

# 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

# ▶ To cite this version:

Lise Lotte Gluud, Ebbe Langholz, Aleksander Krag. Systematic Review with Meta-Analyses of Randomized Trials on Isosorbide-Mononitrate Alone or With Beta-Blockers or Endoscopic Therapy for Esophageal Varices. Alimentary Pharmacology and Therapeutics, 2010, 32 (7), pp.859. 10.1111/j.1365-2036.2010.04418.x. hal-00565916

# HAL Id: hal-00565916 https://hal.science/hal-00565916

Submitted on 15 Feb 2011

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers. L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés. Alimentary Pharmacology & Therapeutic

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



1

3
4
5
6
7
1
8
9
10
11
12
12
13
14
15
16
17
18
10
19
20
21
22
23
24
25
20
26
27
28
29
30
31
20
32
33
34
35
36
37
20
30
39
40
41
42
43
44
15
40
40
47
48
49
50
51
50
52
53
54
55
56
57
58
50
59

60

Systematic Review with Meta-Analyses of Randomized Trials on Isosorbide-Mononitrate Alone or With Beta-Blockers or Endoscopic Therapy for Esophageal Varices LL. Gluud,<sup>1</sup> E. Langholz,<sup>1</sup> A. Krag,<sup>1,2</sup>

<sup>1</sup>Department of Internal Medicine, Copenhagen University Hospital Gentofte, Denmark, <sup>2</sup>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 betablockers 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, <u>Evidence</u> 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 <u>mortality</u> in secondary (RR 0.73, 95% CI 0.59-0.89), but not in primary prevention, <u>The effect of IsMn plus beta-blockers</u> on mortality in secondary prevention was not confirmed in trial sequential analysis.

# CONCLUSIONS

JsMn 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 betablockers 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. ¶

60

Page 3 of 64

#### Alimentary Pharmacology & Therapeutic

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.<sup>1</sup> 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.<sup>2,3</sup> 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.<sup>4,5</sup> Still, the prognosis remains poor. About 50% of patients are non-responders to beta-blockers or cannot continue treatment due to adverse effects.<sup>6</sup> 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.<sup>7</sup> 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.<sup>5</sup> However, one randomized trial found that IsMn increased the risk of bleeding compared with placebo.<sup>8</sup> Other randomized trials on IsMn versus beta-blockers or IsMn plus betablockers versus beta-blockers or endoscopic therapy have reached equivocal results.<sup>9,10</sup> Recent meta-analyses including between four and 25 randomized trials have found that the combination of endoscopic and pharmacological therapy with betablockers alone or combined with IsMn may be more effective in reducing the risk of rebleeding than either therapeutic option used alone.<sup>11-13</sup> 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 <u>in combination</u> with beta blockers or endoscopic therapy for the primary or secondary prevention of <u>bleeding in patients with esophageal varices</u>.

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).

#### **Alimentary Pharmacology & Therapeutic**

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).<sup>14,15</sup> 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 <u>assessed through comparisons between trial</u> 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 metaanalyses 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 (1<sup>2</sup>). 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%.<sup>16</sup>

RESULTS

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

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

#### **Alimentary Pharmacology & Therapeutic**

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.  $^{8-10,\underline{17-42}}$ 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<sup>32</sup> 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, <sup>34,40</sup> 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,<sup>29</sup> 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

#### **Alimentary Pharmacology & Therapeutic**

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 betablockers, 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  $\frac{34.40}{2}$  In the remaining trials, randomization methods were unclear. For two trials  $\frac{27.38}{2}$  there were considerable differences between the characteristics of patients randomized to the treatment and

Deleted: <sup>33,39</sup>
Deleted: <sup>26,37</sup>

#### **Alimentary Pharmacology & Therapeutic**

 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.<sup>8,9,20,23,25,26</sup> One trial was described as single blind without specification of the method of blinding,<sup>20</sup> None of the trials assessed the effect of blinding.

Deleted:	19,22,24
Deleted:	19

Sample size calculations were reported for 18 trials.<sup>8-10,17,18,22-26,30,31,34,36-38,40,41</sup> 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 <sup>25,26</sup> Another trial, which was planned to include 352 patients, was terminated due to low recruitment rates <sup>37</sup> One single centre trial included 137 patients although the reported sample size calculation suggested that the planned size was 120 patients <sup>34</sup> 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. Deleted: <sup>16,</sup> Deleted: <sup>21-25,29</sup> Deleted: <sup>33,35-37,39</sup>

Deleted: <sup>24,</sup> Deleted: <sup>36</sup>

Deleted: 33

Deleted: 23,39

Deleted: <sup>23,39</sup> Deleted: <sup>40</sup>

Deleted: <sup>39</sup>

patients although the reported sample size calculation suggested that the planned size was 120 patients,<sup>34</sup> 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,<sup>24,40,41</sup> All trials were registered after their completion date. Two trials described the same primary outcome measures in the protocol and published report,<sup>24,40</sup> The protocol for one trial defined rebleeding as the primary outcome measure and complications as the secondary outcome measure,<sup>41</sup> 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, <sup>40</sup> An abstract describing the trial reported that the secondary outcomes were complications of cirrhosis including encephalopathy, hepatorenal

## **Alimentary Pharmacology & Therapeutic**

syndrome, spontaneous bacterial peritonitis, and jaundice <sup>42</sup> 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.

### **Primary prevention**

Ten trials on primary prevention reported mortality (**Figure 3**). <u>No apparent effect of</u> <u>IsMn was identified for the intervention comparisons assessed. No</u> 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<sup>2</sup> 0%-6%).

Two meta-analyses included trials with unclear randomization methods 20,21,33Excluding 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).

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

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).

#### Deleted: <sup>19</sup> Deleted: <sup>32</sup>

Deleted: 41

**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

## **Alimentary Pharmacology & Therapeutic**

60

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

<u>Meta-analyses</u> of variceal bleeding <u>found a detrimental effect of IsMn</u> 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. <u>(Table 2). No</u> effects on bleeding-related mortality was seen for any of the treatment comparisons assessed.

#### 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

# **Secondary Prevention**

Sixteen trials on secondary prevention reported mortality in trials on IsMn plus betablockers 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<sup>2</sup> 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: when including all trials Deleted: %) or after

**Deleted:** ). No differences in mortality were seen between IsMn plus beta-blockers versus betablockers (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% Cl 0.56-1.39) or between IsMn plus beta-blockers and banding ligation versus banding ligation (RR 0.86; 95% Cl 0.38-1.94). After excluding trials with unclear

**Deleted:**, there was no apparent difference between IsMn plus betablockers 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 betablockers 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. JsMn 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.

<b>Deleted:</b> Only 13 trials reported variceal bleeding ( <b>Table 2</b> ). The
<b>Deleted:</b> was higher for patients randomized to IsMn plus beta-blockers
Deleted: ) or TIPS (
Deleted: (Table 2).

#### Adverse events

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

compared with placebo (14/67 versus 7/66; RR 1.97; 95% CI 0.85-4.57) or betablockers (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%

analysis
Deleted: the
Deleted: <sup>39,41</sup>
<b>Deleted:</b> 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% Cl 0.60-2.96) or bleeding (19/79 versus 20/92; RR 1.11; 95% Cl 0.64-1.92).
<b>Deleted:</b> Although the definitions and the methods used to register adverse events varied in individual trials, there

Deleted: performed a post hoc

## **Alimentary Pharmacology & Therapeutic**

DISCUSSION

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,  $\frac{17}{4}$  Among 43 patients randomized to sclerotherapy, bleeding ulcers were seen for seven patients and esophageal strictures for 2 patients.

#### Deleted: to

Deleted: 16

#### 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 <u>available evidence presented in this review suggests that IsMn used alone or in</u> <u>combination</u> with beta-blockers <u>has</u> 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.

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,<sup>43</sup> We found similar evidence when comparing published protocols, abstracts and full paper articles, <u>Abstracts often</u> 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, <u>Accordingly</u>, 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. $^{6,44,45}_{r}$ 

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  $\frac{46}{\sqrt{2}}$  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:** <sup>3940,42</sup> 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.<sup>41</sup> 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.<sup>39</sup> A previously reported abstract describing the same trial suggested that there were several losses to follow up.<sup>41</sup> The number of patients randomized to IsMn plus beta-blockers and banding ligation was higher in the published pape 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

14

60

## **Alimentary Pharmacology & Therapeutic**

59 60 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  $\frac{47}{2}$  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. <u>When</u> the <u>calculation is</u> not reported, the reader does not know whether <u>the planned</u> sample size was reached or the trial terminated at an arbitrary time. <u>Two of the trials in</u> the present review were terminated based on <u>concurrent evidence from a concurrent</u> trial suggesting a <u>detrimental effect</u> of the <u>interventions</u> assessed, <sup>25,26</sup> <u>Another trial was</u> 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.<sup>28</sup> 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.<sup>36</sup> The reported sample size calculation for one of the included single centre trials included 137 patients although the planned size was only 120 patients.<sup>33</sup> 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

