Systematic Review with Meta-Analyses of Randomized Trials on Isosorbide-Mononitrate Alone or With Beta-Blockers or Endoscopic Therapy for Esophageal Varices

Lise Lotte Gluud, Ebbe Langholz, Aleksander Krag

Alimentary Pharmacology & Therapeutics

Systematic Review with Meta-Analyses of Randomized Trials on Isosorbide-Mononitrate Alone or With Beta-Blockers or Endoscopic Therapy for Esophageal Varices

Journal:	*Alimentary Pharmacology & Therapeutics*
Manuscript ID:	APT-0303-2010.R1
Wiley - Manuscript type:	Systematic Review
Date Submitted by the Author:	30-Jun-2010
Complete List of Authors:	Gluud, Lise; Department of Internal Medicine Langholz, Ebbe; Department of Internal Medicine Krag, Aleksander; Department of Internal Medicine
Keywords:	Cirrhosis < Hepatology, Portal hypertension < Hepatology, Varices < Hepatology, Liver < Organ-based

Systematic Review with Meta-Analyses of Randomized Trials on Isosorbide-Mononitrate Alone or With Beta-Blockers or Endoscopic Therapy for Esophageal Varices

LL. Gluud,[1] E. Langholz,[1] A. Krag,[1,2]

[1]Department of Internal Medicine, Copenhagen University Hospital Gentofte, Denmark,

[2]Department of Medical Gastroenterology, Copenhagen University Hospital Hvidovre, Denmark

Correspondence: Lise Lotte Gluud, M.D., Dm.Sc., Department of Internal Medicine, Copenhagen University Hospital, Niels Andersens Vej 65, 2900 Hellerup, Denmark. E-mail: liselottegluud@yahoo.dk; fax: +(45) 3977 7121

BACKGROUND

The evidence concerning the use of Isosorbide-Mononitrate (IsMn) for esophageal varices is equivocal.

METHODS

Systematic review with meta-analyses of randomized trials on IsMn alone or with beta-blockers or endoscopic therapy for esophageal varices. Electronic and manual searches were combined. Randomized trials on primary and secondary prevention were included. The primary outcome measure was mortality. Intention-to-treat random effects meta-analyses were performed. The robustness of the results were assessed in trial sequential analyses.

RESULTS

Ten randomized trials on primary and 17 on secondary prevention were included. Evidence of bias was identified. No apparent effect of IsMn on mortality compared with placebo or beta-blockers or IsMn plus beta-blockers versus beta-blockers was identified. Compared with endoscopic therapy, IsMn plus beta-blockers had no apparent effect on bleeding, but did seem to reduce mortality in secondary (RR 0.73, 95% CI 0.59-0.89), but not in primary prevention. The effect of IsMn plus beta-blockers on mortality in secondary prevention was not confirmed in trial sequential analysis.

CONCLUSIONS

IsMn used alone or in combination with beta blockers does not seem to offer any reduction in bleeding in the primary or secondary prevention of esophageal varices. Compared to endoscopic therapy, there may be a survival advantage to using IsMn and beta-blockers, but additional large multicentre trials are needed to verify this finding.

Deleted: Data on all patients randomized were sought and included in intention-to-treat random effects meta-analyses.

Deleted: trials

Deleted: The treatment comparisons included IsMn alone or combined with beta-blockers versus placebo, beta-blockers, banding ligation, sclerotherapy, or transjugular intrahepatic portosystemic shunts. Clear evidence

Deleted:

Deleted: Additional trials on IsMn plus beta-blockers versus beta-blockers are needed before any recommendations can be made. Future trials should only include the combined pharmacological treatment in the control group if a clear benefit of this treatment has been documented. ¶

The prevalence of esophageal varices is about 50% among patients who are diagnosed as having cirrhosis of the liver and at least two thirds of patients with cirrhosis will develop esophageal or gastric varices.[1] The risk of bleeding once the varices are developed, depends on the severity of the liver disease assessed by the Child-Pugh class, the variceal size, severity of red color signs, and the portal pressure.[2,3] Without treatment, about one third of patients with esophageal varices will experience their first bleeding episode within two years after the diagnosis is made. The subsequent risk of rebleeding after one year is about 65% if treatment is not initiated. Treatment with non-selective beta-blockers or endoscopic therapy reduces the risk of bleeding considerably.[4,5] Still, the prognosis remains poor. About 50% of patients are non-responders to beta-blockers or cannot continue treatment due to adverse effects.[6] A meta-analysis of randomized trials on patients with esophageal varices and no history of bleeding have found overall mortality rates of about 34% after banding ligation and 27% after beta-blockers.[7] Although both interventions appear to reduce mortality compared with no treatment, the mortality rates suggest that additional therapeutic options should be assessed. Isosorbide-mononitrate (IsMn) has been suggested used alone or combined with beta-blockers.[5] However, one randomized trial found that IsMn increased the risk of bleeding compared with placebo.[8] Other randomized trials on IsMn versus beta-blockers or IsMn plus beta-blockers versus beta-blockers or endoscopic therapy have reached equivocal results.[9,10] Recent meta-analyses including between four and 25 randomized trials have found that the combination of endoscopic and pharmacological therapy with beta-blockers alone or combined with IsMn may be more effective in reducing the risk of rebleeding than either therapeutic option used alone.[11-13] No clear effect on mortality was identified. The meta-analyses also found considerable inter-trial heterogeneity and

Deleted: severe.

some evidence of bias. Accordingly, we performed a systematic review of randomized trials to evaluate the strength of the evidence on IsMn alone or in combination with beta blockers or endoscopic therapy for the primary or secondary prevention of bleeding in patients with esophageal varices.

Deleted: -

METHODS

The objective of the present review was to assess the effects of IsMn for patients with esophageal varices and no previous bleeding (primary prevention) or previous variceal bleeding (secondary prevention). Randomized trials were included irrespective of publication status or language. The treatment comparisons assessed included IsMn alone or with beta-blockers versus placebo, no intervention, beta-blockers, endoscopic therapy (banding ligation or sclerotherapy), transjugular intrahepatic portosystemic shunts (TIPS), or the combination of IsMn plus beta-blockers and endoscopic therapy. The primary outcome measure was mortality. Secondary outcomes included upper gastrointestinal bleeding, variceal bleeding, bleeding-related mortality, and adverse events. The review is based on a protocol published in the Cochrane Library.

Eligible trials were identified through searches in The Cochrane Hepato-Biliary Group Controlled Trials Register, The Cochrane Library, MEDLINE via PubMed and SilverPlatter, EMBASE, and Science Citation Index Expanded . The last search update was January 2010. The searches were performed with help from the Cochrane Hepato-Biliary Group, Denmark and included the terms ‘isosorbide-mononitrate’ and ‘varices’, combined with a search strategy developed for the identification of randomized trials (http://www.mrw.interscience.wiley.com/cochrane/cochrane_clsysrev_crglist_fs.html).

Manual searches including scanning of reference lists in relevant papers, conference proceedings, correspondence with experts, and online trial registers through controlled-trials.com were also performed. Two authors (LG and AK) searched for eligible trials and extracted data. The primary authors of the included trials were contacted for additional information if data were not included in the published trial reports.

Methodological quality.

Based on previous evidence the primary assessment of bias control focused on randomization methods (allocation sequence generation and allocation concealment).[14,15] The allocation sequence generation was classified as adequate if based on computer generated random numbers, a table of random numbers, or similar. The allocation concealment was classified as adequate if patients were randomized through a central independent unit, serially numbered indistinguishable drug containers or bottles, serially numbered opaque sealed envelopes, or similar. Additional measures of bias control included blinding (whether the trial was double or single blind, whether patients, outcome assessors or other persons involved in the trial were blinded, and whether the effect of blinding was assessed), handling of missing outcome data, reporting of outcome measures (reporting bias), and other apparent biases including sample size calculations and whether the preset sample size was reached. The risk of reporting bias was assessed through comparisons between trial protocols, abstracts, and full paper articles.

Deleted: included

Statistical analysis.

All analyses were performed in RevMan version 5 (The Nordic Cochrane Centre, Copenhagen, Denmark) and STATA version 10.0 (Stata Corp, Texas, USA). Analyses were performed using the intention-to-treat principle including all patients, irrespective of compliance or follow up. For patients with missing outcome data, carry forward of the last observed response was used. Due to expected clinical heterogeneity, all meta-analyses were performed using random effects models. Results were expressed as risk ratios (RR) with 95% confidence intervals (CI) and the degree of intertrial heterogeneity as I-square values (I^2). Meta-analyses of all outcome measures except adverse events were performed stratified for subgroups of trials on primary prevention and secondary prevention. The analyses of adverse events were performed without stratification for previous variceal bleeding. To estimate the potential influence of bias, the primary meta-analyses were repeated including only trials with adequate randomization. Regression analyses of funnel plot asymmetry were performed to assess the risk of bias (or small trial effects). Since we identified discrepancies between the number of patients and events in abstracts and full paper articles, we also performed post hoc analyses including data from the abstracts. We originally planned to perform multiple intervention comparison meta-analyses, but were unable to perform these analyses due to the limited number of trials. To account for multiple comparisons associated with the design of our review, we performed trial sequential analysis for statistically significant outcome measures with alpha set to 5% and power to 80%.[16]

RESULTS

Formatted: Heading 2, None, Space Before: 0 pt, After: 0 pt, Line spacing: single, Don't keep with next

Formatted: Font: Not Bold

Forty-nine of 451 potentially relevant references identified in the electronic and manual searches were retrieved for further assessment (**Figure 1**). Forty-five references

referred to randomized trials that fulfilled our inclusion criteria. One ongoing trial (ISRCTN16334693) had to be excluded (data not yet available). In total, 27 randomized trials (described in 44 references) were included in our analyses.[8-10,17-42] Six trials were published in abstract form.[21,26-28,33,35] Remaining trials were published as full paper articles. One trial was translated from Chinese.[32] Remaining trials were published in English. The trials were performed in Argentina, China, Egypt, France, Great Britain, India, Italy, Pakistan, Spain, and Taiwan. The maximum duration of follow up ranged from 8 to 91 months (median 24 months). Ten trials assessed primary prevention and remaining trials secondary prevention (**Table 1**). Patient characteristics were reported in all full paper articles. In two trials 85 to 86% of included patients had cirrhosis.[34,40] The remaining trials only included patients with cirrhosis. The mean age of included patients ranged from 51 to 66 years and the proportion of men from 53% to 85%. In one trial, all included patients had ascites.[29] In remaining trials, 16% to 67% of included patients had ascites. The proportion of patients with large varices ranged from 36% to 100% in trials on primary prevention and from 77% to 100% in trials on secondary prevention. The reported exclusion criteria included contraindications to IsMn or beta-blockers (heart disease with aortic stenosis or atrioventricular block, peripheral ischemic disease, or chronic pulmonary disease), chronic renal failure, and malignant disease.

All trials used a parallel group design. The number of comparison groups was 2 in 21 trials, 3 in five trials, and 4 in one trial (**Table 1**). Trials on primary prevention assessed IsMn versus placebo, beta-blockers, or banding ligation or IsMn plus beta-blockers versus beta-blockers or banding ligation. Trials on secondary prevention assessed IsMn plus beta-blockers alone or with banding ligation versus beta-blockers,

Deleted: [16-41]
Deleted: [20,25-27,32,34]
Deleted: [31]
Deleted: [33,39]
Deleted: [28]

endoscopic therapy, or TIPS. The initial dose of IsMn ranged from 20 to 40 mg/day. The dose was increased to a maximum of 40 to 80 mg/day. The mean dose administered in the trials ranged from 30 to 73 mg/day. In trials on IsMn and beta-blockers, IsMn was initiated after the maintenance dose of beta-blocker was achieved. The beta-blockers assessed included nadolol and propranolol. The initial dose ranged from 40 to 80 mg/day. In most trials, the dose was adjusted to achieve a resting heart rate of about 55 to 60 beats per minute, a 20% to 25% reduction in the resting heart rate, or a maximum of 160 to 240 mg/day if tolerated. The mean dose of beta-blockers administered in the trials ranged from 40 mg to 125 mg/day. Most trials were initiated after the introduction of multiple band ligation devices in 1995. Patients randomized to endoscopic therapy with banding ligation or sclerotherapy initially underwent endoscopy every two to four weeks until variceal eradication was achieved. Subsequently, control endoscopy was performed monthly to every third month. In trials with long term follow up, patients randomized to endoscopic therapy alone underwent control endoscopy with about six months intervals. The TIPS procedure was performed using radiologic/ultrasonographic guidance using wall-stent endoprosthesis. The diameter was initially dilated to 8 mm in diameter and then to 10 mm if the portocaval pressure gradient remained more than 12 mmHg.

Methodological quality of included trials

Randomization methods (allocation sequence generation and allocation concealment) were classified as adequate in 17 trials (**Figure 2**). Two trials had adequate allocation sequence generation, but unclear allocation concealment.[34,40] In the remaining trials, randomization methods were unclear. For two trials,[27,38] there were considerable differences between the characteristics of patients randomized to the treatment and

Deleted: [33,39]

Deleted: [26,37]

control groups (number of patients and proportion with large varices, respectively). Adequate double blinding of patients and investigators using IsMn placebo was used in six trials.[8,9,20,23,25,26] One trial was described as single blind without specification of the method of blinding.[20] None of the trials assessed the effect of blinding.

