ANNALS of Hepatology

ORIGINAL ARTICLE

May-June, Vol. 11 No.3, 2012: 369-383

Meta-analysis: beta-blockers versus banding ligation for primary prophylaxis of esophageal variceal bleeding

Natalie Funakoshi,* Yohan Duny,** Jean-Christophe Valats,* Frédérique Ségalas-Largey,* Nicolas Flori,* Michael Bismuth,* Jean-Pierre Daurès,** Pierre Blanc*

* Department of Hepato-gastroenterology B, Hôpital Saint Eloi, Centre Hospitalier Universitaire de Montpellier, France.
** Department of Statistics, Centre Hospitalier Universitaire de Nîmes, France.

ABSTRACT

Aim. To perform an updated meta-analysis comparing β-blockers (BB) with endoscopic variceal banding ligation (EVBL) in the primary prophylaxis of esophageal variceal bleeding. **Material and methods.** Randomized controlled trials were identified through electronic databases, article reference lists and conference proceedings. Analysis was performed using both fixed-effect and random-effect models. Heterogeneity and publication bias were systematically taken into account. Main outcomes were variceal bleeding rates and all-cause mortality, calculated overall and at 6, 12, 18 and 24 months. **Results.** 19 randomized controlled trials were analyzed including a total of 1,483 patients. Overall bleeding rates were significantly lower for the EVBL group: odds ratio (OR) 2.06, 95% confidence interval (CI) [1.55-2.73], p < 0.0001, without evidence of publication bias. Bleeding rates were also significantly lower at 18 months (OR 2.20, 95% CI [1.04-4.60], *P* = 0.04), but publication bias was detected. When only high quality trials were taken into account, results for bleeding rates were no longer significant. No significant difference was found for either bleeding-related mortality or for all-cause mortality overall or at 6, 12, 18 or 24 months. BB were associated with more frequent severe adverse events (OR 2.61, 95% CI 1.60-4.40, *P* < 0.0001) whereas fatal adverse events were more frequent with EVBL (OR 0.14, 95% CI 0.02-0.99, *P* = 0.05). **Conclusion.** EVBL appears to be superior to BB in preventing the first variceal bleed, although this finding may be biased as it was not confirmed by high quality trials. No difference was found for mortality. Current evidence is insufficient to recommend EVBL over BB as first-line therapy.

Key words. Variceal bleeding. Banding ligation. β-blockers. Portal hypertension. Cirrhosis.

INTRODUCTION

Bleeding from esophageal varices is a frequent and serious complication of cirrhosis. Upon diagnosis of cirrhosis, esophageal varices are present in 30-40% of compensated patients and in 60% of decompensated patients.[1] The risk of variceal bleeding is approximately 30%, with a mortality rate of 20-50% for each episode.[1] It is estimated that over a five year period, one out of five cirrhotic patients will die from variceal bleeding.[2] Variceal bleeding can also trigger additional complications of cirrhosis, such as hepato-renal syndrome, hepatic encephalopathy and spontaneous bacterial peritonitis. Given the high morbidity and mortality rates, it is essential to ensure adequate primary prophylaxis of variceal bleeding in cirrhotic patients.

Recommendations from the Baveno V Consensus Workshop[3] as well as published practice guidelines[4] conclude that both non-selective β-blockers (BB) and endoscopic variceal banding ligation (EVBL) are effective in preventing first variceal hemorrhage in patients with medium to large esophageal varices. Despite studies confirming their preventative role, β-blockers may be ineffective in up to 30% of patients, for whom decrease in portal pressure is insufficient despite doses adjusted according to reduction of heart rate.[5] They also carry several contra-indications and may cause side effects, leading to poor tolerance and adherence to treatment. Endoscopic variceal banding ligation has been proposed as an alternative method for primary prophylaxis. Although effective, this technique has been associated with severe adverse events (post-ligation bleeding, esophageal perforation), sometimes leading to death.

Correspondence and reprint request: Pierre Blanc, M.D., Ph.D.
Department of Hepato-gastroenterology B. Hôpital Saint Eloi
Centre Hospitalier Universitaire de Montpellier
80 rue Augustin Fliche. 34295 Montpellier Cedex 5, France
Tel.: +334 6733-7077. Fax: +334 6733-7575
E mail: pblanc34@yahoo.fr

Manuscript received: August 01, 2011.
Manuscript accepted: December 14, 2011.