I

# **Alimentary Pharmacology & Therapeutic**

f GA	Alimontary Bharmonology 9 Thereneutic	Deleted: Trial
1 04	Anmentary Pharmacology & Therapeutic	Deleted: Treatment compari
		Image: specific constraints     Image: specific constraints       Image: specific constraints     Image: specific constraints
		h
		Formatted
		Formatted [4]
		Deleted: Abdelfattah
		Field Code Changed
		Formatted
		Deleted: versus banding ligat [ [7]
Table 1. Table of Included R	Randomized Trials	Deleted: Abulfutuh
	174	Field Code Changed
<b>Frials on Pharmacological</b>	Therapy in Primary	Deleted: <sup>32</sup>
	///	Formatted
Prevention		<b>Deleted:</b> propranolol versus [ [10]
		Formatted
<u>Garcia-Pagan et al°</u>	<u>IsMn versus placebo.</u>	Formatted [12]
A		Formatted
Angelico et al <sup>10</sup>	IsMn versus propranolol	Deleted: Agrawal <sup>2723</sup>
Derropi et el <sup>29</sup>		Formatted
Borroni et al	ISIVIN Versus nadolol.	Deleted: banding ligation for [16]
D'Amico et al <sup>25</sup>	leMn plus padolol versus placebo	// Formatted
		Image: Provide the second se
	plus nadolol	Formatted
		Deleted: for primary prevention
Garcia-Pagan et al	IsMn plus propranolol versus	Formatted
		// Deleted: Patti
	placebo plus propranolol,	Leield Code Changed
		// Polotodi <sup>25</sup>
Merkel et al	IsMn plus nadolol versus <u>placebo</u>	
		Formatted [ [22]
27		Formatted ( [23])
<u>Deplano</u> et al <u>-</u>	IsMn plus nadolol versus nadolol	Deleted: for secondary prevention.
	and Factors and Theorem in Prince Provention	Formatted ( [24])
rials on Pharmacological	and Endoscopic Therapy in Primary Prevention	Deleted: Shiha
Mana at al <sup>37</sup>	IoMa alua padalal versus banding	Field Code Changed [25]
wang et al	Isivin plus hadoloi versus banding	Deleted: [26]
		Deleted: for secondary prevention.
	iigation.	Deleted: Full paper articles [27]
lui et al <sup>30</sup>	IsMn versus propranolol versus	Field Code Changed [28]
		Deleted: <sup>38</sup>
	banding ligation	Formatted [29]
		Deleted: plus propranolol
Abdelfattah et al	IsMn versus propranolol versus	[Formatted [30]
#		Deleted: IsMn plus propranolol and
	banding ligation.*	Formatted [31]
		Deleted: versus banding liga [32]
<u>Abulfutuh</u> et al <mark>33</mark>	IsMn versus propranolol <u>versus</u>	Formatted
	7,	Deleted: Angelico
	· //l //1 //1	Field Code Changed
		<b>Deleted:</b> <sup>19</sup>
	17	Formatted
	17	Deleted: for primary provention

# Alimentary Pharmacology & Therapeutic

I

I

	banding ligation.*
rials on Pharmacological Therapy in	
	<b>-</b>
Patti et al <sup>26</sup>	IsMn plus nadolol versus placebo
	plus nadolol
Gournay et al	IsMn plus propranolol versus
	propranolol
Zhang et al	IsMn plus propranolol versus
	propranolol
rials on Pharmacological and Endoscopic	c Therapy in Primary Prevention
Agrawal et al <sup>28</sup>	IsMn plus propranolol versus
	banding ligation
Lo_et al <sup>38</sup>	IsMn plus nadolol versus banding
	ligation
Patch et al	IsMn plus propranolol versus
	banding ligation
<mark>Sarin</mark> et al	,IsMn <mark>plus,</mark> propranolol versus
	banding ligation
<u>Villanueva</u> et al <sup>18</sup>	IsMn plus nadolol versus banding
	ligation.
<u>Villanueva</u> et al <sup>17</sup>	IsMn plus <u>nadolol</u> versus
	<u>sclerotherapy.</u>
	18

Formatted	<b>. . . . . . . . . .</b>
Deleted: Borroni et al	
Deleted: IsMn versus na	dolo [37]
Formatted	[38]
Formatted	<u>[39]</u>
Deleted: D'Amico	
Deleted: <sup>24</sup>	
Formatted	[01]
Field Code Changed	[40]
Deletedu for primary pro	[41]
Corrected: for primary pre	
	[42]
Deleted: Escorsell et al <sup>2</sup>	<u>[</u> [43]
Deleted: 2210	
Formatted	[44]
Deleted: placebo plus	)
Formatted	[45]
Deleted: for primary pre	evention.
Formatted	[[46]
Deleted: Garcia-Pagan	et al <sup>2</sup> $[47]$
Field Code Changed	
Deleted: <sup>10</sup>	[40]
Formattad	
	<u>[ [49]</u>
Deleted: for secondary	prevention.
Formatted	[50]
Deleted: Kumar	
Field Code Changed	[51]
Deleted: 39	
Formatted	[52]
Deleted: and banding lig	ation
Formatted	[[52]
Deleted: for secondary	prevention
Formatted	F=
Formatted	
	( [55]
Field Code Changed	[ [56]
Deleted: 3/	
Formatted	[57]
Formatted	[58]
Deleted: for secondary	prevention.
Formatted	[59]
Deleted: Lo	
Formatted	[60]
Deleted: 4031	
Formatted	[61]
Deleted: nadolol	( [01]
Formatted	
Deleted later i	<u>[ [62]</u>
Formatted	[ [63]
Deleted: for secondary	prevention.
Formatted	[64]
Deleted: Lui <sup>2934</sup>	[65]
Formatted	[66]
Deleted: versus	
Formatted	[[67]
Deleted: for primary pre	evention.
Formatted	
	[68]
Formatt-1	<u>[ [69]</u>
Formatted	[ [70]
<u></u>	[ [71]
For a state of the	[ [72]
Formatted	[ [73]
Formatted	[74]
Formatted	[ [74]
Formatted	[74]
Formatted Formatted	[74] ( [75])
Formatted Formatted Formatted Formatted	[74] [75] [76]

		Deleted: <sup>35</sup>
Romero et al <sup>36</sup>	IsMn plus nadolol versus banding	Formatted: French (France)
		Deleted: for secondary prevention.
	ligation plus sclerotherapy	<b>Formatted:</b> French (France)
		Deleted: Sarin
		<b>Deleted:</b> <sup>33</sup>
	transjugular intrahepatic	Deleted: banding ligation
	portosystemic shunt (TIPS) for	
	secondary prevention.	
		Deleted: Villanueva
<u>Garcia-Pagan</u> et al	IsMn plus nadolol versus IsMn	Deleted: <sup>1624</sup>
	,	Formatted: French (France)
		<b>Deleted:</b> sclerotherapy for secondary prevention.
Lo et al	IsMn plus nadolol versus <u>IsMn</u>	Formatted: French (France)
		Deleted: Villanueva
	plus nadolol and panding ligation	Deleted: <sup>1741</sup>
Kumor et el <sup>40</sup>		Formatted: French (France)
Kumar et al	ISININ PIUS <u>propranoioi and</u>	Formatted: French (France)
	handing lightion vorsus handing	<b>Deleted:</b> for secondary prevention
	banding ligation versus banding	<b>Formatted:</b> French (France)
	ligation	<b>Deleted:</b> Wang
	guile.g	Field Code Changed
Shiha et al <sup>35</sup>	IsMn plus propranolol versus	Deleted: <sup>36</sup>
		Deleted: nadolol
	propranolol versus banding	<b>Deleted:</b> for primary prevention.
	ligation.*	
Abmod at al <sup>39</sup>	loMn plug propropolol vorguo	Deleted: Zhang
		Formatted: French (France)
	propranolol versus IsMn plus	Field Code Changed
	propranolol and banding ligation	Formatted
	versus banding ligation for	Formatted
	versus banding ligation to	Deleted:
	secondary prevention	Formatted: Font: Times New Roma
*Abstract		
	19	

**Table 2.** Random-Effects Meta-Analyses on Variceal Bleeding and Bleeding-Related

Mortality in Randomized Trials on Primary and Secondary Prevention.

Variceal bleeding in trials on primary prevention					
Exp*		Ctr*			
Treatment comparison	n	Ν	n	Ν	RR (95% CI)
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-analys	es of	trial	s on	prima	ary 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 s	econ	dary	prevention
IsMn plus beta-blockers versus beta-blockers	44	141	65	148	0.71 (0.52-0.96)
IsMn plus beta-blockers versus endoscopic	146	445	133	449	1 07 (0 87-1 32)
therapy					(001 1102)
IsMn plus beta-blockers alone or with banding	60	173	38	177	1.61 (1.14-2.27)
ligation		. 5			- ()

IcMn plus bota blockors vorsus TIPS					
ISINIT PIUS DELA-DIOCKEIS VEISUS TIFO	17	44	6	47	3.03 (1.31-6.98)
IsMn plus beta-blockers and banding ligation	11	88	11	89	1 01 (0 46-2 21)
versus banding ligation		00		00	1.01 (0.40 2.21)
Bleeding-related mortality in meta-analys	es o	f trial	s on	prima	ary prevention
IsMn plus beta-blockers versus beta-blockers	13	99	13	100	1.01 (0.49-2.09)
IsMn plus beta-blockers versus endoscopic	22	200	26	208	0.87 (0.50-1.52)
therapy	22	255	20	230	0.07 (0.00-1.02)
IsMn plus beta-blockers alone or with banding					
isivili plus beta bioekers alone or with banding					
ligation	11	138	5	140	1.95 (0.71-5.33)
ligation IsMn plus beta-blockers versus TIPS	11 4	138 44	5 3	140 47	1.95 (0.71-5.33) 1.42 (0.34-6.01)
ligation IsMn plus beta-blockers versus TIPS IsMn plus beta-blockers and banding ligation	11 4	138	5 3	140 47	1.95 (0.71-5.33) 1.42 (0.34-6.01)

Table 3. Random Effects Meta-analyses on Adverse Events in Randomized Trials

for Primary or Secondary Prevention in Esophageal Varices.

