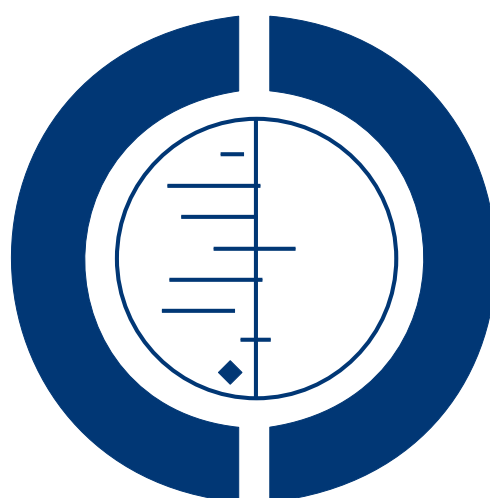# Beta-blocker plus nitrates for secondary prevention of variceal bleeding (Protocol)

Sharma BC, Gluud LL, Sarin SK

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Beta-blocker plus nitrates for secondary prevention of variceal bleeding (Protocol)

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Beta-blocker plus nitrates for secondary prevention of variceal bleeding

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A B S T R A C T

This is the protocol for a review and there is no abstract. The objectives are as follows:

The objectives are to assess the benefits and harms of combination of a beta-blocker plus a nitrate for prevention of variceal rebleeding.

BACKGROUND

Varices are present in 30% of patients with compensated and 60% of patients with decompensated cirrhosis (D'Amico 1997; Tripathi 2001). Variceal bleeding occurs in one-third of these patients with mortality of 50% (Tripathi 2001). Patients with portal hypertension who have bled from oesophageal varices have a very high risk of variceal rebleeding. The risk of recurrence of haemorrhage from oesophageal varices is 60% to 70% at one year, if no therapy for prevention of variceal rebleeding is instituted (Bernard 1997; Bernard-Chabert 2004). Factors determining the high risk of recurrence of variceal hemorrhage are active bleeding on endoscopy, large esophageal varices, severity of index bleed, severity of portal hypertension as determined by hepatic venous pressure gradient (HVPG) measurement, hepatic decompensation, presence of encephalopathy, and renal impairment (Gluud 1988; de Franchis 1992; Zaman 2005). Since there is high risk of recurrence of variceal haemorrhage, patients with variceal bleeding should be given effective therapy to prevent recurrence of variceal bleeding.

For prevention of recurrent variceal haemorrhage, drugs, endoscopic modes of treatment, surgery, or transjugular intrahepatic portosystemic shunt are used (Zaman 2005). Drug therapy in portal hypertension is administered to normalize the increased portal blood inflow by using splanchnic vasoconstrictors like beta-blockers or to reduce intrahepatic vascular resistance by using isosorbide mononitrate. Beta-blockers (propranolol or nadolol) are the most effective agents for prevention of variceal rebleeding (Tripathi 2001). Addition of isosorbide mononitrate increases the efficacy of beta-blockers (Tripathi 2001). The therapeutic goals of drug therapy are to attain reduction in HVPG to 20% of baseline value or to 12 mm Hg to prevent or reduce the risk of rebleeding from varices (Groszmann 1990; Feu 1995). Reduction in HVPG to 12 mm Hg or to 20% of baseline value are criteria used for labelling responders. Patients not showing reduction in HVPG of this degree are called nonresponders. With drug therapy, about 45% to 63% of patients are non-responders, and 46% to 65% of non-responders have recurrence of variceal haemorrhage on drug therapy compared to 7% to 13% of responders (Zaman 2005). It has been found that haemodynamic response to drug therapy of portal hypertension is usually sustained even after a long-term follow-up (Villanueva 2004).