Sample size calculations were reported for 18 trials.[8-10,17,18,22-26,30,31,34,36-38,40,41] Two trials performed simultaneously at one clinical site were terminated prematurely after interim analysis of a similar study suggested that IsMn increases mortality in patients with esophageal varices.[25,26] Another trial, which was planned to include 352 patients, was terminated due to low recruitment rates.[37] One single centre trial included 137 patients although the reported sample size calculation suggested that the planned size was 120 patients.[34] The authors did not describe whether the trial was continued beyond the planned size due to unexpectedly low event rates or for some other reason.

Three trials were included in clinical trial registers.[24,40,41] All trials were registered after their completion date. Two trials described the same primary outcome measures in the protocol and published report.[24,40] The protocol for one trial defined rebleeding as the primary outcome measure and complications as the secondary outcome measure.[41] In the published paper of the trial, the primary outcome measure was variceal rebleeding and the secondary outcome was mortality. The protocol and published report for the second trial defined upper gastrointestinal bleeding due to causes not related to portal hypertension and adverse events requiring treatment discontinuation as the secondary outcomes assessed.[40] An abstract describing the trial reported that the secondary outcomes were complications of cirrhosis including encephalopathy, hepatorenal

Deleted: [19,22,24]
Deleted: [19]
Deleted: [16,]
Deleted: [21-25,29]
Deleted: [33,35-37,39]
Deleted: [24,]
Deleted: [36]
Deleted: [33]
Deleted: [23,39]
Deleted: [23,39]
Deleted: [40]
Deleted: [39]

syndrome, spontaneous bacterial peritonitis, and jaundice.[42] The abstract also reported that the number of patients randomized and the overall mortality rates in the treatment and control group was 9/79 versus 5/92, respectively. In the full paper article the numbers were 2/88 versus 3/89, respectively. The reason for the discrepancy including the total number of patients randomized was not clear. There were no notable differences between the abstracts and published reports of remaining trials.

Deleted: [41]

Primary prevention

Ten trials on primary prevention reported mortality (**Figure 3**). No apparent effect of IsMn was identified for the intervention comparisons assessed. No differences in mortality were seen between IsMn and beta-blockers versus beta-blockers (49/277 versus 50/275; RR 0.95; 95% CI 0.68-1.32), or banding ligation (6/31 versus 8/30; RR 0.73; 95% CI 0.29-1.84). There was little evidence of intertrial heterogeneity (I^2 0%-6%).

Deleted: No differences in mortality rates were seen between IsMn versus placebo (15/67 versus 9/66; RR 1.64; 95% CI 0.77-3.49), beta-blockers (77/261 versus 72/270; RR 1.11; 95% CI 0.84-1.47), or banding ligation (42/177 versus 72/270; RR 0.99; 95% CI 0.67-1.47). Likewise no

Deleted: Likewise, regression analyses of funnel plot asymmetry found little evidence of bias for IsMn versus beta-blockers (P = 0.993), IsMn versus banding ligation (P = 0.107), or IsMn plus beta-blockers versus beta-blockers (P = 0.323).

Two meta-analyses included trials with unclear randomization methods.[20,21,33] Excluding these trials from the meta-analyses did not change the overall conclusions. Regression analyses of funnel plot asymmetry found little evidence of bias (P = 0.323-0.993).

Deleted: [19,]

Deleted: [32]

Deleted: After excluding these trials, no differences in mortality were seen between IsMn versus beta-blockers (RR 1.25; 95% CI 0.59-2.63) or IsMn versus banding ligation (RR 0.91; 95% CI 0.51-1.63

Nine trials reported bleeding (**Figure 3**). IsMn increased the risk of bleeding compared with placebo (RR 2.34; 95% CI 1.10-4.97) or banding ligation (RR 4.33; 95% CI 1.57-11.92). There were no apparent differences between bleeding rates of patients randomized to IsMn alone or with beta-blockers versus beta-blockers or banding

ligation. Considering the small number of trials and patient, we did not perform trial sequential analysis for this outcome measure.

Meta-analyses of variceal bleeding found a detrimental effect of IsMn compared with banding ligation (RR 3.31; 95% CI 1.01-10.84). There was no apparent difference in variceal bleeding for remaining treatment comparisons (**Table 2**). No effects on bleeding-related mortality was seen for any of the treatment comparisons assessed.

Secondary Prevention

Sixteen trials on secondary prevention reported mortality in trials on IsMn plus beta-blockers alone or with endoscopic therapy (**Figure 4**). Random effects meta-analyses found that IsMn plus beta-blockers reduced mortality compared with endoscopic therapy (111/496 versus 137/502; RR 0.73; 95% CI 0.59-0.89; I^2 0%). The findings were confirmed in sensitivity analyses excluding trials on sclerotherapy (RR 0.69; 95% CI 0.55-0.88) and trials without adequate randomization methods (RR 0.76; 95% CI 0.62-0.95). No differences in mortality were seen between remaining intervention comparisons. Regression analyses revealed no clear evidence of bias (P = 0.141-0.291).

We performed a trial sequential analysis to assess the potential effect of the effect of IsMn plus beta-blockers versus endoscopic therapy on mortality. The a priory intervention effect and the control group event rate were based on the findings of the random effects meta-analysis. The analysis confirmed that the cumulated z-curve (the estimated intervention effect) crossed the traditional boundary of 5% significance. However, the z-curve did not cross the trial sequential monitoring boundary, implying

Deleted: The statistical intertrial heterogeneity ranged from 0% to 31%. The trial on IsMn versus placebo

Deleted: report variceal bleeding (**Table 2**). A meta-

Deleted: of three trials reporting

Deleted: found that IsMn increased the risk

Deleted: . No beneficial or detrimental

Deleted: when including all trials

Deleted: %) or after

Deleted:). No differences in mortality were seen between IsMn plus beta-blockers versus beta-blockers (RR 1.04; 95% CI 0.73-1.50), TIPS (RR 0.90; 95% CI 0.45-1.80), or IsMn plus beta-blockers

Deleted: banding ligation (RR 0.88; 95% CI 0.56-1.39) or between IsMn plus beta-blockers and banding ligation versus banding ligation (RR 0.86; 95% CI 0.38-1.94). After excluding trials with unclear

Deleted: , there was no apparent difference between IsMn plus beta-blockers versus beta-blockers (RR 1.34; 95% CI 0.81-2.21) whereas IsMn plus beta-blockers reduced mortality compared with endoscopic therapy

Deleted: IsMn plus beta-blockers versus beta-blockers

Deleted: and IsMn plus beta-blockers versus banding ligation P =

that there is no firm evidence of a survival benefit of IsMn plus beta-blockers when the analysis was adjusted for multiple testing.

Fifteen trials reported overall bleeding (**Figure 4**). The risk of bleeding was higher among patients randomized to IsMn plus beta-blockers compared with TIPS (22/44 versus 8/47, RR 2.94; 95% CI 1.46-5.90). No other differences in bleeding were seen for remaining treatment comparisons. IsMn plus beta-blockers increased the risk of variceal bleeding compared with banding ligation or TIPS (RR 1.61; 95% CI 1.14-2.27 and RR 3.03; 95% CI 1.31-6.98, **Table 2**). No differences in variceal bleeding were seen for the remaining treatment comparisons. The risk of bleeding related mortality did not differ for any of the treatment comparisons assessed.

Deleted: Only 13 trials reported variceal bleeding (**Table 2**). The

Deleted: was higher for patients randomized to IsMn plus beta-blockers

Deleted:) or TIPS (

Deleted: (**Table 2**).

Based on identified discrepancies between the published report and abstract for one of the included trials, we repeated our meta-analyses including data described in the abstract.[40,42] These post hoc analyses did not change our overall conclusions.

Deleted: performed a post hoc analysis

Deleted: the

Deleted: [39,41]

Deleted: The trial compared IsMn plus beta-blockers versus banding ligation versus banding ligation. No differences between the two treatment were seen for mortality (16/116 versus 13/131; RR 1.33; 95% CI 0.60-2.96) or bleeding (19/79 versus 20/92; RR 1.11; 95% CI 0.64-1.92).

Adverse events

A considerable number of adverse events were registered (**Table 3**). There was little evidence of intertrial heterogeneity (I^2 0% in all analyses). There was no clear difference between the total number of adverse events

Deleted: Although the definitions and the methods used to register adverse events varied in individual trials, there

compared with placebo (14/67 versus 7/66; RR 1.97; 95% CI 0.85-4.57) or beta-blockers (30/62 versus 26/66; RR 1.23; 95% CI 0.83-1.82). No differences in the number of withdrawals were seen between IsMn versus placebo (10/67 versus 3/66; RR 3.28; 95% CI 0.95-11.40) or beta-blockers (19/146 versus 32/156; RR 0.63; 95%

CI 0.38-1.05). Compared with beta-blockers, IsMn plus beta-blockers increased the total number of adverse events (96/251 versus 57/251; RR 1.65; 95% CI 1.25-2.17) and the number of withdrawals due to adverse events (49/322 versus 18/325; RR 2.60; 95% CI 1.55-4.38). IsMn used alone or with beta-blockers mainly increased the risk of headache, but was not clearly associated with the risk of hypotension (**Table 3**). As expected, the risk of developing hepatic encephalopathy was lower for patients randomized to IsMn plus beta-blockers compared with TIPS (6/44 versus 18/47; RR 0.36; 95% CI 0.16-0.81). The risk of ascites was not different for these two treatment groups (RR 1.07; 95% CI 0.16-7.26). Among patients randomized to banding ligation, 28 of 442 developed clinically relevant esophageal ulcers (RR 0.10; 95% CI 0.03-0.31) and 10 of 216 dysphagia (RR 0.12; 95% CI 0.02-0.68). One case of perforation of the esophagus and one case of glottis edema was registered following banding ligation. One trial reported adverse events following sclerotherapy.[17] Among 43 patients randomized to sclerotherapy, bleeding ulcers were seen for seven patients and esophageal strictures for 2 patients.

Deleted: to

Deleted: [16]

DISCUSSION

The available evidence presented in this review suggests that IsMn used alone or in combination with beta-blockers has no effect on bleeding in primary or secondary prevention of esophageal varices. In secondary prevention, IsMn plus beta-blockers appeared to reduce mortality compared with endoscopic therapy. The potential improved survival benefit did seem related to a reduced risk of bleeding. The combined evidence does not support the use of IsMn for prevention of esophageal varices, but suggests that additional large randomized trials with long term follow up are warranted.

Deleted: present

Deleted: included data from 27 randomized trials on

Deleted: combined

Deleted: or endoscopic therapy for esophageal varices. The combined evidence does not support the use of IsMn as monotherapy. Likewise, the evidence on IsMn combined with beta-blockers is weak. The combined pharmacological therapy had

Deleted: clear

Deleted: mortality or

Deleted: , but seemed to increase the risk of adverse events.

Deleted: reduced

Deleted: alone, but had no clear effect on remaining outcome measures including overall or variceal bleeding. Whether the effect on mortality is

Deleted: beta-blockers or the combination of IsMn and beta-blockers remains to be established.

The need for additional trials is underlined by the identification of reporting bias. Previous studies have found discrepancies between protocols and full paper articles regarding the defined primary and secondary outcomes.[43] We found similar evidence when comparing published protocols, abstracts and full paper articles. Abstracts often report preliminary data, but may also indicate dropouts or withdrawals. We found evidence of losses to follow up based on the comparison between the abstract and full paper article for one of the included trials. Accordingly, performing intention-to-treat analysis in systematic reviews without the original data may be difficult. Access to individual patient data would also make subgroup analyses possible. Questions such as the benefit of IsMn for patients with gastric as well as esophageal varices would have been interesting to analyze. Unfortunately, the available data did not allow such analyses to be done in a reliable manner.

The present review found that IsMn plus beta-blockers reduced mortality compared with endoscopic therapy, but had no clear effect on overall bleeding. This suggests that the medical therapy had beneficial effects not directly related to a reduced risk of bleeding. For beta-blockers, non-hemodynamic effects such as protection against infections may explain our findings.[6,44,45]

The hemodynamic effects of the medical therapy are related to a reduction in the hepatic venous pressure gradient (HVPG). Clinical studies found that the risk of bleeding is considerably reduced when the HVPG is reduced to less than 12 mmHg or by at least 20% compared with baseline values.[46] The effects of beta-blockers on the portal venous inflow include a decrease in cardiac output and splanchnic

Deleted: [42]

Deleted: One

Deleted: trials in

Deleted: present review was registered three days before

Deleted: trial was submitted for publication.

Deleted: [39,40,42] There were only few discrepancies between the protocol and published paper. However, an abstract describing the same trial revealed clear discrepancies in the outcomes, number of patients randomized, and number of events.[41] The value of entering clinical trials in trial registries after their termination date is debatable. If the trial registration number is published along with the trial report, the date of registration should be noted. ¶ ¶ One of the limitations of the present review is that we did not have the individual patient data. Although a number of authors provided us with additional information, we only had access to the published data for most trials. One of the included trials compared IsMn plus beta-blockers and banding ligation versus banding ligation alone.[39] A previously reported abstract describing the same trial suggested that there were several losses to follow up.[41] The number of patients randomized to IsMn plus beta-blockers and banding ligation was higher in the published paper than in the abstract (88 and 79). Conversely, the number of patients randomized to banding ligation was lower in the paper than in the abstract (89 and 92). For both groups, the mortality rates were lower in the paper than in the abstract (combination therapy versus banding ligation full paper article 2/88 and 3/89 and abstract 9/79 and 5/92). Likewise, the bleeding rates were 14/88 versus 16/89 in the published paper and 19/79 versus 20/92 in the published paper. Including data from the abstract had no clear effect on our overall conclusions. Still, the identified discrepancies support the importance of assessing reporting biases when evaluating the results of clinical trials. ¶ ¶

Deleted: [43,

Deleted: [45

vasoconstriction. IsMn decreases the intra-hepatic resistance through vasodilatation. The addition of IsMn to beta-blockers has a synergistic effect on the portal pressure, but no additional effect on the collateral blood flow.[47] Therefore a combination may not translate into a clinical effect on the risk of variceal bleeding.

