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Banding ligation versus beta-blockers for primary prevention in oesophageal varices in adults (Review)

Gluud LL, Krag A

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[Intervention Review]

Banding ligation versus beta-blockers for primary prevention in oesophageal varices in adults

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ABSTRACT

Background

Non-selective beta-blockers are used as a first-line treatment for primary prevention in patients with medium- to high-risk oesophageal varices. The effect of non-selective beta-blockers on mortality is debated and many patients experience adverse events. Trials on banding ligation versus non-selective beta-blockers for patients with oesophageal varices and no history of bleeding have reached equivocal results.

Objectives

To compare the benefits and harms of banding ligation versus non-selective beta-blockers as primary prevention in adult patients with endoscopically verified oesophageal varices that have never bled, irrespective of the underlying liver disease (cirrhosis or other cause).

Search methods

In Febuary 2012, electronic searches (the Cochrane Hepato-Biliary Group Controlled Trials Register, *The Cochrane Library*, MEDLINE, EMBASE, and Science Citation Index Expanded) and manual searches (including scanning of reference lists in relevant articles and conference proceedings) were performed.

Selection criteria

Randomised trials were included irrespective of publication status, blinding, and language.

Data collection and analysis

Review authors independently extracted data. All-cause mortality was the primary outcome. Intention-to-treat random-effects and fixed-effect model meta-analyses were performed. Results were presented as risk ratios (RR) and 95% confidence intervals (CI) with I^2 statistic values as a measure of intertrial heterogeneity. Subgroup, sensitivity, regression, and trial sequential analyses were performed to evaluate the robustness of the overall results, risks of bias, sources of intertrial heterogeneity, and risks of random errors.

Main results

Nineteen randomised trials on banding ligation versus non-selective beta-blockers for primary prevention in oesophageal varices were included. Most trials specified that only patients with large or high-risk oesophageal varices were included. Bias control was unclear in most trials. In total, 176 of 731 (24%) of the patients randomised to banding ligation and 177 of 773 (23%) of patients randomised to non-selective beta-blockers died. The difference was not statistically significant in a random-effects meta-analysis (RR 1.09; 95% CI 0.92 to 1.30; $I^2 = 0\%$). There was no evidence of bias or small study effects in regression analysis (Egger's test P = 0.997). Trial sequential analysis showed that the heterogeneity-adjusted low-bias trial relative risk estimate required an information size of 3211 patients, that none of the interventions

showed superiority, and that the limits of futility have not been reached. When all trials were included, banding ligation reduced upper gastrointestinal bleeding and variceal bleeding compared with non-selective beta-blockers (RR 0.69; 95% CI 0.52 to 0.91; I^2 = 19% and RR 0.67; 95% CI 0.46 to 0.98; I^2 = 31% respectively). The beneficial effect of banding ligation on bleeding was not confirmed in subgroup analyses of trials with adequate randomisation or full paper articles. Bleeding-related mortality was not different in the two intervention arms (29/567 (5.1%) versus 37/585 (6.3%); RR 0.85; 95% CI 0.53 to 1.39; I^2 = 0%). Both interventions were associated with adverse events.

Authors' conclusions

This review found a beneficial effect of banding ligation on primary prevention of upper gastrointestinal bleeding in patient with oesophageal varices. The effect on bleeding did not reduce mortality. Additional evidence is needed to determine whether our results reflect that non-selective beta-blockers have other beneficial effects than on bleeding.

PLAIN LANGUAGE SUMMARY

Banding ligation versus beta-blockers for primary prevention in oesophageal varices in adults

Non-selective beta-blockers are used as a first-line treatment for primary prevention in patients with medium- to high-risk oesophageal varices. However, the effect of non-selective beta-blockers on mortality is debated and many patients experience adverse events. This review includes 19 randomised trials on banding ligation versus beta-blockers for patients with high-risk oesophageal varices and no history of bleeding. Bias control was unclear in most trials. There was no difference in mortality among the patients randomised to banding ligation compared with beta-blockers. The trials with adequate bias control based on the assessment of randomisation methods found no difference in bleeding rates. The trials with unclear randomisation methods found that banding ligation reduced bleeding. The effect of banding ligation was associated with the duration of follow-up and publication status of the trials. The results of trials with less than 20 months of follow-up found a better effect of banding ligation compared to trials with longer follow-up. Trials published in abstract form were more positive towards the effect of banding ligation than trials published as full paper articles. The combined evidence suggests that banding ligation and beta-blockers may be used as primary prophylaxis in oesophageal varices in adult patients. Additional evidence from trials with adequate bias control and sufficient follow-up is still needed to determine long-term effects.

BACKGROUND

Oesophageal varices is one of the most serious complications to cirrhosis and portal hypertension (Le Moine 1992; Bosch 2003). During a five-year period, about one in five patients with cirrhosis will die from variceal bleeding (Gunnarsdottir 2005). Oesophageal varices develop when the hepatic venous pressure gradient exceeds 10 mmHg (Arguedas 2003). A reduction in the hepatic venous pressure gradient by at least 20% of the baseline pressure or to less than 12 mmHg reduces the risk of bleeding (Turnes 2006). Interventions that decrease portal pressure may, therefore, help to prevent bleeding from oesophageal varices (D'Amico 2006).

Randomised trials and meta-analyses show that non-selective beta-blockers reduce the number of bleeding events when used as primary prevention in oesophageal varices (Cheng 2005). Treatment with non-selective beta-blockers is widely used as a first-line treatment for primary prevention in medium- to high-risk oesophageal varices (Lebrec 2005). However, the effect on mortality is debated and many patients experience adverse events (Garcia-Pagan 2001; Cheng 2005; Lebrec 2005). Banding ligation has been assessed as an alternative treatment, but the results of individual trials are conflicting (Avgerinos 2000; Vlachogiannakos 2000). Previous meta-analyses of randomised trials found no clear difference between banding ligation and beta-blockers regarding mortality (Khuroo 2005; Triantos 2006). However, the frequency of adverse events associated with banding ligation may be underestimated due to the inclusion of selected patient groups and the fact that only experienced operators participated in the trials (Mahadeva 2002; Parente 2005; Lim 2006). In our previous systematic review on banding ligation versus beta-blockers we found that banding ligation may decrease the risk of bleeding (Gluud 2007). However, there was no clear effect on mortality and adverse events were unclearly reported. We, therefore, performed this updated review with inclusion of subsequent trials (Tripathi 2009; Perez 2010).

OBJECTIVES

The objective of this review was to assess the beneficial and harmful effects of banding ligation versus beta-blockers as primary prevention in the management of patients with oesophageal varices and no previous bleeding.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised trials were included regardless of publication status or language.

Types of participants

Adult patients with endoscopically verified oesophageal varices that have never bled were included regardless of the underlying liver disease (cirrhosis or other cause).

Types of interventions

The interventions assessed were randomised comparisons of banding ligation versus non-selective beta-blockers, irrespective of the dose or duration of the intervention.

Types of outcome measures

Primary outcomes

1. All-cause mortality

Secondary outcomes

1. Upper gastrointestinal bleeding (irrespective of bleeding source)
2. Variceal bleeding
3. Bleeding-related mortality
4. Quality of life
5. Adverse events (ICH-GCP 1997)

Search methods for identification of studies

Electronic searches

We searched the Cochrane Hepato-Biliary Group Controlled Trials Register (Gluud 2012), Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*, MEDLINE, EMBASE, and Science Citation Index Expanded (Royle 2003). The search strategies with the time span of the searches are given in Appendix 1.

Searching other resources

Additional trials were identified through scanning of reference lists in relevant papers and conference proceedings. The meta-register at the World Health Organization search portal for clinical trials (http://www.who.int/trialsearch/) was searched for additional ongoing or unpublished trials.

Data collection and analysis

Selection of studies

Two review authors (LG and AK) identified and selected trials, and approved the trials selected for inclusion. Excluded trials were listed with the reasons for exclusion.

Data extraction and management

Review authors independently extracted data. Primary authors of the included trials were contacted for additional information when outcomes or trial methods were not described in the published trial reports.

Assessment of risk of bias in included studies

The risk of bias in included trials was assessed using individual components. The risk of bias was classed as low if the individual components were classed as adequate. Based on previous evidence (Schulz 1995; Moher 1998; Kjaergard 2001; Gluud 2006; Wood 2008), the randomisation methods (allocation sequence generation and concealment) were extracted as the primary measures of bias control. An allocation sequence generation based on a computer, random number table, or similar was classified as adequate. The allocation concealment was classed as adequate if based on a central independent unit, serially numbered opaque sealed envelopes, or on-site locked computer. Additional measures of bias control included blinding, handling of missing data (whether all patients randomised were accounted for in the analyses), and reporting bias (whether the most clinically relevant outcome measures were reported). We also assessed other sources of bias including sample size calculations and comparability between intervention groups (differences between prognostic variables at

baseline may reflect skewed allocation and distort the result of the trial).

Measures of treatment effect

Outcome measures were binary and expressed as relative risks (RR) with 95% confidence intervals (CI).

Unit of analysis issues

The primary unit of analysis was included patients.

Dealing with missing data

Intention-to-treat analyses were performed with carry forward of the last observed response for patients with missing data.

Assessment of heterogeneity

Intertrial heterogeneity was expressed as I^2 statistic values.

Assessment of reporting biases

Trials were classed as having a low risk of publication bias if clinically relevant outcome measures were defined and reported.

Data synthesis

The analyses were performed in Review Manager version 5 (RevMan 2011), STATA version 11 (STATA Corp, Texas USA), and trial sequential analysis (TSA) (CTU 2011; Thorlund 2011). Meta-analyses were performed using random-effects models due to an expected clinical heterogeneity (duration of follow-up and intervention regimens). Results were expressed as relative risks (RR) with 95% confidence intervals (CI), and I^2 as a measure of intertrial heterogeneity. Data on all patients randomised were sought to perform intention-to-treat analyses. Carry forward of the last observed response was used for patients with missing data.

Subgroup analysis and investigation of heterogeneity

Based on peer review comments stressing the importance of analysing the effect of the interventions on bleeding, we performed sensitivity, subgroup, and regression analyses for our primary outcome mortality and for the outcome upper gastrointestinal bleeding. Subgroup and sensitivity analyses were performed to assess the influence of trial characteristics on the overall result and on intertrial heterogeneity (publication status, bias control, duration of follow-up), and regression analyses (Egger's 'test of bias') to evaluate evidence of bias or small trial effects. Differences between subgroups were expressed as P and I^2 values. We also performed trial sequential analyses to assess the risk of random errors due to sparse data and multiple comparisons in our cumulative assessment of the intervention effects (Brok 2008; Wetterslev 2008; Brok 2009; Thorlund 2009, Wetterslev 2009; Higgins 2010; Thorlund 2010; Higgins 2011). The analysis was performed with alpha set to 5% and power to 80%, and with a model-based heterogeneity correction. The proportion of patients with the outcome in the non-selective beta-blockers control group and the estimated intervention effect were set in accordance with the meta-analysis of all trials and the meta-analysis including trials with adequate bias control.

Sensitivity analysis

Sensitivity analyses were conducted using fixed-effect models to analyse the robustness of the results.The fixed-effect model meta-analyses were only reported when the conclusions of the results differed from the random-effects model.

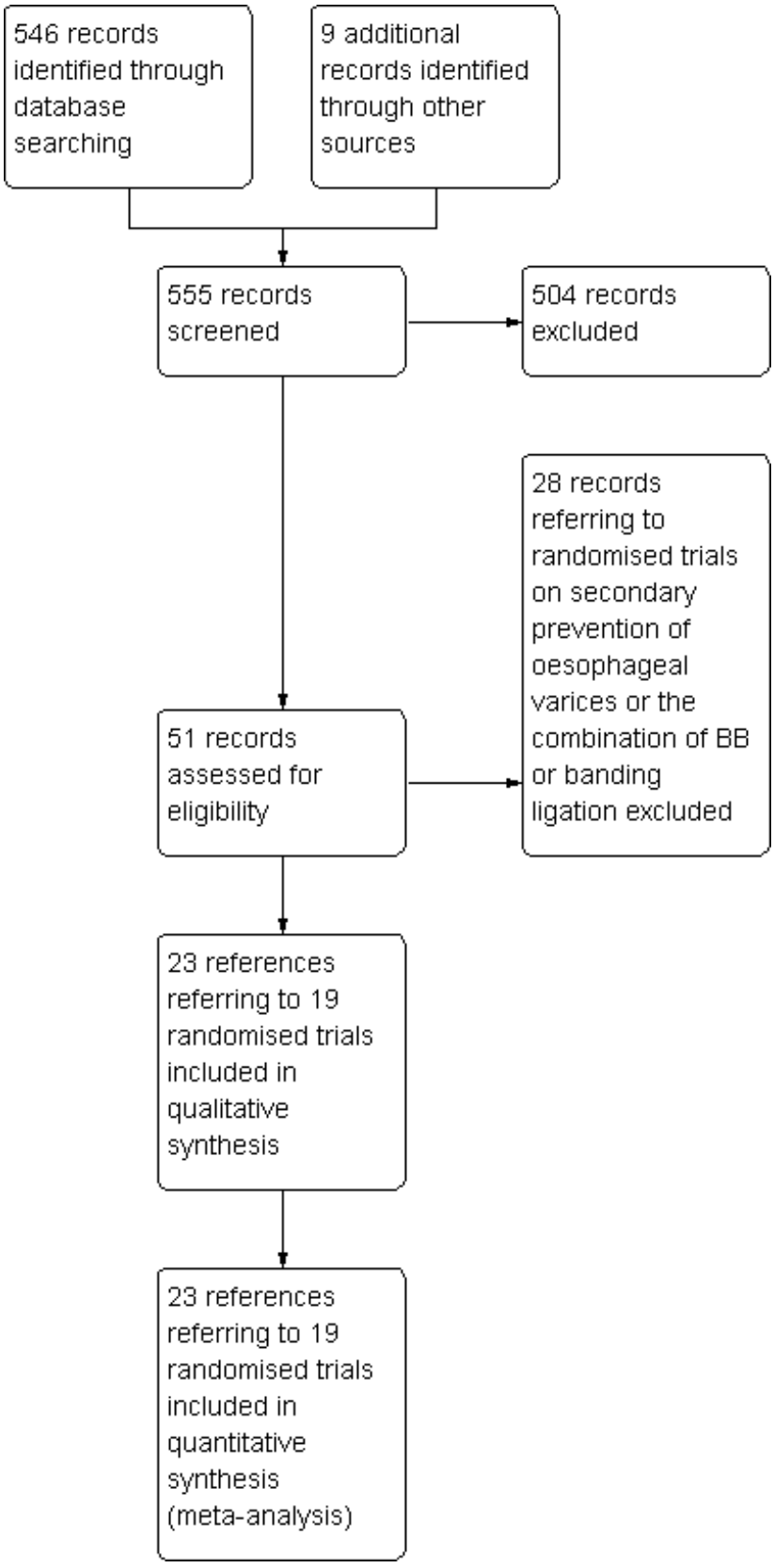
RESULTS

Description of studies

Results of the search

The electronic searches identified 555 references (Figure 1). After reading the titles and abstracts, duplicates and references that did not refer to randomised trials were excluded. Subsequently, 51 references were retrieved for further assessment. After excluding references on secondary prevention or the combination of beta-blockers and banding ligation, we included 23 references referring to 19 randomised trials on banding ligation versus non-selective beta-blockers for primary prevention in adult patients with oesophageal varices (Chen 1998; De 1999; Sarin 1999; Mora 2000; Song 2000; Gheorghe 2002; Lui 2002; Abulfutuh 2003; Lo 2004; Schepke 2004; Drastich 2005; Jutabha 2005; Psilopoulos 2005; Thuluvath 2005; Abdelfattah 2006; Lay 2006; Norberto 2007; Tripathi 2009; Perez 2010).

Figure 1. Study flow diagram.



Included studies

Thirteen trials (72%) were performed as single centre trials. The remaining five trials included two to 13 clinical sites. The mean sample size was 79 patients (range 24 to 152). All trials assessed primary prevention in the management of patients with oesophageal varices and no previous bleeding. Included patients with cirrhosis were diagnosed based on clinical, biochemical, or histological signs. Most trials specified that 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 (red wale markings, cherry red spots, or haematocystic spots), tortuous varices protruding as far as at least one third of the oesophageal lumen, or pseudotumorous varices (also known as F2 or F3 varices). Other trials classified varices 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. The reported exclusion criteria were contraindications to beta-blockers or severe concurrent illnesses, such as renal or malignant disease. In two trials, all patients were eligible for liver transplantation (Gheorghe 2002; Norberto 2007). The mean age for patients randomised to banding ligation was 53 years (range 42 to 62) and to beta-blockers 52 years (range 39 to 59). Most patients were men (mean proportion 66%) and few had alcoholic liver disease (mean 22%). Seven trials (37%) were published in abstract form and the remaining trials as full paper articles during the period 1998 to 2010 (Characteristics of included studies). The trials were performed in Egypt (n = 2), Great Britain (n = 2), India (n = 2), Mexico (n = 2), Taiwan (n = 2), USA (n = 2), China (n = 1), Czech Republic (n = 1), Germany (n = 1), Greece (n = 1), Italy (n = 1), Korea (n = 1), and Romania (n = 1).

Banding ligation was performed with conventional or multiband ligators and was repeated at three to four week intervals until the varices were eradicated. On average, two to three sessions were necessary to achieve variceal eradication. Subsequently, patients were followed at three to six month intervals and banding ligation was repeated in the case of variceal recurrence.

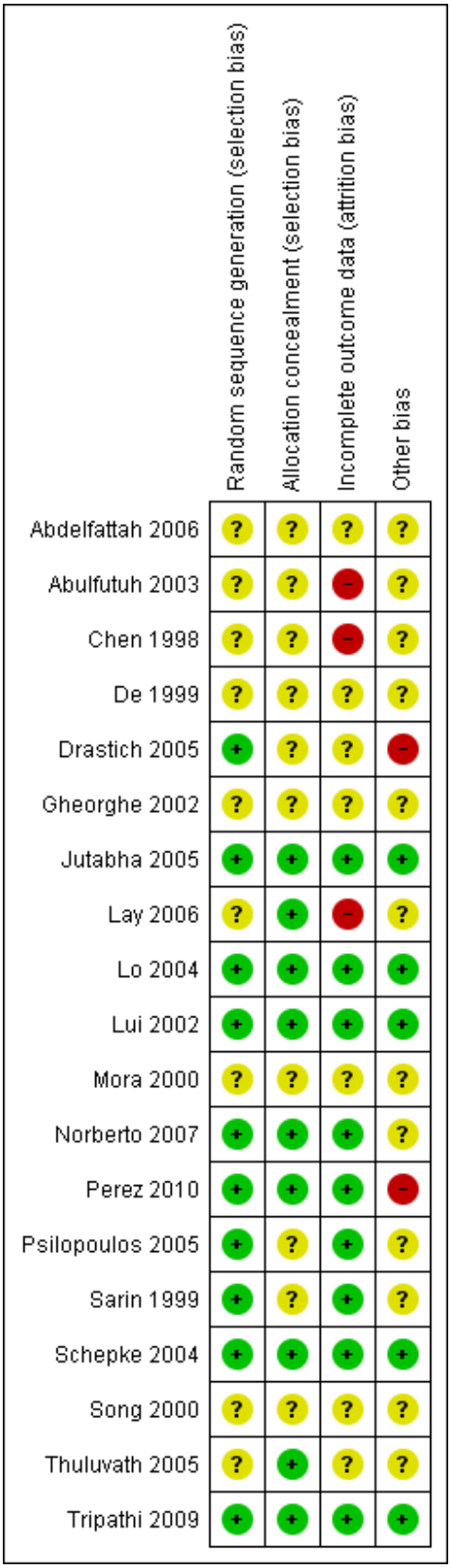
One trial assessed nadolol (Lo 2004). The initial daily dose was 40 mg adjusted based on the heart rate (mean 60 mg). One trial assessed carvedilol (Tripathi 2009). The initial daily dose of carvedilol was 6.25 mg. The dose was increased to 12.5 mg if tolerated (the mean dose was not reported). The remaining 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).