Results of randomized controlled trials comparing β-blockers with EVBL have been conflicting. Four previous meta-analyses[6-9] have shown a reduction in bleeding in favor of EVBL; however, this advantage disappears when only trials with adequate bias control or with follow-up longer than 20 months are taken into account.[6] As yet, no significant difference in mortality has been demonstrated between the two treatments. In view of these results, we performed an updated meta-analysis of β-blockers versus EVBL for primary prophylaxis of esophageal variceal bleeding. As results seem to vary according to the length of follow-up, we evaluated the incidence of first variceal bleed and mortality both overall and at different time-points (6, 12, 18 and 24 months).

MATERIAL AND METHODS

Data sources and searches

Randomized controlled trials comparing BB with EVBL for primary prophylaxis of esophageal variceal bleeding were identified through the electronic databases Medline (1950-2011), Web of Science (1991-2011), EMBASE and the Cochrane Central Register of Controlled Trials. The search strategy is shown in Appendix. We manually searched conference abstracts from the Digestive Disease Week (2001-2011), American Association for the Study of Liver Disease (2003-2010), European Association for the Study of the Liver (2000-2011), United European Gastroenterological Federation (2006-2010), British Society of Gastroenterology (2001-2011), French Society of Gastroenterology (2001-2011), and the Asia-Pacific Association of Gastroenterology (2002-2010). Reference lists from retrieved articles and previous meta-analyses were scanned, and clinical trial registries at www.controlled-trials.com and www.clinicaltrials.gov were searched. The final search was performed on 1 June 2011.

Study selection

The following selection criteria were applied:

- Randomized controlled trials published as abstracts or as peer-reviewed articles.
- Population: patients with esophageal varices secondary to portal hypertension with no evidence of prior variceal bleeding.
- Interventions: treatment with either EVBL or non-selective beta-blockers alone for primary prophylaxis of the first variceal bleed. No language restrictions were applied.

Data extraction and quality assessment

Data were extracted by two independent reviewers (N. Funakoshi, P. Blanc). Discrepancies were resolved through discussion before analyses. Quality assessment of studies was based on the guidelines of the Cochrane Handbook of Systematic Reviews of Interventions.[10] The following domains were evaluated for each study: adequate sequence generation, allocation concealment, selective outcome reporting, handling of incomplete data, intention-to-treat analysis and sample size calculation. For each domain, the risk of bias was evaluated as either high, low or unclear.[10-11]

Data synthesis and analysis

Primary end-points were first variceal bleed and all-cause mortality, both evaluated overall and at 6, 12, 18 and 24 months. For each time-point, results were extracted directly from the text when stated explicitly or from data provided by authors when available. If this was not possible, results were extrapolated from Kaplan-Meier survival curves. Extrapolation was performed by three different reviewers (N. Funakoshi, P. Blanc, JP. Daurès), and the result was obtained by calculating the mean of the results obtained by each reviewer. Secondary end-points were bleeding-related mortality (linked to variceal or non-variceal upper gastro-intestinal bleeding) and frequency of adverse events. Adverse events were classified according to severity:[12]

- **Mild.** Transient or mild discomfort, not interfering with the patient's daily activities.
- **Severe.** Marked limitation in activity, necessitating treatment discontinuation.
- **Fatal.** Leading to the death of the patient.

All results were expressed as odds ratios (OR), with a 95% confidence interval (CI). Results were first calculated using a fixed-effect model (Yusuf and Peto[13]). Heterogeneity was calculated using Breslow-Day's test. When significant heterogeneity was found, both the OR and *P*-heterogeneity were subsequently calculated using a random-effect model (Der Simonian and Laird).[14] This model takes into account heterogeneity by providing a more conservative estimate of treatment effect with wider confidence intervals in order to adjust for in-

ter-trial variability. *P*-heterogeneity was initially considered significant if < 0.05; however, when *P*-heterogeneity tended towards significance (ie. between 0.05 and 0.10), we preferred to take the precaution of calculating results using the random-effect model. The percentage of variability beyond chance was estimated using the I^2 statistic.[15] Publication bias was assessed using the Egger Test[16] and represented graphically using funnel plots[17] plotting the natural log of the OR versus its standard error. The Trim and Fill analysis for publication bias was performed using Duval and Tweedie's methods, which allows to compensate for funnel plot asymmetry.[18] Additionally, the fail safe number according to Orwin's formula[19] was calculated, which represents the number of non-significant studies which would be necessary to reduce the effect size to a non-significant value. All analyses were performed using Comprehensive Meta-analysis software (version 2.2.048 New Jersey, USA, 2008).