Sample size calculations are an essential part of the planning of randomized trials. When the calculation is not reported, the reader does not know whether the planned sample size was reached or the trial terminated at an arbitrary time. Two of the trials in the present review were terminated based on concurrent evidence from a concurrent trial suggesting a detrimental effect of the interventions assessed.[25,26] Another trial was planned to include 352 patients, but was terminated after inclusion of 61 patients due to low recruitment rates. Less than one third of included trials reported sample size calculations or achieved the planned size. We cannot exclude that the total number of patients in the individual subgroups was too low to determine intervention effects with sufficient power. The combined considerations suggests that additional trials are warranted before IsMn can be recommended for prevention in esophageal varices.

Deleted: [46]

Deleted: Likewise,

Deleted: reported sample size calculations are essential to the assessment of clinical trials. When sample size calculations are

Deleted: a sample size was performed, whether the required

Deleted: Alternatively, trials may be stopped prematurely based on the preliminary results or accumulating evidence from other trials. In

Deleted: , about one third of the included trials did not report sample size calculations. None of the included trials

Deleted: interim analyses

Deleted: benefit

Deleted: treatments

Deleted: [47]

Deleted: Two were terminated based on concurrent evidence from a trial suggesting a detrimental effect of the interventions assessed.

Deleted: [24,2537] One trial was performed without preliminary sample size calculations size since the authors expected recruitment rates would be insufficient.[28] The trial included 52 patients. Another trial was planned to include 352 patients, but was terminated after inclusion of 61 patients due to low recruitment rates.[36] The reported sample size calculation for one of the included single centre trials included 137 patients although the planned size was only 120 patients.[33] The authors do not describe whether the trial was continued beyond the planned size due to unexpectedly low event rates or for some other reason. Accordingly, the total number of trials that reported sample size calculations and achieved the required sample size was lower than one third. The benefit of performing a systematic review is that the statistical power of the overall conclusions is increased. The limitation of the review process is that individual patient data are rarely available. Although we found no evidence of statistical heterogeneity, the inclusion criteria and trial settings suggested that clinical heterogeneity was present. Likewise, since we only had access to the published data from most trials, we were unable to ensure adequate bias control. Likewise, although we attempted to perform intention to treat analyses, based on the available data, we were unable to ensure that all patients randomized had actually been included in our analyses. These combined considerations support additional trials to assess the effect of IsMn for esophageal varices. ¶

CONFLICT OF INTEREST

Author contributions: study concept and design: L.Gluud and A. Krag. Data extraction, analysis and interpretation of data: L.Gluud, E. Langholz, A. Krag. Drafting of the review: L. Gluud. All authors have read and approved the paper.

Financial support: this study received no external funding

Potential competing interests: there were no conflicts of interest.

Formatted: Normal, Line spacing: single

Table 1. Table of Included Randomized Trials

Trials on Pharmacological Therapy in Primary Prevention	
Garcia-Pagan et al[8]	IsMn versus placebo.
Angelico et al[20]	IsMn versus propranolol.
Borroni et al[29]	IsMn versus nadolol.
D'Amico et al[25]	IsMn plus nadolol versus placebo plus nadolol.
Garcia-Pagan et al	IsMn plus propranolol versus placebo plus propranolol.
Merkel et al	IsMn plus nadolol versus placebo plus nadolol.
Deplano et al[27]	IsMn plus nadolol versus nadolol.*
Trials on Pharmacological and Endoscopic Therapy in Primary Prevention	
Wang et al[37]	IsMn plus nadolol versus banding ligation.
Lui et al[30]	IsMn versus propranolol versus banding ligation.
Abdelfattah et al[21]	IsMn versus propranolol versus banding ligation.*
Abulfutuh et al[33]	IsMn versus propranolol versus

Deleted: Trial
Deleted: Treatment comparis... [1]
Formatted ... [2]
Deleted: Abstract
Formatted ... [3]
Formatted ... [4]
Deleted: Abdelfattah
Field Code Changed ... [5]
Formatted ... [6]
Deleted: versus banding ligat... [7]
Deleted: Abulfutuh
Field Code Changed ... [8]
Deleted: [32]
Formatted ... [9]
Deleted: propranolol versus I... [10]
Formatted ... [11]
Formatted ... [12]
Formatted ... [13]
Deleted: Agrawal…[2723] ... [14]
Formatted ... [15]
Deleted: banding ligation for ... [16]
Formatted ... [17]
Deleted: Deplano…[269] ... [18]
Formatted ... [19]
Deleted: for primary prevention.
Formatted ... [20]
Deleted: Patti
Field Code Changed ... [21]
Deleted: [25]
Formatted ... [22]
Deleted: placebo plus
Formatted ... [23]
Deleted: for secondary prevention.
Formatted ... [24]
Deleted: Shiha
Field Code Changed ... [25]
Deleted: [34]... [26]
Deleted: for secondary prevention.
Deleted: Full paper articles ... [27]
Field Code Changed ... [28]
Deleted: [38]
Formatted ... [29]
Deleted: plus propranolol
Formatted ... [30]
Deleted: IsMn plus propranolol and
Formatted ... [31]
Deleted: versus banding liga... [32]
Formatted ... [33]
Deleted: Angelico
Field Code Changed ... [34]
Deleted: [19]
Formatted ... [35]
Deleted: for primary prevention.

	banding ligation.*
Trials on Pharmacological Therapy in Secondary Prevention	
Patti et al[26]	IsMn plus nadolol versus placebo plus nadolol.*
Gournay et al	IsMn plus propranolol versus propranolol.
Zhang et al[32]	IsMn plus propranolol versus propranolol.
Trials on Pharmacological and Endoscopic Therapy in Primary Prevention	
Agrawal et al[28]	IsMn plus propranolol versus banding ligation.*
Lo et al[38]	IsMn plus nadolol versus banding ligation.
Patch et al	IsMn plus propranolol versus banding ligation.
Sarin et al	IsMn plus propranolol versus banding ligation.
Villanueva et al[18]	IsMn plus nadolol versus banding ligation.
Villanueva et al[17]	IsMn plus nadolol versus sclerotherapy.

Formatted ... [36]
Deleted: Borroni et al[25]
Deleted: IsMn versus nadolo ... [37]
Formatted ... [38]
Formatted ... [39]
Deleted: D'Amico
Deleted: [24]
Formatted ... [40]
Field Code Changed ... [41]
Deleted: for primary prevention.
Formatted ... [42]
Deleted: Escorsell et al[21] ... [43]
Deleted: [2210]
Formatted ... [44]
Deleted: placebo plus
Formatted ... [45]
Deleted: for primary prevention.
Formatted ... [46]
Deleted: Garcia-Pagan et al[20] ... [47]
Field Code Changed ... [48]
Deleted: [10]
Formatted ... [49]
Deleted: for secondary prevention.
Formatted ... [50]
Deleted: Kumar
Field Code Changed ... [51]
Deleted: [39]
Formatted ... [52]
Deleted: and banding ligation
Formatted ... [53]
Deleted: for secondary prevention.
Formatted ... [54]
Formatted ... [55]
Field Code Changed ... [56]
Deleted: [37]
Formatted ... [57]
Formatted ... [58]
Deleted: for secondary prevention.
Formatted ... [59]
Deleted: Lo
Formatted ... [60]
Deleted: [4031]
Formatted ... [61]
Deleted: nadolol
Formatted ... [62]
Deleted: IsMn plus nadolol and
Formatted ... [63]
Deleted: for secondary prevention.
Formatted ... [64]
Deleted: Lui…[2934] ... [65]
Formatted ... [66]
Deleted: versus
Formatted ... [67]
Deleted: for primary prevention.
Formatted ... [68]
... [69]
Formatted ... [70]
... [71]
Formatted ... [72]
... [73]
Formatted ... [74]
Formatted ... [75]
... [76]
Formatted ... [77]

Romero et al[36]	IsMn plus nadolol versus banding ligation plus sclerotherapy
Escorsell et al[22]	IsMn plus propranolol versus transjugular intrahepatic portosystemic shunt (TIPS) for secondary prevention.
Garcia-Pagan et al	IsMn plus nadolol versus IsMn plus nadolol and banding ligation.
Lo et al	IsMn plus nadolol versus IsMn plus nadolol and banding ligation.
Kumar et al[40]	IsMn plus propranolol and banding ligation versus banding ligation.
Shiha et al[35]	IsMn plus propranolol versus propranolol versus banding ligation.*
Ahmad et al[39]	IsMn plus propranolol versus propranolol versus IsMn plus propranolol and banding ligation versus banding ligation for secondary prevention.

*Abstract

Deleted: [35]
Formatted: French (France)
Deleted: for secondary prevention.
Formatted: French (France)
Deleted: Sarin
Deleted: [33]
Deleted: banding ligation
Deleted: Villanueva
Deleted: [1624]
Formatted: French (France)
Deleted: sclerotherapy for secondary prevention.
Formatted: French (France)
Deleted: Villanueva
Deleted: [1741]
Formatted: French (France)
Formatted: French (France)
Deleted: for secondary prevention
Formatted: French (France)
Deleted: Wang
Field Code Changed
Deleted: [36]
Deleted: nadolol
Deleted: for primary prevention.
Deleted: Zhang
Formatted: French (France)
Field Code Changed
Deleted: [31]
Formatted
Formatted
Deleted: .
Formatted: Font: Times New Roman

Table 2. Random-Effects Meta-Analyses on Variceal Bleeding and Bleeding-Related Mortality in Randomized Trials on Primary and Secondary Prevention.

	Exp*		Ctr*		
Treatment comparison	**n**	**N**	**n**	**N**	**RR (95% CI)**
Variceal bleeding in trials on primary prevention					
IsMn versus placebo	15	67	7	66	2.11 (0.92-4.84)
IsMn versus beta-blockers	44	181	33	193	1.41 (0.94-2.11)
IsMn versus banding ligation	28	124	7	88	2.82 (1.29-6.16)
IsMn plus beta-blockers versus beta-blockers	28	279	38	273	0.71 (0.45-1.13)
IsMn plus beta-blockers versus banding ligation	7	31	3	30	2.26 (0.64-7.93)
Bleeding-related mortality in meta-analyses of trials on primary prevention					
IsMn versus placebo	4	67	1	66	3.94 (0.45-34.33)
IsMn versus beta-blockers	12	146	12	152	1.04 (0.33-3.26)
IsMn versus banding ligation	1	62	2	44	0.35 (0.03-3.79)
IsMn plus beta-blockers versus beta-blockers	11	279	8	273	1.30 (0.52-3.25)
Variceal bleeding in meta-analyses of trials on secondary prevention					
IsMn plus beta-blockers versus beta-blockers	44	141	65	148	0.71 (0.52-0.96)
IsMn plus beta-blockers versus endoscopic therapy	146	445	133	449	1.07 (0.87-1.32)
IsMn plus beta-blockers alone or with banding ligation	60	173	38	177	1.61 (1.14-2.27)

IsMn plus beta-blockers versus TIPS	17	44	6	47	3.03 (1.31-6.98)
IsMn plus beta-blockers and banding ligation versus banding ligation	11	88	11	89	1.01 (0.46-2.21)
Bleeding-related mortality in meta-analyses of trials on primary prevention					
IsMn plus beta-blockers versus beta-blockers	13	99	13	100	1.01 (0.49-2.09)
IsMn plus beta-blockers versus endoscopic therapy	22	299	26	298	0.87 (0.50-1.52)
IsMn plus beta-blockers alone or with banding ligation	11	138	5	140	1.95 (0.71-5.33)
IsMn plus beta-blockers versus TIPS	4	44	3	47	1.42 (0.34-6.01)
IsMn plus beta-blockers and banding ligation versus banding ligation	4	79	1	92	4.66 (0.53-40.82)

*Number of events (n) and patients (N) in the experimental (exp) and control (group).

Table 3. Random Effects Meta-analyses on Adverse Events in Randomized Trials for Primary or Secondary Prevention in Esophageal Varices.