Combination drug therapy for prevention of rebleeding comprises a vasoconstrictor (a beta-blocker: propranolol or nadolol) and a nitrovasodilator (isosorbide mononitrate). The combination of a beta-blocker and a nitrate leads to synergistic effect on reduction of portal pressure. The combination of propranolol and isosorbide mononitrate leads to greater reduction in portal pressure, better haemodynamic control and more clinical benefits than achieved with propranolol alone (Feu 1995; Villanueva 1996; Villanueva 2001; Tripathi 2001; Bureau 2002; Patch 2002; Zaman 2005). In patients not responding to beta-blockers, isosorbide mononitrate should be added. But this requires HVPG measurement before adding isosorbide mononitrate. HVPG measurement should be repeated within 1 to 2 weeks of starting treatment because the risk of rebleeding is very high in the first six weeks after index bleed. Other workers prefer to add isosorbide mononitrate to all the patients, thus avoiding repeat HVPG measurements. The studies have shown that addition of isosorbide mononitrate to beta-blockers increase response rates in patients who do not show target reduction in HVPG with beta-blockers (Bureau 2002). About one-third of non-responders to beta-blockers respond after addition of isosorbide mononitrate.

Randomised trials and reviews have found combined drug therapy to be effective for prevention of rebleeding from oesophageal varices. However, the therapeutic effects in different trials are variable, controversial and contradictory. The present Cochrane systemic review will study the beneficial and harmful effects of combined drug therapy for prevention of rebleeding from varices.

OBJECTIVES

The objectives are to assess the benefits and harms of combination of a beta-blocker plus a nitrate for prevention of variceal rebleeding.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised clinical trials irrespective of blinding, publication status, or language.

Types of participants

We will include patients with portal hypertension of any aetiology having oesophageal varices with history of upper gastrointestinal bleeding, that is likely to be variceal in origin.

Types of interventions

We will make the following comparisons:
- Combination of a beta-blocker plus a nitrate versus no intervention
- Combination of a beta-blocker plus a nitrate versus placebo
- Combination of a beta-blocker plus a nitrate versus a beta-blocker.

Other co-interventions will be allowed if used equally in the interventions arms.

Types of outcome measures

Primary outcome measure

(1) Rebleeding diagnosed by endoscopy or identification of hae-matemesis, maelena, or gastric aspirate containing blood.

(2) All-cause mortality (at maximum follow-up).

Secondary outcome measures

(3) Rebleeding-related mortality.

(4) Adverse events. They will be defined as any untoward medical occurrence not necessarily having a causal relationship with the treatment, but resulting in a dose reduction or discontinuation of the intervention (ICH-GCP 1997).

(5) Quality-of-life measures (as reported by authors).

Search methods for identification of studies

We will search for eligible trials in *The Cochrane Hepato-Biliary Group Controlled Trials Register*, the *Cochrane Central Register of Controlled Trials* in *The Cochrane Library*, *MEDLINE*, *EMBASE*, and *Science Citation Index Expanded* (Royle 2003). The preliminary search strategies are given in Appendix 1. Additional trials will be identified through scanning of reference lists in relevant papers and conference proceedings and correspondence with experts and pharmaceutical companies.

Data collection and analysis

One author (BCS) will develop the search strategies. Two authors (BCS and SKS) will do the literature searches and extract data. Disagreements will be resolved through discussion. LLG will serve as adjudicator. Excluded trials will be listed with the reason for exclusion. Primary authors of the included trials will be contacted for additional information if outcome measures are not included in the published trial reports.

Generation of allocation sequence, allocation concealment, blinding, and follow-up will be extracted as measures of bias control (Gluud 2001; Kjaergard 2001) using the following definitions:

Generation of the allocation sequence

• Adequate, if the allocation sequence was generated by a computer or random number table. Drawing of lots, tossing of a coin, shuffling of cards, or throwing dice will be considered as adequate if a person who was not otherwise involved in the recruitment of participants performed the procedure.

• Unclear, if the trial was described as randomised, but the method used for the allocation sequence generation was not described.