	Ехр		Ctr		
Treatment comparison	n	N	n	N	RR (95% CI)
Isl	Mn vers	us beta	-blocke	ers	
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 b	eta-bloc	kers ve	rsus be	eta-bloc	kers
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	2	27	4	30	0.56 (0.11-2.80)
trial					
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	-blocker	s versu	s endo	scopic	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	44	61	39	60	1.11 (0.87-1.41)
trial					
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).

#### 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. Paquiaro L. Bosch J

. 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.¶

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 betablockers. *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 ret(....[78]

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

- 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 metaanalytic 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* <u>2007;46:922-938.</u>
- 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.

24

1 2 3	7
3 4 5 6 7 8 9 10 11	<u>8</u>
12 13 14 15 16 17 18 19 20	<u>ç</u>
21 22 23 24 25 26 27 28	_1(
29 30 31 32 33 34 35 36	11
37 38 39 40 41 42 43 44	12
45 46 47 48 49 50 51 52	
53 54 55 56 57 58 59	

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

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

- 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.
- 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.
- Gonzalez R, Zamora J, Gomez-Camarero J, Molinero LM, Banares R, Albillos
   <u>A. Meta-analysis: Combination endoscopic and drug therapy to prevent variceal</u> 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. <u>Gastrointest Endosc 2009;70:658-664.</u>

Formatted: Danish
Formatted: Danish

Formatted: Danish
Formatted: Danish

	mononitrate and endoscopic band ligation for prophylaxis of esophageal variceal rebleeding: a meta-analysis World J Gastroenterol 2009:15:2151-2155		
		,	Formatted: Danish
14.	Gluud LL. Bias in clinical intervention research. Am J Epidemiol 2006;163:493-	-1.	Formatted: Danish
	501.		
		1	Formatted: Danish
<u>15.</u>	Wood L, Egger M, Gluud LL et al. Empirical evidence of bias in treatment effect	1	Formatted: Danish
1	estimates in controlled trials with different interventions and outcomes: meta-		
	epidemiological study BMJ 2008:336:601-605		
-			
<b>16</b> .	Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may		
	establish when firm evidence is reached in cumulative meta-analysis. J Clin	1	Formatted: Danish
•		-	
	<u>Epidemiol 2008;61:64-75.</u>		
17	Villanueva C. Balanzo J. Novella MT et al. Nadolol plus isosorbide mononitrate	1	Formatted: Danish
			Formatted: Danish
!	compared with sclerotherapy for the prevention of variceal rebleeding. <u>N Engl J</u>	1,	Formatted: Danish
	Med 1996;334:1624-1629.		
	•	_	
		,	Formatted: Danish
<u>18.</u>	Villanueva C. Minana J. Ortiz J et al. Endoscopic ligation compared with	1	Formatted: Danish
	combined treatment with nadelel and isosorbide menopitrate to provent	,	Formatted: Danish
		11	Formatted: Danish
<u> </u>	recurrent variceal bleeding. <u>N Engl J Med</u> 2001;345:647-655.		
10	Villanueva C. Aracil C. Colomo A et al. Clinical trial: a randomized controlled	1	Formatted: Danish
13.		2	Formatted: Danish
1	study on prevention of variceal rebleeding comparing nadolol + ligation vs.		

	hepatic venous pressure gradient-guided pharmacological therapy. Aliment
	Pharmacol Ther 2009;29:397-408.
<b>20</b> .	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.
<b>22</b> .	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.
<b>23</b> .	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.
<b>24</b> .	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.
<b>25</b> .	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
	27

57 58 59

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
Formatted: Danish

	mononitrate plus propranolol compared with propranolol alone for the	
	provention of variceal reblooding. Zhanghua Vi Yua Za Zhi 2002:82:1157.1159	
<b>33</b> .	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.	
<u>34.</u>	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. <i>Dig Dis Sci</i> 2005;50:1538-1547.	
<b>35</b> .	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	Form Form
	randomised trial. Gut 2005;44:A6.	
<u>36.</u>	Romero G, Kravetz D, Argonz J et al. Comparative study between nadolol and	  Form
	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.	
<b>37</b> .	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.	
	29	
	29	

3
1
4
5
6
7
8
0
9
10
11
12
12
13
14
15
16
17
10
18
19
20
21
22
22
23
24
25
26
20
27
28
29
30
24
51
32
33
34
35
33
36
37
38
39
40
40
41
42
43
44
 /
40
46
47
48
10
49
50
51
52
52
55
54
55
-0
56
56 57

1
2

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. <u>Hepatology</u> 2007;46:250A,

<u>43.</u> 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

1	portal hypertension: rational basis, available treatments and future options. J	
1	Hepatol 2008;48 Suppl 1:S68-S92.	
<u>45. (</u>	Senzolo M, Cholongitas E, Burra P et al. Beta-Blockers protect against	Formatted: Danish
5	spontaneous bacterial peritonitis in cirrhotic patients: a meta-analysis. Liver Int	Formatted: Danish
		/
	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.



Page	32	of	64

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 particoutcomes, 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	pecify study characteristics (e.g., PICOS, length of follow-up) and report Formatted: Font color: Black, anguage, publication status) used as criteria for eligibility, giving rationale English (Canada)			
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact vadditional 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 system included in the meta-analysis).			
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently 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, in (e.g., I <sup>2</sup> ) for each meta-analysis.			
		Page 1 of 2			
Section/topic	#	Checklist item			
Disk of hiss same staff	45				

	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).		
I	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 review each stage, ideally with a flow diagram.		

Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study : 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	<u>.</u>	
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-levidentified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and
FUNDING	<u>1</u>	
Funding	27	Describe sources of funding for the systematic review and other support (e.g., sup systematic review.

 

 PRISMA Group

 unvisit:
 www.prisma.stat.

 Page 2 of 2

 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 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: sing	le		
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: sing	le		
Page 17: [7] Deleted	Lise Lotte	6/26/2010 6:03:00 PM		
versus handing ligation for primary	prevention			
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.

1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24 25	
20	
20	
28	
20	
30	
31	
32	
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48 40	
49 50	
50	
52	
52 53	
54	
55	
56	
57	
58	
59	
60	

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: singl	e		
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		
		0, 20, 2020 0100100 111		
Font: Ariai, 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				

1
2
3
4
5
6
7
1
8
9
10
11
12
13
14
15
16
17
18
19
20
20
∠ I 20
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
30
37
38
39
40
41
42
43
44
45
46
47
48
49
50
50
51
ບ∠ ≂ົ
53
54
55
56
57
58
59
60

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		
Fuil paper articles		
AhmadAbdelfattah et	IsMn plus propranolol versu	us propranolol versus
al <sup>3821</sup>	IsMn plus propranolol and I	panding ligation versus
	banding ligation for second	ary 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	r 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

5/2010 6:03:00 PM
5/2010 6:03:00 PM
5/2010 6:03:00 PM
5/2010 6:03:00 PM
olocker (proprano
ılar intrahepatic
nunt (TIPS) for
ention.
cebo for primary

et al <sup>2210</sup>	propranolol for primary pr	revention
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 <sup>23</sup>	IsM	n plus nadolol versus IsMn plu
	nad	olol and banding ligation for
	sec	ondary prevention.
GournayZhang et	IsMn plus propranolol ver	sus propranolol for
al <sup>1032</sup>	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		

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 sec	condary prevention.	
Page 18: [77] Formatted	Unknown	
French (France)		4
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
3
1
4
5
6
7
8
0
9
10
11
12
10
13
14
15
16
17
10
10
19
20
21
22
22
23
24
25
20
20
27
28
29
23
30
31
32
33
24
34
35
36
37
20
38
39
40
11
40
42
43
44
45
16
40
47
48
49
50
50
51
52
53
54
54
55
56
57
58
50
59
60

- 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.
- 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.
- 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.
- 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.
- 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.

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

- Ding SH, Liu J, Wang JP. Efficacy of beta-adrenergic blocker plus 5isosorbide mononitrate and endoscopic band ligation for prophylaxis of esophageal variceal rebleeding: a meta-analysis. *World J Gastroenterol* 2009;15:2151-2155.
  - Gluud LL. Bias in clinical intervention research. *Am J Epidemiol* 2006;163:493-501.
  - 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.
  - 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.
  - 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.
  - 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.

- 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.
  - 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.
- 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.
- 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.
- 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.
- 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.

- 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.
- 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.
- 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.