Subgroup analyses were performed in order to determine whether the dosage of β-blockers or the length of the interval between banding sessions affected bleeding rates, as it has been suggested that bleeding following banding ligation is less frequent with longer intervals between banding sessions.[20] An additional subgroup analysis was performed for bleeding rates and mortality according to the methodological quality of the studies.

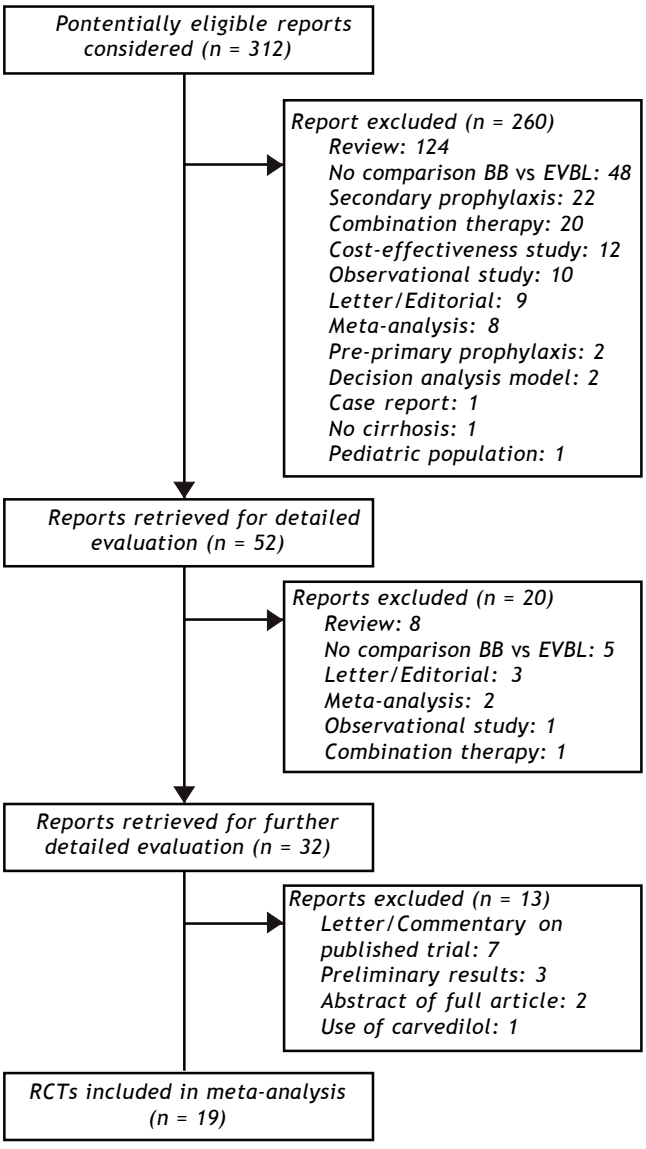
RESULTS

Study identification and selection

Our search identified 312 potentially relevant references. 260 reports were excluded when it was obvious they did not meet inclusion criteria; a further 20 reports were excluded after retrieval. A total of 32 reports were considered for detailed analysis: seven were commentaries on published trials, three were abstracts containing preliminary results, and three were abstracts of studies later published as full articles. Nineteen studies were included in the meta-analysis. The flow diagram of the study selection process is shown in figure 1.

Study and patient characteristics

The nineteen randomized controlled trials included in the meta-analysis were published between 1999-2011, of which twelve were published as full articles[21-31] and seven as abstracts[32-38] (Table 1). A total of 1,483 patients were randomized, 762 to β-blockers and 721 to EVBL. The number of patients included in each study ranged from 31 to 156 (mean 81). Five studies were multicentre trials.[23,25,27,31,39] All trials included patients with portal hypertension due to proven cirrhosis, with the exception of Sarin, *et al.*,[22] who included six patients with extra-hepatic portal vein obstruction and one patient with non-cirrhotic portal fibrosis. Exclusion criteria generally included contra-indications to β-blockers or severe co-morbidities. One trial included only patients on a liver-transplant



RCT: randomized controlled trial.

***Figure 1**. Study selection flow diagram.*

Table 1. Characteristics of studies included.