Risk of bias in included studies

Allocation

Ten trials reported adequate allocation sequence generation and seven adequate allocation concealment (Figure 2).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Blinding

As expected, none of the trials were double blind. None of the trials reported blinded outcome assessment.

Incomplete outcome data

Nine trials reported intention-to-treat analyses that accounted for all patients randomised. The method used to account for patients with missing data appeared to be carry forward of the last observed event although this was not specifically stated. Five trials did not describe losses to follow-up or the analytical strategy. In the remaining trials, there were no apparent losses to follow-up although this was not specifically described.

Selective reporting

All trials reported mortality and bleeding in both allocation groups. We were able to extract data on adverse events from 10 trials (De 1999; Sarin 1999; Lui 2002; Lo 2004; Schepke 2004; Drastich 2005; Jutabha 2005; Psilopoulos 2005; Lay 2006; Tripathi 2009). The definitions of adverse events varied between trials.

Other potential sources of bias

Ten trials did not report a sample size calculation or whether trials were terminated early, after the planned sample size was achieved, or if the trials were terminated at an arbitrary point. In nine trials, sample size calculations were reported. Three of these trials were terminated after the planned sample size was achieved. The remaining six trials were terminated early because event rates were lower than expected, because there was no apparent difference between the interventions being compared, or due to high failure rates in the propranolol group. None of the trials reported clear differences between the baseline characteristics of patients randomised to banding ligation or non-selective beta-blockers.

Effects of interventions

Mortality

In total, 176 of 731 patients (24%) randomised to banding ligation versus 177 of 773 patients (23%) randomised to non-selective beta-blockers died (Analysis 1.1). Random-effects model meta-analysis showed no difference in mortality between the intervention groups (RR 1.09; 95% CI 0.92 to 1.30) and little evidence of intertrial heterogeneity (I^2 = 0%).

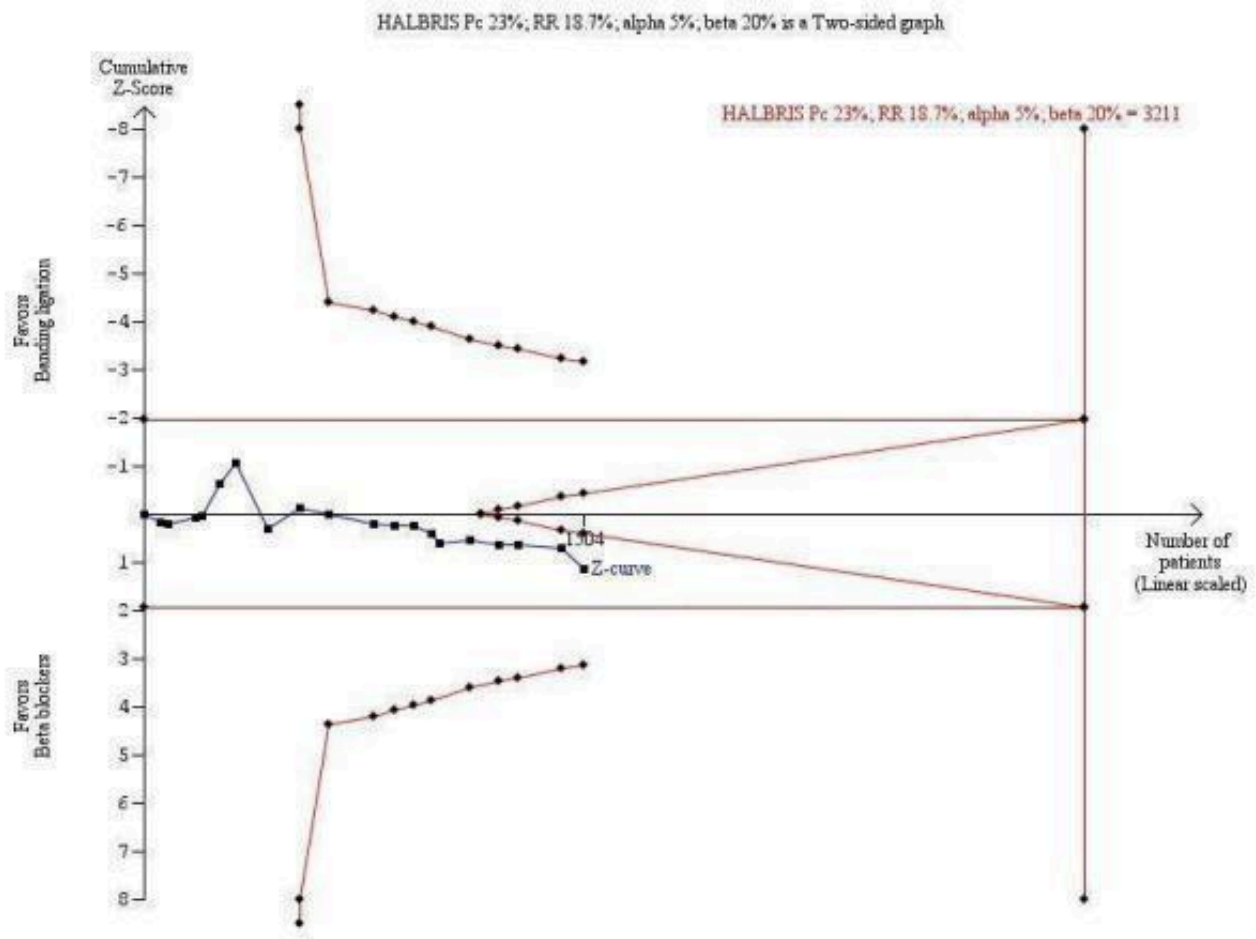
Subgroup, sensitivity, regression, and trial sequential analyses

In subgroup analyses (Analysis 1.2), there was no difference between banding ligation and non-selective beta-blockers in trials with a low risk of selection bias (RR 1.18; 95% CI 0.95 to 1.47) or an unclear risk of selection bias (RR 0.96; 95% CI 0.72 to 1.28). The test of subgroup differences found little difference between these subgroups of trials (P = 0.27; I^2 = 17.8%). A similar result was achieved when the analysis was repeated for subgroups of trials stratified according to the risk of attrition bias (Analysis 1.3), and in trials published as full-paper articles or abstracts (Analysis 1.4).

No clear evidence of bias or small study effects was identified in regression analysis (Egger's test P = 0.997).

The trial sequential analysis (Figure 3) showed that the heterogeneity-adjusted low-bias trial relative risk estimate required an information size (HALBRIS) of 3211 patients. The cumulative Z curve did not cross any of the boundaries, showing that none of the interventions showed superiority and the limits of futility had not been reached.

Figure 3. Banding ligation versus non-selective beta blockers for primary prevention in patients with oesophageal varices. The outcome is all-cause mortality. The heterogeneity-adjusted low-bias trial relative risk estimate required information size (HALBRIS) is 3211 patients. The calculation is based on 0% heterogeneity; a proportion of people dying in the control group (Pc) of 23%; a relative risk reduction of 18.7% based on the intervention effect in trials with a low risk of bias; an alpha of 5%; and a beta of 20%. The red lines sloping towards a Z value of 1.96 and -1.96 are the trial-sequential alpha spending monitoring boundaries. The red lines originating from the Z line of 0 broadening towards the HALBRIS are the beta spending monitoring boundaries. The blue line is the cumulative Z curve, which does not cross the alpha or beta spending boundaries.



Upper gastrointestinal bleeding

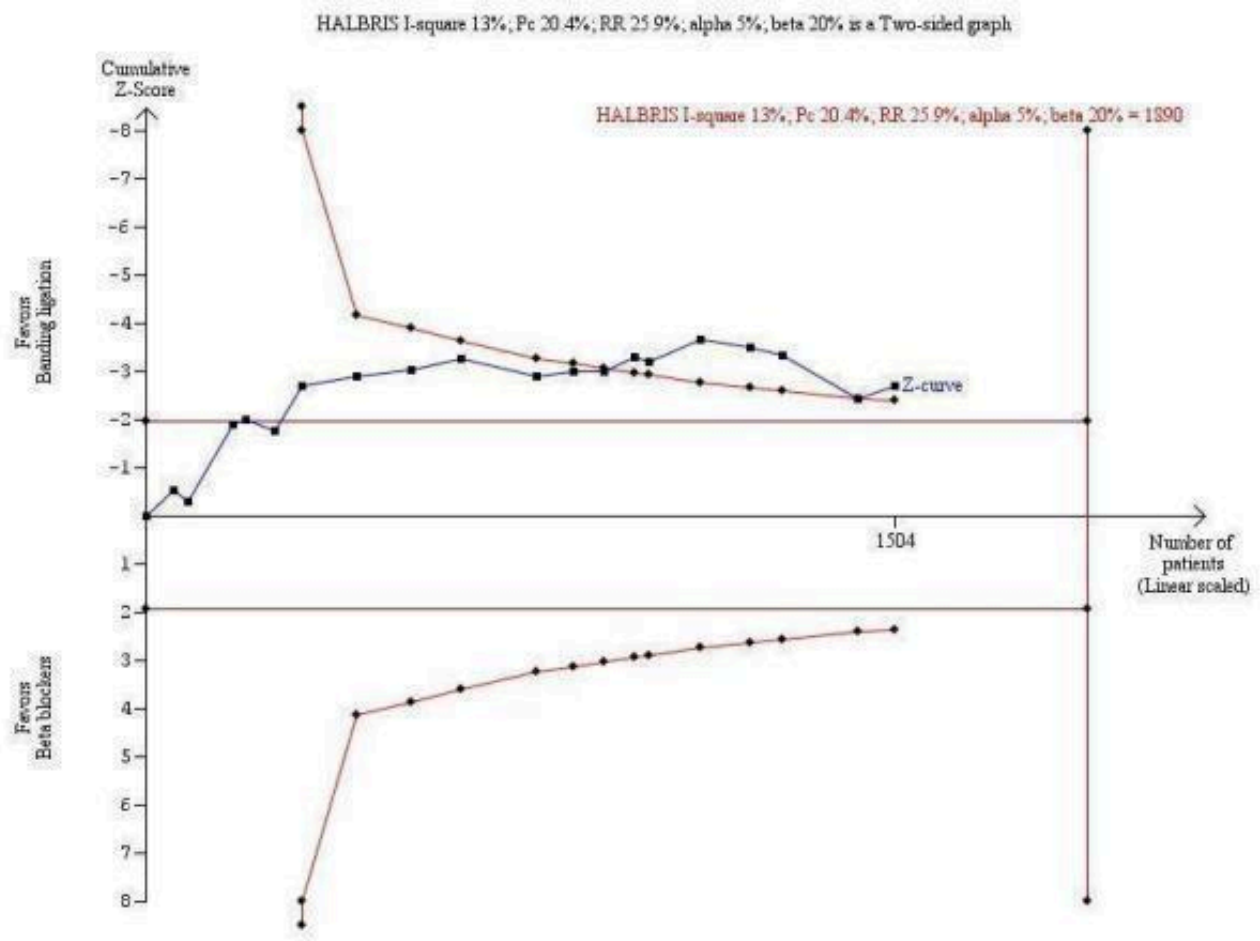
Upper gastrointestinal bleeding was diagnosed for 103 of 731 patients (14%) in the banding ligation group and 158 of 773 patients (20%) in the non-selective beta-blocker group (Analysis 1.5). Banding ligation appeared to have a beneficial effect on this outcome measure (RR 0.68; 95% CI 0.52 to 0.90; I^2 = 19%).

Subgroup, sensitivity, regression, and trial sequential analyses

In subgroup analyses (Analysis 1.6), trials with a low risk of selection bias found no difference in upper gastrointestinal bleeding among patients randomised to banding ligation versus non-selective beta-blockers (RR 0.84; 95% CI 0.53 to 1.33). Trials with an unclear risk of selection bias found that banding ligation reduced the risk of bleeding (RR 0.57; 0.40 to 0.80). The difference between subgroups of trials with a low or unclear risk of bias was not statistically significant (P = 0.18; I^2 = 44.1%). A similar result was reached when comparing subgroups of trials stratified according to the risk of attrition bias (Analysis 1.11) or publication status (Analysis 1.8). No clear evidence of bias or small study effects were identified in regression analysis (Egger's test P = 0.434).

The trial sequential analysis (Figure 4) showed that banding ligation was associated with a lower risk of upper gastrointestinal bleeding. The HALBRIS was 1883 patients. The Z curve crossed the conventional boundary after the sixth trial (314 patients) and the alpha spending monitoring boundary after the 13th trial (981 patients) showing that the superiority of banding ligation versus beta blockers was not likely to be due to random error.

Figure 4. Banding ligation versus non-selective beta blockers for primary prevention in patients with oesophageal varices. The outcome is upper gastrointestinal bleeding. The heterogeneity-adjusted low-bias trial relative risk estimate required information size (HALBRIS) is 1890 patients. The calculation is based on 13% heterogeneity; a proportion of people with upper gastrointestinal bleeding in the control group (Pc) of 20.4%; a relative risk reduction of 25.9% based on the intervention effect in trials with a low risk of bias; an alpha of 5%; and a beta of 20%. The red lines sloping towards a Z value of 1.96 and -1.96 are the trial sequential alpha spending monitoring boundaries. The blue line is the cumulative Z curve, which crosses the conventional boundary after the sixth trial (314 patients) and the alpha spending boundary after the 13th trial (981 patients).



Variceal bleeding

Three trials did not report the outcome measure variceal bleeding (Analysis 1.9). Banding ligation appeared to reduce variceal bleeding compared with beta-blockers (75 of 590 (13%) versus 113 of 611(19%) patients (RR 0.66; 95% CI 0.45 to 0.96; I^2 = 31%).

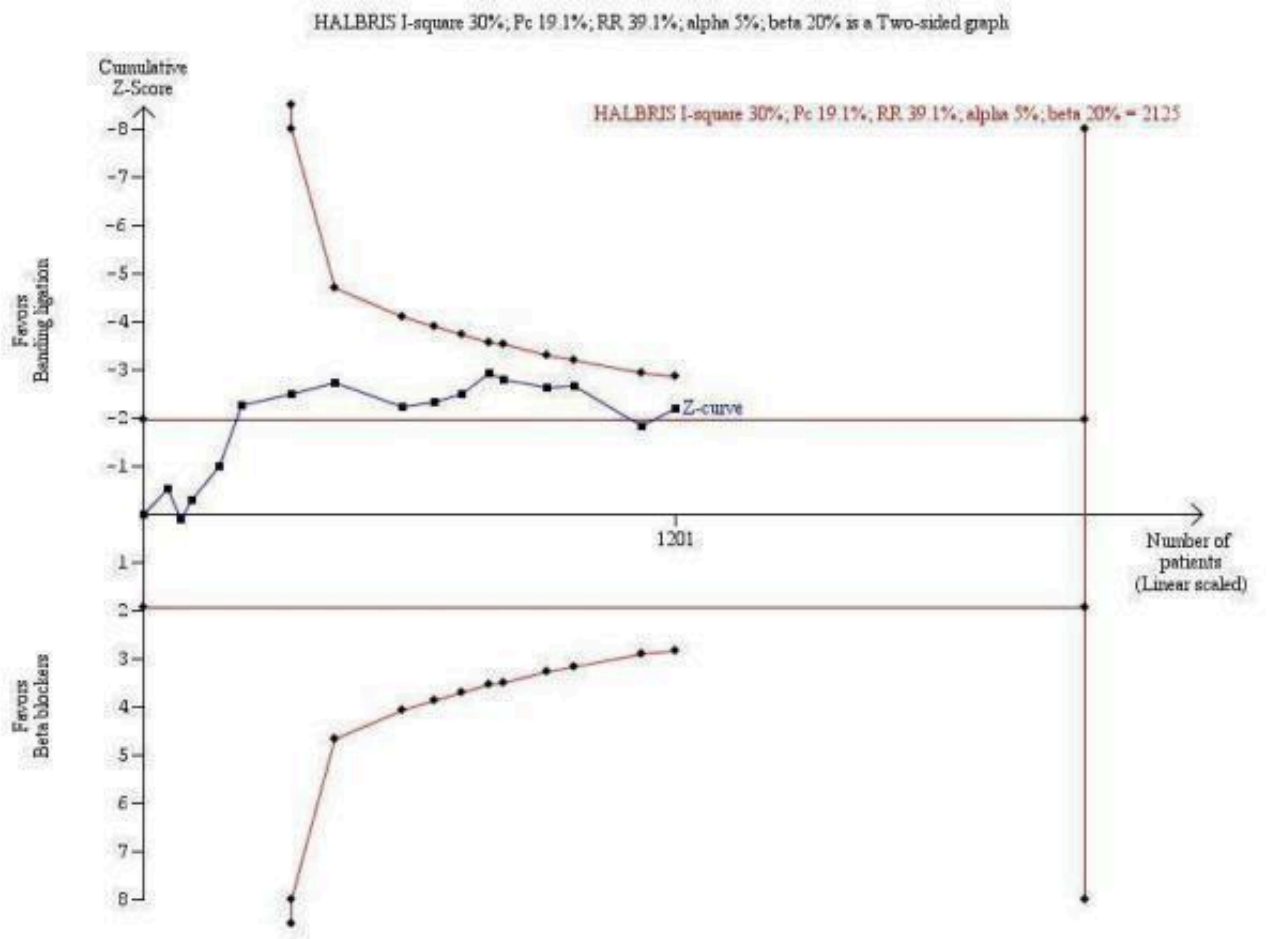
Subgroup, sensitivity, regression and trial sequential analyses

Trials with a low risk of selection bias found no difference between intervention groups whereas trials with an unclear risk of selection bias found that banding ligation reduced the risk of variceal bleeding (Analysis 1.10) (test for subgroup differences P = 0.72; I^2 = 0%). A similar result was reached when comparing subgroups of trials stratified according to the risk of attrition bias (Analysis 1.11) or publication status (Analysis 1.12).

No clear evidence of bias or small study effects was identified in a regression analysis (Egger's test P = 0.397).

The trial sequential analysis (Figure 5) showed that the HALBRIS was 2125 patients. The Z curve crossed the conventional boundary after the fifth trial (224 patients) but not the trial sequential alpha spending monitoring boundary, showing that the apparent superiority of banding ligation versus beta blockers on variceal bleeding (based on the conventional 5% boundary) could be due to random error.

Figure 5. Banding ligation versus beta blockers for primary prevention in patients with oesophageal varices. The outcome is variceal bleeding. The heterogeneity-adjusted low-bias trial relative risk estimate required information size (HALBRIS) is 2125 patients. The calculation is based on 30% heterogeneity; a proportion of people with upper gastrointestinal bleeding in the control group (Pc) of 19.1%; a relative risk reduction of 39.1% based on the intervention effect in trials with low risk of bias; an alpha of 5%; and a beta of 20%. The red lines sloping towards a Z value of 1.96 and -1.96 are the trial sequential alpha spending monitoring boundaries. The blue line is the cumulative Z curve, which crosses the conventional boundary after the fifth trial (224 patient), but not the alpha spending monitoring boundaries.



Bleeding-related mortality

No difference was seen between the two interventions regarding bleeding-related mortality (29/567 (5.1%) versus 37/585 (6.3%); RR 0.85; 95% CI 0.53 to 1.39; I^2 = 0%; reported in 13 trials) (Analysis 1.13).