2		
3	35.	Romero G, Kravetz D, Argonz J et al. Comparative study between nadolol
5		
6		and 5-isosorbide mononitrate vs. endoscopic band ligation plus
7		
8 9		sclerotherapy in the prevention of variceal rebleeding in cirrhotic patients:
10		a randomized controlled trial Aliment Pharmacel Ther 2006:24:601 611
11		
12		
14		
15	<b>36</b> .	Wang HM, Lo GH, Chen WC et al. Comparison of endoscopic variceal
16 17		lighting and a deletation in a solution. The experiments in the eventer of first
18		ligation and nadolol plus isosorbide-5-mononitrate in the prevention of first
19		variceal bleeding in cirrhotic patients J Chin Med Assoc 2006:69:453-460
20 21		
22		
23	07	
24 25	37.	Lo GH, Chen WC, Lin CK et al. Improved survival in patients receiving
26		medical therapy as compared with banding ligation for the prevention of
27		medical therapy as compared with banding ligation for the prevention of
28 29		esophageal variceal rebleeding. Hepatology 2008;48:580-587.
30		
31		
33	38	Abmad I Khan AA Alam A Butt AK Shafaat E Sarwar S Propranolol
34	50.	Animad I, Mian AA, Alam A, Bult AR, Shaiqat I, Saiwai S. I Topianoloi,
35		isosorbide mononitrate and endoscopic band ligation - alone or in varying
37		
38		combinations for the prevention of esophageal variceal rebleeding. J Coll
39		Physiciana Come Balt 0000-10-000 000
41		Physicians Surg Pak 2009;19:283-286.
42		
43 44		
45	<b>39</b> .	Kumar A, Jha SK, Sharma P et al. Addition of propranolol and isosorbide
46		
48		mononitrate to endoscopic variceal ligation does not reduce variceal
49		rebleeding incidence Gastroenterology 2009:137:892-901
50		
52		
53	40	La Old Oban MO. Oban III at al Avendaria d'a sentrella ditrial af
54 55	40.	LOGH, Unen WU, Unan HH et al. A randomized, controlled trial of
56		handing ligation plus drug therapy versus drug therapy alone in the
57		שמוימויש וושמוטרו אושש מושע נוופומאי יפושטש טושע נוופומאי מוטוופ ווו נוופ
58 59		

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.
- 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



44 references referring to 27 randomized trials included

 Page Break
Figure 2 Bias assessment of randomized trials
Allocation sequence generation
Blinding
Incomplete outcome data addressed
Free of selective reporting
Adequate/yes Unclear No

-----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**

E	хрелп	nental	Con 1	rol			
E	vents	Total	Events	Total	Weight I	RR, Random, 95%CI	R R, Rand om, 95% C
IsMn v ersus placeb	D						
Garcia-Pagan 2001	15	67	9	66	100.0%	1.64[0.77, 3.49]	
Sub total (95% CI)		67		66	100.0%	1.64 [0.77, 3.49]	
lotalevents	15		9				
Heterogeneity: Notap Test for overall effect	Z = 1.	e 29 (P -	0.20)				
lsMn v ersus beta-bl	ockers	8					
Abdelfattah 2001	6	53	5	52	6.0%	1.18[0.38, 3.62]	
Abulfutuh 2003	18	62	24	66	27.6%	0.80[0.48, 1.32]	
Angelico 1997	28	57	24	61	40.0%	1.25[0.83, 1.88]	
Borrani 2002	7	27	8	25	10.1%	0.81[0.34, 1.91]	
Lui 2002 Sub total (95% CI)	18	62 261	11	66 270	16.4%	1.74[0.90, 3.39] 1.11 (0.84, 1.47]	<b>•</b>
Total events	77		72				ſ
Heterogeneity: TauF -	0.01;	OhF = 4	4.26,d	t = 4 (	P = 0.37)	;F = 6%	
Test for overall effect	Z = 0.	75 (P =	0.45)				
lsMn v ersus bandin	g ligati	ion					
Abdelfattah 2001	6	53	4	51	10.7%	1.44[0.43,4.82]	
Abulfutuh 2003	18	62	13	44	43.3%	0.98[0.54, 1, 79]	<b>-</b>
Lui 2002	18	62	14	44	46.0%	0.91[0.51, 1.63]	_ <b>_</b>
Sub total (95% CI)		177		139	100.0%	0.99 [0.67, 1.47]	-
Total events	42		31				
Heterogeneity: Tau? -	0.00;	OhF = 0	0.45,d	1 = 2 (	P = 0.80)	;F = 0%	
Test for overall effect	Z = 0.	05 (P =	0.96)				
IsMn plus beta-blod	kers ve	ersus b	eta-bl	ocke	rs		
D Amico 2002	10	30	9	27	20.0%	1 00[0 48 2 09]	
Garcia-Pagan 2003	14	175	11	174	18.7%	1.27[0.59.2.71]	
Merkel 2000	25	72	30	74	61.3%	0.86[0.56, 1.30]	-0-
Sub total (95% CI)		277		275	100.0%	0.95 [0.68, 1.32]	•
Total events	49		50				1
Heterogeneity: TauF -	0.00;	ChF = 0	D.80,d	1 - 2 (	P = 0.67)	;F = 0%	
Test for overall effect	Z = 0.	30 (P =	0.76)				
IsMn plus beta-blod	kers ve	ersus b	andin	g liga	tion		_
Wang 2006 Sub total (95% (1)	6	31	8	30	100.0%	0.73 0.29, 1.84	
Table star(55,5 Gr)	~	0.			100.070	0.10 [0.20, 1.04]	_
Hotorogomity Notor	o I co bi	10	0				
Test for overall off est	7 0	67 (D	0.50)				
rea loi overali elicu	2=0.	0r (r =	0.00)				
						H	
						0.1 0	2 0.5 1 2 5
						Favors	experimental Favorsco

#### Bleeding

E	Experime	ntal	Con tr	ol						
E	Events T	otal	Events	Total	Weight	RR,Random,95	%CI RI	R, Randor	n,95%C	(
IsMn versus placebo	<b>b</b>								_	
Garcia-Pagan 2001 Subtotal (95% CI)	19	67 67	8	66 66	100.0% 100.0%	2.34 (1.10, 4.9 2.34 (1.10, 4.9	7] 7]			
Total events Heterogeneity:Notap	19 plicable		8							
Testfor overalleffect	Z=221(	P = 0	103)							
IsMn versus beta-blo	ockers									
Abdelfat tah 2001	18	53	13	52	44.5%	1.36 0.74, 2.4	8]	-+0	_	
Argelico 1997	16	57	14	61	43.1%	1.22 [0.66, 2.2	7]		_	
Borioni 2002	10	27	2	25	12.4%	4.63 [1.12, 19.1	0]	-	•	-
Subtotal (95% CI)		137		138	100.0%	1.51 0.89,2.5	7j	-		
Total events	44		29							
Heterogeneity : Tau <sup>2</sup> =	0.07;Chi	<sup>2</sup> = 2!	91, df =	2 (P -	0.23); F	- 31%				
Testfor overalleffect	Z=1.52 (	(P = 0	113)							
lsMn plus beta-block	ersversu	us be	ta-bloci	kers						
DAmico 2002	9	30	13	27	28.9%	0.62 (0.32, 1.2	2]	-0		
Deplano 2001	2	14	3	22	4.7%	1.05 [0.20, 5.5	0]	-		
Garcia-Pagan 2003	18	175	18	174	34.1%	0.99 (0.54, 1.8	5]		-	
Merkel 2000	13	72	18	74	32.3%	0.74 [0.39, 1.4	0] -	-		
Subtotal (95% CI)		291		297	100.0%	0.79 [0.55, 1.1	s]	-		
Total events	42		52							
Heterogeneity : Tau <sup>2</sup> =	0.00;Chi	<sup>2</sup> = 1.	16, df =	3 (P -	- 0.76); F	- 0%				
Testfor overalleffect	Z = 126 (	(P = 0	121)							
1.2.4 IsMn plus beta-	blockers	vers	u sband	ling li	gation			_	-	
Wang 2006	8	31	5	30	100.0%	1.55 [0.57, 4.2	0]			
Subtotal (95% CI)		31		30	100.0%	1.55 [0.57, 4.2	0]		_	
Total events	8		5							
Heterogeneity:Notap	plicable									
Testfor overalleffect	Z=0.86 (	(P = 0	139)							
1.2.5 IsMn versus ba	nding liga	ation							_	
Abdelfattah 2001 Subtotal (95% Cit	18	53 53	4	51	100.0%	4.33 [1.57, 11.9	2]			_
Trtal events	18		4		100.0 /0	4.00[1.07,11.0	-			
Heterogeneity:Notan	nic shla		4							
Testfor overalleffect	Z=2.84 (	P = 0	1005)							
			.,							
							0102	0.5 1	2 5	
						F	0.102	imental F	avorecor	tro