Author, year of publication	Country	Publication type	Number of patients (BB/EVBL)	Length of follow-up Range or SD (months)
Chen, 1998	Taiwan	Abstract	56 (30/26)	12
De, 1999	India	Article	30 (15/15)	17.6 ± 4.7
Sarin, 1999	India	Article	89 (44/45)	18
Song, 2000	Korea	Abstract	61 (30/31)	18
Lopez-Acosta, 2002	Mexico	Abstract	56 (28/28)	26 (2-48)
Gheorghe, 2002	Romania	Abstract	53 (28/25)	15
Lui, 2002	Scotland	Article	110 (66/44)	19.7 ± 17,6
Abulfutuh, 2003	Egypt	Abstract	110 (66/44)	30.1 ± 27.4
Lo, 2004	Taiwan	Article	100 (50/50)	22
Schepke, 2004	Germany	Article	152 (77/75)	34.4 ± 18.9
Thuluvath, 2005	USA	Article	31 (15/16)	27.4 ± 12.9
Jutabha, 2005	USA	Article	62 (31/31)	15
Psilopoulos, 2005	Greece	Article	60 (30/30)	27.5 ± 14.6
Lay, 2006	Taiwan	Article	100 (50/50)	35
Abdelfattah, 2006	Egypt	Abstract	156 (52/51)	18-24
Gill, 2006	Pakistan	Abstract	100 (50/50)	24
Norberto, 2007	Italy	Article	62 (31/31)	14.6
Perez-Ayuso, 2010	Chile	Article	75 (36/39)	55 ± 36.5
Drastich, 2011	Czech Republic	Article	73 (33/40)	10

BB: β-blockers. EVBL: endoscopic variceal banding ligation. SD: standard deviation.

waiting list,[30] whereas this population was excluded in another trial.[25] Three trials excluded patients with hepatic decompensation.[24,27-28] Follow-up ranged between 10 and 55 months.

As shown in table 2, the mean age of patients ranged from 39 to 62 years, with a majority of males (≥ 50%) when patient gender was reported (12 trials). Viral cirrhosis was predominant in the majority of trials.[22-24,26-30,36] Child B patients were predominant in a majority of seven trials.[21-23,26-27,30,36] All trials included patients with high risk varices, except for two[32,38] which did not specify whether varices were high risk or not. Criteria used to evaluate the degree of risk were size (grade II or higher, ≥ 5 mm or ≥ 2 mm with one red color sign), presence of red color signs and tortuosity. Varices were mainly grade II in four trials,[23-24,28,30] grade III in four trials[22,25,27,34] and grade IV in one trial;[21] grading was not reported in eleven trials.

Treatment protocols

All trials used propranolol except for one trial which used nadolol.[24] Long-acting propranolol was used in two trials;[26,27] the rest used standard propranolol with doses adjusted to achieve a reduction in heart rate of 20-25%, or a heart rate at 55-60 bpm. Mean daily dose ranged from 30-113.5 mg. Compliance was reported in six trials,[21,23,25,27,29-30] either by direct reporting from patients or pill counting, and was estimated at 91-100%.

Endoscopic variceal band ligation was performed using either single-band[22,29] or multi-band ligators[24-28,30-31,35,39]; one trial[23] first used single-band ligators, then multi-band ligators from 1995 onwards. Protocols varied according to the interval between each ligation session (range one week[25] to 4-5 weeks[27]) and the maximum number of bands placed in a single session (range 4[22, 24] to 10[25, 29]). Complete eradication was achieved in five trials,[21-22,26,31-32] whereas other trials reported eradication rates varying between 71 and 93.5%. Recurrence of esophageal varices was noted in twelve trials in 6.5 to 75% of patients; this information was not reported in the seven other trials.

Quality assessment

Quality assessment is shown in figures 2 and 3. Successful randomization was completed in all trials. None of the trials assessed were double-blinded due to the nature of the interventions. Baseline characteristics of treatment groups were balanced in all trials except for two[33,35] in which their comparability was not mentioned. Sample size was calculated in eight trials,[23-27,30-31,39] five of which were terminated prematurely when interim analyses

Table 2. Patient characteristics.