Quality of life

None of the included trials assessed this outcome.

Adverse events

Several adverse events were reported (Analysis 1.14). Treatment with non-selective beta-blockers was associated with dizziness, hypotension, impotence, lethargy, and peripheral oedema. Banding ligation was associated with clinically important bleeding and retrosternal pain. One patient with oesophageal perforation was registered after insertion of the overtube during banding ligation.

DISCUSSION

The present review compared the effects of banding ligation versus non-selective beta-blockers for patients with oesophageal varices and no history of bleeding. The overall analyses suggested that banding ligation reduced upper gastrointestinal bleeding and variceal bleeding compared with non-selective beta-blockers. However, this effect did not reflect reduced mortality suggesting that non-selective beta-blockers may have beneficial effects that are not related to bleeding. An alternative reason could be the potential influence of bias since the effect of banding ligation on bleeding could not be confirmed when the analysis was limited to trials with a low risk of selection bias. None of the included trials reported baseline differences between intervention groups regarding prognostic factors such as variceal size or Child-Pugh score. However, without adequate randomisation, the subgroup analyses suggest that the distribution of unknown and known factors may influence the overall result. Non-comparability

between intervention groups may be the reason why trials with an unclear control of selection bias found a clear benefit of banding ligation on bleeding.

Adverse events are likely to influence compliance with the intervention assessed. Due to the variation in reporting, we were unable to determine whether an increased risk of adverse events (for example, in trials using a high dose of beta-blockers) led to reduced compliance. The assessment of adverse events in meta-analyses of published trials is often difficult. One of the reasons for this is the lack of consensus regarding the classification of serious and non-serious adverse events. In the ICH-GCP guidelines, adverse events leading to death, hospitalisation, or prolongation of existing hospitalisation are classified as serious (ICH-GCP 1997). None of the included trials used these definitions. The lack of agreement on definitions is likely to explain the differences in the reported frequencies of adverse events.

For example, one trial classified the development of hypotension and first degree heart block after treatment with beta-blockers as serious adverse events but not the development of melena after banding ligation (Jutabha 2005). The trial did not register any serious adverse events after banding (Jutabha 2005) whereas a similar trial registered five serious adverse events in the form of bleeding occurring after banding (Schepke 2004). A trial comparing banding ligation with no intervention for patients with contraindications to beta-blockers found high iatrogenic bleeding rates (that is, after banding ligation) (Triantos 2005). This trial was terminated early. A potential explanation for differences between trials is related to the types of band ligators that were used. The conventional banding devices involved insertion of an overtube, which increased the risk of bleeding and oesophageal perforation. The currently used multiband devices do not involve this procedure. Accordingly, a randomised trial found that the multiband device was safer to use than the conventional device (Wong 2000).

One trial assessed the effect of banding versus no intervention for primary prophylaxis of bleeding in patients intolerant to beta-blockers (Triantos 2005). The trial was stopped prematurely because of unacceptably high iatrogenic bleeding rates after banding. The reason may be the high proportion of patients with small varices in the trial. Similar results were found in a large randomised trial showing that sclerotherapy should not be used for prevention of bleeding from small varices (PROVA 1991). Likewise, a randomised, double-blind trial found no benefit of treating patients with cirrhosis and no or small oesophageal varices with propanolol (Cales 1999). Overall, the evidence suggests that interventions for primary prophylaxis should mainly be considered for patient with varices that have a high risk of bleeding.

The fact that no significant difference is found between the two treatments regarding mortality does not necessarily mean that the treatments are equally effective. The objective of non-inferiority trials is to ensure that an experimental treatment is not worse than the established treatment by more than a prespecified delta value. The delta value is also known as the non-inferiority margin which is included in the sample size calculation (Henaff 2006). Non-inferiority trials generally require larger sample sizes than superiority trials. In a number of the included trials, the authors concluded that banding was 'as effective and safe' as treatment with non-selective beta-blockers (Lui 2002; Lo 2004; Lay 2006). These conclusions are debatable as none of the trials were designed to establish non-inferiority. In one of the included trials (Thuluvath 2005), investigators estimated that 90 patients in each intervention group would be required to show a difference in bleeding. The trial was prematurely terminated due to the observed bleeding rates which occurred in 2 of 16 patients randomised to banding ligation and 1 of 15 patients randomised to beta-blockers. Despite the selection of high-risk patients, the number of events were lower than anticipated. The authors concluded that 424 patients would be required in each arm to show a clinically relevant difference (Thuluvath 2005).

The assessment of bleeding varied considerably in the included trials. Two trials did not specify whether variceal or non-variceal bleeding was assessed (Mora 2000; Abdelfattah 2006). Four trials reported both incident variceal and non-variceal bleeding (Sarin 1999; Song 2000; Lo 2004; Psilopoulos 2005). The remaining trials only reported incident variceal bleeding. Both outcome measures seem relevant. For example, some trials suggest that banding ligation may accentuate portal hypertensive gastropathy (Lo 2001). We originally planned to analyse bleeding using the BAVENO criteria (de Franchis 2001; de Franchis 2005), but we were unable to do so because none of the trials provided the necessary data.

AUTHORS' CONCLUSIONS

Implications for practice

This review suggests that banding ligation and beta-blockers may be considered as primary prophylaxis for large oesophageal varices with a high risk of bleeding in adult patients.

Implications for research

Long-term randomised trials are needed on banding ligation versus beta-blockers for primary prevention in adult patients with oesophageal varices.

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Wetterslev 2009

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Wong 2000

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Wood 2008

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Gluud 2009

Gluud LL, Klingenberg SL, Nikolova D, Gluud C. Endoscopic therapy or beta-blockers for primary prevention of bleeding oesophageal varices. *Cochrane Database of Systematic Reviews* 2009, Issue 1. [DOI: 10.1002/14651858.CD004544]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abdelfattah 2006

Methods	- Randomised trial including patients with cirrhosis and high-risk varices.
Participants	- Characteristics not reported.
Interventions	- Type of beta-blocker: propanolol. - Remaining intervention characteristics are not reported.
Outcomes	- Duration of follow-up: 18 to 24 months (mean not reported).
Country of origin	- Egypt.
Publication status	- Abstract.
Number of clinical sites	- Single centre.
Notes	- Funding: not reported. - The trial included a third intervention group in which patients were randomised to IsMn.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported.

Abdelfattah 2006 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up and analytical strategy: unclear.
Other bias	Unclear risk	- Sample size calculation: not reported. - Differences between allocation groups: the text states that there were no differences without providing the specific data. - Registered in trial database: no.

Abulfutuh 2003

Methods	- Randomised trial including patients with cirrhosis and large oesophageal varices.
Participants	- Mean age: 55 years (not reported separately for allocation groups). - Remaining characteristics not reported.
Interventions	- Type of beta-blocker: propranolol. - Remaining intervention characteristics are not reported.
Outcomes	- Mean duration of follow-up: 30 months (range not reported).
Country of origin	- Egypt.
Publication status	- Abstract.
Number of clinical sites	- Single centre.
Notes	- Funding: not reported. - The trial also included a third intervention arm in which patients were randomised to IsMn.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	High risk	The number of treatment withdrawals only reported for patients randomised to propranolol.
Other bias	Unclear risk	- Sample size calculation: not reported. - Differences between allocation groups: the text states that there were no differences without providing the specific data.

Abulfutuh 2003 *(Continued)*

	- Registered in trial database: no. - The reason why a relatively small proportion of patients were randomised to banding ligation compared with the other intervention groups is not clarified.

Chen 1998

Methods	- Randomised trial including patients with cirrhosis and oesophageal varices.
Participants	- The mean age and number of patients with alcoholic liver disease: not reported.
Interventions	- Type of beta-blocker: propanolol. - Remaining intervention characteristics are not reported.
Outcomes	- Duration of follow-up: mean 12 months.
Country of origin	- Taiwan.
Publication status	- Abstract.
Number of clinical sites	- Single centre.
Notes	- Funding: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	Losses to follow-up only reported for the propranolol group. Whether these patients were included in the analyses is unclear.
Other bias	Unclear risk	- Sample size calculations: not reported. - Differences between allocation groups: the text states that there were no differences without providing the specific data. - Registered in trial database: no.

De 1999

Methods	- Randomised trial including patients with cirrhosis and grade 3 or 4 oesophageal varices.
Participants	- Mean age banding ligation: 42 years. - Mean age propanolol: 39 years. - Proportion of men: 73%.

De 1999 *(Continued)*

	- Proportion with alcoholic liver disease: 17%.
Interventions	- Type of beta-blocker: propanolol. - The initial dose of propanolol: 120 mg daily. The dose was titrated to achieve a 25% decrease in heart rate (mean 73 mg daily).
Outcomes	- Duration of follow-up: mean 18 months (range not reported).
Country of origin	- India.
Publication status	- Full paper.
Number of clinical sites	- Single centre trial.
Notes	- Funding: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up and analytical strategy: unclear.
Other bias	Unclear risk	- Sample size calculation: not reported. - Differences between allocation groups: none identified. - Registered in trial database: no.

Drastich 2005

Methods	- Randomised trial including patients with cirrhosis and high-risk oesophageal varices.
Participants	- Mean age banding ligation: 57 years. - Mean age beta-blocker: 56 years. - Proportion of men: 70%. - Proportion with alcoholic liver disease: 49%.
Interventions	- Type of beta-blocker: propanolol. - The initial dose of propanolol: not reported. The dose was titrated to achieve a 25% decrease in heart rate (mean 67 mg daily).
Outcomes	- Duration of follow-up: median 10 months.
Country of origin	- Czech Republic.

Drastich 2005 *(Continued)*

Publication status	- Full-paper article.
Number of clinical sites	- Six clinical sites.
Notes	- Funded by non-profit organisation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated table of random numbers.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up and analytical strategy: unclear.
Other bias	High risk	- Sample size calculation: 44 patients required per intervention group. This goal was not reached. - Differences between allocation groups: none identified. - Registered in trial database: no.

Gheorghe 2002

Methods	- Randomised trial including patients who were identified on a liver transplantation list and had high-risk oesophageal varices.
Participants	- Patient characteristics not reported.
Interventions	- Type of beta-blocker: propanolol. - Remaining intervention characteristics: not reported.
Outcomes	- Duration of follow-up: mean 15 months (range not reported).
Country of origin	- Romania.
Publication status	- Abstract.
Number of clinical sites	- Single centre.
Notes	- Funding: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported.

Gheorghe 2002 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up and analytical strategy: unclear.
Other bias	Unclear risk	- Sample size calculation: not reported. - Differences between allocation groups: none identified. - Registered in trial database: no.

Jutabha 2005

Methods	- Randomised trial including patients with cirrhosis and large oesophageal varices.
Participants	- Mean age banding ligation: 54 years. - Mean age propanolol: 55 years. - Proportion of men: 71%. - Proportion with alcoholic liver disease: 11%.
Interventions	- Type of beta-blocker: propanolol. - The initial daily dose of propanolol was 80 mg. The dose was titrated to achieve a 25% reduction in heart rate or to a maximum of 160 mg (mean 87 mg).
Outcomes	- Duration of follow-up: mean 12 months (range 1 to 61 months).
Country of origin	- USA.
Publication status	- Full paper.
Number of clinical sites	- Three clinical sites.
Notes	- Funded by non-profit organisations.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random numbers, permuted blocks.
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients randomised accounted for in intention-to-treat analyses.
Other bias	Low risk	- Sample size calculation reported, but not achieved since the trial was stopped prematurely after a preplanned interim analysis showing considerably higher failure rates in the propanolol group.

Jutabha 2005 *(Continued)*

	- Differences between allocation groups: none identified. - Registered in trial database: no.

Lay 2006

Methods	- Randomised trial including patient with cirrhosis and high-risk oesophageal varices.
Participants	- Mean age banding ligation: 56 years. - Mean age propanolol: 55 years. - Proportion of men: 78% - Proportion with alcoholic liver disease: 31%.
Interventions	- Type of beta-blocker: propanolol. - The initial daily dose of propanolol was 80 mg. The dose was titrated to achieve a 20% reduction in heart rate (mean 68 mg).
Outcomes	- Duration of follow-up: mean 35 months (range 1 to 72 months).
Country of origin	- China and Taiwan.
Publication status	- Full paper.
Number of clinical sites	- Unclear.
Notes	- No funding reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes.
Incomplete outcome data (attrition bias) All outcomes	High risk	Five patients with missing data are not included in the analyses.
Other bias	Unclear risk	- Sample size calculation: not reported. - Differences between allocation groups: none identified. - Registered in trial database: no.

Lo 2004

Methods	- Randomised trial including patients with cirrhosis and at least moderately-sized oesophageal varices.
Participants	- Mean age banding ligation: 55 years.

Lo 2004 *(Continued)*

	- Mean age nadolol: 57 years. - Proportion of men: 77%. - Proportion with alcoholic liver disease: 20%.
Interventions	- Type of beta-blocker: nadolol. - The initial daily dose of nadolol was 40 mg. The dose was titrated to achieve a 25% reduction in heart rate or a reduction to < 56 bpm (mean 60 mg).
Outcomes	- Duration of follow-up: mean 23 months.
Country of origin	- Taiwan.
Publication status	- Full paper.
Number of clinical sites	- Single centre.
Notes	- No funding reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers.
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients randomised included in intention-to-treat analyses.
Other bias	Low risk	- Sample size calculation: reported and achieved. - Differences between allocation groups: none identified. - Registered in trial database: no.

Lui 2002

Methods	- Randomised trial including patients with cirrhosis and high-risk varices.
Participants	- Mean age banding ligation: 54 years. - Mean age propanolol 55 years. - Proportion of men 60%. - Proportion with alcoholic liver disease: 72%.
Interventions	- Type of beta-blocker: propanolol. - The initial daily dose of propanolol: 80 mg. The dose was increased to 160 mg if tolerated (mean not described).
Outcomes	- Duration of follow-up: mean 20 months (range 1 to 48 months).

Lui 2002 *(Continued)*

Country of origin	- Great Britain.
Publication status	- Full paper.
Number of clinical sites	- Six clinical sites.
Notes	- No finding reported. - The trial also included a third group of patients randomised to IsMn.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers.
Allocation concealment (selection bias)	Low risk	Central independent unit.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients randomised accounted for in intention-to-treat analyses.
Other bias	Low risk	- Sample size calculation: performed and achieved. - Differences between allocation groups: none identified. - Registered in trial database: no.

Mora 2000

Methods	- Randomised trial including patients with cirrhosis and large high-risk oesophageal varices.
Participants	- Median age banding ligation: 50 years. - Mean age propanolol 45 years. - Remaining patient characteristics: not reported.
Interventions	- Type of beta-blocker: propanolol. - The initial daily dose of propanolol: not reported. The dose was titrated to achieve a 20% reduction in heart rate or to less than 60 beats per minute.
Outcomes	- Duration of follow-up: mean not reported (range1 to 19 months).
Country of origin	- Mexico.
Publication status	- Abstract.
Number of clinical sites	- Not reported.
Notes	- Funding: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement

Mora 2000 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up and analytical strategy: unclear.
Other bias	Unclear risk	- Sample size calculation: not reported. - Differences between allocation groups: none identified. - Registered in trial database: no.

Norberto 2007

Methods	- Randomised trial including patients who had cirrhosis and large high-risk oesophageal varices and were classified as candidates for liver transplantation.
Participants	- Mean age banding ligation: 53 years. - Mean age propranolol: 53 years. - Remaining patient characteristics: not reported.
Interventions	- Type of beta-blocker: propanolol. - The initial daily dose of propanolol: 20 mg. The dose was titrated to achieve a 25% decrease in heart rate (mean 30 mg daily).
Outcomes	- Duration of follow-up: 14 months (range not reported).
Country of origin	- Italy.
Publication status	- Full paper.
Number of clinical sites	- Single centre.
Notes	- Funding not reported.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers.
Allocation concealment (selection bias)	Low risk	Serially numbered opaque sealed envelopes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for in intention-to-treat analyses.

Norberto 2007 *(Continued)*

Other bias	Unclear risk	- Sample size calculation: performed, but not achieved. The trial was terminated after a preplanned interim analysis showed no differences between allocation groups. - Differences between allocation groups: none identified. - Registered in trial database: no.

Perez 2010

Methods	- Randomised trial including patients with cirrhosis and large high-risk oesophageal varices.
Participants	- Mean age banding ligation: 60 years. - Mean age propranolol: 58 years. - Proportion of men: 49%. - Proportion of patients with alcoholic liver disease: 24%.
Interventions	- Type of beta-blocker: propranolol. - The initial daily dose of propanolol: 40 mg. The dose was titrated to achieve a 25% reduction in heart rate, to a heart rate < 55 bpm, to a systolic blood pressure < 90 mmHg or a maximum of 320 mg daily (mean 88 mg daily).
Outcomes	- Duration of follow-up 55 months (range 1 to 119 months).
Country of origin	- Mexico.
Publication status	- Full paper.
Number of clinical sites	- Single centre.
Notes	- No funding reported.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers.
Allocation concealment (selection bias)	Low risk	Serially numbered opaque sealed envelopes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients randomised included in intention-to-treat analyses.
Other bias	High risk	- Sample size calculation reported. Although the trial was extended due to low recruitment rates the trial had to be terminated before the planned sample size was reached. In total, 75 patients were randomised (to achieve sufficient power 72 patients were needed according to sample size calculations). - Registered in trial database: no.

Perez 2010 *(Continued)*

	- Two patients were crossed over between intervention arms. These patients are analysed in the group to which they were originally assigned.

Psilopoulos 2005

Methods	- Randomised trial including patients with cirrhosis and high-risk oesophageal varices.
Participants	- Mean age banding ligation: 62 years. - Mean age propanolol: 59 years. - Proportion of men: 70%. - Proportion with alcoholic liver disease: 25%.
Interventions	- Type of beta-blocker: propranolol. - The initial daily dose of propanolol: 40 mg. The dose was titrated to achieve a 25% reduction in heart rate (mean 70 mg).
Outcomes	- Duration of follow-up: 28 months (range 0.5 to 52 months).
Country of origin	- Greece.
Publication status	- Full paper
Number of clinical sites	- Single centre.
Notes	- No funding reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers.
Allocation concealment (selection bias)	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients randomised included in intention-to-treat analyses.
Other bias	Unclear risk	- Sample size calculation: not reported. - Differences between allocation groups: none identified. - Registered in trial database: no.

Sarin 1999

Methods	- Randomised trial including patients with cirrhosis and large high-risk oesophageal varices.
Participants	- Mean age banding ligation: 44 years.

Sarin 1999 *(Continued)*

	- Mean age propanolol: 39 years. - Proportion of men: 73%. - Proportion with alcoholic liver disease: 20%.
Interventions	- Type of beta-blocker: propranolol. - The initial daily dose of propanolol: 40 mg. The dose was titrated to achieve a 25% reduction in heart rate (mean 60 mg).
Outcomes	- Duration of follow-up: mean not reported (range 0.5 to 18 months).
Country of origin	- India.
Publication status	- Full paper.
Number of clinical sites	- Single centre.
Notes	- No funding reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients randomised included in intention-to-treat analyses.
Other bias	Unclear risk	- Sample size calculation: not reported. - Differences between allocation groups: none identified. - Registered in trial database: no.

Schepke 2004

Methods	- Randomised trial including patients with cirrhosis and high-risk oesophageal varices.
Participants	- Mean age banding ligation: 54 years. - Mean age propanolol: 57 years. - Proportion of men:69%. - Proportion with alcoholic liver disease: 51%
Interventions	- Type of beta-blocker: propanolol. - The initial daily dose of propanolol: 80 mg. The dose was titrated to achieve a 20% decrease in heart rate (mean 77 mg).
Outcomes	- Duration of follow-up: mean 34 months (0,1 to 73 months).