---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

	Exp er im	en tal	Contro	6			
latte a lua hata h la	Ev ent s	Total	Events 1	'o tal	Weight	RR, Random, 95% CI	RR, Random, 95
ISMn plus beta-bio	cke is ver:	uspe	a-biooke	rs			
Ahmad 2009	6	35	9	39	15.4%	0.74 [0.2.9, 1.88]	
Gournay 2 000	11	46	11	49	24.6%	1.07 [0.51,2.22]	
F all 2001			10	60	20.0%	0.92 10.27 1.921	
3mm - 0000		~		00	44.000	0.70 (0.07, 0.00)	
Subtotal (95% C)	5	228	0	231	1 00.0%	1.04[0.73, 1.50]	÷
Total events	48		47	_			
Hereio generty: Tau-	= 0.0 0; Ci	P = 2 i	52,01=4	(P =	0.58); P	- 0%	
lest for overall effect	20 Z = 0.23	(P = 0	182)				
IsMn nius betable	rke is ver	aisha	ndina lia	ation	or sole	n the ran v	
A nawal 2 002	7	51	7	53	40%	104 0 39 2751	
Ahmad 2009	6	35	8	39	42%	0.84 (0.32, 2.17)	
Lo 20 08	30	61	42	60	41.5%	0.70 10.5 2.0.951	-0-
Patch 200.2	17	51	17	51	12 76	100 0 58 1731	-+
Romer o 2 006	11	57	10	52	6.5%	1.00 [0.46, 2.17]	
Sarin 2 005	4	66	6	71	2.6%	0.72 [0.21, 2.43]	
Shiha 200 5	9	60	8	61	4.9%	1.14 [0.47, 2.77]	
Villaru ele 1 996	4	43	9	43	32%	0.44 [0.1 5, 1.33]	
Vilanu ele 2 001	23	72	30	72	20.4%	0.77 [0.5.0, 1.18]	
Subtotal (95% C)		496		502	1 00.0%	0.79[0.65, 0.96]	•
Total events	111		137				
Hetero geneity: Tau <sup>2</sup>	= 0.0 0; CI	1 <sup>2</sup> = 3.7	74, d1 = 8	(P =	0.88); F	- 0%	
IsMn plus betabloe	kers vers	us TIP:	5				1
Escorsell 200 2	11	44	13	47	100.0%	0.90 [0.4 5, 1.80 ]	
Subtotal (95% C)		44		47	1 00.0%	0.90[0.45, 1.80]	-
Total events	11		13				
Hetero geneity: Not	applicable						
Test for overall effect	t Z= 0.29	(P = 0	L77)				
IsMn plus betabloo	kers vers	us IsM	n plus be	t abli	ockers a	nd banding ligation	
Garcia-Pagan 2009	15	78	16	80	50.5%	0.96 [0.5 1, 1.81 ]	
Lo 20 09	13	60	16	60	49.5%	0.81 [0.43, 1.54]	
Subtotal (95% C)		138		140	1 00.0%	0.88[0.56, 1.39]	-
Total events	28		32				
Hetero geneity: Tau <sup>3</sup>	= 0.0 0; Cl	s <sup>2</sup> = 0.	14, df = 1	(P =	0.71); P	- 0%	
test tor overall effect	st ∠= 0.53	(P = 0	L 569)				
lette plus betable	deam and	handi	na Ea alla		couch a	ntion lie affen	
Abread 2009	7	27	-gao	20	70.00	0.02 0.27 2 201	
Kumar 2009	2	88	3	89	21 0%	0.67 [0.12.394]	
Subtotal (95% C)	-	125		128	1 00.0%	0.8510.38.1.941	-
Total events Hetern neneity: Tau?	9	e =0 ·	11 10 df = 1	(P =	0.78) P	. 0%	
Total events Hetero geneity: Tau <sup>3</sup> Test for overall effer	9 = 0.0 0; Ci	P = 0.	11 10, df = 1	(P =	0.76); P	0%	
Total events Hetero geneity: Tau <sup>3</sup> Test for overall effect	9 = 0.0 0; Cl ct Z= 0.36	s <sup>p</sup> = 0. (P = 0	11 10, d f = 1 172)	(P =	0.76); P	- 0%	
Total events Hetero geneity: Tau <sup>2</sup> Test for overall effec	9 = 0.0 0; Cl st Z = 0.36	6 <sup>2</sup> = 0. (P = 0	11 10, d f = 1 1.72)	(P =	0.76); P	- 0%	, ,
Total events Hetero geneity: Tau <sup>3</sup> Test for overall effec	9 = 0.0 0; Cl at Z = 0.36	s <sup>p</sup> = 0. (P = 0	11 10, d f = 1 172)	(P =	0.76); P	0%	2 05 1 2

Bleeding





# Figure 1 Flow chart of trials

423 potentially relevant references identified through electronic searches 28 potentially relevant references identified through manual searches 60 references retrieved for further assessment 15 references excluded (referred to observational studies 1 ongoing randomised trial on IsMn plus propranolol versus or randomised trials that did not assess IsMn or patients transjugular intrahepatic shunts excluded (data not yet available) with oesophageal varices) 44 references referring to 27 randomized trials included

# Figure 2 Bias assessment of randomized trials



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

E	xperim	ental	Co	ontrol	Risk Ratio	Risk Ratio
	n	N	n	N		
Isin versus places	00					
Garcia-Pagan 2001 Total (95% CI)	15	67 67	9	66 66	1.64 [0.77, 3.49] 1.64 [0.77, 3.49]	
Total events	15		9			
Heterogeneity: Not a	applicat	ole				
Test for overall effect	xt: Z = 1	.29 (P	= 0.20	))		
IsMn versus betabl	lockers	5				
Abdelfattah 2001	6	53	5	52	1.18 [0.38, 3.62]	
Abulfutuh 2003	18	62	24	66	0.80 [0.48, 1.32]	
Angelico 1997	28	57	24	61	1.25 [0.83, 1.88]	-+ <b>B</b>
Borroni 2002	7	27	8	25	0.81 [0.34, 1.91]	
Lui 2002	18	62	11	66	1.74 [0.90, 3.39]	
Total (95% CI)		261		270	1.11 [0.84, 1.47]	●
Total events	77		72			
Heterogeneity: Tau <sup>2</sup>	= 0.01	; Chi² =	4.26,	df = 4	(P = 0.37); I <sup>2</sup> = 6%	
Test for overall effect	ct: Z = 0	.75 (P	= 0.45	5)		
IsMn versus bandii	ng ligat	tion				
Abdelfattah 2001	6	53	4	51	1.44 [0.43, 4.82]	<b>-</b>
Abulfutuh 2003	18	62	13	44	0.98 [0.54, 1.79]	
Lui 2002 Total (95% CI)	18	62 177	14	44 139	0.91 [0.51, 1.63] <b>0.99 [0.67, 1.47]</b>	•
Total events	42		31			
Heterogeneity: Tau <sup>2</sup> Test for overall effect	= 0.00; t: Z = 0	Chi² = .05 (P	= 0.45, = 0.96	df = 2 3)	(P = 0.80); I <sup>2</sup> = 0%	
IsMn plus betabloc	kers ve	ersus I	betab	locker	s	
D Amico 2002	10	30	9	27	1.00 [0.48, 2.09]	<b>•</b>
Garcia-Pagan 2003	14	175	11	174	1.27 [0.59, 2.71]	
Merkel 2000	25	72	30	74	0.86 [0.56, 1.30]	
Total (95% CI)		277		275	0.95 [0.68, 1.32]	<b>•</b>
Total events	49		50			
Heterogeneity: Tau <sup>2</sup>	= 0.00	Chi² =	= 0.80,	df = 2	(P = 0.67); l <sup>2</sup> = 0%	
Test for overall effect	ct: Z = 0	.30 (P	= 0.76	6)		
IsMn plus betabloc	kers ve	ersus l	bandi	ng liga	ition	
Wang 2006 Total (95% CI)	6	31 31	8	30 <b>30</b>	0.73 [0.29, 1.84] <b>0.73 [0.29</b> , <b>1.84]</b>	
Total events	6		8			
Heterogeneity: Not a Test for overall effect	applicat t: Z = 0	ole .67 (P	= 0.50	))		
					0.10	
					Eavors exp	perimental Favors control

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

E	perim	ental	Contr	ol	Risk Ratio	Risk Ratio
	n	Ν	n	Ν		
IsMn versus placebo						
Garcia-Pagan 2001 Total (95% CI)	19	67 67	8	66 66	2.34 [1.10, 4.97] 2.34 [1.10, 4.97]	-
Total events	19		8			
Heterogeneity: Not app	licable					
Test for overall effect: 2	Z = 2.2'	1 (P = 0	0.03)			
IsMn versus betabloc	kers					
Abdelfattah 2001	18	53	13	52	1.36 [0.74, 2.48]	-+=
Angelico 1997	16	57	14	61	1.22 [0.66, 2.27]	
Borroni 2002	10	27	2	25	4.63 [1.12, 19.10]	
Total (95% CI)		137		138	1.51 [0.89, 2.57]	►
Total events	44		29			
Heterogeneity: Tau <sup>2</sup> = 0	0.07; C	hi² = 2.	91, df =	2 (P =	0.23); I <sup>2</sup> = 31%	
Test for overall effect: 2	Z = 1.52	2 (P = 0	).13)			
IsMn plus betablocke	rs vers	us bet	ablock	ers		
D Amico 2002	9	30	13	27	0.62 [0.32, 1.22]	— <b>•</b> +
Deplano 2001	2	14	3	22	1.05 [0.20, 5.50]	
Garcia-Pagan 2003	18	175	18	174	0.99 [0.54, 1.85]	<b>-</b>
Merkel 2000	13	72	18	74	0.74 [0.39, 1.40]	<b>e</b> +-
Total (95% CI)		291		297	0.79 [0.55, 1.14]	◆
Total events	42		52			
Heterogeneity: Tau <sup>2</sup> = 0	0.00; C	hi² = 1.	16, df =	3 (P =	0.76); l <sup>2</sup> = 0%	
Test for overall effect: 2	Z = 1.26	6 (P = 0	).21)			
IsMn plus betablocke	rs vers	us bar	nding li	gation		
Wang 2006	8	31	5	30	1.55 [0.57, 4.20]	
Total (95% CI)	-	31	5	30	1.55 [0.57, 4.20]	
Total events	8		5			
Heterogeneity: Not app	licable					
Test for overall effect: 2	Z = 0.86	6 (P = 0	).39)			
IsMn versus banding	ligatio	n				
Abdelfattah 2001	18	53	4	51	4 33 [1 57 11 92]	
Total (95% CI)	10	53	-7	51	4.33 [1.57, 11.92]	
Total events	18		4		,	-
Heterogeneity: Not app	licable		,			
Test for overall effect: 7	Z = 2.84	4 (P = 0	).005)			
					H	
					(	0.05 0.2 1 5 20
					Fav	ours experimental Favours control