	Exp		Ctr		
Treatment comparison	**n**	**N**	**n**	**N**	**RR (95% CI)**
IsMn versus beta-blockers					
Ascites, 1 trial	12	57	10	61	1.28 (0.60-2.74)
Asthenia or dizziness, 3 trials	15	146	12	152	1.34 (0.66-2.74)
Diarrhea, 1 trial	3	62	0	66	7.44 (0.39-141.26)
Dyspnea, 2 trials	5	89	25	91	0.23 (0.10-0.54)
Heart failure, 1 trial	0	57	2	61	0.21 (0.01-4.36)
Hypotension2 trials	2	84	3	86	0.72 (0.14-3.65)
Impotence, 2 trials	0	84	2	86	0.33 (0.04-3.12)
Insomnia, 1 trial	4	62	3	66	1.42 (0.33-6.09)
Nausea, 1 trial	3	62	4	66	0.80 (0.19-3.42)
Poor memory, 1 trial	0	62	3	66	0.15 (0.01-2.88)
Headache, 1 trial	16	119	0	127	11.69 (1.21-113.15)
IsMn plus beta-blockers versus beta-blockers					
Ascites, 3 trials	29	155	23	152	1.23 (0.74-2.03)
Angina or stroke, 3 trials	5	251	2	250	1.94 (0.48-7.80)
Asthenia or dizziness, 3 trials	21	240	22	240	0.94 (0.53-1.67)
Bradycardia, 3 trials	4	256	7	262	0.67 (0.19-2.35)
Arrhythmia, 1 trial	1	30	0	27	2.71 (0.12-63.84)
Cutaneous reaction, 1 trial	0	175	4	174	0.11 (0.01-2.04)

Dyspnea, 2 trials	4	76	1	76	2.46 (0.33-18.12)
Hypotension, 1 trial	3	30	0	27	6.32 (0.34-117.09)
Hepatic encephalopathy, 1 trial	2	27	4	30	0.56 (0.11-2.80)
Impotence, 1 trial	0	46	1	49	0.35 (0.01-8.49)
Nausea, 1 trial	1	30	0	27	2.71 (0.12-63.84)
Raynaud, 1 trial	0	46	1	49	0.35 (0.01, 8.49)
Headache, 5 trials	56	385	17	363	2.92 (1.77-4.82)
IsMn plus beta-blockers versus endoscopic therapy					
Ascites, 2 trials	59	104	57	103	1.06 (0.85-1.32)
Asthenia or dizziness, 2 trials	14	161	0	155	9.04 (1.69-48.50)
Bradycardia, 2 trials	4	100	0	95	4.55 (0.53-39.28)
Dyspnea, 3 trials	8	160	0	165	6.43 (1.16-35.57)
Headache, 3 trials	16	174	0	174	9.86 (1.81-53.72)
Hypotension, 1 trial	5	51	0	51	11.00 (0.62, 193.90)
Hepatic encephalopathy, 1 trial	44	61	39	60	1.11 (0.87-1.41)
Impotence, 2 trials	2	100	0	95	2.87 (0.30-27.10)
Headache, 3 trials	16	174	0	174	9.86 (1.81-53.72)

*Number of events (n) and patients (N) in the experimental (exp) and control (group).

Reference List

1. de Franchis R, Primignani M. Natural history of portal hypertension in patients with cirrhosis. *Clin Liver Dis* 2001;5:645-663.

2. Merkel C, Zoli M, Siringo S et al. Prognostic indicators of risk for first variceal bleeding in cirrhosis: a multicenter study in 711 patients to validate and improve the North Italian Endoscopic Club (NIEC) index. *Am J Gastroenterol* 2000;95:2915-2920.

3. D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: a meta-analytic review. *Hepatology* 1995;22:332-354.

4. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology* 2007;46:922-938.

5. Garcia-Tsao G, Bosch J, Groszmann RJ. Portal hypertension and variceal bleeding--unresolved issues. Summary of an American Association for the study of liver diseases and European Association for the study of the liver single-topic conference. *Hepatology* 2008;47:1764-1772.

6. Thalheimer U, Bosch J, Burroughs AK. How to prevent varices from bleeding: shades of grey--the case for nonselective beta blockers. *Gastroenterology* 2007;133:2029-2036.

Deleted: References¶

¶
. **1**. . de Franchis R, Primignani M. Natural history of portal hypertension in patients with cirrhosis. *Clin Liver Dis* 2001;5:645-663.¶
. **2**. . Merkel C, Zoli M, Siringo S et al. Prognostic indicators of risk for first variceal bleeding in cirrhosis: a multicenter study in 711 patients to validate and improve the North Italian Endoscopic Club (NIEC) index. *Am J Gastroenterol* 2000;95:2915-2920.¶
. **3**. . D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: a meta-analytic review. *Hepatology* 1995;22:332-354.¶
. **4**. . Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology* 2007;46:922-938.¶
. **5**. . Garcia-Tsao G, Bosch J, Groszmann RJ. Portal hypertension and variceal bleeding--unresolved issues. Summary of an American Association for the study of liver diseases and European Association for the study of the liver single-topic conference. *Hepatology* 2008;47:1764-1772.¶
. **6**. . Thalheimer U, Bosch J, Burroughs AK. How to prevent varices from bleeding: shades of grey--the case for nonselective beta blockers. *Gastroenterology* 2007;133:2029-2036.¶
. **7**. . Gluud LL, Klingenberg S, Nikolova D, Gluud C. Banding ligation versus beta-blockers as primary prophylaxis in esophageal varices: systematic review of randomized trials. *Am J Gastroenterol* 2007;102:2842-2848.¶
. **8**. . Garcia-Pagan JC, Villanueva C, Vila MC et al. Isosorbide mononitrate in the prevention of first variceal bleed in patients who cannot receive beta-blockers. *Gastroenterology* 2001;121:908-914.¶
. **9**. . Merkel C, Marin R, Sacerdoti D et al. Long-term results of a clinical trial of nadolol with or without isosorbide mononitrate for primary prophylaxis of variceal bleeding in cirrhosis. *Hepatology* 2000;31:324-329.¶
. **10**. . Gournay J, Masliah C, Martin T, Perrin D, Galmiche JP. Isosorbide mononitrate and propranolol compared with propranolol alone for the prevention of variceal rebleeding. *Hepatology* 2000;31:1239-1245.¶
. **11**. . Gonzalez R, Zamora J, Gomez-Camarero J, Molinero LM, Banares R, Albillos A. Meta-analysis: Combination endoscopic and drug therapy to prevent variceal reb

... [78]

Formatted: Danish

Formatted: Danish

Formatted: Danish

Formatted: Danish

7. Gluud LL, Klingenberg S, Nikolova D, Gluud C. Banding ligation versus beta-blockers as primary prophylaxis in esophageal varices: systematic review of randomized trials. *Am J Gastroenterol* 2007;102:2842-2848.

8. Garcia-Pagan JC, Villanueva C, Vila MC et al. Isosorbide mononitrate in the prevention of first variceal bleed in patients who cannot receive beta-blockers. *Gastroenterology* 2001;121:908-914.

9. Merkel C, Marin R, Sacerdoti D et al. Long-term results of a clinical trial of nadolol with or without isosorbide mononitrate for primary prophylaxis of variceal bleeding in cirrhosis. *Hepatology* 2000;31:324-329.

10. Gournay J, Masliah C, Martin T, Perrin D, Galmiche JP. Isosorbide mononitrate and propranolol compared with propranolol alone for the prevention of variceal rebleeding. *Hepatology* 2000;31:1239-1245.

11. Gonzalez R, Zamora J, Gomez-Camarero J, Molinero LM, Banares R, Albillos A. Meta-analysis: Combination endoscopic and drug therapy to prevent variceal rebleeding in cirrhosis. *Ann Intern Med* 2008;149:109-122.

12. Ravipati M, Katragadda S, Swaminathan PD, Molnar J, Zarling E. Pharmacotherapy plus endoscopic intervention is more effective than pharmacotherapy or endoscopy alone in the secondary prevention of esophageal variceal bleeding: a meta-analysis of randomized, controlled trials. *Gastrointest Endosc* 2009;70:658-664.

Formatted: Danish
Formatted: Danish
Formatted: Danish
Formatted: Danish

13. Ding SH, Liu J, Wang JP. Efficacy of beta-adrenergic blocker plus 5-isosorbide mononitrate and endoscopic band ligation for prophylaxis of esophageal variceal rebleeding: a meta-analysis. *World J Gastroenterol* 2009;15:2151-2155.

14. Gluud LL. Bias in clinical intervention research. *Am J Epidemiol* 2006;163:493-501.

15. Wood L, Egger M, Gluud LL et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ* 2008;336:601-605.

16. Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *J Clin Epidemiol* 2008;61:64-75.

17. Villanueva C, Balanzo J, Novella MT et al. Nadolol plus isosorbide mononitrate compared with sclerotherapy for the prevention of variceal rebleeding. *N Engl J Med* 1996;334:1624-1629.

18. Villanueva C, Minana J, Ortiz J et al. Endoscopic ligation compared with combined treatment with nadolol and isosorbide mononitrate to prevent recurrent variceal bleeding. *N Engl J Med* 2001;345:647-655.

19. Villanueva C, Aracil C, Colomo A et al. Clinical trial: a randomized controlled study on prevention of variceal rebleeding comparing nadolol + ligation vs.

Formatted: Danish
Formatted: Danish
Formatted: Danish
Formatted: Danish
Formatted: Danish
Formatted: Danish
Formatted: Danish
Formatted: Danish
Formatted: Danish
Formatted: Danish
Formatted: Danish
Formatted: Danish
Formatted: Danish
Formatted: Danish
Formatted: Danish
Formatted: Danish

hepatic venous pressure gradient-guided pharmacological therapy. *Aliment Pharmacol Ther* 2009;29:397-408.

20. Angelico M, Carli L, Piat C, Gentile S, Capocaccia L. Effects of isosorbide-5-mononitrate compared with propranolol on first bleeding and long-term survival in cirrhosis. *Gastroenterology* 1997;113:1632-1639.

21. Abdelfattah MH, Rashed MA, Elfakhry AA, Soliman MA, Shiha GE. Endoscopic variceal ligation versus pharmacologic treatment of primary prophylaxis of variceal bleeding: a randomised study. *J Hepatol* 2001;44:S83.

22. Escorsell A, Banares R, Garcia-Pagan JC et al. TIPS versus drug therapy in preventing variceal rebleeding in advanced cirrhosis: a randomized controlled trial. *Hepatology* 2002;35:385-392.

23. Garcia-Pagan JC, Morillas R, Banares R et al. Propranolol plus placebo versus propranolol plus isosorbide-5-mononitrate in the prevention of a first variceal bleed: a double-blind RCT. *Hepatology* 2003;37:1260-1266.

24. Garcia-Pagan JC, Villanueva C, Albillos A et al. Nadolol plus isosorbide mononitrate alone or associated with band ligation in the prevention of recurrent bleeding: A multicenter randomized controlled trial. *Gut* 2009;58:1144-1150.

25. D'Amico G, Pasta L, Politi F et al. Isosorbide mononitrate with nadolol compared to nadolol alone for prevention of the first bleeding in cirrhosis. A double-blind

placebo-controlled randomised trial. *Gastroenterology International* 2002;15:40-50.

26. Patti R, Pasta L, D'Amico G et al. Isosorbide mononitrate with nadolol compared to nadolol alone for prevention of recurrent bleeding in cirrhosis. A double blind placebo controlled randomized trial. Final report. *J Hepatol* 2001;34:63.

27. Deplano A, Careddu G, Reho A et al. The long-term variceal pressure response to nadolol alone vs. nadolol plus isosorbide mononitrate. *J Hepatol* 2001;34:53.

28. Agrawal SA, Gupta R, Murthy NS, Sarin SK. Comparable efficacy of propranolol plus isosorbide mononitrate and variceal ligation in prevention of variceal rebleed. *J Hepatol* 2002;36:178-179.

29. Borroni G, Salerno F, Cazzaniga M et al. Nadolol is superior to isosorbide mononitrate for the prevention of the first variceal bleeding in cirrhotic patients with ascites. *J Hepatol* 2002;37:315-321.

30. Lui HF, Stanley AJ, Forrest EH et al. Primary prophylaxis of variceal hemorrhage: a randomized controlled trial comparing band ligation, propranolol, and isosorbide mononitrate. *Gastroenterology* 2002;123:735-744.

31. Patch D, Sabin CA, Goulis J et al. A randomized, controlled trial of medical therapy versus endoscopic ligation for the prevention of variceal rebleeding in patients with cirrhosis. *Gastroenterology* 2002;123:1013-1019.

Formatted: Danish
Formatted: Danish
Formatted: Danish
Formatted: Danish
Formatted: Danish
Formatted: Danish
Formatted: Danish
Formatted: Danish

32. Zhang Q, Yuan R, Wang H. The randomized controlled trial of isosorbide mononitrate plus propranolol compared with propranolol alone for the prevention of variceal rebleeding. *Zhonghua Yi Xue Za Zhi* 2002;82:1157-1159.

33. Abulfutuh AR, Morsy A, Solyman AEG et al. Study of variceal band ligation, propranolol and isosorbide mononitrate in the prevention of the first variceal bleeding. *Gastroenterology* 2003;124:A780.

34. Sarin SK, Wadhawan M, Gupta R, Shahi H. Evaluation of endoscopic variceal ligation (EVL) versus propanolol plus isosorbide mononitrate/nadolol (ISMN) in the prevention of variceal rebleeding: comparison of cirrhotic and noncirrhotic patients. *Dig Dis Sci* 2005;50:1538-1547.

35. Shiha G, Menesy A, Seef S, Elfakhry AA, Khalek EA, Khalil N. Endoscopic ligation compared with propranolol and combined isosorbide mononitrates (ISMM) and propranolol to prevent recurrent variceal bleeding: A prospective randomised trial. *Gut* 2005;44:A6.

36. Romero G, Kravetz D, Argonz J et al. Comparative study between nadolol and 5-isosorbide mononitrate vs. endoscopic band ligation plus sclerotherapy in the prevention of variceal rebleeding in cirrhotic patients: a randomized controlled trial. *Aliment Pharmacol Ther* 2006;24:601-611.