Schepke 2004 *(Continued)*

Country of origin	- Germany.
Publication status	- Full paper.
Number of clinical sites	- 27 clinical sites.
Notes	- Funded by non-profit organisations.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated.
Allocation concealment (selection bias)	Low risk	Central independent unit.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients randomised included in intention-to-treat analyses.
Other bias	Low risk	- Sample size calculation: performed, but not achieved. The trial was terminated prematurely after an interim analysis showed no difference between intervention groups. - Differences between allocation groups: none identified. - Registered in trial database: no.

Song 2000

Methods	- Randomised trial including patients with cirrhosis and high risk oesophageal varices.
Participants	- Patient characteristics: not reported.
Interventions	- Intervention comparison: banding versus propanolol. - The dose of propanolol: not described.
Outcomes	- Duration of follow-up: unclear.
Country of origin	- Korea.
Publication status	- Abstract.
Number of clinical sites	- Single centre.
Notes	- No funding reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported.

Song 2000 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up and analytical strategy: unclear.
Other bias	Unclear risk	- Sample size calculation: not reported. - Differences between allocation groups: not reported. - Registered in trial database: no.

Thuluvath 2005

Methods	- Randomised trial including patients with cirrhosis and large oesophageal varices.
Participants	- Mean age banding ligation: 50 years. - Mean age propanolol: 54 years. - Proportion of men: 55%. - Proportion with alcoholic liver disease: 19%.
Interventions	- Type of beta-blocker: propanolol. - The initial daily dose of propanolol: not reported. The dose was titrated to achieve a 25% reduction in heart rate or a reduction in heart rate to less than 60 beats per minute (mean 93 mg).
Outcomes	- Duration of follow-up: mean 27 months.
Country of origin	- USA.
Publication status	- Full paper.
Number of clinical sites	- Single centre.
Notes	- No funding reported.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up and analytical strategy: unclear.
Other bias	Unclear risk	- Sample size calculation: reported, but not achieved. The trial was terminated prematurely after an interim analysis showed considerably lower event rates than expected.

Thuluvath 2005 *(Continued)*

	- Differences between allocation groups: none identified. - Registered in trial database: no.

Tripathi 2009

Methods	- Randomised trial including patients with cirrhosis and large oesophageal varices.
Participants	- Mean age banding ligation: 55 years. - Mean age carvedilol: 54 years. - Proportion of men: 54%. - Proportion with alcoholic liver disease: 73%.
Interventions	- Type of beta-blocker: carvedilol. - Initial daily dose of carvedilol: 6.25 mg. The dose was adjusted to 12.5 mg if tolerated (mean not reported).
Outcomes	- Duration of follow-up: mean 26 months (range not reported).
Country of origin	- Great Britain.
Publication status	- Full paper.
Number of clinical sites	- Five clinical sites.
Notes	- Funded by non-profit organisation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers.
Allocation concealment (selection bias)	Low risk	Serially numbered opaque sealed envelopes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for in intention-to-treat analyses.
Other bias	Low risk	- Sample size calculation: reported and achieved. - Differences between allocation groups: none identified. - Registered in trial database: yes.

IsMn: isosorbide mononitrate.
bpm = beats per minute.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Andreani 1990	Randomised trial on propranolol versus sclerotherapy versus placebo for primary prevention of bleeding oesophageal varices.
Angelico 1997	Randomised trial on isosorbide mononitrate versus propranolol for primary prevention of bleeding oesophageal varices.
Avgerinos 2000	Randomised trial on sclerotherapy plus propranolol versus propranolol for primary prevention of bleeding oesophageal varices.
Borroni 2002	Randomised trial on nadolol versus isosorbide mononitrate for primary prevention of bleeding oesophageal varices.
Cales 1999	Randomised trial on propranolol versus placebo for primary prevention of development of oesophageal varices.
Colman 1990	Randomised trial on propanolol versus no intervention for primary prevention of bleeding oesophageal varices.
Conn 1991	Randomised trial on propanolol versus placebo for primary prevention of bleeding oesophageal varices.
Garcia-Pagan 1991	Randomised trial on propanolol versus propanolol plus isosorbide mononitrate for primary prevention of bleeding oesophageal varices.
Garcia-Pagan 2003	Randomised trial on propanolol plus placebo versus propanolol plus isosorbide mononitrate for primary prevention of bleeding oesophageal varices.
Garcia-Pagan 2006	Randomised trial on nadolol plus isosorbide mononitrate without or with endoscopic band ligation in the prevention of rebleeding oesophageal varices.
Gournay 2000	Randomised trial on propanolol versus propanolol plus isosorbide mononitrate for primary prevention of bleeding oesophageal varices.
Groszmann 2003	Randomised trial on propanolol for primary prevention of bleeding oesophageal varices.
Hayes 1987	Randomised trial on propranolol for primary prevention of bleeding oesophageal varices.
Ideo 1988	Randomised trial on nadolol for primary prevention of bleeding oesophageal varices.
IMPPPB 1989	Randomised trial on propranolol for primary prevention of bleeding oesophageal varices.
Ink 1992	Randomised trial on sclerotherapy plus propranolol versus propranolol for prevention of rebleeding oesophageal varices.
Lebrec 1988	Randomised trial on nadolol for prevention of rebleeding oesophageal varices.
Lo 2000	Randomised trial on banding ligation plus nadolol and sucralfate versus banding ligation for prevention of rebleeding oesophageal varices.
Lo 2001	Randomised trial on banding ligation plus beta-blockers for prevention of rebleeding oesophageal varices.
Lo 2002	Randomised trial on banding ligation versus nadolol plus isosorbide mononitrate for prevention of rebleeding oesophageal varices.

Study	Reason for exclusion
Merkel 1996	Randomised trial on nadolol plus isosorbide mononitrate versus nadolol for primary prevention of bleeding oesophageal varices.
Merkel 2003	Randomised trial on nadolol for primary prevention of bleeding oesophageal varices.
Pascal 1987	Randomised trial on propanolol for primary prevention of bleeding oesophageal varices.
Patch 2002	Randomised trial on propanolol plus isosorbide mononitrate versus banding ligation for prevention of rebleeding oesophageal varices.
Pena 2005	Randomised trial on propanolol plus banding ligation versus banding ligation for prevention of rebleeding oesophageal varices.
PROVA 1991	Randomised trial on propanolol versus sclerotherapy versus propanolol plus sclerotherapy for primary prevention of bleeding oesophageal varices.
Rossle 1997	Randomised trial of transjugular intrahepatic portosystemic shunt versus endoscopy (banding ligation and sclerotherapy) plus propranolol for prevention of rebleeding oesophageal varices.
Sarin 2005	Randomised trial on banding ligation plus beta-blockers for oesophageal varices.
Sarin 2010	Randomised trial on secondary prevention of variceal bleeding.
Sauer 2002	Randomised trial on banding ligation plus propranolol versus transjugular intrahepatic portosystemic stent for prevention of rebleeding oesophageal varices.
Shashidhar 1999	Randomised trial on propanolol for primary prevention of bleeding oesophageal varices. The trial includes children.
Strauss 1988	Two randomised trials on sclerotherapy versus no intervention and propanolol versus no intervention for primary prevention of bleeding oesophageal varices.
Strauss 1999	Randomised trial on sclerotherapy for primary prevention of bleeding oesophageal varices.
Tomikawa 2004	Randomised trial on sclerotherapy versus propanolol for primary prevention of bleeding oesophageal varices.
Triantos 2005	Randomised trial on banding. Beta blocker not assessed.
Villanueva 2001	Randomised trial on banding ligation versus nadolol plus isosorbide mononitrate for prevention of rebleeding oesophageal varices.

DATA AND ANALYSES

Comparison 1. Banding ligation versus non-selective beta-blockers

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	19	1504	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.92, 1.30]

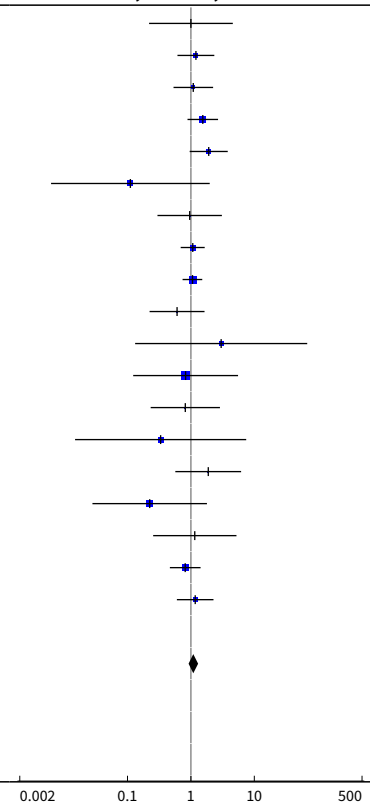
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Mortality stratified by selection bias	19	1504	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.92, 1.30]
2.1 Low risk of selection bias	7	713	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.95, 1.47]
2.2 Unclear risk of selection bias	12	791	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.72, 1.28]
3 Mortality stratified by attrition bias	19	1504	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.92, 1.30]
3.1 Low risk of attrition bias	9	863	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.96, 1.44]
3.2 Unclear risk of attrition bias	7	375	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.46, 1.46]
3.3 High risk of attrition bias	3	266	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.64, 1.44]
4 Mortality in full-paper articles and abstracts	19	1504	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.92, 1.30]
4.1 Full-paper articles	13	1097	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.98, 1.44]
4.2 Abstracts	6	407	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.49, 1.13]
5 Upper gastrointestinal bleeding	19	1504	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.52, 0.91]
6 Upper gastrointestinal bleeding stratified by selection bias	19	1504	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.52, 0.91]
6.1 Low risk of selection bias	7	713	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.53, 1.33]
6.2 Unclear risk of selection bias	12	791	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.40, 0.80]
7 Upper gastrointestinal bleeding stratified by attrition bias	19	1504	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.52, 0.91]
7.1 Low risk of selection bias	9	863	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.46, 1.09]
7.2 Unclear risk of selection bias	7	375	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.31, 0.89]
7.3 High risk of attrition bias	3	266	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.44, 1.41]
8 Upper gastrointestinal bleeding in full-paper articles and abstracts	19	1504	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.52, 0.91]
8.1 Full-paper articles	13	1097	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.56, 1.07]
8.2 Abstracts	6	407	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.29, 0.78]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9 Variceal bleeding	16	1201	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.46, 0.98]
10 Variceal bleeding stratified by selection bias	16	1201	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.46, 0.98]
10.1 Low risk of selection bias	7	713	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.38, 1.29]
10.2 Unclear risk of selection bias	9	488	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.38, 0.96]
11 Variceal bleeding stratified by attrition bias	16	1201	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.46, 0.98]
11.1 Low risk of attrition bias	8	773	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.33, 1.12]
11.2 Unclear risk of attrition bias	6	272	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.27, 1.03]
11.3 High risk of attrition bias	2	156	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.44, 1.75]
12 Variceal bleeding in full-paper articles and abstracts	16	1201	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.46, 0.98]
12.1 Full-paper articles	13	1011	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.42, 1.01]
12.2 Abstracts	3	190	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.23, 1.99]
13 Bleeding-related mortality	14	1152	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.53, 1.38]
13.1 Trials with lower risk of bias	11	966	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.55, 1.46]
13.2 Trials with higher risk of bias	3	186	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.04, 3.10]
14 Adverse events	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
14.1 Bleeding after banding ligation	4	397	Risk Ratio (M-H, Random, 95% CI)	5.18 [1.13, 23.78]
14.2 Bradycardia	3	255	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.02, 4.33]
14.3 Dizziness	4	425	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.11, 0.64]
14.4 Exanthema	1	152	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.27]
14.5 Fever	1	90	Risk Ratio (M-H, Random, 95% CI)	6.70 [0.36, 126.13]
14.6 Gastrointestinal discomfort	4	477	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.55, 1.63]
14.7 Hypotension	6	656	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.03, 0.25]
14.8 Impotence	4	494	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.04, 0.85]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.9 Lethargy	2	163	Risk Ratio (M-H, Random, 95% CI)	0.04 [0.01, 0.28]
14.10 Peripheral oedema	2	252	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.03, 0.35]
14.11 Perforation of the oesophagus	1	110	Risk Ratio (M-H, Random, 95% CI)	4.47 [0.19, 107.22]
14.12 Shortness of breath	3	342	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.04, 1.45]
14.13 Transient dysphagia or retrosternal pain	5	475	Risk Ratio (M-H, Random, 95% CI)	18.33 [5.19, 64.70]
14.14 Peripheral vascular disease	1	152	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.01, 2.79]
15 Adverse events	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

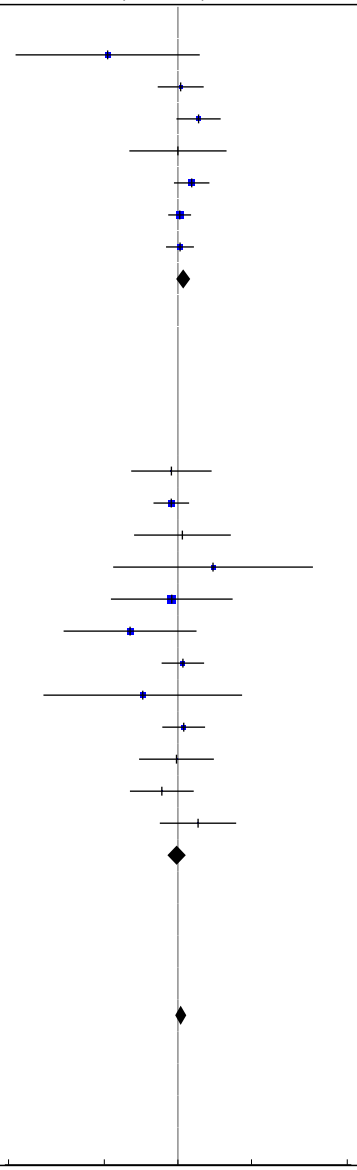
Analysis 1.1. Comparison 1 Banding ligation versus non-selective beta-blockers, Outcome 1 Mortality.

Study or subgroup	Banding n/N	Beta-blockers n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Norberto 2007	3/31	3/31		1.31%	1[0.22,4.58]
Psilopoulos 2005	12/30	10/30		6.79%	1.2[0.61,2.34]
Lo 2004	12/50	11/50		5.9%	1.09[0.53,2.24]
Perez 2010	20/39	12/36		9.91%	1.54[0.88,2.68]
Lui 2002	14/44	11/66		6.36%	1.91[0.96,3.81]
Jutabha 2005	0/31	4/31		0.37%	0.11[0.01,1.98]
Sarin 1999	5/46	5/44		2.23%	0.96[0.3,3.08]
Tripathi 2009	27/75	26/77		16.1%	1.07[0.69,1.65]
Schepke 2004	34/75	33/77		23.71%	1.06[0.74,1.51]
Song 2000	5/31	8/30		3.05%	0.6[0.22,1.64]
De 1999	1/15	0/15		0.31%	3[0.13,68.26]
Drastich 2005	2/40	2/33		0.84%	0.83[0.12,5.54]
Abdelfattah 2006	4/51	5/52		1.93%	0.82[0.23,2.87]
Mora 2000	0/12	1/12		0.32%	0.33[0.01,7.45]
Thuluvath 2005	6/16	3/15		2.14%	1.88[0.57,6.19]
Gheorghe 2002	1/25	5/28		0.7%	0.22[0.03,1.79]
Chen 1998	3/26	3/30		1.33%	1.15[0.25,5.23]
Abulfutuh 2003	13/44	24/66		9.81%	0.81[0.47,1.42]
Lay 2006	14/50	12/50		6.9%	1.17[0.6,2.27]
Total (95% CI)	**731**	**773**		**100%**	**1.09[0.92,1.3]**
Total events: 176 (Banding), 178 (Beta-blockers)					
Heterogeneity: Tau^2=0; Chi^2=13.44, df=18(P=0.76); I^2=0%					
Test for overall effect: Z=1.01(P=0.31)					



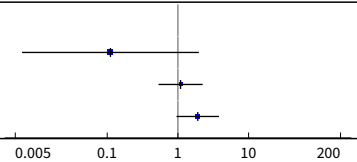
Analysis 1.2. Comparison 1 Banding ligation versus non-selective beta-blockers, Outcome 2 Mortality stratified by selection bias.

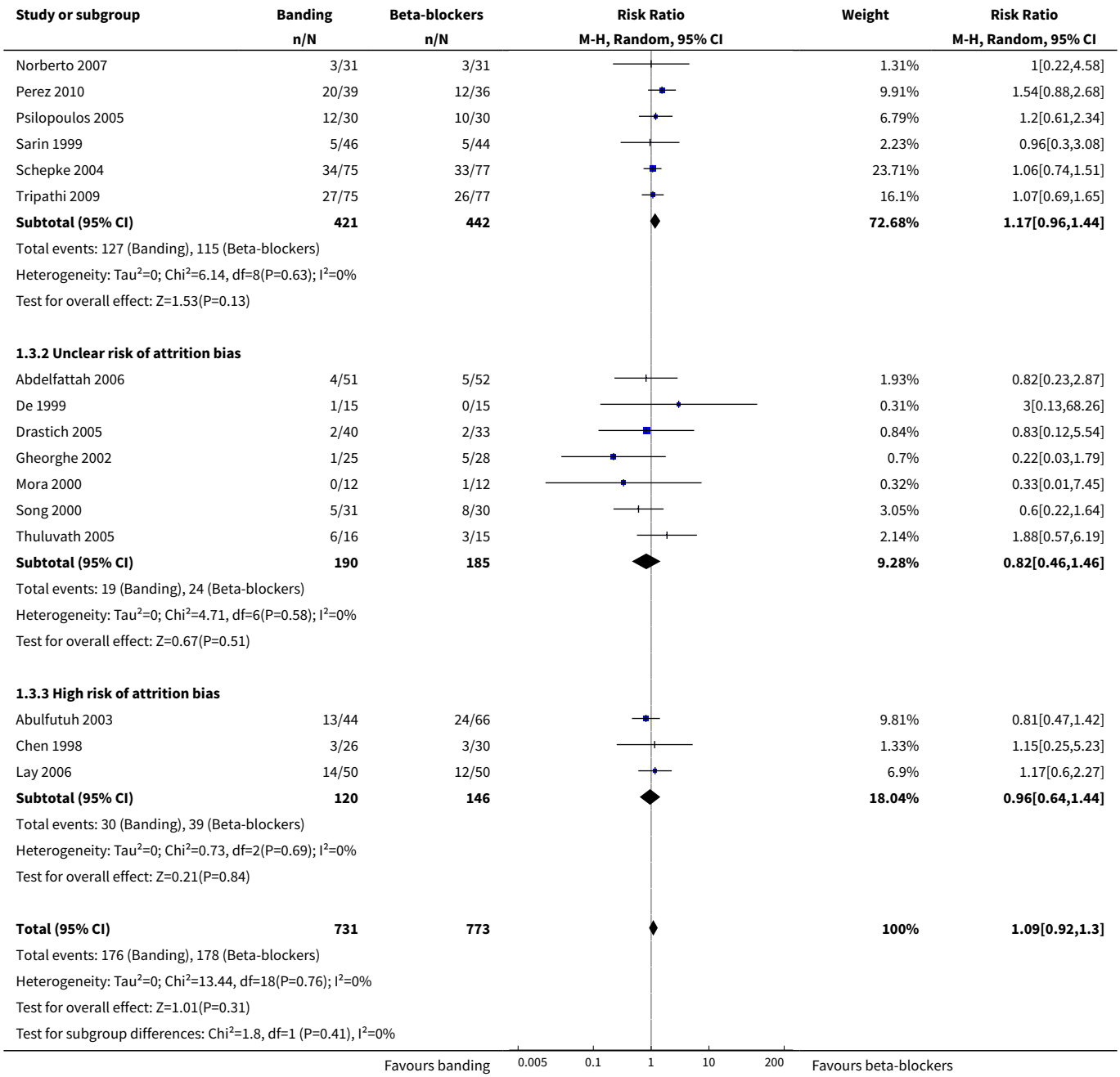
Study or subgroup	Banding n/N	Beta-blockers n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Low risk of selection bias					
Jutabha 2005	0/31	4/31		0.37%	0.11[0.01,1.98]
Lo 2004	12/50	11/50		5.9%	1.09[0.53,2.24]
Lui 2002	14/44	11/66		6.36%	1.91[0.96,3.81]
Norberto 2007	3/31	3/31		1.31%	1[0.22,4.58]
Perez 2010	20/39	12/36		9.91%	1.54[0.88,2.68]
Schepke 2004	34/75	33/77		23.71%	1.06[0.74,1.51]
Tripathi 2009	27/75	26/77		16.1%	1.07[0.69,1.65]
Subtotal (95% CI)	**345**	**368**		**63.66%**	**1.18[0.95,1.47]**
Total events: 110 (Banding), 100 (Beta-blockers)					
Heterogeneity: Tau^2=0; Chi^2=6.01, df=6(P=0.42); I^2=0.22%					
Test for overall effect: Z=1.47(P=0.14)					
1.2.2 Unclear risk of selection bias					
Abdelfattah 2006	4/51	5/52		1.93%	0.82[0.23,2.87]
Abulfutuh 2003	13/44	24/66		9.81%	0.81[0.47,1.42]
Chen 1998	3/26	3/30		1.33%	1.15[0.25,5.23]
De 1999	1/15	0/15		0.31%	3[0.13,68.26]
Drastich 2005	2/40	2/33		0.84%	0.83[0.12,5.54]
Gheorghe 2002	1/25	5/28		0.7%	0.22[0.03,1.79]
Lay 2006	14/50	12/50		6.9%	1.17[0.6,2.27]
Mora 2000	0/12	1/12		0.32%	0.33[0.01,7.45]
Psilopoulos 2005	12/30	10/30		6.79%	1.2[0.61,2.34]
Sarin 1999	5/46	5/44		2.23%	0.96[0.3,3.08]
Song 2000	5/31	8/30		3.05%	0.6[0.22,1.64]
Thuluvath 2005	6/16	3/15		2.14%	1.88[0.57,6.19]
Subtotal (95% CI)	**386**	**405**		**36.34%**	**0.96[0.72,1.28]**
Total events: 66 (Banding), 78 (Beta-blockers)					
Heterogeneity: Tau^2=0; Chi^2=6.16, df=11(P=0.86); I^2=0%					
Test for overall effect: Z=0.27(P=0.79)					
Total (95% CI)	**731**	**773**		**100%**	**1.09[0.92,1.3]**
Total events: 176 (Banding), 178 (Beta-blockers)					
Heterogeneity: Tau^2=0; Chi^2=13.44, df=18(P=0.76); I^2=0%					
Test for overall effect: Z=1.01(P=0.31)					
Test for subgroup differences: Chi^2=1.22, df=1 (P=0.27), I^2=17.82%					