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

	Experin	nental	Cont	rol	Risk Ratio	Risk Ratio
IsMn nlus betablor		N reus he	n	kors		
Abmod 2000	6	343 50	0	30	0 74 [0 20 1 88]	
Gourpay 2000	11	46	11	40	1 07 [0 51 2 22]	
Botti 2001	17	40	10	49	1.07 [0.01, 2.22]	
Falli 2001	17	55	10	01	0.00[0.07, 4.00]	
5hina 2005 Zhana 2002	9	00		00	0.82 [0.37, 1.83]	
Total (95% CI)	5	228	0	32 231	1.04 [0.73, 1.50]	•
Total events	48		47			
Heterogeneity: Tau <sup>2</sup>	= 0.00;	Chi <sup>2</sup> = 2	.82, df	= 4 (P	= 0.59); l <sup>2</sup> = 0%	
Test for overall effect	ct: Z = 0.2	23 (P =	0.82)			
IsMn plus beta-blo	ckers ve	rsus b	andino	ligatio	on or sclerotherapy	
Agrawal 2002	7	51	7	53	1 04 [0 30 2 75]	
Agrawal 2002	6	25	,	20	0.94[0.33, 2.73]	
-1111du 2009	20	55	40	39	0.04 [0.02, 2.17]	
LU 2008	30	51	42	6U E1	0.70[0.52, 0.95]	
	17	51	1/	51	1.00 [0.56, 1.73]	
Romero 2006	11	57	10	52	1.00 [0.46, 2.17]	
Sarin 2005	4	66	6	/1	0.72[0.21, 2.43]	
Shiha 2005	9	60	8	61	1.14[0.47, 2.77]	
Villanueva 1996	4	43	9	43	0.44 [0.15, 1.33]	•
Villanueva 2001 Total (95% CI)	23	72 496	30	72 502	0.77 [0.50, 1.18] 0.79 [0.65, 0.96]	•
Total events	111		137			
Heterogeneity: Tau <sup>2</sup>	<sup>e</sup> = 0.00; (	Chi² = 3	.74, df	= 8 (P	= 0.88); l <sup>2</sup> = 0%	
Heterogeneity: Tau <sup>2</sup> Test for overall effections SMn plus betabloc	* = 0.00; ( ct: Z = 2.; ckers ver	Chi² = 3 34 (P = rsus TI	.74, df 0.02) PS	= 8 (P	= 0.88); l <sup>2</sup> = 0%	
Heterogeneity: Tau <sup>2</sup> Test for overall effect IsMn plus betabloc Escorsell 2002 Total (95% CI)	<sup>t</sup> = 0.00; ( ct: Z = 2.3 ckers ver 11	Chi <sup>2</sup> = 3 34 (P = rsus TI 44 44	8.74, df 0.02) PS 13	= 8 (P 47 47	= 0.88); l <sup>2</sup> = 0% 0.90 [0.45, 1.80] 0.90 [0.45, 1.80]	*
Heterogeneity: Tau <sup>2</sup> Test for overall effect IsMn plus betabloc Escorsell 2002 Fotal (95% CI) Fotal events	t = 0.00; 0 ct: Z = 2.3 ckers ver 11	Chi <sup>2</sup> = 3 34 (P = rsus TI 44 44	5.74, df 0.02) PS 13 13	= 8 (P 47 47	= 0.88); l <sup>2</sup> = 0% 0.90 [0.45, 1.80] <b>0.90 [0.45, 1.80]</b>	-
Heterogeneity: Tau <sup>2</sup> Test for overall effect IsMn plus betabloc Escorsell 2002 Total (95% CI) Total events Heterogeneity: Not a	t = 0.00; 0 ct: Z = 2.3 ckers ver 11 11 applicabl	Chi <sup>2</sup> = 3 34 (P = rsus TI 44 44 e	5.74, df 0.02) PS 13 13	= 8 (P 47 47	= 0.88); l <sup>2</sup> = 0% 0.90 [0.45, 1.80] <b>0.90 [0.45, 1.80]</b>	-
Heterogeneity: Tau <sup>2</sup> Test for overall effect sMn plus betabloc Escorsell 2002 Total (95% CI) Total events Heterogeneity: Not a Test for overall effect	<pre>E = 0.00; 0 ct: Z = 2.3 ckers ver</pre>	Chi <sup>2</sup> = 3 34 (P = rsus TI 44 44 44 e 29 (P =	5.74, df 0.02) PS 13 13 0.77)	= 8 (P 47 47	= 0.88); l <sup>2</sup> = 0% 0.90 [0.45, 1.80] <b>0.90 [0.45, 1.80]</b>	-
Heterogeneity: Tau <sup>2</sup> Test for overall effect IsMn plus betabloc Escorsell 2002 Total (95% CI) Total events Heterogeneity: Not a Test for overall effect isMn plus betabloc	<pre>2 = 0.00; 0 ct: Z = 2.3 ckers ver 11 11 applicabl ct: Z = 0.3 ckers ver</pre>	Chi <sup>2</sup> = 3 34 (P = rsus TI 44 44 44 e 29 (P = rsus Isl	.74, df 0.02) PS 13 13 0.77) Vin plu	= 8 (P 47 47 5 betal	= 0.88); I <sup>2</sup> = 0% 0.90 [0.45, 1.80] 0.90 [0.45, 1.80]	ng ligation
Heterogeneity: Tau <sup>2</sup> Test for overall effect IsMn plus betabloc Escorsell 2002 Total (95% CI) Total events Heterogeneity: Not a Fest for overall effect isMn plus betabloc Garcia-Pagan 2009	<ul> <li>= 0.00; (</li> <li>ct: Z = 2.3</li> <li>ckers ver</li> <li>11</li> <li>applicabl</li> <li>ct: Z = 0.2</li> <li>ckers ver</li> <li>15</li> </ul>	Chi <sup>2</sup> = 3 34 (P = rsus TI 44 44 44 e 29 (P = rsus Isl 78	5.74, df 0.02) PS 13 13 0.77) Vin plu 16	= 8 (P 47 47 5 betal 80	= 0.88); I <sup>2</sup> = 0% 0.90 [0.45, 1.80] 0.90 [0.45, 1.80] blockers and bandir 0.96 [0.51, 1.81]	ng ligation
Heterogeneity: Tau <sup>2</sup> Test for overall effect skIn plus betabloc Escorsell 2002 Total (95% C1) Total events Heterogeneity: Not a Test for overall effect skIn plus betabloc Garcia-Pagan 2009 .o 2009	<ul> <li>= 0.00; (</li> <li>t: Z = 2.3</li> <li>t: Skers ver</li> <li>11</li> <li>applicabl</li> <li>ct: Z = 0.3</li> <li>ckers ver</li> <li>15</li> <li>13</li> </ul>	Chi <sup>2</sup> = 3 34 (P = rsus TI 44 44 29 (P = rsus Isl 78 60	5.74, df 0.02) PS 13 13 0.77) Vin plu 16 16	= 8 (P 47 47 5 betal 80 60	= 0.88); I <sup>2</sup> = 0% 0.90 [0.45, 1.80] 0.90 [0.45, 1.80] 0.045, 1.80] 0.056 [0.51, 1.81] 0.81 [0.43, 1.54]	ng ligation
Heterogeneity: Tau <sup>2</sup> Test for overall effect IsMn plus betabloc Escorsell 2002 Total (95% Cl) Total events -leterogeneity: Not i Test for overall effect isMn plus betabloc Garcia-Pagan 2009 .o 2009 Subtotal (95% Cl)	<ul> <li>= 0.00; (ct: Z = 2.3)</li> <li>ckers ver</li> <li>11</li> <li>applicabil</li> <li>ct: Z = 0.3)</li> <li>ckers ver</li> <li>15</li> <li>13</li> </ul>	Chi <sup>2</sup> = 3 34 (P = rsus TI 44 44 29 (P = rsus Isl 78 60 138	5.74, df 0.02) PS 13 13 0.77) Vin plu 16 16	= 8 (P 47 47 5 betal 80 60 140	= 0.88); I <sup>2</sup> = 0% 0.90 [0.45, 1.80] 0.90 [0.45, 1.80] blockers and bandir 0.96 [0.51, 1.81] 0.81 [0.43, 1.54] 0.88 [0.65, 1.39]	ng ligation
Heterogeneity: Tau <sup>2</sup> Test for overall effect IsMn plus betabloc Escorsell 2002 Total (95% CI) Total events Heterogeneity: Not a Test for overall effect IsMn plus betabloc Garcia-Pagan 2009 .o 2009 Subtotal (95% CI) Total events	2 = 0.00; ( ct: Z = 2.3 ckers ver 11 11 applicabl ct: Z = 0.3 ckers ver 15 13 28	Chi <sup>2</sup> = 3 34 (P = rsus TI 44 44 e 29 (P = rsus Isl 78 60 138	5.74, df 0.02) PS 13 13 0.77) Vin plu 16 16 32	= 8 (P 47 47 5 betal 80 60 140	<ul> <li>0.88); l<sup>2</sup> = 0%</li> <li>0.90 [0.45, 1.80]</li> <li>0.90 [0.45, 1.80]</li> <li>blockers and bandir</li> <li>0.96 [0.51, 1.81]</li> <li>0.81 [0.43, 1.54]</li> <li>0.88 [0.56, 1.39]</li> </ul>	ng ligation
Heterogeneity: Tau <sup>2</sup> Test for overall effect IsMn plus betabloc Escorsell 2002 Total (95% CI) Total events Heterogeneity: Not a Fest for overall effect isMn plus betabloc Garcia-Pagan 2009 0 2009 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup>	= 0.00; ( ct: Z = 2.3 ckers ver 11 11 applicabl ct: Z = 0.3 ckers ver 15 13 28 c = 0.00; (	Chi <sup>2</sup> = 3 34 (P = rsus TI 44 44 29 (P = rsus Isl 78 60 138 Chi <sup>2</sup> = 0	5.74, df 0.02) PS 13 13 0.77) Vin plu 16 16 32 5.14, df	= 8 (P 47 47 5 betal 80 60 140 = 1 (P	= 0.88); I <sup>2</sup> = 0% 0.90 [0.45, 1.80] 0.90 [0.45, 1.80] 0.90 [0.45, 1.80] 0.06 [0.51, 1.81] 0.81 [0.43, 1.54] 0.88 [0.56, 1.39] = 0.71); I <sup>2</sup> = 0%	ngligation
Heterogeneity: Tau <sup>2</sup> Test for overall effect IsMn plus betabloc Escorsell 2002 Total (95% CI) Total events Heterogeneity: Not <i>i</i> Test for overall effect isMn plus betabloc Garcia-Pagan 2009 .0 2009 Subtotal (95% CI) Total events -leterogeneity: Tau <sup>2</sup> Test for overall effect	<ul> <li>= 0.00; (ct; Z = 2.3)</li> <li>= 2.3</li> <li>= 2</li></ul>	Chi <sup>2</sup> = 3 34 (P = rsus TI 44 44 29 (P = rsus Isl 78 60 138 Chi <sup>2</sup> = 0 53 (P =	5.74, df 0.02) <b>PS</b> 13 13 0.77) <b>Vin plu</b> 16 16 16 32 5.14, df 0.59)	= 8 (P 47 47 5 betal 80 60 140 = 1 (P	0.90 [0.45, 1.80] 0.90 [0.45, 1.80] 0.90 [0.45, 1.80] 0.90 [0.45, 1.80] 0.00 [0.51, 1.81] 0.81 [0.43, 1.54] 0.81 [0.43, 1.54] 0.88 [0.56, 1.39] = 0.71); I <sup>2</sup> = 0%	ng ligation