Study, Year (Reference)	Mean age (range or SD), years		Men (%)		Alcoholic liver disease (%)		Child class C (%)		Size of varices grades I-II /III /IV (%)	
	BB	EVBL	BB	EVBL	BB	EVBL	BB	EVBL	BB	EVBL
Chen, 1998	-	-	-	-	-	-	-	-	-	-
De, 1999	39.2 ± 16.6	41.6 ± 12.5	75	66	86.7	80	13.3	13.3	0/13.3/86.7	0/26.7/73.3
Sarin, 1999	39 ± 7	44 ± 12	73	73	20.5	24.4	30	33	0/77/23	0/71/29
Song, 2000	-	-	-	-	-	-	-	-	-	-
Lopez-Acosta, 2002	-	-	-	-	-	-	-	-	0/100/0	0/100/0
Gheorghe, 2002	-	-	-	-	-	-	-	-	-	-
Lui, 2002	55.2 ± 10.5	53.6 ±10.2	53	61	62.1	70.5	35	33.3	81.8/18.2/0	90.0/9.1/0
Abulfutuh, 2003	Overall: 55 ± 11	-	-	-	-	-	-	-	-	-
Lo, 2004	57 ± 11	55 ± 12	80	74	20	20	18	14	64/36/0	58/42/0
Schepke, 2004	57.3 ± 9.7	54.3 ± 10.5	70.1	66.7	49.4	53.3	11.7	13.3	45.5/54.5/0	42.7/57.3/0
Thuluvath, 2005	53.5 ± 10.5	50 ± 10	47	62	7	31	Overall: 19.4		-	-
Jutabha, 2005	54.9 ± 2.2	54.3 ± 1.7	74	68	12.9	9.7	25.8	22.6	9.7/74.2/16.1	3.2/83.9/12.9
Psilopoulos, 2005	59.3 ± 9.48	61.5 ± 8.25	66.7	73.3	23.3	26.7	10	16.7	76.7/23.3/0	76.7/23.3/0
Lay, 2006	55 ± 11	56 ± 10	80	76	22	20	18	14	-	-
Abdelfattah, 2006	-	-	-	-	-	-	-	-	-	-
Gill, 2006	-	-	-	-	-	-	-	-	-	-
Norberto, 2007	51.7 ± 8.0	52.5 ± 6.1	-	-	-	-	-	-	84/16/0	87/13/0
Perez-Ayuso, 2010	58 ± 9	60 ± 7	50	48	27.8	20.5	11.1	5.1	-	-
Drastich, 2011	56 ± 10	57 ± 9	82	60	61.6	65	9	5	-	-

BB: β-blockers. EVBL: endoscopic variceal banding ligation. SD: standard deviation.