• Inadequate, if a system involving dates, names, or admittance numbers were used for the allocation of patients. These studies are known as quasi-randomised and will be excluded from the review.

Allocation concealment

• Adequate, if the allocation of patients involved a central independent unit, on-site locked computer, or sealed envelopes.

• Unclear, if the trial was described as randomised, but the method used to conceal the allocation was not described.

• Inadequate, if the allocation sequence was known to the investigators who assigned participants. Such studies will be excluded.

Blinding

• Adequate, if blinded outcome assessment, data extraction, or data analysis was reported. The nature of the interventions assessed precludes adequate blinding of patients and health care providers.

Follow-up

• Adequate, if the numbers and reasons for dropouts and withdrawals in all intervention groups were described or if it was specified that there were no dropouts or withdrawals.

• Unclear, if the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated.

• Inadequate, if the number or reasons for dropouts and withdrawals were not described.

The number and reasons for losses to follow-up will be extracted to assess the risk of attrition bias.

From the individual trials we will also extract data on the baseline characteristics of patients (inclusions criteria, mean age, sex, and number of patients with alcoholic liver disease), treatments (type and dose of therapy), and trials (country of origin, publication status, funding, duration of follow up, and all outcomes).

Further, we will extract information on whether sample-size and intention-to-treat analysis were performed in the trials.

Statistical analyses

The analyses will be performed in RevMan (RevMan 2003) and STATA version 8.0 for Windows. Results of meta-analyses will be presented as relative risks (RR) with 95% confidence intervals (95% CI). Random-effects models will be used in the primary analyses because of the expected clinical heterogeneity. Chi-squared analyses will be performed to estimate inter-trial heterogeneity. All analyses will be performed using the intention-to-treat principle including all randomised patients irrespective of compliance or follow-up. For patients with missing data, carry forward of the last observed response will be used. Worst-case scenario analyses in which patients with missing data will be counted as treatment failures will be performed to assess the risk of attrition bias. Random-effects meta-regression analyses will be performed to assess the potential sources of heterogeneity. Fixed-effect meta-analyses will be performed in which trials will be grouped according to significant predictors of heterogeneity identified in the meta-regression analyses. The risk of bias will be evaluated in regression analyses of funnel plot asymmetry and in subgroup meta-analyses

with trials stratified by publication status and allocation concealment. The outcome measure in the regression and subgroup analyses will be rebleeding and mortality.

REFERENCES

Additional references

Bernard 1997
Bernard B, Lebrec D, Mathurin P, Opolon P, Poynard T. ß-adrenergic antagonists in the prevention of gastrointestinal rebleeding in patients with cirrhosis: a meta-analysis. *Hepatology* 1997;**25**:63–70.

Bernard-Chabert 2004
Bernard-Chabert B, Sauerbruch T, Lo GH, Sanyal AJ, Henderson M, Shiha G, et al.Prevention of rebleeding. Portal hypertension IV. Proceedings of the fourth Baveno international consensus workshop on methodology of diagnosis and treatment. Oxford: UK: Blackwell Science, 2004:262–84.

Bureau 2002
Bureau C, Peron JM, Alric L, Morales J, Sanchez J, Barange K, et al."A la carte" treatment of portal hypertension: adapting medical therapy to hemodynamic response for the prevention of bleeding. *Hepatology* 2002;**36**:1361–6.

D'Amico 1997
D'Amico G, Luca A. Natural history: clinical-haemodynamic correlations: prediction of the risk of bleeding. *Baillieres Clinical Gastroenterology* 1997;**11**:243–56.

de Franchis 1992
de Franchis R, Primignani M. Why do varices bleed?. *Gastroenterology Clinics of North America* 1992;**21**:85–101.

Feu 1995
Feu F, Garcia-Pagan JC, Bosch J, Luca A, Teres J, Escorsell A, et al.Relationship between portal pressure response to pharmacotherapy and risk of recurrent variceal haemorrhage in patients with cirrhosis. *Lancet* 1995;**346**(8982):1056–9.