Heterogeneity: Tau <sup>2</sup> Test for overall effect IsMn plus betabloc Escorsell 2002 Total (95% CI) Total events Heterogeneity: Not i Test for overall effect isMn plus betabloc Sarcia-Pagan 2009 .o 2009 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> Test for overall effect isMn plus betabloc	= 0.00; f ct; Z = 2.3 ckers veri 11 applicabl ct; Z = 0.3 ckers veri 15 13 28 = 0.00; f ct; Z = 0.3 ckers and ct; Z = 0.3	Chi <sup>2</sup> = 3 34 (P = rsus TI 44 44 e 29 (P = rsus Isl 78 60 138 Chi <sup>2</sup> = 0 53 (P = d band	5.74, df 0.02) PS 13 13 0.77) Vin plu 16 16 16 32 1.14, df 0.59) ing liga	= 8 (P 47 47 s betal 80 60 140 = 1 (P ation v	<ul> <li>0.88); I<sup>2</sup> = 0%</li> <li>0.90 [0.45, 1.80]</li> <li>0.90 [0.45, 1.80]</li> <li>0.90 [0.45, 1.80]</li> <li>0.96 [0.51, 1.81]</li> <li>0.81 [0.43, 1.54]</li> <li>0.88 [0.56, 1.39]</li> <li>= 0.71); I<sup>2</sup> = 0%</li> <li>ersus banding ligati</li> </ul>	ng ligation
Heterogeneity: Tau <sup>2</sup> Test for overall effect IsMn plus betabloc Escorsell 2002 Total (95% CI) Total events Heterogeneity: Not a Test for overall effec isMn plus betabloc Garcia-Pagan 2009 .o 2009 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> Test for overall effec isMn plus betabloc Amad 2009	<ul> <li>= 0.00;</li> <li>= 0.00;</li> <li>= 2.3</li> <li>= 11</li> <li>= 11</li></ul>	Chi <sup>2</sup> = 3 34 (P = rsus TI 44 44 e 29 (P = rsus Isl 78 60 138 Chi <sup>2</sup> = 0 53 (P = d band 37	5.74, df 0.02) PS 13 13 0.77) VIn plu 16 16 32 5.14, df 0.59) ing liga	= 8 (P 47 47 s betal 80 60 140 = 1 (P 39	<ul> <li>0.88); I<sup>2</sup> = 0%</li> <li>0.90 [0.45, 1.80]</li> <li>0.90 [0.45, 1.80]</li> <li>blockers and bandir</li> <li>0.96 [0.51, 1.81]</li> <li>0.81 [0.43, 1.54]</li> <li>0.88 [0.56, 1.39]</li> <li>= 0.71); I<sup>2</sup> = 0%</li> <li>ersus banding ligati</li> <li>0.92 [0.37, 2.20]</li> </ul>	ng ligation
Heterogeneity: Tau <sup>2</sup> Test for overall effect IsMn plus betabloc Escorsell 2002 Total (95% CI) Total events Heterogeneity: Not a Test for overall effect IsMn plus betabloc Garcia-Pagan 2009 0 2009 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> Test for overall effect IsMn plus betabloc Ahmad 2009	<ul> <li>= 0.00; t</li> <li>= 2.3</li> <li>ckers ver</li> <li>11</li> <li>11</li> <li>applicable</li> <li>ckers ver</li> <li>15</li> <li>13</li> <li>28</li> <li>= 0.00; t</li> <li>ct: Z = 0.4</li> <li>ckers and</li> <li>7</li> <li>2</li> </ul>	Chi <sup>2</sup> = 3 34 (P = rsus TI 44 44 29 (P = rsus Isl 78 60 138 Chi <sup>2</sup> = 0 53 (P = d band 37 89	.74, df 0.02) PS 13 13 0.77) VIn plu 16 16 32 1.14, df 0.59) ing lig: 8 2	= 8 (P 47 47 5 betal 80 140 = 1 (P ation vo 39	<ul> <li>0.88); I<sup>2</sup> = 0%</li> <li>0.90 [0.45, 1.80]</li> <li>0.90 [0.45, 1.80]</li> <li>0.90 [0.45, 1.80]</li> <li>0.90 [0.51, 1.81]</li> <li>0.81 [0.43, 1.54]</li> <li>0.88 [0.56, 1.39]</li> <li>= 0.71); I<sup>2</sup> = 0%</li> <li>ersus banding ligati</li> <li>0.92 [0.37, 2.29]</li> <li>0.67 [0.12, 2.64]</li> </ul>	ng ligation
Heterogeneity: Tau <sup>2</sup> Test for overall effect IsMn plus betabloc Escorsell 2002 Total (95% CI) Total events Heterogeneity: Not 1 Test for overall effect IsMn plus betabloc Sarcia-Pagan 2009 .o 2009 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> Test for overall effect IsMn plus betabloc Ahmad 2009 Kumar 2009 Subtotal (95% CI)	<ul> <li>= 0.00; t</li> <li>= 2.3</li> <li>ckers ver</li> <li>11</li> <li>11</li> <li>applicabl</li> <li>ct: Z = 0.2</li> <li>ckers ver</li> <li>15</li> <li>13</li> <li>28</li> <li>= 0.00; t</li> <li>ct: Z = 0.2</li> <li>ckers and</li> <li>7</li> <li>2</li> </ul>	Chi <sup>2</sup> = 3 34 (P = sus TI 44 44 44 e 29 (P = crsus Isl 60 138 Chi <sup>2</sup> = 0 Chi <sup>2</sup> = 0 Chi <sup>2</sup> = 0 37 88 225	<ul> <li>.74, df</li> <li>.0.02)</li> <li>PS</li> <li>13</li> <li>13</li> <li>0.77)</li> <li>Mn plu</li> <li>16</li> <li>16</li> <li>32</li> <li>1.14, df</li> <li>0.59)</li> <li>ing ligation and a second s</li></ul>	47 47 47 80 140 = 1 (P 39 128	<ul> <li>0.88); I<sup>2</sup> = 0%</li> <li>0.90 [0.45, 1.80]</li> <li>0.90 [0.45, 1.80]</li> <li>0.90 [0.45, 1.80]</li> <li>0.96 [0.51, 1.81]</li> <li>0.81 [0.43, 1.54]</li> <li>0.88 [0.56, 1.39]</li> <li>= 0.71); I<sup>2</sup> = 0%</li> <li>arsus banding ligati</li> <li>0.92 [0.37, 2.29]</li> <li>0.67 [0.12, 3.94]</li> <li>0.88 [0.38, 1.94]</li> </ul>	ng ligation
Heterogeneity: Tau <sup>2</sup> Test for overall effect IsMn plus betabloc Escorsell 2002 Total (95% CI) Total events Heterogeneity: Not a Test for overall effect IsMn plus betabloc Garcia-Pagan 2009 .o 2009 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> Test for overall effect IsMn plus betabloc Ahmad 2009 Kumar 2009 Subtotal (95% CI) Total events	<ul> <li>= 0.00;</li> <li>:= 0.00;</li> <li>:: Ct: Z = 2.:</li> <li>: Ckers ver</li> <li>11</li> <li>11</li> <li>applicable</li> <li>: Ckers ver</li> <li>15</li> <li>13</li> <li>: 28</li> <li>: 20.00;</li> <li>: Ckers and</li> <li>: Ckers and</li> <li>: Ckers and</li> <li>: 2</li> <li>: Ckers and</li> <li>: 2</li> <li>: 2</li> <li>: 2</li> <li>: 2</li> <li>: 3</li> </ul>	Chi <sup>2</sup> = 3 34 (P = rsus TI 44 44 e 29 (P = rsus Isl 78 60 138 Chi <sup>2</sup> = C 53 (P = 37 88 125	.74, df 0.02) PS 13 13 0.77) VIn plu 16 16 32 .14, df 0.59) ing liga 8 3 11	47 47 47 80 60 140 = 1 (P 39 89 128	<ul> <li>0.88); I<sup>2</sup> = 0%</li> <li>0.90 [0.45, 1.80]</li> <li>0.90 [0.45, 1.80]</li> <li>0.90 [0.45, 1.80]</li> <li>0.96 [0.51, 1.81]</li> <li>0.81 [0.43, 1.54]</li> <li>0.88 [0.56, 1.39]</li> <li>= 0.71); I<sup>2</sup> = 0%</li> <li>ersus banding ligati</li> <li>0.92 [0.37, 2.29]</li> <li>0.67 [0.12, 3.94]</li> <li>0.86 [0.38, 1.94]</li> </ul>	ng ligation
Heterogeneity: Tau <sup>2</sup> Test for overall effect IsMn plus betabloc Escorsell 2002 Total (95% CI) Total events Heterogeneity: Not a Test for overall effect IsMn plus betabloc Garcia-Pagan 2009 0 2009 Subtotal (95% CI) Total events - Heterogeneity: Tau <sup>2</sup> Test for overall effect Subtotal (95% CI) Total events - Heterogeneity: Tau <sup>2</sup> Fest for overall effect	= 0.00; t = 0.	Chi <sup>2</sup> = 3 34 (P = $rsus TI$ 44 44 44 e 29 (P = $rsus Isl$ 60 138 Chi <sup>2</sup> = 0 53 (P = $rsus Isl$ 78 60 138 Chi <sup>2</sup> = 0 37 88 125 Chi <sup>2</sup> = 0 Chi <sup></sup>	.74, df 0.02) PS 13 13 0.77) In plu 16 16 16 32 1.14, df 0.59) ing liga 8 3 11 1.10, df 0.72)	47 47 5 betal 80 140 = 1 (P 39 89 128 = 1 (P	$\begin{array}{l} 0.88); \ l^2 = 0\%\\ 0.90 \ [0.45, 1.80]\\ 0.90 \ [0.45, 1.80]\\ 0.90 \ [0.45, 1.80]\\ 0.90 \ [0.45, 1.80]\\ 0.81 \ [0.43, 1.54]\\ 0.81 \ [0.43, 1.54]\\ 0.81 \ [0.43, 1.54]\\ 0.81 \ [0.43, 1.54]\\ 0.81 \ [0.56, 1.39]\\ 0.81 \ [0.43, 1.54]\\ 0.81 \ [0.56, 1.39]\\ 0.81 \ [0.56, 1.39]\\ 0.81 \ [0.56, 1.39]\\ 0.81 \ [0.56, 1.39]\\ 0.81 \ [0.56, 1.39]\\ 0.81 \ [0.58, 1.94]\\ 0.86 \ [0.38, 1.94]\\ 0.86 \ [0.58, 1.94]\\ 0.86$	ng ligation
Heterogeneity: Tau <sup>2</sup> Test for overall effect IsMn plus betabloc Escorsell 2002 Total (95% Cl) Total events Heterogeneity: Not i Test for overall effect IsMn plus betabloc Garcia-Pagan 2009 Lo 2009 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> Test for overall effect Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> Test for overall effect	= 0.00; t = 0.00; t t: $Z = 2.3$ ters ver 11 11 applicabl t: $Z = 0.3$ ters ver 15 13 28 = 0.00; t ct: $Z = 0.3$ ters and 7 2 9 = 0.00; t ct: $Z = 0.3$	Chi <sup>2</sup> = 3 34 (P = 44 44 44 e 29 (P = 78 60 138 Chi <sup>2</sup> = C 53 (P = 125 Chi <sup>2</sup> = C 37 88 125 Chi <sup>2</sup> = C 36 (P =	.74, df 0.02) PS 13 13 0.77) Mn plu 16 16 16 32 .14, df 0.59) s 11 1,10, df 10, 0,72)	47 47 47 s betall 80 60 140 = 1 (P 39 89 128 = 1 (P	$\begin{array}{l} 0.38); \ l^2 = 0\%\\ 0.90 \ [0.45, 1.80]\\ 0.90 \ [0.45, 1.80]\\ 0.90 \ [0.45, 1.80]\\ 0.96 \ [0.51, 1.81]\\ 0.81 \ [0.43, 1.54]\\ 0.88 \ [0.56, 1.39]\\ = 0.71); \ l^2 = 0\%\\ \end{array}$	ng ligation