Analysis 1.3. Comparison 1 Banding ligation versus non-selective beta-blockers, Outcome 3 Mortality stratified by attrition bias.

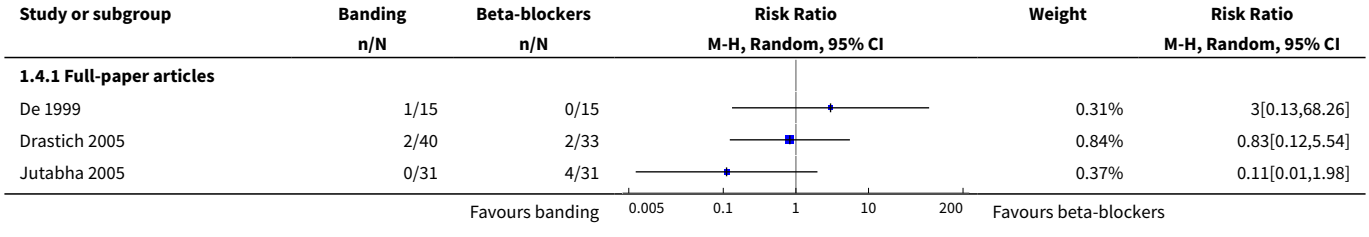
Study or subgroup	Banding n/N	Beta-blockers n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Low risk of attrition bias					
Jutabha 2005	0/31	4/31		0.37%	0.11[0.01,1.98]
Lo 2004	12/50	11/50		5.9%	1.09[0.53,2.24]
Lui 2002	14/44	11/66		6.36%	1.91[0.96,3.81]



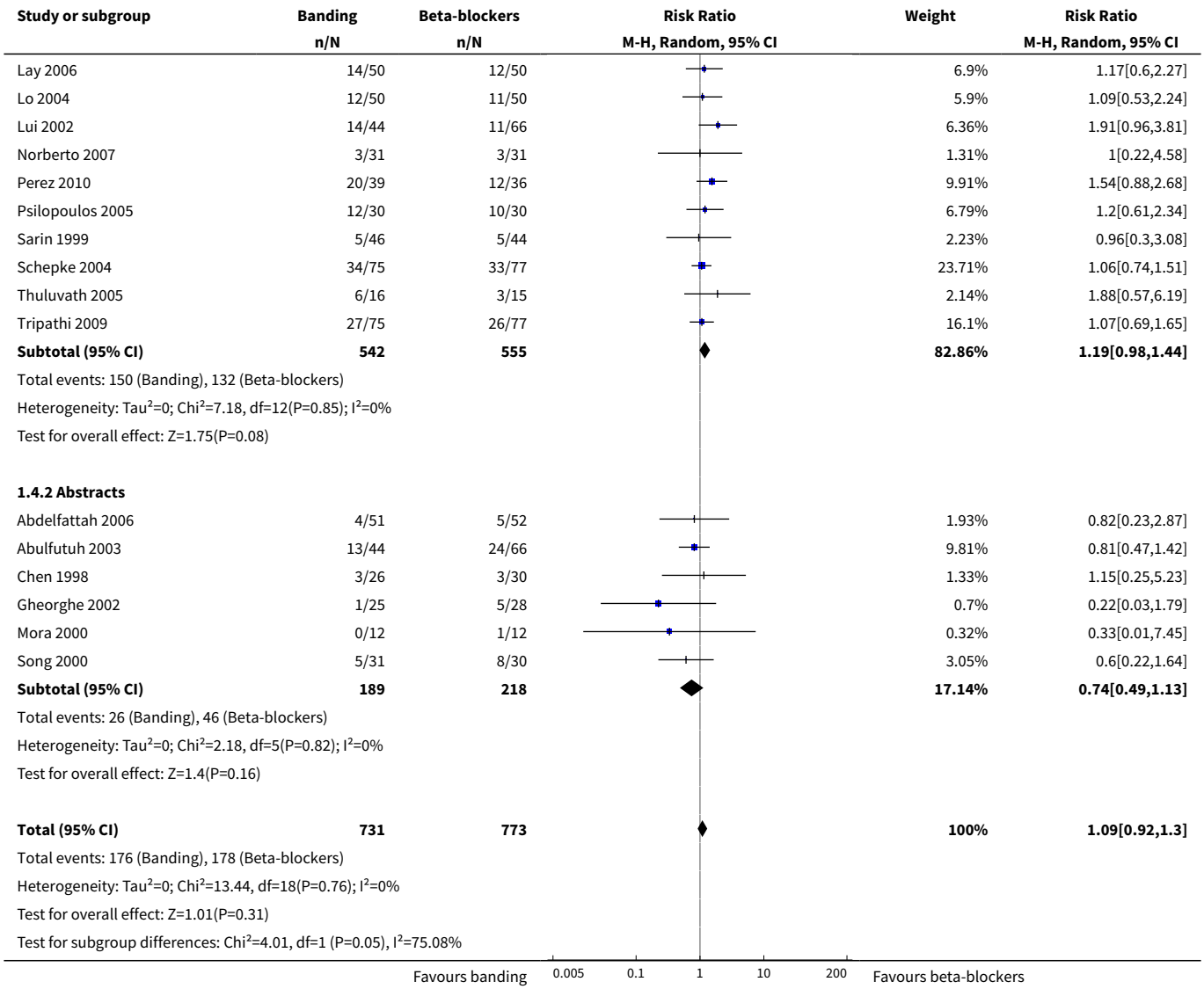


Study or subgroup	Banding n/N	Beta-blockers n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Norberto 2007	3/31	3/31		1.31%	1[0.22,4.58]
Perez 2010	20/39	12/36		9.91%	1.54[0.88,2.68]
Psilopoulos 2005	12/30	10/30		6.79%	1.2[0.61,2.34]
Sarin 1999	5/46	5/44		2.23%	0.96[0.3,3.08]
Schepke 2004	34/75	33/77		23.71%	1.06[0.74,1.51]
Tripathi 2009	27/75	26/77		16.1%	1.07[0.69,1.65]
Subtotal (95% CI)	**421**	**442**		**72.68%**	**1.17[0.96,1.44]**
Total events: 127 (Banding), 115 (Beta-blockers)					
Heterogeneity: Tau^2=0; Chi^2=6.14, df=8(P=0.63); I^2=0%					
Test for overall effect: Z=1.53(P=0.13)					
1.3.2 Unclear risk of attrition bias					
Abdelfattah 2006	4/51	5/52		1.93%	0.82[0.23,2.87]
De 1999	1/15	0/15		0.31%	3[0.13,68.26]
Drastich 2005	2/40	2/33		0.84%	0.83[0.12,5.54]
Gheorghe 2002	1/25	5/28		0.7%	0.22[0.03,1.79]
Mora 2000	0/12	1/12		0.32%	0.33[0.01,7.45]
Song 2000	5/31	8/30		3.05%	0.6[0.22,1.64]
Thuluvath 2005	6/16	3/15		2.14%	1.88[0.57,6.19]
Subtotal (95% CI)	**190**	**185**		**9.28%**	**0.82[0.46,1.46]**
Total events: 19 (Banding), 24 (Beta-blockers)					
Heterogeneity: Tau^2=0; Chi^2=4.71, df=6(P=0.58); I^2=0%					
Test for overall effect: Z=0.67(P=0.51)					
1.3.3 High risk of attrition bias					
Abulfutuh 2003	13/44	24/66		9.81%	0.81[0.47,1.42]
Chen 1998	3/26	3/30		1.33%	1.15[0.25,5.23]
Lay 2006	14/50	12/50		6.9%	1.17[0.6,2.27]
Subtotal (95% CI)	**120**	**146**		**18.04%**	**0.96[0.64,1.44]**
Total events: 30 (Banding), 39 (Beta-blockers)					
Heterogeneity: Tau^2=0; Chi^2=0.73, df=2(P=0.69); I^2=0%					
Test for overall effect: Z=0.21(P=0.84)					
Total (95% CI)	**731**	**773**		**100%**	**1.09[0.92,1.3]**
Total events: 176 (Banding), 178 (Beta-blockers)					
Heterogeneity: Tau^2=0; Chi^2=13.44, df=18(P=0.76); I^2=0%					
Test for overall effect: Z=1.01(P=0.31)					
Test for subgroup differences: Chi^2=1.8, df=1 (P=0.41), I^2=0%					

Analysis 1.4. Comparison 1 Banding ligation versus non-selective beta-blockers, Outcome 4 Mortality in full-paper articles and abstracts.

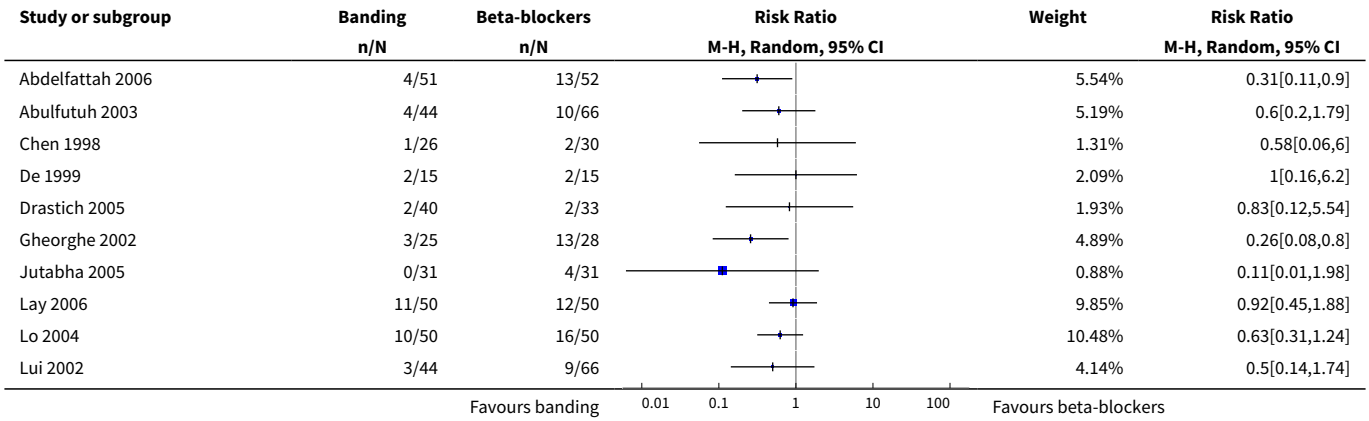


Study or subgroup	Banding n/N	Beta-blockers n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Full-paper articles					
De 1999	1/15	0/15		0.31%	3[0.13,68.26]
Drastich 2005	2/40	2/33		0.84%	0.83[0.12,5.54]
Jutabha 2005	0/31	4/31		0.37%	0.11[0.01,1.98]

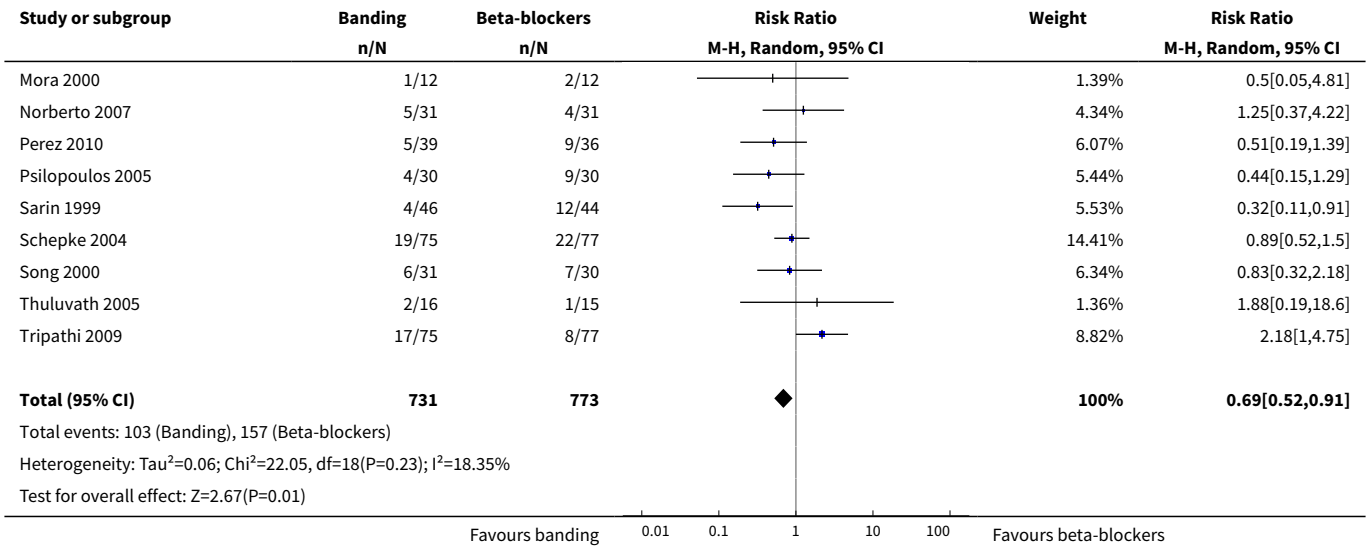


Study or subgroup	Banding n/N	Beta-blockers n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Lay 2006	14/50	12/50		6.9%	1.17[0.6,2.27]
Lo 2004	12/50	11/50		5.9%	1.09[0.53,2.24]
Lui 2002	14/44	11/66		6.36%	1.91[0.96,3.81]
Norberto 2007	3/31	3/31		1.31%	1[0.22,4.58]
Perez 2010	20/39	12/36		9.91%	1.54[0.88,2.68]
Psilopoulos 2005	12/30	10/30		6.79%	1.2[0.61,2.34]
Sarin 1999	5/46	5/44		2.23%	0.96[0.3,3.08]
Schepke 2004	34/75	33/77		23.71%	1.06[0.74,1.51]
Thuluvath 2005	6/16	3/15		2.14%	1.88[0.57,6.19]
Tripathi 2009	27/75	26/77		16.1%	1.07[0.69,1.65]
Subtotal (95% CI)	**542**	**555**		**82.86%**	**1.19[0.98,1.44]**
Total events: 150 (Banding), 132 (Beta-blockers)					
Heterogeneity: Tau^2=0; Chi^2=7.18, df=12(P=0.85); I^2=0%					
Test for overall effect: Z=1.75(P=0.08)					
1.4.2 Abstracts					
Abdelfattah 2006	4/51	5/52		1.93%	0.82[0.23,2.87]
Abulfutuh 2003	13/44	24/66		9.81%	0.81[0.47,1.42]
Chen 1998	3/26	3/30		1.33%	1.15[0.25,5.23]
Gheorghe 2002	1/25	5/28		0.7%	0.22[0.03,1.79]
Mora 2000	0/12	1/12		0.32%	0.33[0.01,7.45]
Song 2000	5/31	8/30		3.05%	0.6[0.22,1.64]
Subtotal (95% CI)	**189**	**218**		**17.14%**	**0.74[0.49,1.13]**
Total events: 26 (Banding), 46 (Beta-blockers)					
Heterogeneity: Tau^2=0; Chi^2=2.18, df=5(P=0.82); I^2=0%					
Test for overall effect: Z=1.4(P=0.16)					
Total (95% CI)	**731**	**773**		**100%**	**1.09[0.92,1.3]**
Total events: 176 (Banding), 178 (Beta-blockers)					
Heterogeneity: Tau^2=0; Chi^2=13.44, df=18(P=0.76); I^2=0%					
Test for overall effect: Z=1.01(P=0.31)					
Test for subgroup differences: Chi^2=4.01, df=1 (P=0.05), I^2=75.08%					

Analysis 1.5. Comparison 1 Banding ligation versus non-selective beta-blockers, Outcome 5 Upper gastrointestinal bleeding.