37. Wang HM, Lo GH, Chen WC et al. Comparison of endoscopic variceal ligation and nadolol plus isosorbide-5-mononitrate in the prevention of first variceal bleeding in cirrhotic patients. *J Chin Med Assoc* 2006;69:453-460.

Formatted: Danish
Formatted: Danish
Formatted: Danish
Formatted: Danish

38. Lo GH, Chen WC, Lin CK et al. Improved survival in patients receiving medical therapy as compared with banding ligation for the prevention of esophageal variceal rebleeding. *Hepatology* 2008;48:580-587.

39. Ahmad I, Khan AA, Alam A, Butt AK, Shafqat F, Sarwar S. Propranolol, isosorbide mononitrate and endoscopic band ligation - alone or in varying combinations for the prevention of esophageal variceal rebleeding. *J Coll Physicians Surg Pak* 2009;19:283-286.

40. Kumar A, Jha SK, Sharma P et al. Addition of propranolol and isosorbide mononitrate to endoscopic variceal ligation does not reduce variceal rebleeding incidence. *Gastroenterology* 2009;137:892-901.

41. Lo GH, Chen WC, Chan HH et al. A randomized, controlled trial of banding ligation plus drug therapy versus drug therapy alone in the prevention of esophageal variceal rebleeding. *J Gastroenterol Hepatol* 2009;24:982-987.

42. Jha SK, Kumar A, Sharma BC, Sarin SK. Endoscopic Variceal Ligation (EVL) plus Propranolol (P) and Isosorbide Mononitrate (ISMN) versus EVL Alone in Secondary Prophylaxis of Variceal Bleeding: A Prospective RCT. *Hepatology* 2007;46:250A.

43. Dwan K, Altman DG, Arnaiz JA et al. Systematic review of the empirical evidence of study publication bias and outcome reporting bias. *PLoS One* 2008;3:e3081.

Formatted: Danish
Formatted: Danish
Formatted: Danish
Formatted: Danish

44. Bosch J, Berzigotti A, Garcia-Pagan JC, Abraldes JG. The management of portal hypertension: rational basis, available treatments and future options. *J Hepatol* 2008;48 Suppl 1:S68-S92.

45. Senzolo M, Cholongitas E, Burra P et al. Beta-Blockers protect against spontaneous bacterial peritonitis in cirrhotic patients: a meta-analysis. *Liver Int* 2009;29:1189-1193.

46. Feu F, Garcia-Pagan JC, Bosch J et al. Relation between portal pressure response to pharmacotherapy and risk of recurrent variceal haemorrhage in patients with cirrhosis. *Lancet* 1995;346:1056-1059.

47. Garcia-Pagan JC, Feu F, Bosch J, Rodes J. Propranolol compared with propranolol plus isosorbide-5-mononitrate for portal hypertension in cirrhosis. A randomized controlled study. *Ann Intern Med* 1991;114:869-873.

Formatted: Danish
Formatted: Danish
Formatted: Danish
Formatted: Danish

Section/topic	#	Checklist item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; da participants, and interventions; study appraisal and synthesis methods; results; lim implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to parti outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web adc registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limi repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in syste included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independentl for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sour simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including s done at the study or outcome level), and how this information is to be used in any
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, i (e.g., I^2) for each meta-analysis.

Formatted: Font color: Black, English (Canada)

Formatted: Font color: Black, English (Canada)

Formatted: Font color: Black, English (Canada)

Section/topic	#	Checklist item
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e. reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, m which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the revi each stage, ideally with a flow diagram.

Formatted: Font color: Black, English (Canada)

Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study s provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level ass
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simp intervention group (b) effect estimates and confidence intervals, ideally with a fore
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and me
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses,
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main out key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-le identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., sup systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Formatted

Page 2 of 2

Page 17: [1] Deleted **Lise Lotte** **6/26/2010 6:03:00 PM**

Treatment comparison and patient characteristics

Page 17: [2] Formatted **Lise Lotte** **6/26/2010 6:03:00 PM**

Indent: Left: 0 pt

Page 17: [3] Formatted **Unknown**

Font: Not Bold

Page 17: [4] Formatted **Lise Lotte** **6/26/2010 6:03:00 PM**

Normal, Space Before: Auto, After: Auto, Line spacing: single

Page 17: [5] Change **Unknown**

Field Code Changed

Page 17: [6] Formatted **Lise Lotte** **6/26/2010 6:03:00 PM**

Normal, Space Before: Auto, After: Auto, Line spacing: single

Page 17: [7] Deleted **Lise Lotte** **6/26/2010 6:03:00 PM**

versus banding ligation for primary prevention.

Page 17: [8] Change **Unknown**

Field Code Changed

Page 17: [9] Formatted **Lise Lotte** **6/26/2010 6:03:00 PM**

French (France)

Page 17: [10] Deleted **Lise Lotte** **6/26/2010 6:03:00 PM**

propranolol versus banding ligation for primary prevention.

Page 17: [11] Formatted **Lise Lotte** **6/26/2010 6:03:00 PM**

French (France)

Page 17: [12] Formatted **Lise Lotte** **6/26/2010 6:03:00 PM**

Normal, Space Before: Auto, After: Auto, Line spacing: single

Page 17: [13] Formatted **Lise Lotte** **6/26/2010 6:03:00 PM**

French (France)

Page 17: [14] Deleted **Lise Lotte** **6/26/2010 6:03:00 PM**

Agrawal

Page 17: [14] Deleted **Lise Lotte** **6/26/2010 6:03:00 PM**

2723

Page 17: [15] Formatted **Lise Lotte** **6/26/2010 6:03:00 PM**

Font: Arial, French (France)

Page 17: [16] Deleted **Lise Lotte** **6/26/2010 6:03:00 PM**

banding ligation for secondary prevention.

Page 17: [17] Formatted **Unknown**

French (France)

Page 17: [18] Deleted **Lise Lotte** **6/26/2010 6:03:00 PM**

Deplano

Page 17: [18] Deleted **Lise Lotte** **6/26/2010 6:03:00 PM**

269

Page 17: [19] Formatted **Lise Lotte** **6/26/2010 6:03:00 PM**

Font: Arial, French (France)

Page 17: [19] Formatted **Lise Lotte** **6/26/2010 6:03:00 PM**

Font: Arial, French (France)

Page 17: [20] Formatted **Unknown**

French (France)

Page 17: [21] Change **Unknown**

Field Code Changed

Page 17: [22] Formatted **Lise Lotte** **6/26/2010 6:03:00 PM**

Font: Arial, French (France)

Page 17: [23] Formatted **Lise Lotte** **6/26/2010 6:03:00 PM**

Font: Arial, French (France)

Page 17: [24] Formatted **Unknown**

French (France)

Page 17: [25] Change **Unknown**

Field Code Changed

Page 17: [26] Deleted **Lise Lotte** **6/26/2010 6:03:00 PM**

34

Page 17: [26] Deleted **Lise Lotte** **6/26/2010 6:03:00 PM**

plus propranolol

Page 17: [27] Deleted **Lise Lotte** **6/26/2010 6:03:00 PM**

Full paper articles	
AhmadAbdelfattah et al[3821]	IsMn plus propranolol versus propranolol versus IsMn plus propranolol and banding ligation versus banding ligation for secondary prevention.*

Page 17: [28] Change	Unknown	
Field Code Changed		
Page 17: [29] Formatted	**Lise Lotte**	**6/26/2010 6:03:00 PM**
French (France)		
Page 17: [30] Formatted	**Lise Lotte**	**6/26/2010 6:03:00 PM**
French (France)		
Page 17: [31] Formatted	**Lise Lotte**	**6/26/2010 6:03:00 PM**
French (France)		
Page 17: [32] Deleted	**Lise Lotte**	**6/26/2010 6:03:00 PM**
versus banding ligation for secondary prevention		
Page 17: [33] Formatted	**Unknown**	
French (France)		
Page 17: [34] Change	**Unknown**	
Field Code Changed		
Page 17: [35] Formatted	**Lise Lotte**	**6/26/2010 6:03:00 PM**
French (France)		
Page 18: [36] Formatted	**Lise Lotte**	**6/26/2010 6:03:00 PM**

Font: Times New Roman, French (France)

Page 18: [37] Deleted	Lise Lotte	6/26/2010 6:03:00 PM

IsMn versus nadolol for primary prevention.

Page 18: [38] Formatted	Lise Lotte	6/26/2010 6:03:00 PM

Indent: Left: 0 pt

Page 18: [39] Formatted	Lise Lotte	6/26/2010 6:03:00 PM

Font: Bold

Page 18: [40] Formatted	Lise Lotte	6/26/2010 6:03:00 PM

French (France)

Page 18: [41] Change	Unknown

Field Code Changed

Page 18: [42] Formatted	Unknown

French (France)

Page 18: [43] Deleted	Lise Lotte	6/26/2010 6:03:00 PM

Escorsell et al[21]	IsMn plus beta-blocker (propranolol) versus transjugular intrahepatic portosystemic shunt (TIPS) for secondary prevention.
Garcia-Pagan et al[8]	IsMn versus placebo for primary prevention.
Garcia-PaganGournay	IsMn plus propranolol versus placebo plus

et al[2210]	propranolol for primary prevention..

Page 18: [44] Formatted **Lise Lotte** **6/26/2010 6:03:00 PM**

French (France)

Page 18: [45] Formatted **Lise Lotte** **6/26/2010 6:03:00 PM**

French (France)

Page 18: [46] Formatted **Unknown**

French (France)

Page 18: [47] Deleted **Lise Lotte** **6/26/2010 6:03:00 PM**

Garcia-Pagan et al[23]	IsMn plus nadolol versus IsMn plus nadolol and banding ligation for secondary prevention.
GournayZhang et al[1032]	IsMn plus propranolol versus propranolol for secondary prevention..

Page 18: [48] Change **Unknown**

Field Code Changed

Page 18: [49] Formatted **Lise Lotte** **6/26/2010 6:03:00 PM**

French (France)

Page 18: [50] Formatted **Unknown**

French (France)

Page 18: [51] Change **Unknown**

Field Code Changed

Page 18: [52] Formatted **Lise Lotte** **6/26/2010 6:03:00 PM**

French (France)

Page 18: [53] Formatted **Lise Lotte** **6/26/2010 6:03:00 PM**

French (France)

Page 18: [54] Formatted **Unknown**

French (France)

Page 18: [55] Formatted **Lise Lotte** **6/26/2010 6:03:00 PM**

French (France)

Page 18: [56] Change **Unknown**

Field Code Changed

Page 18: [57] Formatted **Unknown**

French (France)

Page 18: [58] Formatted **Lise Lotte** **6/26/2010 6:03:00 PM**

French (France)

Page 18: [59] Formatted **Unknown**

French (France)

Page 18: [60] Formatted **Lise Lotte** **6/26/2010 6:03:00 PM**

French (France)

Page 18: [61] Formatted **Lise Lotte** **6/26/2010 6:03:00 PM**

French (France)

Page 18: [62] Formatted **Lise Lotte** **6/26/2010 6:03:00 PM**

French (France)

Page 18: [63] Formatted **Lise Lotte** **6/26/2010 6:03:00 PM**

French (France)

Page 18: [64] Formatted **Unknown**

French (France)

Page 18: [65] Deleted **Lise Lotte** **6/26/2010 6:03:00 PM**

Lui

Page 18: [65] Deleted **Lise Lotte** **6/26/2010 6:03:00 PM**

2934

Page 18: [66] Formatted **Lise Lotte** **6/26/2010 6:03:00 PM**

French (France)

Page 18: [67] Formatted **Lise Lotte** **6/26/2010 6:03:00 PM**

French (France)

Page 18: [68] Formatted **Unknown**

French (France)

Page 18: [69] Deleted **Lise Lotte** **6/26/2010 6:03:00 PM**

Merkel

Page 18: [69] Deleted **Lise Lotte** **6/26/2010 6:03:00 PM**

9

Page 18: [70] Formatted **Lise Lotte** **6/26/2010 6:03:00 PM**

French (France)

Page 18: [71] Deleted **Lise Lotte** **6/26/2010 6:03:00 PM**

placebo plus nadolol for primary prevention.

Page 18: [72] Formatted	Unknown	

French (France)

Page 18: [73] Deleted	Lise Lotte	6/26/2010 6:03:00 PM

Patch

Page 18: [73] Deleted	Lise Lotte	6/26/2010 6:03:00 PM

30

Page 18: [74] Formatted	Lise Lotte	6/26/2010 6:03:00 PM

French (France)

Page 18: [75] Formatted	Lise Lotte	6/26/2010 6:03:00 PM

French (France)

Page 18: [76] Deleted	Lise Lotte	6/26/2010 6:03:00 PM

banding ligation for secondary prevention.

Page 18: [77] Formatted	Unknown	

French (France)

Page 24: [78] Deleted	Lise Lotte	6/26/2010 6:03:00 PM

References

1. de Franchis R, Primignani M. Natural history of portal hypertension in patients with cirrhosis. *Clin Liver Dis* 2001;5:645-663.

2. Merkel C, Zoli M, Siringo S et al. Prognostic indicators of risk for first variceal bleeding in cirrhosis: a multicenter study in 711 patients to validate and improve the North Italian Endoscopic Club (NIEC) index. *Am J Gastroenterol* 2000;95:2915-2920.