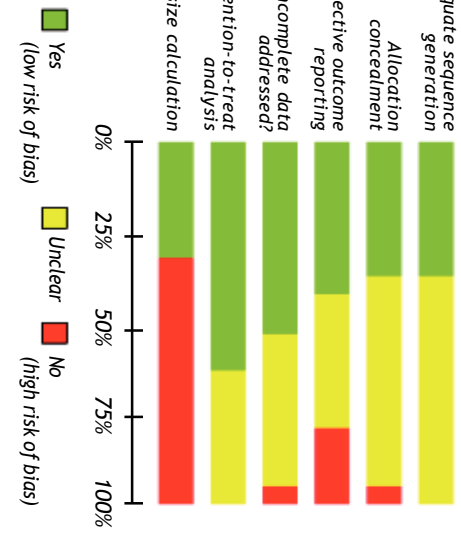


Figure 2. *Quality assessment graph.*

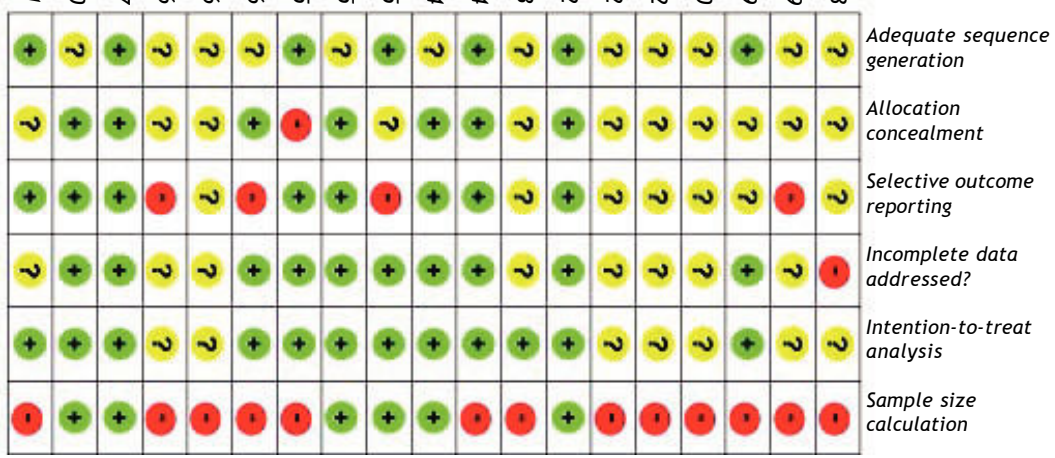


Figure 3. *Quality assessment table.*

showed that sample size had been grossly underestimated due to minimal differences in outcomes between the two treatment groups.[25-27,30-31] The trial of Jutabha, *et al.*,[27] was terminated prematurely on ethical grounds as mortality and bleeding rates were found to be significantly lower in the EVBL group after interim analysis. Only two studies[24,30] were classified as low risk in all domains evaluated.

Outcome measures

- **First variceal bleed.** All nineteen trials evaluated first variceal bleeding as an outcome measure. A total of 155 patients bled in the β-blocker group (20.3%), compared with 80 in the EVBL group (11.1%). In individual trials, bleeding rates ranged from 7 to 46% for β-blockers, and from 0 to 25% for EVBL. Eight trials demonstrated a reduction in bleeding rates in favor of EVBL; this difference was significant in six trials[22,27-28,32,35,38-39] whereas two trials did not state whether the difference was significant or not.[33,37] Eleven trials did not show any significant difference in bleeding rates between the treatment arms.[21,23-26,29-31,34,36]
  When overall bleeding rates were taken into account, bleeding was found to be significantly lower in the EVBL group (OR 2.06, 95% CI [1.55-2.73], p < 0.0001), as shown in table 3 and figure 4. No significant heterogeneity was found (*P*-heterogeneity = 0.70) and the results were therefore calculated with the fixed-effect method. There was no evidence of publication bias (*P*-Eggers = 0.33). After recalculation with Duval and Tweedie's trim and fill method,[18] the result remained significant (OR 2.10, 95% CI [1.60-1.80]). Using Orwin's method,[19] it was estimated that 27 additional medium-sized non-significant studies would need to be added in order to cancel out significance of the result (fail safe number).

When results were analyzed at different timepoints, significant heterogeneity was found with the fixed-effect method. Accordingly, results were recalculated using the random-effect method. A tendency towards reduced bleeding rates for the EVBL group was present at all time points (6, 12, 18 and 24 months), but the difference was only significant at 18 months (Table 3): OR 2.20, 95% CI [1.04-4.60], *P* = 0.04 (Figure 5). However, the Eggers test showed evidence of funnel plot asymmetry (*P*-Eggers = 0.03), indicating possible publication bias. When results were

Table 3. Meta-analysis for bleeding rates, mortality, bleeding-related mortality and adverse events.

	BB, n/N (%)	EVBL, n/N (%)	Number of trials analyzed	OR (OR 95%CI)	P for heterogeneity	I^2 (%)	P-value
• First variceal bleed							
6 months	35/442 (7.9)	17/387 (3.5)	10	1.90 [0.88-4.00] *	0.08	42.9	0.10
12 months	59/472 (12.5)	37/453 (8.2)	11	1.60 [0.82-3.31] *	0.04	48.1	0.16
18 months	80/412 (19.4)	44/396 (11.1)	9	2.19 [1.04- 4.60] *	0.008	61.2	0.04
24 months	60/304 (19.7)	35/280 (12.5)	6	2.10 [0.92- 4.70] *	0.03	58.7	0.08
Overall	155/762 (20.3)	80/721 (11.1)	19	2.06 [1.55-2.73] †	0.70	0	<0.0001
• Mortality							
6 months	16/384 (7.4)	26/371 (7.0)	9	0.58 [0.31-1.09] †	0.23	24.0	0.09
12 months	38/414 (9.2)	47/397 (11.8)	10	0.71 [0.45-1.11] †	0.25	20.6	0.14
18 months	64/428 (15.0)	73/416 (17.5)	10	0.77 [0.53-1.12] †	0.14	34.0	0.17
24 months	66/290 (22.8)	69/269 (25.7)	6	0.82 [0.56-1.22] †	0.19	32.5	0.33
Overall	162/697 (23.2)	148/656 (22.6)	17	1.01 [0.78-1.32] †	0.69	0	0.93
• Bleeding-related mortality	33/448 (7.3)	23/435 (5.3)	10	1.43 [0.83-2.46] †	0.80	0	0.20
• Adverse events							
Total	154/474 (32.5)	134/450 (29.8)	11	0.97 [0.38-2.50] *	< 0.0001	84.8	0.94
Severe	49/365 (13.4)	17/345 (4.9)	8	2.61 [1.60- 4.40] †	0.24	23.4	< 0.0001
Fatal	0/141 (0)	4/146 (2.7)	3	0.14 [0.02- 0.99] †	0.99	0	0.05