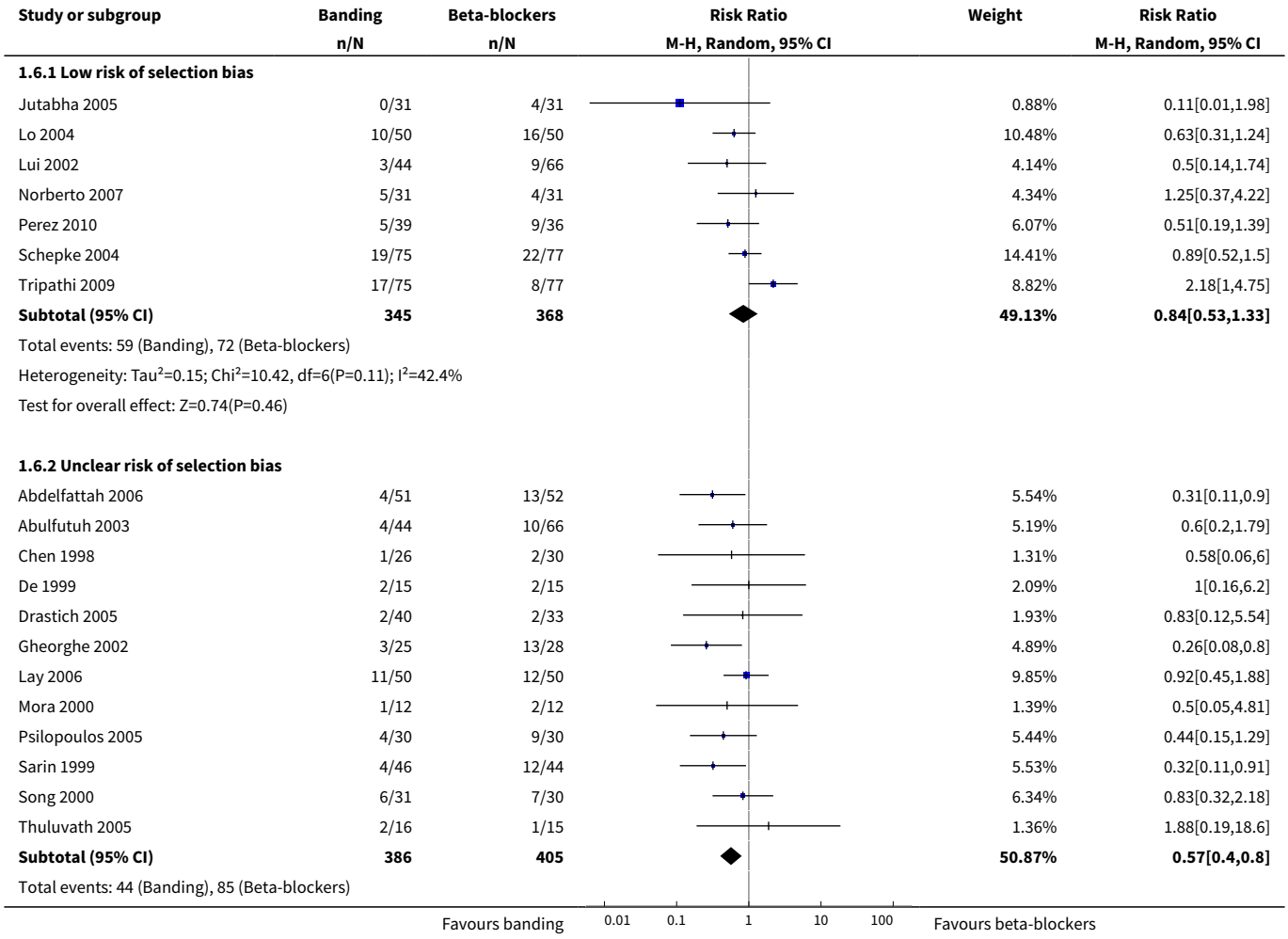


Study or subgroup	Banding n/N	Beta-blockers n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Abdelfattah 2006	4/51	13/52		5.54%	0.31[0.11,0.9]
Abulfutuh 2003	4/44	10/66		5.19%	0.6[0.2,1.79]
Chen 1998	1/26	2/30		1.31%	0.58[0.06,6]
De 1999	2/15	2/15		2.09%	1[0.16,6.2]
Drastich 2005	2/40	2/33		1.93%	0.83[0.12,5.54]
Gheorghe 2002	3/25	13/28		4.89%	0.26[0.08,0.8]
Jutabha 2005	0/31	4/31		0.88%	0.11[0.01,1.98]
Lay 2006	11/50	12/50		9.85%	0.92[0.45,1.88]
Lo 2004	10/50	16/50		10.48%	0.63[0.31,1.24]
Lui 2002	3/44	9/66		4.14%	0.5[0.14,1.74]



Study or subgroup	Banding n/N	Beta-blockers n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Mora 2000	1/12	2/12		1.39%	0.5[0.05,4.81]
Norberto 2007	5/31	4/31		4.34%	1.25[0.37,4.22]
Perez 2010	5/39	9/36		6.07%	0.51[0.19,1.39]
Psilopoulos 2005	4/30	9/30		5.44%	0.44[0.15,1.29]
Sarin 1999	4/46	12/44		5.53%	0.32[0.11,0.91]
Schepke 2004	19/75	22/77		14.41%	0.89[0.52,1.5]
Song 2000	6/31	7/30		6.34%	0.83[0.32,2.18]
Thuluvath 2005	2/16	1/15		1.36%	1.88[0.19,18.6]
Tripathi 2009	17/75	8/77		8.82%	2.18[1,4.75]
Total (95% CI)	**731**	**773**		**100%**	**0.69[0.52,0.91]**
Total events: 103 (Banding), 157 (Beta-blockers)					
Heterogeneity: Tau^2=0.06; Chi^2=22.05, df=18(P=0.23); I^2=18.35%					
Test for overall effect: Z=2.67(P=0.01)					

Analysis 1.6. Comparison 1 Banding ligation versus non-selective beta-blockers, Outcome 6 Upper gastrointestinal bleeding stratified by selection bias.



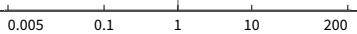
Study or subgroup	Banding n/N	Beta-blockers n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Low risk of selection bias					
Jutabha 2005	0/31	4/31		0.88%	0.11[0.01,1.98]
Lo 2004	10/50	16/50		10.48%	0.63[0.31,1.24]
Lui 2002	3/44	9/66		4.14%	0.5[0.14,1.74]
Norberto 2007	5/31	4/31		4.34%	1.25[0.37,4.22]
Perez 2010	5/39	9/36		6.07%	0.51[0.19,1.39]
Schepke 2004	19/75	22/77		14.41%	0.89[0.52,1.5]
Tripathi 2009	17/75	8/77		8.82%	2.18[1,4.75]
Subtotal (95% CI)	**345**	**368**		**49.13%**	**0.84[0.53,1.33]**
Total events: 59 (Banding), 72 (Beta-blockers)					
Heterogeneity: Tau^2=0.15; Chi^2=10.42, df=6(P=0.11); I^2=42.4%					
Test for overall effect: Z=0.74(P=0.46)					
1.6.2 Unclear risk of selection bias					
Abdelfattah 2006	4/51	13/52		5.54%	0.31[0.11,0.9]
Abulfutuh 2003	4/44	10/66		5.19%	0.6[0.2,1.79]
Chen 1998	1/26	2/30		1.31%	0.58[0.06,6]
De 1999	2/15	2/15		2.09%	1[0.16,6.2]
Drastich 2005	2/40	2/33		1.93%	0.83[0.12,5.54]
Gheorghe 2002	3/25	13/28		4.89%	0.26[0.08,0.8]
Lay 2006	11/50	12/50		9.85%	0.92[0.45,1.88]
Mora 2000	1/12	2/12		1.39%	0.5[0.05,4.81]
Psilopoulos 2005	4/30	9/30		5.44%	0.44[0.15,1.29]
Sarin 1999	4/46	12/44		5.53%	0.32[0.11,0.91]
Song 2000	6/31	7/30		6.34%	0.83[0.32,2.18]
Thuluvath 2005	2/16	1/15		1.36%	1.88[0.19,18.6]
Subtotal (95% CI)	**386**	**405**		**50.87%**	**0.57[0.4,0.8]**
Total events: 44 (Banding), 85 (Beta-blockers)					

Study or subgroup	Banding n/N	Beta-blockers n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0; Chi²=8.38, df=11(P=0.68); I²=0%					
Test for overall effect: Z=3.24(P=0)					
Total (95% CI)	**731**	**773**		**100%**	**0.69[0.52,0.91]**
Total events: 103 (Banding), 157 (Beta-blockers)					
Heterogeneity: Tau²=0.06; Chi²=22.05, df=18(P=0.23); I²=18.35%					
Test for overall effect: Z=2.67(P=0.01)					
Test for subgroup differences: Chi²=1.79, df=1 (P=0.18), I²=44.12%					

Favours banding — Favours beta-blockers

Analysis 1.7. Comparison 1 Banding ligation versus non-selective beta-blockers, Outcome 7 Upper gastrointestinal bleeding stratified by attrition bias.

Study or subgroup	Banding n/N	Beta-blockers n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 Low risk of selection bias					
Jutabha 2005	0/31	4/31		0.88%	0.11[0.01,1.98]
Lo 2004	10/50	16/50		10.48%	0.63[0.31,1.24]
Lui 2002	3/44	9/66		4.14%	0.5[0.14,1.74]
Norberto 2007	5/31	4/31		4.34%	1.25[0.37,4.22]
Perez 2010	5/39	9/36		6.07%	0.51[0.19,1.39]
Psilopoulos 2005	4/30	9/30		5.44%	0.44[0.15,1.29]
Sarin 1999	4/46	12/44		5.53%	0.32[0.11,0.91]
Schepke 2004	19/75	22/77		14.41%	0.89[0.52,1.5]
Tripathi 2009	17/75	8/77		8.82%	2.18[1,4.75]
Subtotal (95% CI)	**421**	**442**		**60.1%**	**0.71[0.46,1.09]**
Total events: 67 (Banding), 93 (Beta-blockers)					
Heterogeneity: Tau²=0.18; Chi²=14.71, df=8(P=0.06); I²=45.63%					
Test for overall effect: Z=1.56(P=0.12)					
1.7.2 Unclear risk of selection bias					
Abdelfattah 2006	4/51	13/52		5.54%	0.31[0.11,0.9]
De 1999	2/15	2/15		2.09%	1[0.16,6.2]
Drastich 2005	2/40	2/33		1.93%	0.83[0.12,5.54]
Gheorghe 2002	3/25	13/28		4.89%	0.26[0.08,0.8]
Mora 2000	1/12	2/12		1.39%	0.5[0.05,4.81]
Song 2000	6/31	7/30		6.34%	0.83[0.32,2.18]
Thuluvath 2005	2/16	1/15		1.36%	1.88[0.19,18.6]
Subtotal (95% CI)	**190**	**185**		**23.55%**	**0.53[0.31,0.89]**
Total events: 20 (Banding), 40 (Beta-blockers)					
Heterogeneity: Tau²=0; Chi²=5.19, df=6(P=0.52); I²=0%					
Test for overall effect: Z=2.41(P=0.02)					
1.7.3 High risk of attrition bias					
Abulfutuh 2003	4/44	10/66		5.19%	0.6[0.2,1.79]
Chen 1998	1/26	2/30		1.31%	0.58[0.06,6]
Lay 2006	11/50	12/50		9.85%	0.92[0.45,1.88]
Subtotal (95% CI)	**120**	**146**		**16.35%**	**0.79[0.44,1.41]**
Total events: 16 (Banding), 24 (Beta-blockers)					



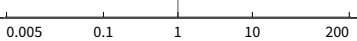
Favours banding — Favours beta-blockers

Study or subgroup	Banding n/N	Beta-blockers n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0; Chi²=0.48, df=2(P=0.79); I²=0%					
Test for overall effect: Z=0.79(P=0.43)					
Total (95% CI)	**731**	**773**		**100%**	**0.69[0.52,0.91]**
Total events: 103 (Banding), 157 (Beta-blockers)					
Heterogeneity: Tau²=0.06; Chi²=22.05, df=18(P=0.23); I²=18.35%					
Test for overall effect: Z=2.67(P=0.01)					
Test for subgroup differences: Chi²=1.18, df=1 (P=0.56), I²=0%					

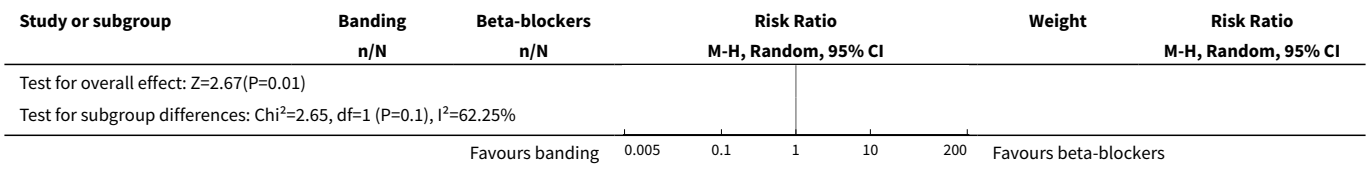
Favours banding — Favours beta-blockers

Analysis 1.8. Comparison 1 Banding ligation versus non-selective beta-blockers, Outcome 8 Upper gastrointestinal bleeding in full-paper articles and abstracts.

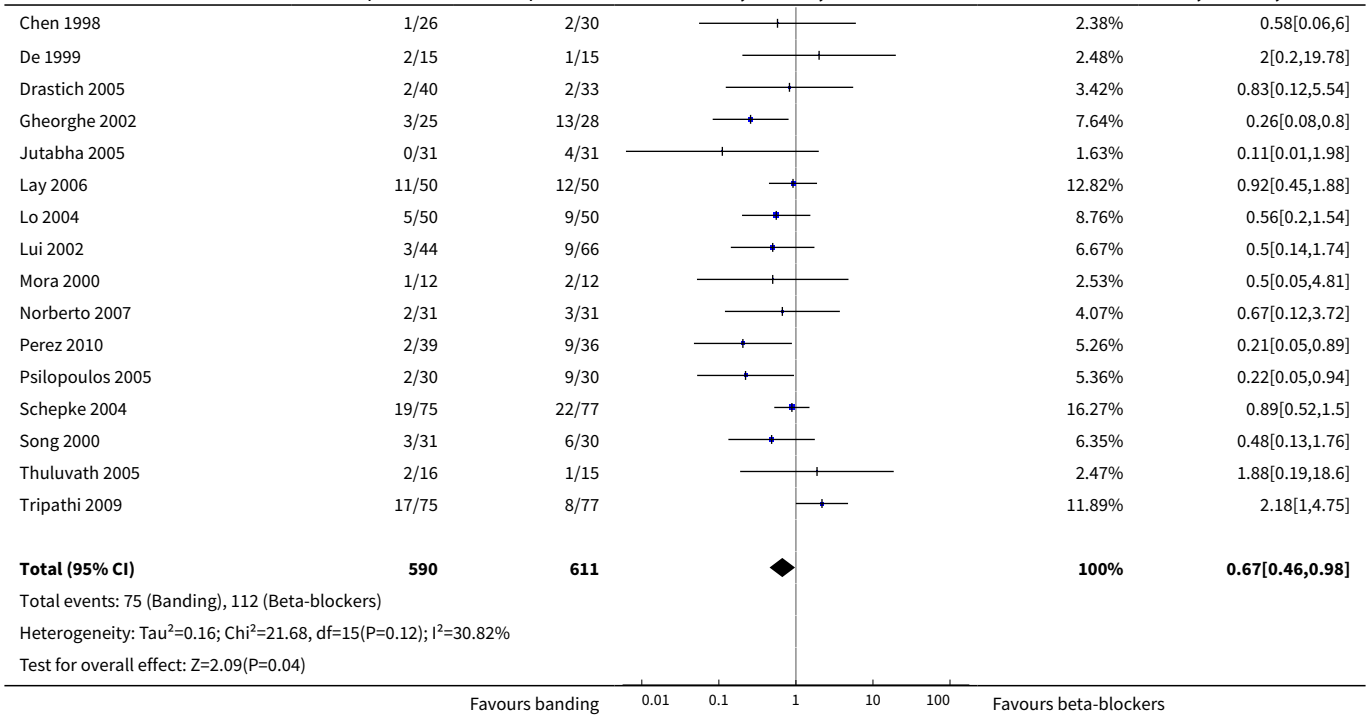
Study or subgroup	Banding n/N	Beta-blockers n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Full-paper articles					
Jutabha 2005	0/31	4/31		0.88%	0.11[0.01,1.98]
Lo 2004	10/50	16/50		10.48%	0.63[0.31,1.24]
Tripathi 2009	17/75	8/77		8.82%	2.18[1,4.75]
Lui 2002	3/44	9/66		4.14%	0.5[0.14,1.74]
Schepke 2004	19/75	22/77		14.41%	0.89[0.52,1.5]
Perez 2010	5/39	9/36		6.07%	0.51[0.19,1.39]
Thuluvath 2005	2/16	1/15		1.36%	1.88[0.19,18.6]
Norberto 2007	5/31	4/31		4.34%	1.25[0.37,4.22]
Lay 2006	11/50	12/50		9.85%	0.92[0.45,1.88]
De 1999	2/15	2/15		2.09%	1[0.16,6.2]
Sarin 1999	4/46	12/44		5.53%	0.32[0.11,0.91]
Psilopoulos 2005	4/30	9/30		5.44%	0.44[0.15,1.29]
Drastich 2005	2/40	2/33		1.93%	0.83[0.12,5.54]
Subtotal (95% CI)	**542**	**555**		**75.34%**	**0.78[0.56,1.07]**
Total events: 84 (Banding), 110 (Beta-blockers)					
Heterogeneity: Tau²=0.07; Chi²=15.53, df=12(P=0.21); I²=22.73%					
Test for overall effect: Z=1.53(P=0.13)					
1.8.2 Abstracts					
Mora 2000	1/12	2/12		1.39%	0.5[0.05,4.81]
Chen 1998	1/26	2/30		1.31%	0.58[0.06,6]
Abulfutuh 2003	4/44	10/66		5.19%	0.6[0.2,1.79]
Abdelfattah 2006	4/51	13/52		5.54%	0.31[0.11,0.9]
Song 2000	6/31	7/30		6.34%	0.83[0.32,2.18]
Gheorghe 2002	3/25	13/28		4.89%	0.26[0.08,0.8]
Subtotal (95% CI)	**189**	**218**		**24.66%**	**0.47[0.29,0.78]**
Total events: 19 (Banding), 47 (Beta-blockers)					
Heterogeneity: Tau²=0; Chi²=3.21, df=5(P=0.67); I²=0%					
Test for overall effect: Z=2.92(P=0)					
Total (95% CI)	**731**	**773**		**100%**	**0.69[0.52,0.91]**
Total events: 103 (Banding), 157 (Beta-blockers)					
Heterogeneity: Tau²=0.06; Chi²=22.05, df=18(P=0.23); I²=18.35%					