3. D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: a meta-analytic review. *Hepatology* 1995;22:332-354.

4. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology* 2007;46:922-938.

5. Garcia-Tsao G, Bosch J, Groszmann RJ. Portal hypertension and variceal bleeding--unresolved issues. Summary of an American Association for the study of liver diseases and European Association for the study of the liver single-topic conference. *Hepatology* 2008;47:1764-1772.

6. Thalheimer U, Bosch J, Burroughs AK. How to prevent varices from bleeding: shades of grey--the case for nonselective beta blockers. *Gastroenterology* 2007;133:2029-2036.

7. Gluud LL, Klingenberg S, Nikolova D, Gluud C. Banding ligation versus beta-blockers as primary prophylaxis in esophageal varices: systematic review of randomized trials. *Am J Gastroenterol* 2007;102:2842-2848.

8. Garcia-Pagan JC, Villanueva C, Vila MC et al. Isosorbide mononitrate in the prevention of first variceal bleed in patients who cannot receive beta-blockers. *Gastroenterology* 2001;121:908-914.

9. Merkel C, Marin R, Sacerdoti D et al. Long-term results of a clinical trial of nadolol with or without isosorbide mononitrate for primary prophylaxis of variceal bleeding in cirrhosis. *Hepatology* 2000;31:324-329.

10. Gournay J, Masliah C, Martin T, Perrin D, Galmiche JP. Isosorbide mononitrate and propranolol compared with propranolol alone for the prevention of variceal rebleeding. *Hepatology* 2000;31:1239-1245.

11. Gonzalez R, Zamora J, Gomez-Camarero J, Molinero LM, Banares R, Albillos A. Meta-analysis: Combination endoscopic and drug therapy to prevent variceal rebleeding in cirrhosis. *Ann Intern Med* 2008;149:109-122.

12. Ravipati M, Katragadda S, Swaminathan PD, Molnar J, Zarling E. Pharmacotherapy plus endoscopic intervention is more effective than pharmacotherapy or endoscopy alone in the secondary prevention of esophageal variceal bleeding: a meta-analysis of randomized, controlled trials. *Gastrointest Endosc* 2009;70:658-664.

13. Ding SH, Liu J, Wang JP. Efficacy of beta-adrenergic blocker plus 5-isosorbide mononitrate and endoscopic band ligation for prophylaxis of esophageal variceal rebleeding: a meta-analysis. *World J Gastroenterol* 2009;15:2151-2155.

14. Gluud LL. Bias in clinical intervention research. *Am J Epidemiol* 2006;163:493-501.

15. Wood L, Egger M, Gluud LL et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ* 2008;336:601-605.

16. Villanueva C, Balanzo J, Novella MT et al. Nadolol plus isosorbide mononitrate compared with sclerotherapy for the prevention of variceal rebleeding. *N Engl J Med* 1996;334:1624-1629.

17. Villanueva C, Minana J, Ortiz J et al. Endoscopic ligation compared with combined treatment with nadolol and isosorbide mononitrate to prevent recurrent variceal bleeding. *N Engl J Med* 2001;345:647-655.

18. Villanueva C, Aracil C, Colomo A et al. Clinical trial: a randomized controlled study on prevention of variceal rebleeding comparing nadolol + ligation vs. hepatic venous pressure gradient-guided pharmacological therapy. *Aliment Pharmacol Ther* 2009;29:397-408.

19. Angelico M, Carli L, Piat C, Gentile S, Capocaccia L. Effects of isosorbide-5-mononitrate compared with propranolol on first bleeding and long-term survival in cirrhosis. *Gastroenterology* 1997;113:1632-1639.

20. Abdelfattah MH, Rashed MA, Elfakhry AA, Soliman MA, Shiha GE. Endoscopic variceal ligation versus pharmacologic treatment of primary prophylaxis of variceal bleeding: a randomised study. *J Hepatol* 2001;44:S83.

21. Escorsell A, Banares R, Garcia-Pagan JC et al. TIPS versus drug therapy in preventing variceal rebleeding in advanced cirrhosis: a randomized controlled trial. *Hepatology* 2002;35:385-392.

22. Garcia-Pagan JC, Morillas R, Banares R et al. Propranolol plus placebo versus propranolol plus isosorbide-5-mononitrate in the prevention of a first variceal bleed: a double-blind RCT. *Hepatology* 2003;37:1260-1266.

23. Garcia-Pagan JC, Villanueva C, Albillos A et al. Nadolol plus isosorbide mononitrate alone or associated with band ligation in the prevention of recurrent bleeding: A multicenter randomized controlled trial. *Gut* 2009;58:1144-1150.

24. D'Amico G, Pasta L, Politi F et al. Isosorbide mononitrate with nadolol compared to nadolol alone for prevention of the first bleeding in cirrhosis.

A double-blind placebo-controlled randomised trial. *Gastroenterology International* 2002;15:40-50.

25. Patti R, Pasta L, D'Amico G et al. Isosorbide mononitrate with nadolol compared to nadolol alone for prevention of recurrent bleeding in cirrhosis. A double blind placebo controlled randomized trial. Final report. *J Hepatol* 2001;34:63.

26. Deplano A, Careddu G, Reho A et al. The long-term variceal pressure response to nadolol alone vs. nadolol plus isosorbide mononitrate. *J Hepatol* 2001;34:53.

27. Agrawal SA, Gupta R, Murthy NS, Sarin SK. Comparable efficacy of propranolol plus isosorbide mononitrate and variceal ligation in prevention of variceal rebleed. *J Hepatol* 2002;36:178-179.

28. Borroni G, Salerno F, Cazzaniga M et al. Nadolol is superior to isosorbide mononitrate for the prevention of the first variceal bleeding in cirrhotic patients with ascites. *J Hepatol* 2002;37:315-321.

29. Lui HF, Stanley AJ, Forrest EH et al. Primary prophylaxis of variceal hemorrhage: a randomized controlled trial comparing band ligation, propranolol, and isosorbide mononitrate. *Gastroenterology* 2002;123:735-744.

30. Patch D, Sabin CA, Goulis J et al. A randomized, controlled trial of medical therapy versus endoscopic ligation for the prevention of variceal rebleeding in patients with cirrhosis. *Gastroenterology* 2002;123:1013-1019.

31. Zhang Q, Yuan R, Wang H. The randomized controlled trial of isosorbide mononitrate plus propranolol compared with propranolol alone for the prevention of variceal rebleeding. *Zhonghua Yi Xue Za Zhi* 2002;82:1157-1159.

32. Abulfutuh AR, Morsy A, Solyman AEG et al. Study of variceal band ligation, propranolol and isosorbide mononitrate in the prevention of the first variceal bleeding. *Gastroenterology* 2003;124:A780.

33. Sarin SK, Wadhawan M, Gupta R, Shahi H. Evaluation of endoscopic variceal ligation (EVL) versus propanolol plus isosorbide mononitrate/nadolol (ISMN) in the prevention of variceal rebleeding: comparison of cirrhotic and noncirrhotic patients. *Dig Dis Sci* 2005;50:1538-1547.

34. Shiha G, Menesy A, Seef S, Elfakhry AA, Khalek EA, Khalil N. Endoscopic ligation compared with propranolol and combined isosorbide mononitrates (ISMM) and propranolol to prevent recurrent variceal bleeding: A prospective randomised trial. *Gut* 2005;44:A6.

35. Romero G, Kravetz D, Argonz J et al. Comparative study between nadolol and 5-isosorbide mononitrate vs. endoscopic band ligation plus sclerotherapy in the prevention of variceal rebleeding in cirrhotic patients: a randomized controlled trial. *Aliment Pharmacol Ther* 2006;24:601-611.

36. Wang HM, Lo GH, Chen WC et al. Comparison of endoscopic variceal ligation and nadolol plus isosorbide-5-mononitrate in the prevention of first variceal bleeding in cirrhotic patients. *J Chin Med Assoc* 2006;69:453-460.

37. Lo GH, Chen WC, Lin CK et al. Improved survival in patients receiving medical therapy as compared with banding ligation for the prevention of esophageal variceal rebleeding. *Hepatology* 2008;48:580-587.

38. Ahmad I, Khan AA, Alam A, Butt AK, Shafqat F, Sarwar S. Propranolol, isosorbide mononitrate and endoscopic band ligation - alone or in varying combinations for the prevention of esophageal variceal rebleeding. *J Coll Physicians Surg Pak* 2009;19:283-286.

39. Kumar A, Jha SK, Sharma P et al. Addition of propranolol and isosorbide mononitrate to endoscopic variceal ligation does not reduce variceal rebleeding incidence. *Gastroenterology* 2009;137:892-901.

40. Lo GH, Chen WC, Chan HH et al. A randomized, controlled trial of banding ligation plus drug therapy versus drug therapy alone in the

prevention of esophageal variceal rebleeding. *J Gastroenterol Hepatol* 2009;24:982-987.

41. Jha SK, Kumar A, Sharma BC, Sarin SK. Endoscopic Variceal Ligation (EVL) plus Propranolol (P) and Isosorbide Mononitrate (ISMN) versus EVL Alone in Secondary Prophylaxis of Variceal Bleeding: A Prospective RCT. *Hepatology* 2007;46:250A.

42. Dwan K, Altman DG, Arnaiz JA et al. Systematic review of the empirical evidence of study publication bias and outcome reporting bias. *PLoS One* 2008;3:e3081.

43. Bosch J, Berzigotti A, Garcia-Pagan JC, Abraldes JG. The management of portal hypertension: rational basis, available treatments and future options. *J Hepatol* 2008;48 Suppl 1:S68-S92.

44. Senzolo M, Cholongitas E, Burra P et al. Beta-Blockers protect against spontaneous bacterial peritonitis in cirrhotic patients: a meta-analysis. *Liver Int* 2009;29:1189-1193.

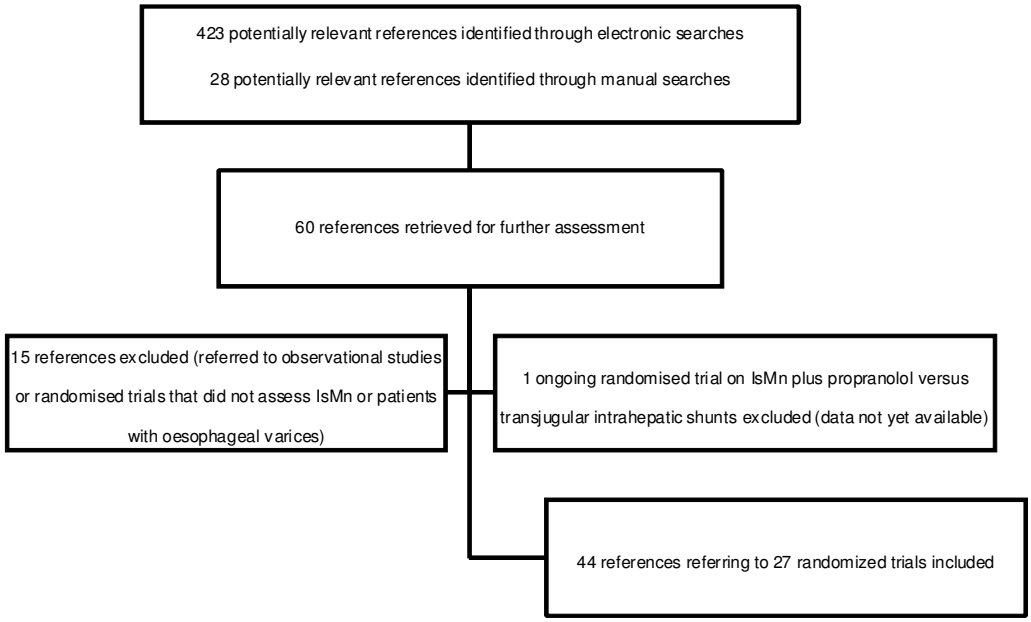
45. Feu F, Garcia-Pagan JC, Bosch J et al. Relation between portal pressure response to pharmacotherapy and risk of recurrent variceal haemorrhage in patients with cirrhosis. *Lancet* 1995;346:1056-1059.

46. Garcia-Pagan JC, Feu F, Bosch J, Rodes J. Propranolol compared with propranolol plus isosorbide-5-mononitrate for portal hypertension in cirrhosis. A randomized controlled study. *Ann Intern Med* 1991;114:869-873.

47. Briel M, Lane M, Montori VM et al. Stopping randomized trials early for benefit: a protocol of the Study Of Trial Policy Of Interim Truncation-2 (STOPIT-2). *Trials* 2009;10:49.