Gluud 1988
Gluud C, Henriksen JH, Nielsen G, The Copenhagen Study Group For Liver Diseases. Prognostic indicators in alcoholic cirrhotic men. *Hepatology* 1988;**8**(2):222–7.

Gluud 2001
Gluud C. Alcoholic hepatitis: no glucocorticosteroids?. *Steatohepatitis (NASH and ASH) - Falk Symposium 121*. Lancaster: Kluwer Academic Publisher, 2001:322–42.

Groszmann 1990
Groszmann RJ, Bosch J, Grace ND, Conn HO, Garcia-Tsao G, Navasa M, et al.Hemodynamic events in a prospective randomised trial of propranolol versus placebo in the prevention of a first variceal hemorrhage. *Gastroenterology* 1990;**99**(5):1401–7.

ICH-GCP 1997
International Conference on Harmonisation Expert Working Group. *Code of Federal Regulations & International Conference on Harmonization Guidelines*. Media: Parexel Barnett, 1997.

Kjaergard 2001
Kjaergard LL, Villumsen J, Gluud C. Reported methodological quality and discrepancies between large and small randomised trials in meta-analyses. *Annals of Internal Medicine* 2001;**135**(11):982–9. [MEDLINE: 11730399]

Patch 2002
Patch D, Sabin CA, Goulis J, Gerunda G, Greenslade L, Merkel C, 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**:1013–9.

RevMan 2003
Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 4.2 for Windows. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2003.

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

Tripathi 2001
Tripathi D, Hayes PC. A drug therapy for the prevention of variceal hemorrhage. *Alimentary Pharmacology and Therapeutics* 2001;**15**: 291–310.

Villanueva 1996
Villanueva C, Balanzo J, Novella MT, Soriano G, Sainz S, Torras X, et al.Nadolol plus isosorbide mononitrate compared with sclerotherapy for the prevention of variceal rebleeding. *New England Journal of Medicine* 1996;**334**(25):1624–9.

Villanueva 2001
Villanueva C, Minana J, Ortiz J, Gallego A, Soriano G, Torras X, et al.Endoscopic ligation compared with combined treatment with nadolol and isosorbide mononitrate to prevent recurrent variceal bleeding. *New England Journal of Medicine* 2001;**345**:647–55.

Villanueva 2004
Villanueva C, Lopez-Balaguer JM, Aracil C, Kolle L, Gonzalez B, Minana J, et al.Maintenance of hemodynamic response to treatment for portal hypertension and influence on complications of cirrhosis. *Journal of Hepatology* 2004;**40**:757–65.

Zaman 2005
Zaman A, Chalasani N. Bleeding caused by portal hypertension. *Gastroenterology Clinics of North America* 2005;**34**:623–42.

* Indicates the major publication for the study

APPENDICES

Appendix 1. Search Strategies

Database	Date of search	Search terms	Number of hits
The Cochrane Hepatobiliary Group Controlled Trials Register		(beta-blocker* OR 'adrenergic beta antagonist*' OR propranolol OR atenolol OR nadolol OR metoprolol OR bisoprolol OR carvedilol OR tertatolol OR nipradilol OR penbutolol OR timolol OR mepindolol OR 'isosorbid* mononitrat*' OR imdur OR ismo OR monoket) AND '*esophageal varic*' OR variceal rebleeding OR secondary prophylaxis for variceal bleeding	
The Cochrane Library (Issue 2, 2006)		#1 MeSH descriptor Adrenergic beta-Antagonists explode all trees in MeSH products 8076 #2 MeSH descriptor Propranolol explode all trees in MeSH products 2376 #3 MeSH descriptor Atenolol explode all trees in MeSH products 1464 #4 MeSH descriptor Nadolol explode all trees in MeSH products 153 #5 MeSH descriptor Metoprolol explode all trees in MeSH products 1183 #6 MeSH descriptor Bisoprolol explode all trees in MeSH products 183 #7 MeSH descriptor Penbutolol explode all trees in MeSH products 51 #8 MeSH descriptor Timolol explode all trees in MeSH products 720 #9 beta-blocker* or adrenergic beta antagonist* or propranolol or atenolol or nadolol or metoprolol or bisoprolol or carvedilol or tertatolol or nipradilol or penbutolol or timolol or mepindolol in All Fields in all products 10724 #10 isosorbid* mononitrat* or imdur or ismo or monoket in All Fields in all products 217 #11 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10) 12599 #12 MeSH descriptor Esophageal and	