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

	Experim	ental	Cont	rol	Risk Ratio	Risk Ratio
		N	n	N		
ISMn plus betabloo	kers vers	us beta	ablocke	ers		-
Gournay 2000	18	46	28	49	0.68 [0.44, 1.06]	
Patti 2001	30	53	25	51	1.15 [0.80, 1.66]	
Shiha 2005	25	60	31	60	0.81 [0.55, 1.19]	
Zhang 2002	7	34	13	32	0.51 [0.23, 1.11]	
Total (95% CI)		193		192	0.82[0.60, 1.11]	<b>—</b>
Total events	80		97			
Heterogeneity: I au <sup>2</sup>	= 0.04; Cf	ייי = 5.4 גער	40, df =	3 (P = 0	).15); l² = 44%	
l est for overall effec	ct: Z = 1.29	(P = 0)	.20)			
IsMn plus betabloo	kers vers	us ban	dinalia	ation	or sclerotherapy	
Agrawal 2002	13	51	10	53	1 35 [0 65 2 80]	<b>_</b>
0 2008	10	61	28	60	1 72 [1 28 2 32]	
Patch 2002	10	51	20	51	0.70[0.45 1.00]	_ <b>_</b>
Romero 2006	27	57	24	52	1 03 [0.40, 1.09]	_ <b>_</b>
Sarin 2005	18	66	10	71	1 94 [0 96 3 89]	
Shiha 2005	25	60	17	61	1.54 [0.50, 5.05]	<b>-</b>
Villanuova 1006	11	43	23	43	0.48[0.27_0.86]	<b>_</b>
Villanueva 1990	26	72	20	72	0.40 [0.27, 0.00]	
Total (95% CI)	20	461	50	463	1.06 [0.75, 1.48]	•
Total events	188		175			T
Heterogeneity: Tau <sup>2</sup>	- 0 17· Cł	ni2 – 20	52 df -	- 7 (P -	0 0001): 12 - 76%	
Test for overall effer	z = 0.17, 01	(P=0	.76)	- / (i =	0.0001),1 = 7070	
			- /			
IsMn plus betabloo	kers vers	us IsM	n plus l	oetablo	ckers and banding li	gation
Garcia-Pagan 2009	27	78	22	80	1.26 [0.79, 2.01]	
Lo 2009	31	60	23	60	1.35 [0.90, 2.02]	+=-
Total (95% CI)		138		140	1.31 [0.96, 1.78]	◆
Total events	58		45			
Heterogeneity: Tau <sup>2</sup>	= 0.00; Cł	ni² = 0.0	05, df =	1 (P = 0	0.83); I <sup>2</sup> = 0%	
Test for overall effect	ct: Z = 1.73	(P = 0	.08)			
IsMn plus betabloo	kers vers	us TIP	S			
Escorsell 2002	22	44	8	47	2.94 [1.46, 5.90]	
Subtotal (95% CI)		44		47	2.94 [1.46, 5.90]	$\bullet$
Total events	22		8			
Heterogeneity: Not a	applicable					
Test for overall effect	ct: Z = 3.03	6 (P = 0	.002)			
In Manuface In start 1		h a n al '			ue hen dien line (*	
isiwin plus betabloo	kers and	pandin	ig ligati	on vers	us panding ligation	
Kumar 2009	14	88	16	89	0.88 [0.46, 1.70]	
Subtotal (95% CI)		88		89	0.68 [0.46, 1.70]	
Total events	14		16			
Heterogeneity: Not a	applicable					
I est for overall effect	ct: $Z = 0.37$	(P = 0	.71)			
						0.1 0.2 0.5 1 2 5 1
						Favours experimental Favours control

1	
2	
2	
3	
4	
5	
6	
7	
<i>'</i>	
8	
9	
1	0
1	1
1	2
1	3
1	4
1	5
1	6
1	7
1	8
1	9
2	0
2	1
2	2
2	2 2
2	3
2	4
2	5
2	6
2	7
~	1
2	8
2	9
3	0
2	1
5	2
3	2
3	3
3	4
3	5
3	6
3	7
2	, 0
3	0
3	9
4	0
4	1
4	2

# 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 nonspecific 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 guestion, 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.