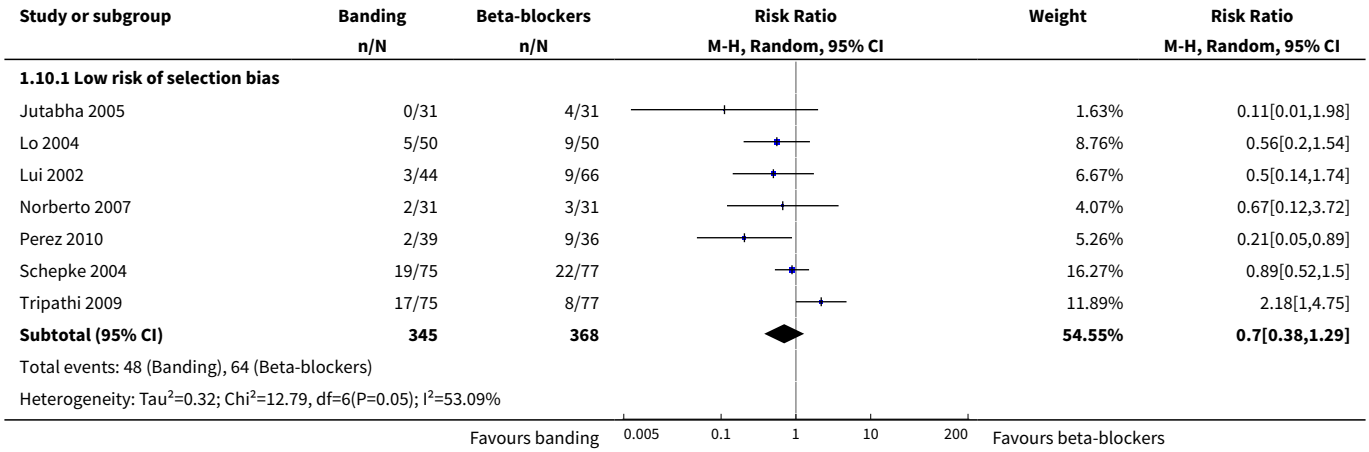
Favours banding — Favours beta-blockers

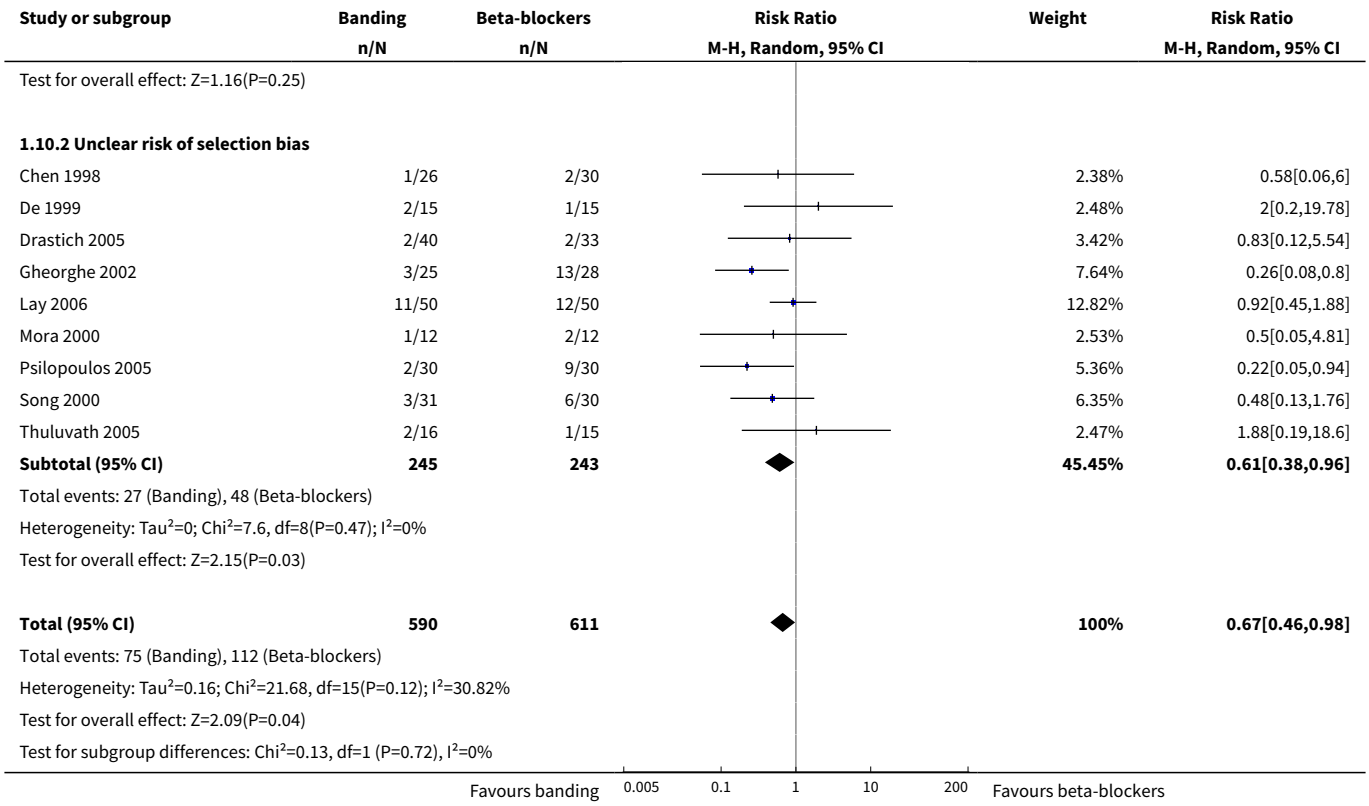


Analysis 1.9. Comparison 1 Banding ligation versus non-selective beta-blockers, Outcome 9 Variceal bleeding.

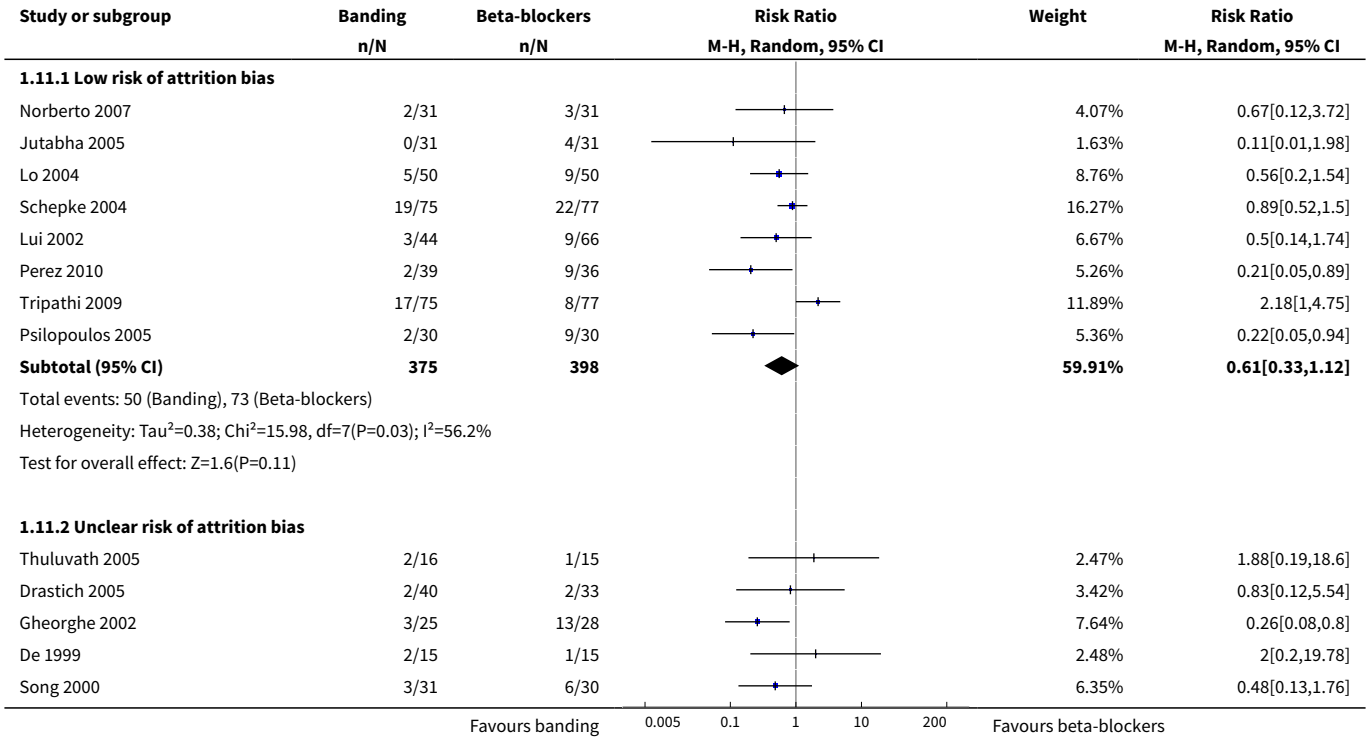


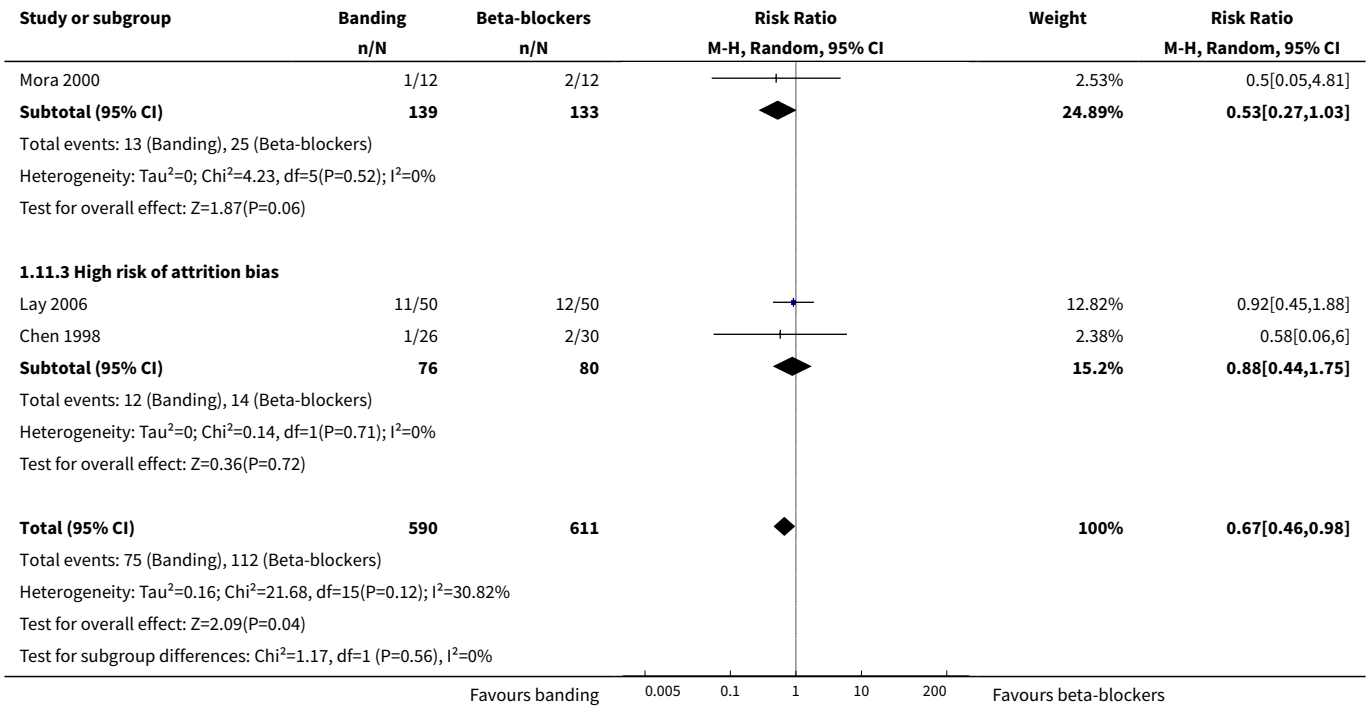
Analysis 1.10. Comparison 1 Banding ligation versus non-selective beta-blockers, Outcome 10 Variceal bleeding stratified by selection bias.



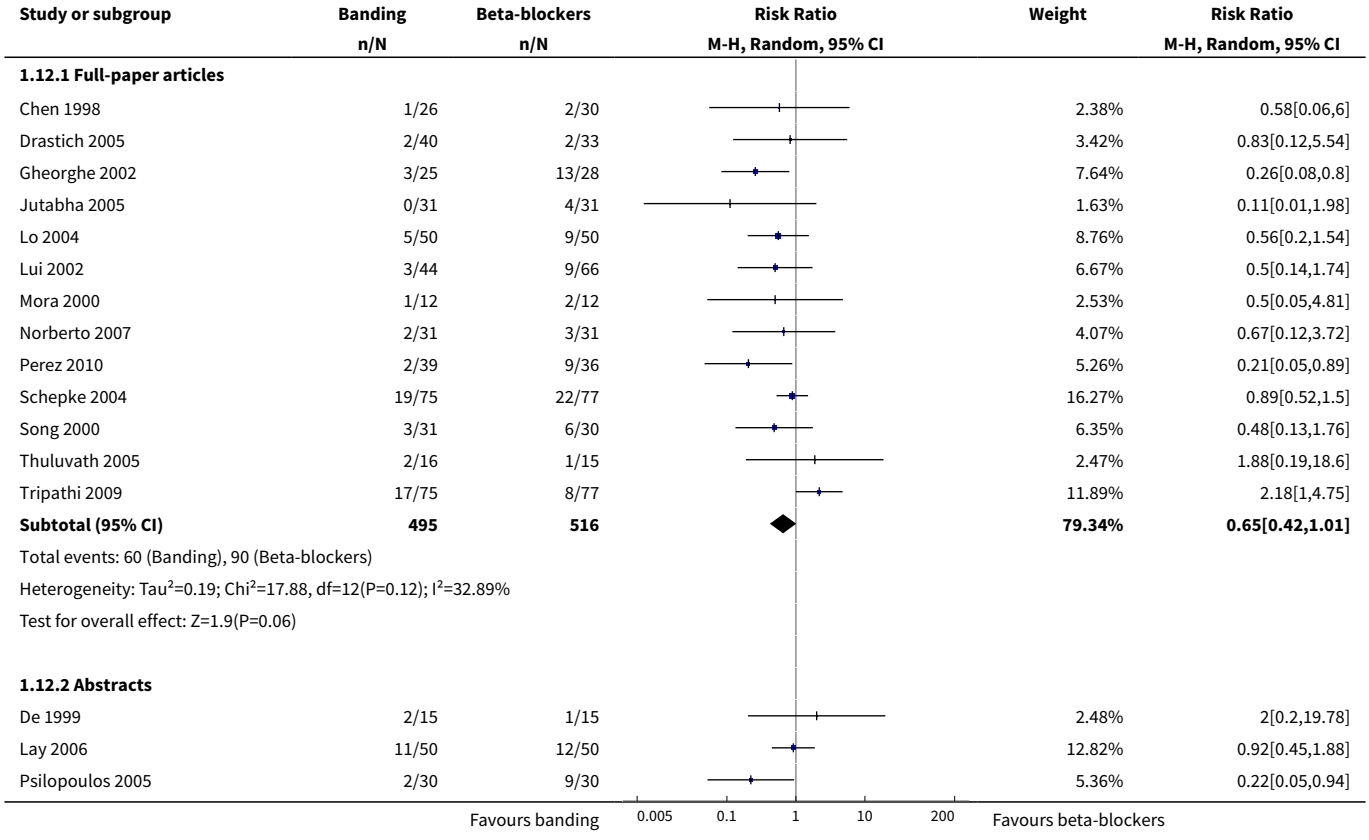


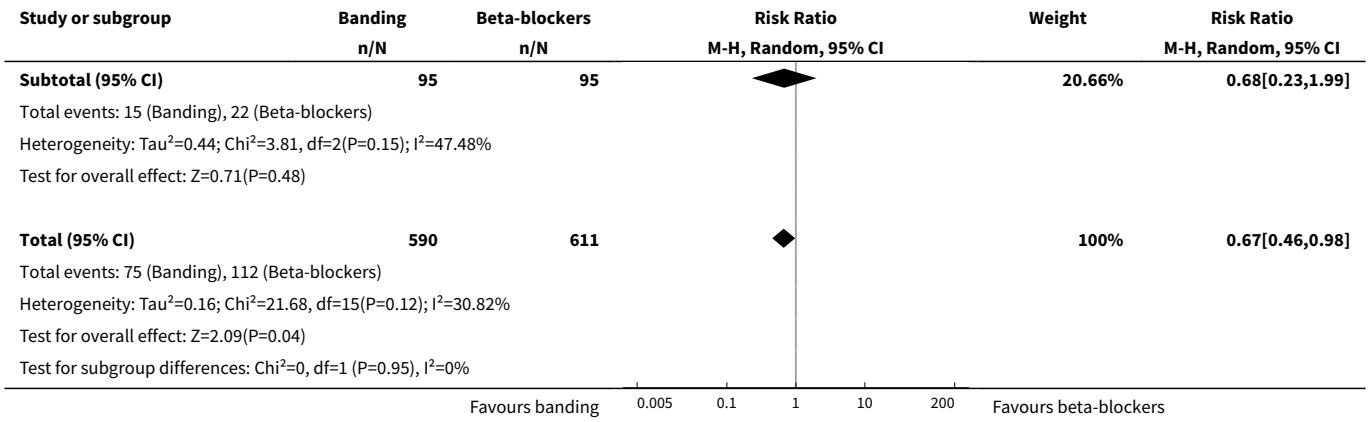
Analysis 1.11. Comparison 1 Banding ligation versus non-selective beta-blockers, Outcome 11 Variceal bleeding stratified by attrition bias.



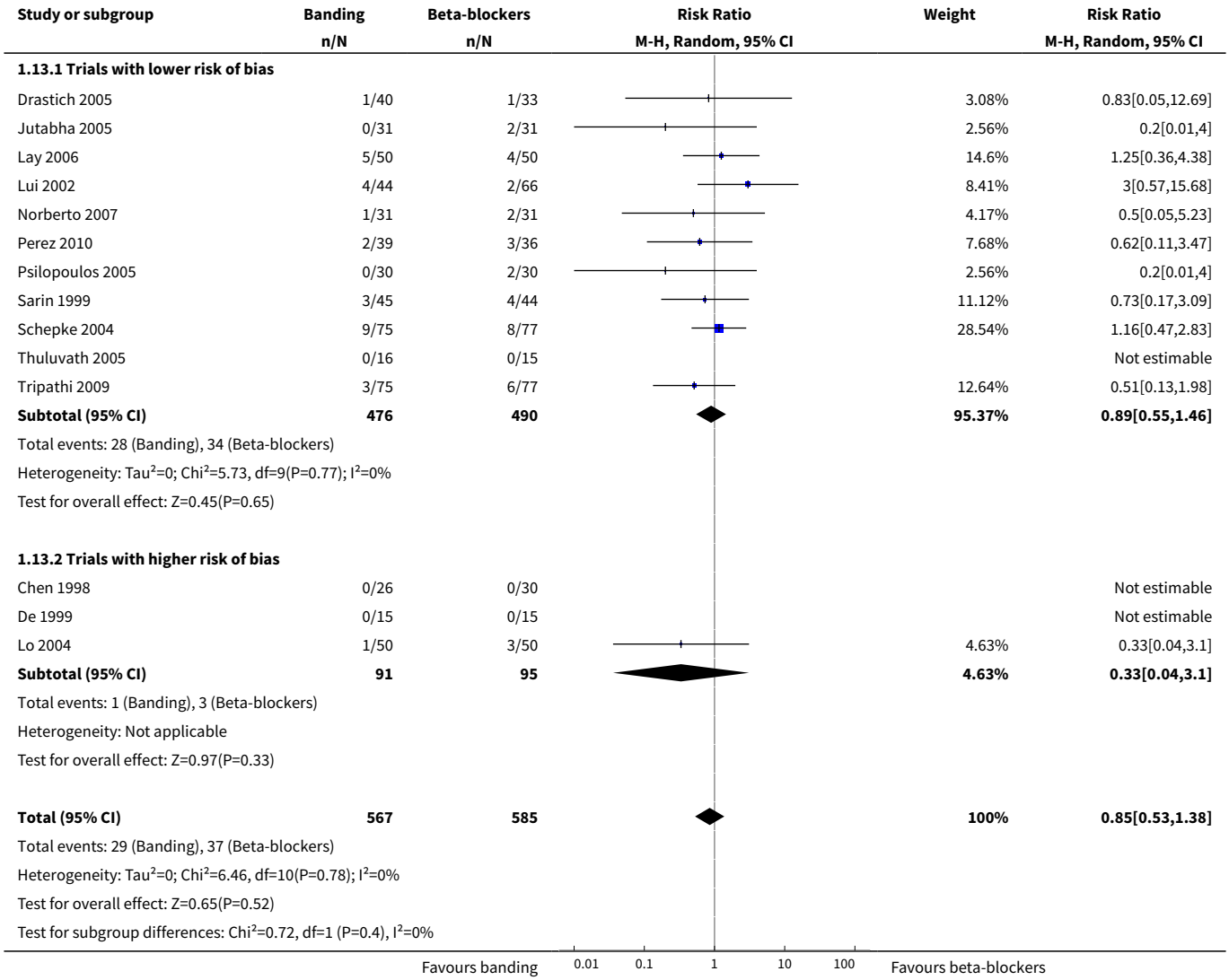


Analysis 1.12. Comparison 1 Banding ligation versus non-selective beta-blockers, Outcome 12 Variceal bleeding in full-paper articles and abstracts.