(Continued)

		Gastric Varices explode all trees in MeSH products 641 #13 *esophageal varic* in All Fields in all products 1099 #14 (#12 OR #13) 1099 #15 (#11 AND #14) 226	
MEDLINE		#127853explode "Adrenergic-beta-Antagonists"/all subheadings #228459explode "Propranolol"/all subheadings #33938explode "Atenolol"/all subheadings #4662explode "Nadolol"/all subheadings #53712explode "Metoprolol"/all subheadings #6534explode "Bisoprolol"/all subheadings #7173explode "Penbutolol"/all subheadings #82593explode "Timolol"/all subheadings #9 71892beta-blocker* or adrenergic beta antagonist* or propranolol or atenolol or nadolol or metoprolol or bisoprolol or carvedilol or tertatolol or nipradilol or penbutolol or timolol or mepindolol #10834isosorbid* mononitrat* or imdur or ismo or monoket #1172593#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 #129288explode "Esophageal-and-Gastric-Varices"/all subheadings #1310983(oesophageal or esophageal) and varic* #1410983#12 or #13 #15592#11 and #14 #16536388random* or blind* or placebo* or meta-analysis #17210#15 and #16	
EMBASE		#1125183explode "beta-adrenergic-receptor-blocking-agent"/all subheadings #252448explode "propranolol"/all subheadings #316176explode "atenolol"/all sub-	

(*Continued*)

		headings #43420explode "nadolol"/all subheadings #515176explode "metoprolol"/all subheadings #62659explode "bisoprolol"/all subheadings #73995explode "carvedilol"/all subheadings #8283explode "tertatolol"/all subheadings #9280explode "nipradilol"/all subheadings #10680explode "penbutolol"/all subheadings #116887explode "timolol"/all subheadings #12207explode "mepindolol"/all subheadings #1386717beta-blocker* or adrenergic beta antagonist* or propranolol or atenolol or nadolol or metoprolol or bisoprolol or carvedilol or tertatolol or nipradilol or penbutolol or timolol or mepindolol #141548isosorbid* mononitrat* or imdur or ismo or monoket #15129630#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 #166445explode "esophagus-varices"/all subheadings #174791(oesophageal or esophageal) and varic* #187440#16 or #17 #19994#15 and #18 #20469358random* or blind* or placebo* or meta-analysis #21288#19 and #20	
Science Citation Index Expanded		#7 289 #6 AND #5 #6 >100,000 TS=(random* or blind* or placebo* or meta-analysis) #5 491 #4 AND #3 #4 5,557 TS=((oesophageal or esophageal)and varic*) #3 41,346 #2 OR #1 #2 349 TS=(isosorbid* mononitrat* or imdur or ismo or monoket)	

(Continued)

		#1 41,109 TS=(beta-blocker* or adrenergic beta antagonist* or propranolol or atenolol or nadolol or metoprolol or bisoprolol or carvedilol or tertatolol or nipradilol or penbutolol or timolol or mepindolol)	

WHAT'S NEW

21 October 2008	Amended	Converted to new RevMan 5 format

HISTORY

Protocol first published: Issue 3, 2007

CONTRIBUTIONS OF AUTHORS

BCS wrote the protocol. SKS approved the contents of the protocol.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital, Rigshospitalet, Denmark.