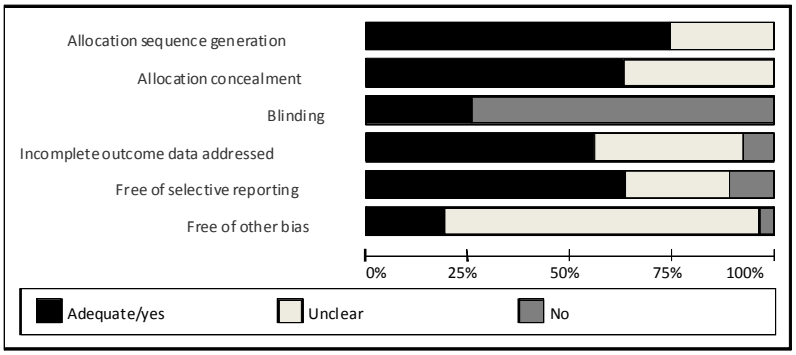
Page Break

Figure 1 Flow chart of trials



Page Break

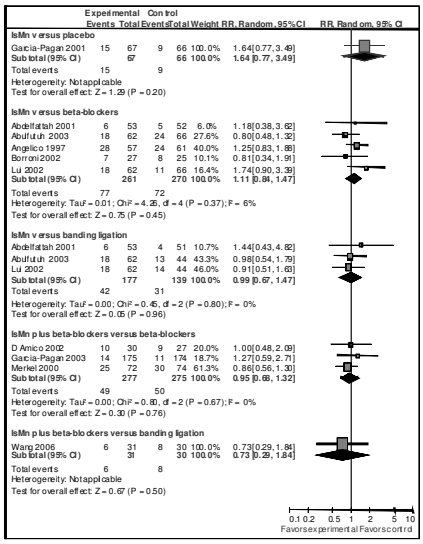
Figure 2 Bias assessment of randomized trials



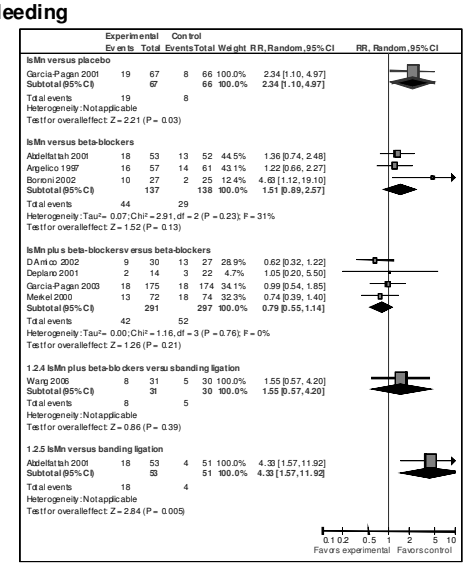
Page Break

Figure 3 Random effect meta-analyses of randomized trials on IsMn alone or with beta-blockers or endoscopic therapy for primary prevention in variceal bleeding

Mortality



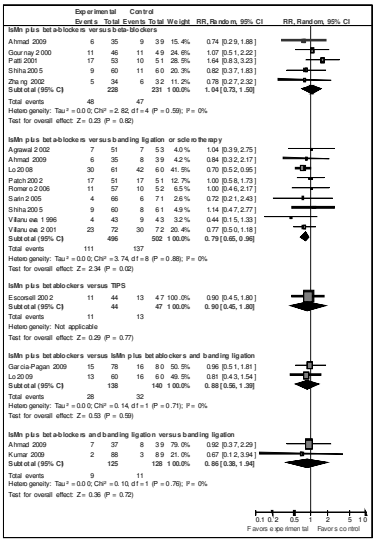
Bleeding



Page Break

Figure 4 Random effect meta-analyses of randomized trials on IsMn alone or with beta-blockers or endoscopic therapy for secondary prevention in variceal bleeding

Mortality



Bleeding

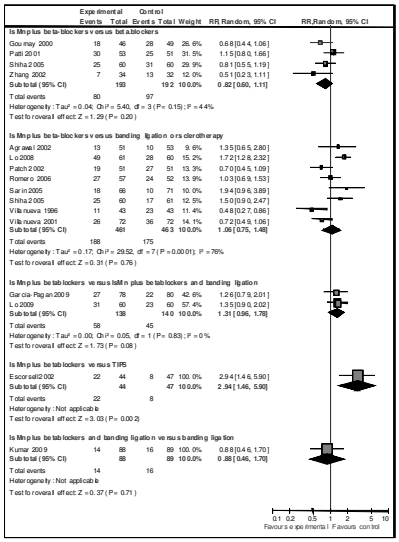


Figure 1 Flow chart of trials

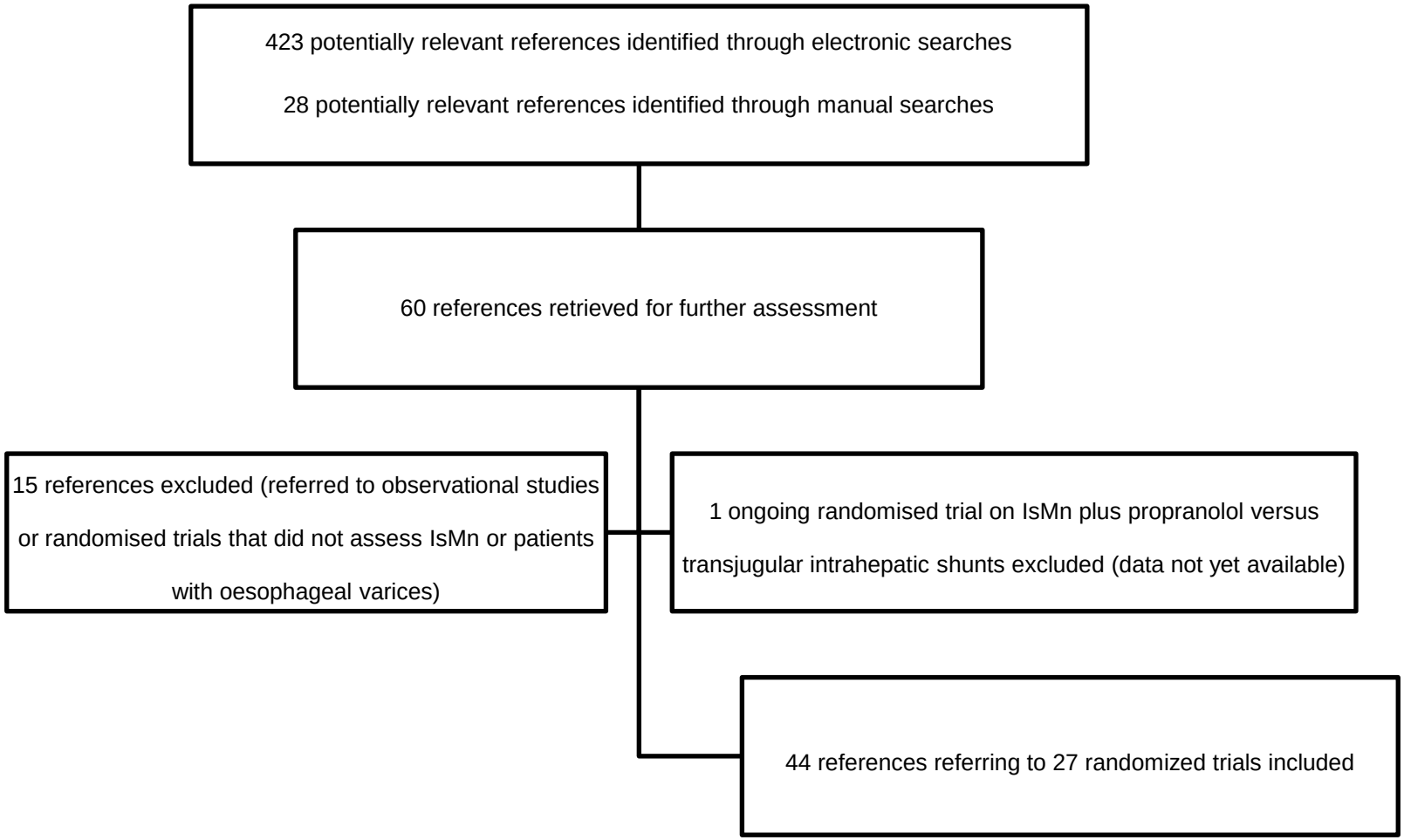


Figure 2 Bias assessment of randomized trials

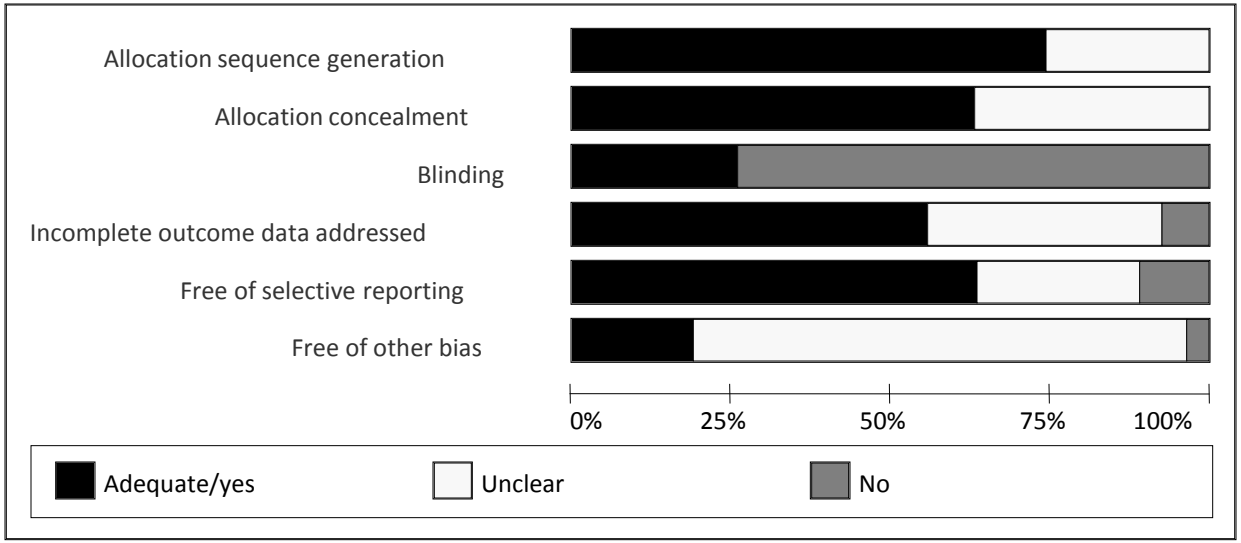


Figure 3 Random effect meta-analyses of mortality in randomized trials on IsMn alone or with beta-blockers or endoscopic therapy for primary prevention in esophageal varices.

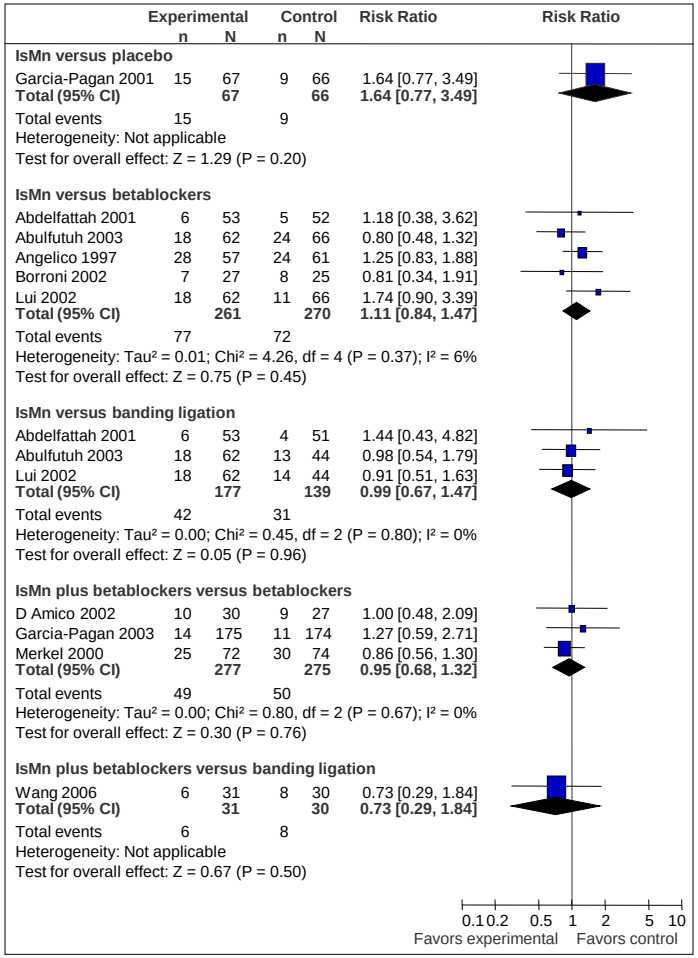


Figure 4 Random effect meta-analyses of bleeding in randomized trials on IsMn alone or with beta-blockers or endoscopic therapy for primary prevention in esophageal varices.