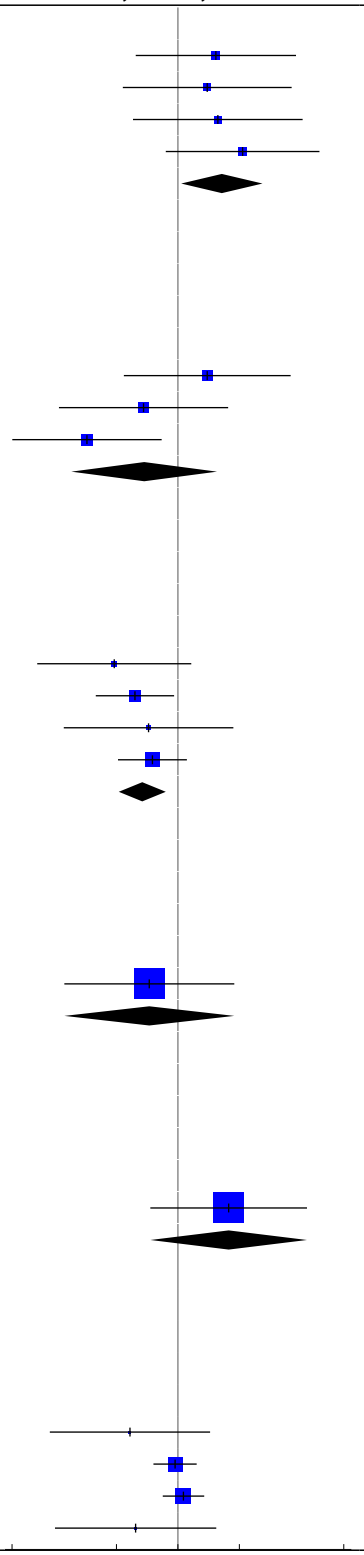


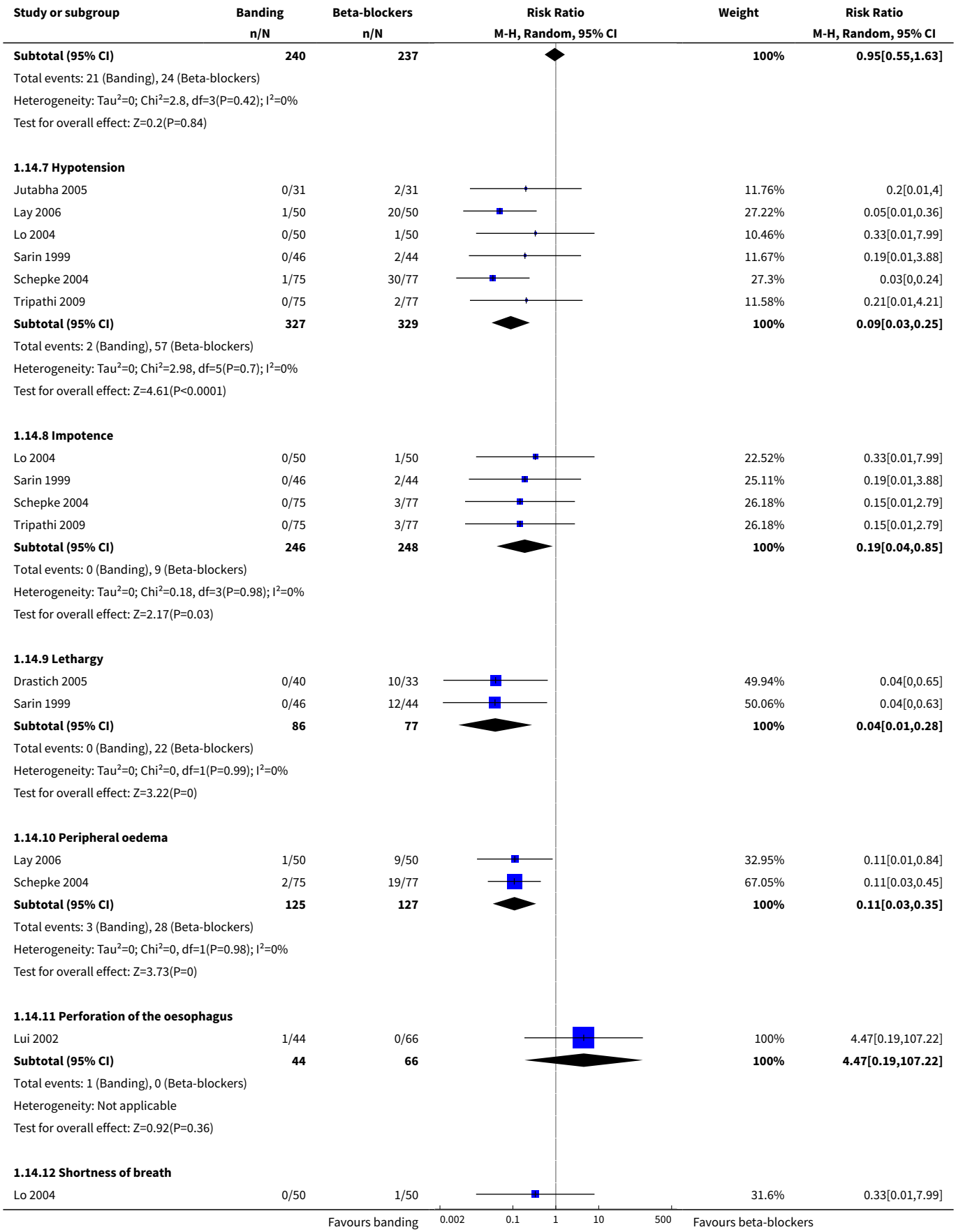
Analysis 1.13. Comparison 1 Banding ligation versus non-selective beta-blockers, Outcome 13 Bleeding-related mortality.

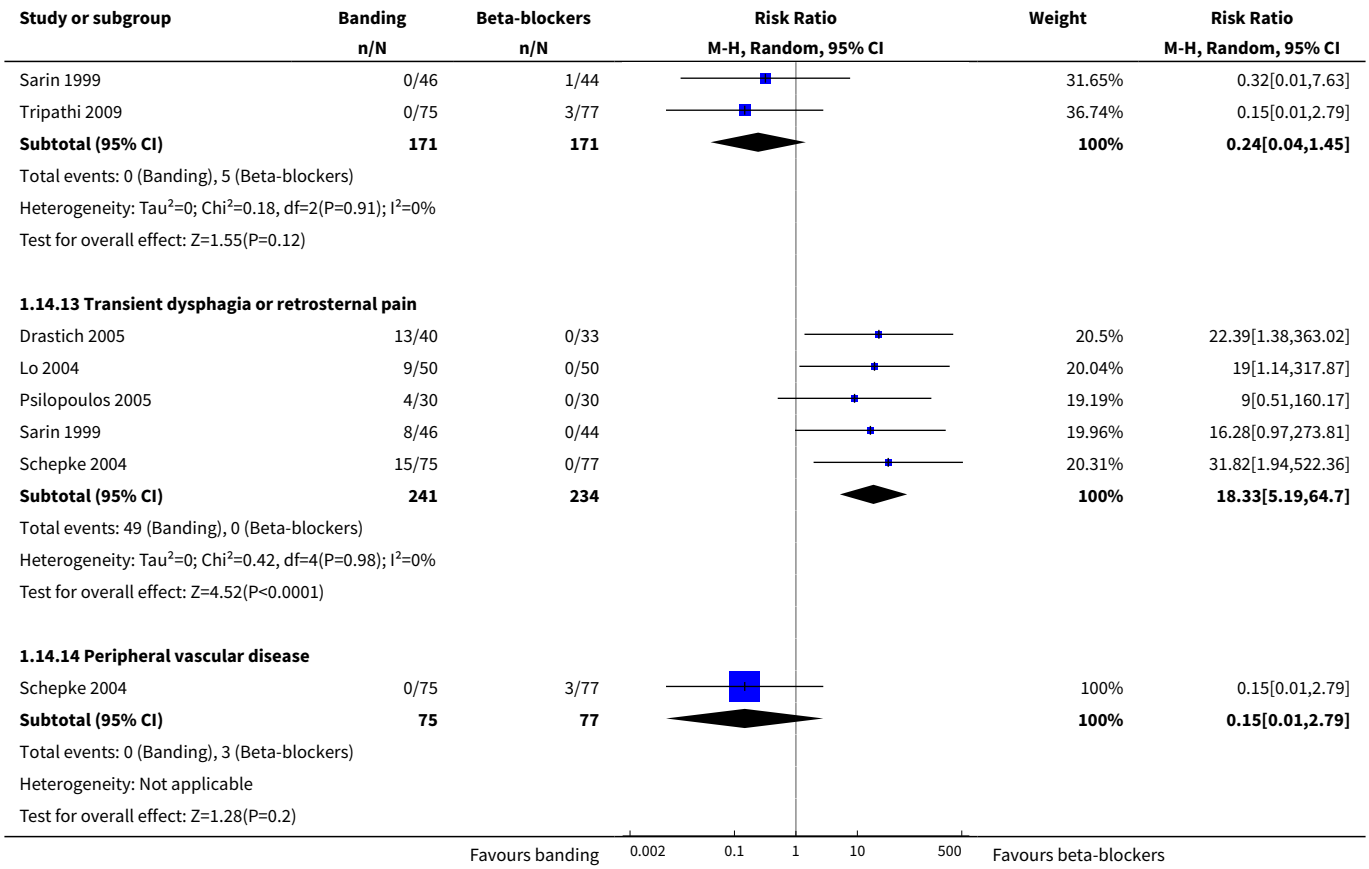


Analysis 1.14. Comparison 1 Banding ligation versus non-selective beta-blockers, Outcome 14 Adverse events.

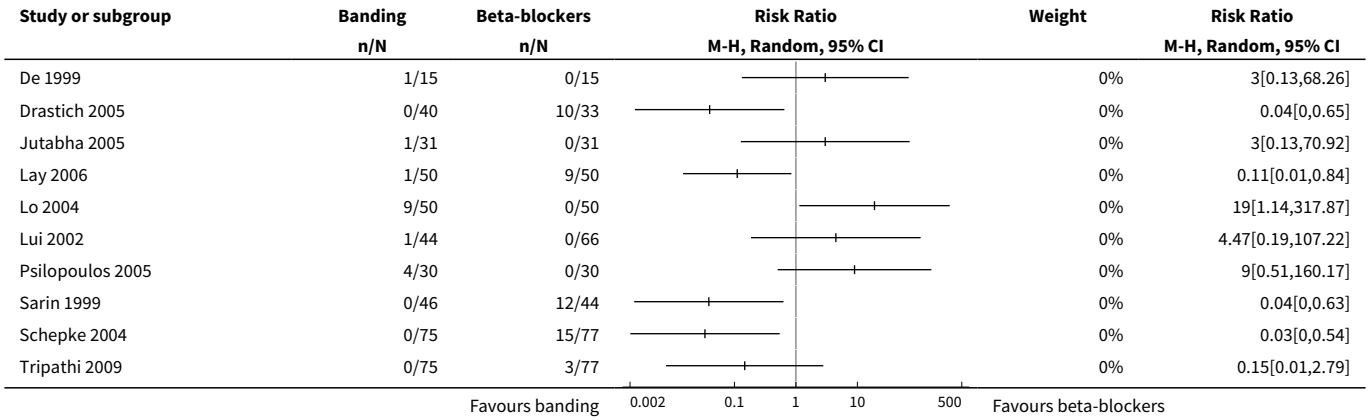
Study or subgroup	Banding n/N	Beta-blockers n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.14.1 Bleeding after banding ligation					
Drastich 2005	2/40	0/33		25.76%	4.15[0.21,83.46]
Jutabha 2005	1/31	0/31		23.21%	3[0.13,70.92]
Lui 2002	1/44	0/66		22.99%	4.47[0.19,107.22]
Schepke 2004	5/75	0/77		28.04%	11.29[0.64,200.67]
Subtotal (95% CI)	**190**	**207**		**100%**	**5.18[1.13,23.78]**
Total events: 9 (Banding), 0 (Beta-blockers)					
Heterogeneity: Tau²=0; Chi²=0.44, df=3(P=0.93); I²=0%					
Test for overall effect: Z=2.12(P=0.03)					
1.14.2 Bradycardia					
De 1999	1/15	0/15		32.47%	3[0.13,68.26]
Drastich 2005	0/40	1/33		32.08%	0.28[0.01,6.57]
Schepke 2004	0/75	15/77		35.45%	0.03[0,0.54]
Subtotal (95% CI)	**130**	**125**		**100%**	**0.28[0.02,4.33]**
Total events: 1 (Banding), 16 (Beta-blockers)					
Heterogeneity: Tau²=3.43; Chi²=4.88, df=2(P=0.09); I²=59.03%					
Test for overall effect: Z=0.91(P=0.36)					
1.14.3 Dizziness					
Drastich 2005	0/40	4/33		9.33%	0.09[0.01,1.65]
Lay 2006	2/50	10/50		36.13%	0.2[0.05,0.87]
Lo 2004	0/50	1/50		7.7%	0.33[0.01,7.99]
Schepke 2004	3/75	8/77		46.84%	0.39[0.11,1.4]
Subtotal (95% CI)	**215**	**210**		**100%**	**0.26[0.11,0.64]**
Total events: 5 (Banding), 23 (Beta-blockers)					
Heterogeneity: Tau²=0; Chi²=1.02, df=3(P=0.8); I²=0%					
Test for overall effect: Z=2.97(P=0)					
1.14.4 Exanthema					
Schepke 2004	0/75	1/77		100%	0.34[0.01,8.27]
Subtotal (95% CI)	**75**	**77**		**100%**	**0.34[0.01,8.27]**
Total events: 0 (Banding), 1 (Beta-blockers)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.66(P=0.51)					
1.14.5 Fever					
Sarin 1999	3/46	0/44		100%	6.7[0.36,126.13]
Subtotal (95% CI)	**46**	**44**		**100%**	**6.7[0.36,126.13]**
Total events: 3 (Banding), 0 (Beta-blockers)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.27(P=0.2)					
1.14.6 Gastrointestinal discomfort					
Drastich 2005	0/40	2/33		3.26%	0.17[0.01,3.34]
Lay 2006	9/50	10/50		44.75%	0.9[0.4,2.02]
Schepke 2004	12/75	10/77		48.76%	1.23[0.57,2.68]
Tripathi 2009	0/75	2/77		3.23%	0.21[0.01,4.21]







Analysis 1.15. Comparison 1 Banding ligation versus non-selective beta-blockers, Outcome 15 Adverse events.



APPENDICES

Appendix 1. Search strategies

Database	Time span	Search Terms
Cochrane Hepato-Biliary Group Controlled Trials Register.	February 2012.	(band* OR ligat*) AND (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 OR 'isosorbid* mononitrat*' OR imdur OR ismo OR monoket) AND '*esophageal varic*'
Cochrane Central Register of Controlled Trials in *The Cochrane Library.*	Issue 1, 2012.	#1 MeSH descriptor Ligation explode all trees #2 band* OR ligat* #3 MeSH descriptor Adrenergic beta-Antagonists explode all tree #4 MeSH descriptor Propranololexplode all trees #5 MeSH descriptor Atenololexplode all trees #6 MeSH descriptor Nadolol explode all trees #7 MeSH descriptor Metoprolol explode all trees #8 MeSH descriptor Bisoprolol explode all trees #9 MeSH descriptor Penbutolol explode all trees #10 MeSH descriptor Timololexplode all trees #11 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 #12 isosorbid* mononitrat* or imdur or ismo or monoket #13 MeSH descriptor Esophageal and Gastric Varices explode all trees #14 *esophageal varic* #15 (#1 OR #2) #16 (#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12) #17 (#13 OR #14) #18 (#15 AND #16 AND #17)
MEDLINE (Ovid SP).	1946 to February 2012.	1. exp Ligation/ 2. (band* or ligat*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 3. 1 or 2 4. exp Adrenergic beta-Antagonists/ 5. exp Propranolol/ 6. exp Atenolol/ 7. exp Nadolol/ 8. exp Metoprolol/ 9. exp Bisoprolol/ 10. exp Penbutolol/

(Continued)

		11. exp Timolol/ 12. (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] 13. (isosorbid* mononitrat* or imdur or ismo or monoket).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 14. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 15. exp "Esophageal and Gastric Varices"/ 16. *esophageal varic*/ 17. 15 or 16 18. 3 and 14 and 17 19. (random* or blind* or placebo* or meta-analysis).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 20. 18 and 19
EMBASE (Ovid SP)	1974 to February 2012	1. exp LIGATION/ 2. (band* or ligat*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer] 3. 1 or 2 4. exp beta adrenergic receptor blocking agent/ 5. exp PROPRANOLOL/ 6. exp ATENOLOL/ 7. exp NADOLOL/ 8. exp METOPROLOL/ 9. exp BISOPROLOL/ 10. exp CARVEDILOL/ 11. exp TERTATOLOL/ 12. exp NIPRADILOL/ 13. exp PENBUTOLOL/ 14. exp TIMOLOL/ 15. exp MEPINDOLOL/ 16. (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, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]

(Continued)

		17. (isosorbid* mononitrat* or imdur or ismo or monoket).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer] 18. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 19. exp esophagus varices/ 20. ((oesophageal or esophageal) and varic*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer] 21. 19 or 20 22. 3 and 18 and 21 23. (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] 24. 22 and 23
Science Citation Index Expanded (http://apps.webofknowledge.com)	1900 to February 2012	# 6 #5 AND #4 # 5 TS=(random* or blind* or placebo* or meta-analysis) # 4 #1 AND #2 AND #3 # 3 TS=((oesophageal or esophageal) and varic*) # 2 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 OR 'isosorbid* mononitrat*' OR imdur OR ismo OR monoket) # 1 TS=(band* OR ligat*)

CONTRIBUTIONS OF AUTHORS

Lise Lotte Gluud drafted the review based on a protocol by LL Gluud et al (Gluud 2009) which in turn was based on the abandoned by Wendong Chen et al protocol with a title 'Beta-blockers for cirrhotic patients with oesophageal varices that have never bled' (last published in Issue 4, 2006, no longer published on *The Cochrane Library*). Lise Lotte Gluud and Aleksander Krag participated in the literature search and data extraction. All authors participated in the revision of the review and have approved the final version.

DECLARATIONS OF INTEREST

None of the authors have financial or other conflicts of interest with regard to the present work.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol for the present review assessed the beneficial and harmful effects of beta-blockers alone or combined with endoscopic interventions for primary prevention in variceal bleeding (Gluud 2009). Due to the large number of possible combinations and the fact that

there may be interactions between interventions for variceal bleeding, the original protocol has been split into more specific protocols and reviews.

The methods and analytical strategy in the present review has been updated to comply with the most recent recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions* (including addition of regression analyses to detect small study effects, trial sequential analyses, and additional markers of bias control).

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic beta-Antagonists [*therapeutic use]; Esophageal and Gastric Varices [*drug therapy] [mortality] [*surgery]; Gastrointestinal Hemorrhage [mortality] [*prevention & control]; Ligation [methods]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans