichotomous data (Fisher 1922), and Student's t-test for continuous data (Student 1908).

Subgroup analysis and investigation of heterogeneity

We will perform subgroup analyses in order to compare the intervention effect for the following subgroups.

- Trials at low risk of bias (see above) compared to trials at high risk of bias. This is because trials at high risk of bias are likely to over-estimate intervention effects (Savović 2018).
- Trials without industry-sponsorship compared to industry-sponsored trials. This is because trials sponsored by industry

are likely to be biased, and thus introduce heterogeneity (Lundh 2018).

- Selective surgical shunts compared with non-selective surgical shunts in cirrhotic portal hypertension and in non-cirrhotic portal hypertension. This is because cirrhotic and non-cirrhotic portal hypertension differ in their geographical locations, age of presentation, and severity of liver dysfunction (Ede 2018).
- Selective TIPS compared with non-selective TIPS in cirrhotic portal hypertension. This is because radiologic shunt is less invasive than surgical shunts, and TIPS is commonly advocated in cirrhotic portal hypertension (Sauerbruch 2018).
- Trials subgrouped according to the interventions in the experimental and control groups.

We will attempt to perform the subgroup analyses for only two of our primary outcomes -- all-cause mortality up to 5 years and variceal rebleeding up to 30 days following intervention.

Sensitivity analysis

We will perform sensitivity analyses to assess the robustness of our conclusions to decisions made during the review process. We will repeat the meta-analysis, re-exploring our decisions for included studies, participants, data imputations, and method of analysis. We will also explore the cause of heterogeneity in sensitivity analysis by considering clinical diversity across studies (i.e. differences in type of participants, types of interventions, and outcomes measured). We will also consider methodological diversity (i.e. the bias risk of trials, trial design, tools for measurement of outcomes). For our sensitivity analyses, we plan to perform meta-analysis both with and without the following.

- Trials with participants aged less than 18 years
- Trials of non-cirrhotic portal hypertension
- Trials of shunts, irrespective of radiologic or surgical shunts
- Assessment of outcomes at different time points
- Trials at high risk of bias
- Trials with lack of blinding of participants, or personnel
- Trials with outlying results

We will attempt to perform the sensitivity analyses for only two of our primary outcomes -- all-cause mortality up to 5 years and variceal rebleeding up to 30 days following intervention.

Summary of findings tables

We will create 'Summary of findings' tables for the following outcomes: all-cause mortality up to 5 years; variceal rebleeding up to 30 days; health-related quality of life; procedure-related mortality up to 30 days; post-shunt encephalopathy up to 1 year; post-shunt ascites up to 1 year; and irreversible shunt occlusion up to 5 years, as our primary time points, using GRADEpro GDT software

(GRADEpro GDT). We will provide the time ranges for the primary time points. Using GRADE, we will appraise the certainty of the body of evidence by considering the following: within-study risk of bias (methodological quality), indirectness of the evidence (population, intervention, control, outcomes), unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses); imprecision of effect estimates (wide CIs), and probability of publication bias (Balshem 2011; Guyatt 2011a; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2011h; Andrews 2013; Guyatt 2013a; Guyatt 2013b; Guyatt 2013c; Guyatt 2013d; Mustafa 2013; Guyatt 2017). We will follow the recommendations of section 8.5 and chapter 12 of the *Cochrane Handbook* (Higgins 2019). We will classify the certainty of evidence as 'high', 'moderate', 'low', or 'very low' (see below).

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

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A P P E N D I C E S

Appendix 1. Search strategy

Database	Time span	Search strategy
Cochrane Hepato-Biliary Group Controlled Trials Register	Date will be given at the review stage.	((selective or non-selective or port*systemic or splenorenal or surgical) and (shunt* or anastomos*)) AND (varic* and (h*emorrhag* or bleed* or rebleed*))
Cochrane Central Register of Controlled Trials	Latest issue	#1 MeSH descriptor: [Anastomosis, Surgical] explode all trees #2 ((selective or non-selective or port*systemic or splenorenal or surgical) and (shunt* or anastomos*))

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(Continued)

(CENTRAL) in the Cochrane Library		#3 #1 or #2
		#4 MeSH descriptor: [Esophageal and Gastric Varices] explode all trees
		#5 (varic* and (h*emorrhag* or bleed* or rebleed*))
		#6 #4 or #5
		#7 #3 and #6
MEDLINE Ovid	1946 to the date of the search	1. exp Anastomosis, Surgical/
		2. ((selective or non-selective or port*systemic or splenorenal or surgical) and (shunt* or anastomos*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
		3. 1 or 2
		4. exp "Esophageal and Gastric Varices"/
		5. (varic* and (h*emorrhag* or bleed* or rebleed*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
		6. 4 or 5
		7. 3 and 6
		8. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
		9. 7 and 8
Embase Ovid	1974 to the date of the search	1. exp anastomosis/
		2. ((selective or non-selective or port*systemic or splenorenal or surgical) and (shunt* or anastomos*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
		3. 1 or 2
		4. exp esophagus varices/
		5. (varic* and (h*emorrhag* or bleed* or rebleed*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
		6. 4 or 5
		7. 3 and 6
		8. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
		9. 7 and 8
LILACS (Bireme)	1982 to the date of the search	((selective or non-selective or port$systemic or splenorenal or surgical) and (shunt$ or anastomos$)) [Words] and (varic$ and (h$emorrhag$ or bleed$ or rebleed$)) [Words]

(Continued)

Science Citation Index Expanded (Web of Science)	1900 to the date of the search	#5 #4 AND #3
		#4 TS=(random* or blind* or placebo* or meta-analys*)
		#3 #2 AND #1
		#2 TS=(varic* and (h*emorrhag* or bleed* or rebleed*))
		#1 TS=((selective or non-selective or port*systemic or splenorenal or surgical) and (shunt* or anastomos*))
Conference Proceedings Citation Index – Science (Web of Science)	1990 to the date of the search	#5 #4 AND #3
		#4 TS=(random* or blind* or placebo* or meta-analys*)
		#3 #2 AND #1
		#2 TS=(varic* and (h*emorrhag* or bleed* or rebleed*))
		#1 TS=((selective or non-selective or port*systemic or splenorenal or surgical) and (shunt* or anastomos*))

CONTRIBUTIONS OF AUTHORS

CJE drafted the protocol.
RE contributed in drafting the protocol.
MB made suggestions to the protocol.

All authors approved the protocol for publication.

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