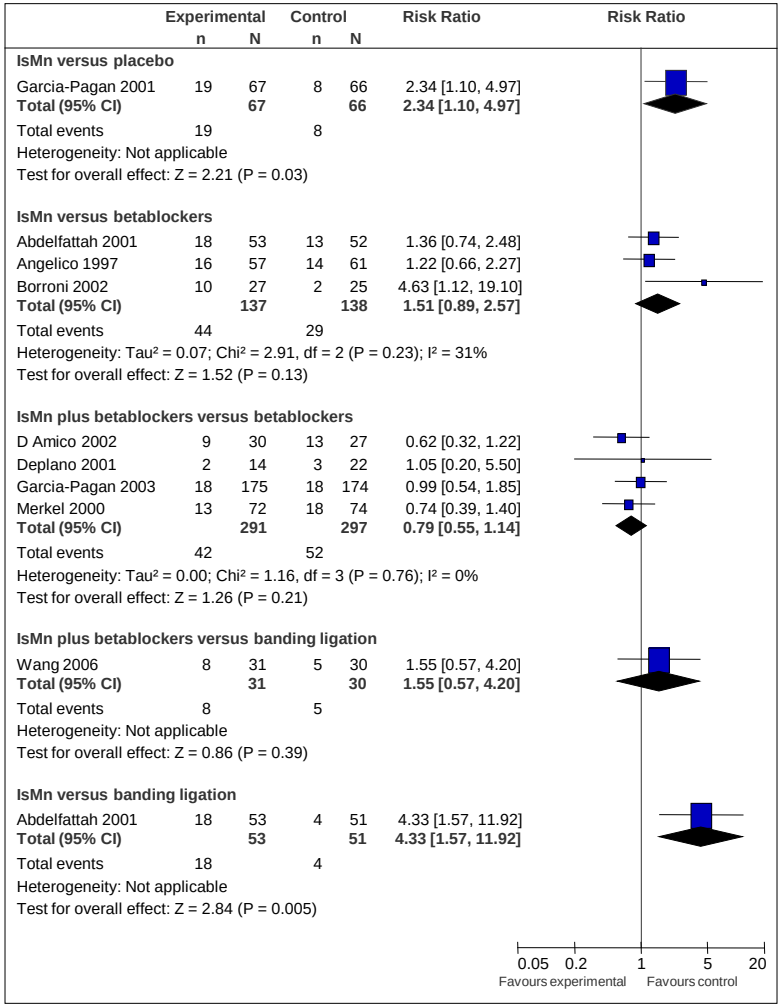


Figure 5 Random effect meta-analyses of mortality in randomized trials on IsMn alone or with beta-blockers or endoscopic therapy for secondary prevention in esophageal varices.

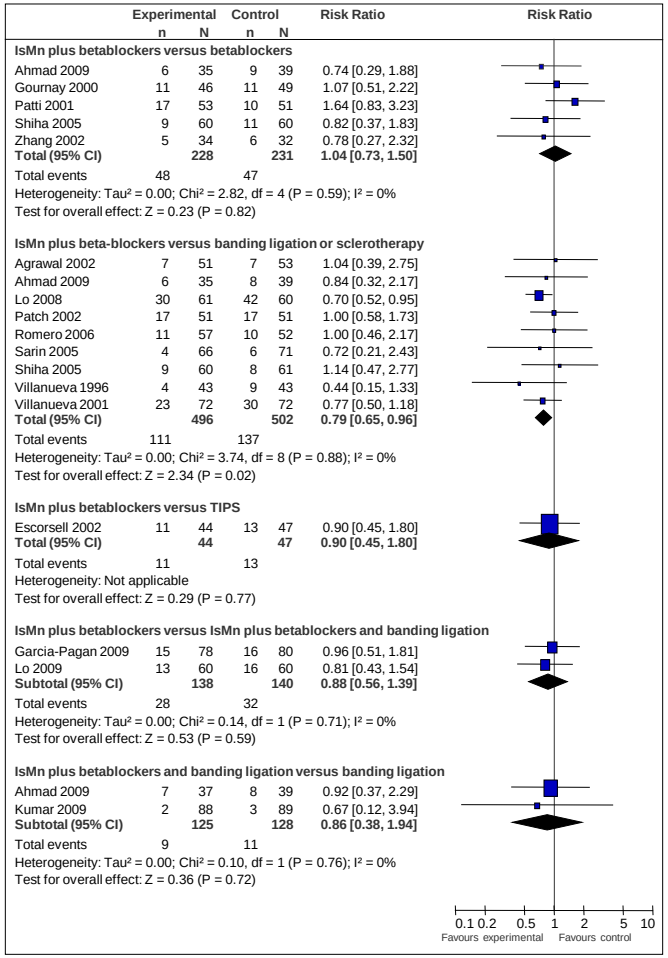
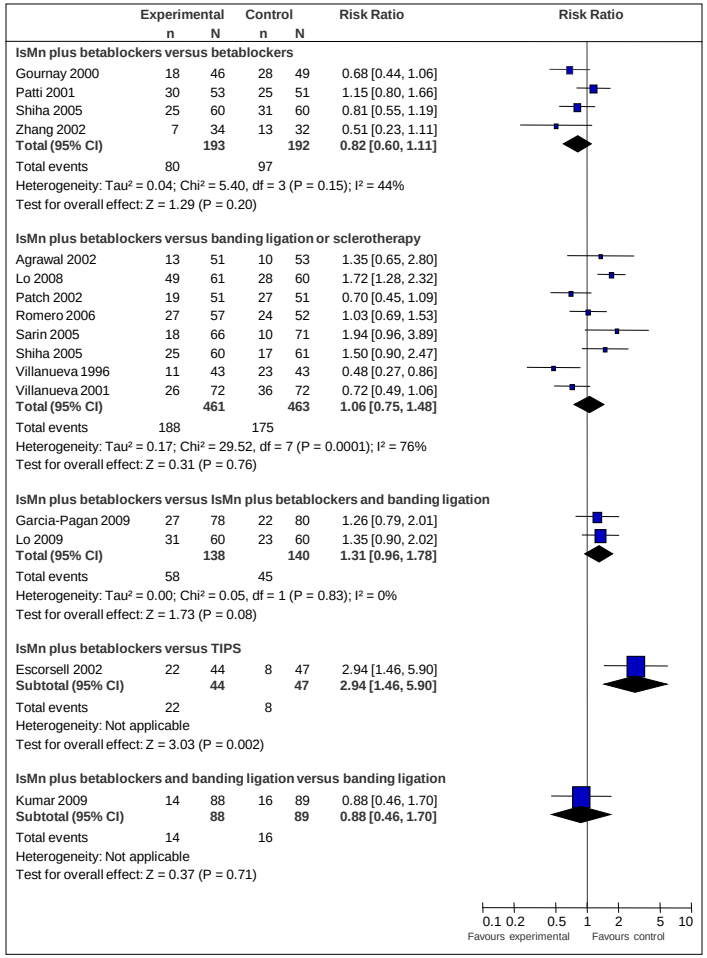


Figure 5 Random effect meta-analyses of bleeding in randomized trials on IsMn alone or with beta-blockers or endoscopic therapy for secondary prevention in esophageal varices.



09/06/2010

APT-0303-2010 Reply with point-to-point responses and corresponding revisions to submitted paper

Dear Professor Fennerty

We are grateful for the opportunity to resubmit our paper entitled Systematic Review with Meta-Analyses of Randomized Trials on Isosorbide-Mononitrate Alone or With Beta-Blockers or Endoscopic Therapy for Esophageal Varices to Alimentary Pharmachology & Therapeutics. We found that the peer review comments were very thorough and helpful and have included a letter specifying our point to point replies and corresponding revisions in the paper.

Yours sincerely

Lise Lotte Gluud

EDITOR'S COMMENTS TO AUTHOR:

REVIEWERS' COMMENTS TO AUTHOR:

Reviewer: 1
Comments for Transmission to the Authors

Gluud and colleagues present a comprehensive systematic review of meta-analyses of randomised trials of isosorbide mononitrate alone or in combination with beta blockers in the primary and secondary prevention of bleeding from oesphageal varices. To this effect, 10 trials were included on primary prevention and 17 on secondary prevention of bleeding/re-bleeding. The authors found a number of deficiencies in the published trials including bias and a clear lack of adequate power calculations to assess sample sizes needed to demonstrate differences in mortality and bleeding rates. No apparent effect was found on mortality alone, or in combination with beta blockers. When compared with endoscopic therapy alone the combination of isosorbide and beta blockers did seem to reduce mortality but this was not due to a reduction in overall bleeding.

There is no doubt that these authors have great experience in the performance of high quality meta-analyses and systematic review in collaboration with the Cochrane

Hepatobiliary Trials Group; systematic review offering the highest level of evidence when judging the merits of an individual therapy. It is therefore difficult to criticise their robust methodology and statistical expertise.

I have just a few comments to make.

I find the concluding statement in the abstract and discussion overall to be non-specific and unhelpful. Readers are looking for guidance on 'which side of the fence to sit' and I would therefore suggest that the authors revise their concluding statements to the effect of: 'Based on the current evidence base, isosorbide mononitrate used alone or in combination with beta blockers does not offer any reduction in bleeding in the primary or secondary prevention of oesphageal varices. Compared to endoscopic therapy, there may be a survival advantage to using isosorbide mononitrate in combination with beta blockers but this is not directly related to a reduction in bleeding'..... 'Further large multicentre trials comparing combined pharmacological therapy with isosorbide mononitrate and non-specific beta blockers may therefore be warranted. **Reply: we agree and have changed the wording of our conclusion as suggested.**

I found it very difficult to 'wade through' this manuscript and to differentiate the large number of trials listed in the manuscript body and tables. Can the manuscript be shortened or simplified in any way to help the reader make sense of the data? **Reply: we acknowledge the problem and have done our best to abbreviate the text and clarify the results.**

This systematic review focuses on oesphageal varices but how many of the included trials had patients with gastric varices as well that may or may not have bled? Were gastric varices an exclusion in any of the trials that were included? Moreover, does isosorbide mononitrate offer any advantage/disadvantage in the management of gastric varices over and above oesphageal varices? **Reply: this is a very good question, which we – unfortunately- are unable to analyse sufficiently. One trial on primary prevention (Garcia-Pagan 2003) included patients with esophageal or gastric varices, but did not report the proportion of patients in the two groups or stratified results for patients with esophageal or gastric varices. One trial on pharmaceutical therapy and sclerotherapy (Romero 2006) excluded patients with gastric fundal varices. Other trials on pharmaceutical end endoscopic therapy (Lui 2002; Sarin 2005; Wang 2006;) included patients included patients with esophageal varices irrespective of whether gastric varices were also present. The proportion with gastric varices in these trials ranged from about 7% to 50%. Most trials did not report the proportion of patients with gastric varices and we were unable to identify data allowing us to perform a subgroup analysis. Additional research seems necessary to determine this question, which has now been addressed in the discussion section.**

What is the relevance of comparing data in abstracts and full published papers of the same trial? Abstracts generally report the preliminary data (which is sometimes prepared in a hurry for conference deadlines) of a trial that may not have been fully completed or been subjected to a thorough final analysis by all authors. **Reply: although abstract present preliminary data, they should be considered in systematic reviews. Previous studies have shown that trials are more likely published if the results are statistically significant. Trials without significant results are more likely to remain unpublished or to be published in abstract form only. Excluding abstracts in systematic reviews may lead to overestimated intervention benefits. On the other hand, as found in the present work, abstracts may present preliminary data. A lower number of events in the abstract is likely to reflect shorter follow up compared with the subsequent full paper article making the data presented in the abstract less interesting. However, if a higher number of events of patients are reported in the abstract, this may help us identify losses to follow up in order to perform intention to treat analyses. These aspects are now clarified in the paper.**

I could not read Figures 3 and 4 which were very small and poorly transcribed onto the pdf provided. **Reply: we have changed the format of the figures and hope that they now read better.**

Minor Comments:
Page 3, line 25. I think it would read better if 'Still, the prognosis remains severe' was replaced with 'Still, the prognosis remains poor'. **Reply: we have changed the sentence as suggested.**
Page 4, line 8. I think the last line of the introduction would read better as...' Accordingly, we performed a systematic review of randomised trials to evaluate the strength of the evidence on IsMn alone or in combination with beta blockers or endoscopic therapy for the primary or secondary prevention of bleeding in patients with oesphageal varices.' **Reply: we have changed the sentence as suggested.**
Page 5, line 38. The last sentence does not make sense. Please remove the word 'was'. **Reply: we have changed the wording of the sentence.**
Table 1 - Can the studies be listed by treatment comparison rather than be listed in alphabetical order. Even better, can headings of the different comparisons be put at the top of a grid table with ticks for each study where applicable. This will make it easier for the reader to interpret. **Reply: we have made several changes to the tables to make them easier to read.**
Page 12, lines 25-27 does not make sense. Should it read 'The trial compared IsMn, beta blockers and banding ligation versus banding ligation alone. No differences between the two treatment arms were seen for mortality....' ??? **Reply: we have changed the wording (attempting to make it easier to read - including abbreviations as suggested above).**
Page 13, line 15. The word 'to' should be replaced by 'two'. **Reply: we have changed the sentence as suggested.**
Page 13, line 54. Should the sentence conclude 'measures including overall mortality or

variceal bleeding'? **Reply; we have changed the first paragraph of the discussion as previously suggested.**
Page 15, line 51. 'sample size' should be replaced with 'power calculation'. **Reply: we have changed the wording of the paragraph including the suggested sentence.**

Reviewer: 2
Comments for Transmission to the Authors
I have checked the data and references for this manuscript.

The authors acknowledge the three previous meta-analyses addressing the impact of endoscopic and pharmacologic therapy (beta-blockers alone or combined with ISMN) on bleeding and mortality in patients with oesophageal varices (References 11 to 13 in this manuscript).

The last search update for this meta-analysis was January 2010. I have not identified any further trials published since then that may be eligible for inclusion.

I have only two minor comments:

Page 10, Paragraph 2 (Primary prevention):
The mortality rate for banding ligation in the primary prevention studies was 31/139. This is recorded as 72/270 in this paragraph (see Figure 3). **Reply: when changing the wording as suggested by reviewer 1, we have gone through the data again and corrected the identified error.**
Figure 4:
Lo et al. 2009: The mortality rates for the ISMN plus beta blockers group versus banding ligation were 30/61 and 42/60, respectively. The rebleeding rates were 49/61 and 28/60, respectively. **Reply: we have rechecked the figures and presented them in a different format to make them more readable.**

The remainder of the data and references are correct.