*Random-effect model, shown when *P*-heterogeneity is significant with the fixed-effect model. †Fixed-effect model. BB: β-blockers. EVBL: endoscopic variceal banding ligation. OR: odds ratio. An odds ratio < 1 indicates the event is more frequent in the EVBL group.

Table 4. Meta-analysis for bleeding rates according to dose of propranolol and length of interval between banding sessions.

	BB, n/N (%)	EVBL, n/N (%)	N° of trials analyzed	OR (OR 95%CI)	P for heterogeneity	I^2 (%)	P-value
• Low dose propranolol (< 75 mg/day)							
6 months	17/188 (9.1)	7/196 (3.6)	5	2.57 [1.12-5.92] †	0.25	25.9	0.03
12 months	25/188 (13.3)	10/196 (5.1)	5	2.66 [1.32-5.35] †	0.65	0	0.006
18 months	46/188 (24.5)	22/196 (11.2)	5	2.52 [1.48-4.28] †	0.11	46.1	0.001
24 months	25/111 (22.5)	13/111 (11.7)	3	3.15 [0.48-20.8]*	0.03	70	0.23
Overall	36/203 (17.7)	18/211 (8.5)	6	2.21 [1.25-3-93] †	0.49	0	0.007
• High dose propranolol (≥ 75 mg/day)							
6 months	11/174 (6.3)	9/150 (0.06)	3	1.20 [0.26-5-51]*	0.02	75.8	0.81
12 months	17/174 (9.8)	17/150 (11.3)	3	0.83 [0.22-3.23]*	0.001	87.2	0.78
18 months	25/174 (14.4)	17/150 (11.3)	3	1.65 [0.37-7.26]*	0.001	85.4	0.51
24 months	26/143 (18.2)	18/119 (15.1)	2	1.59 [0.30-8.56]*	0.04	75.6	0.59
Overall	45/225 (20.0)	29/205 (14.1)	5	1.5 [0.9-2.6] †	0.47	0	0.13
• Short interval between banding sessions (≤ 2 weeks)							
6 months	21/268 (7.8)	14/245 (5.7)	5	1.44 [0.44-4.70] *	0.03	63.3	0.55
12 months	29/268 (10.8)	24/245 (9.8)	5	1.33 [0.44-4.02] *	0.01	68.6	0.61
18 months	47/268 (17.5)	36/245 (14.7)	5	1.34 [0.55-3.31] *	0.03	64	0.51
24 months	43/224 (19.2)	30/200 (15.0)	4	1.62 [0.6-4.4] *	0.05	62.2	0.34
Overall	59/311 (19.0)	28/288 (9.7)	7	1.59 [1.02-2.50] †	0.65	0	0.04
• Long interval between banding sessions (>2 weeks)							
6 months	11/144 (7.6)	5/151 (3.3)	4	2.29 [0.84-6.28] †	0.25	26.2	0.11
12 months	24/174 (13.8)	10/177 (5.6)	5	2.51 [1.23-5.11] †	0.17	38.3	0.01
18 months	33/144 (22.9)	8/151 (5.3)	4	4.26 [2.21-8.21] †	0.31	15.9	0.0001
24 months	18/80 (22.5)	5/80 (6.3)	2	3.48 [1.44-8.41] †	0.28	14.3	0.006
Overall	53/253 (20.9)	22/257 (8.6)	8	2.73 [1.66-4.51] †	0.55	0	0.0001

* Random-effect model, shown when P-heterogeneity is significant with the fixed-effect model. † Fixed-effect model. BB: β-blockers. EVBL: endoscopic variceal banding ligation. OR: odds ratio. An odds ratio < 1 indicates the event is more frequent in the EVBL group.

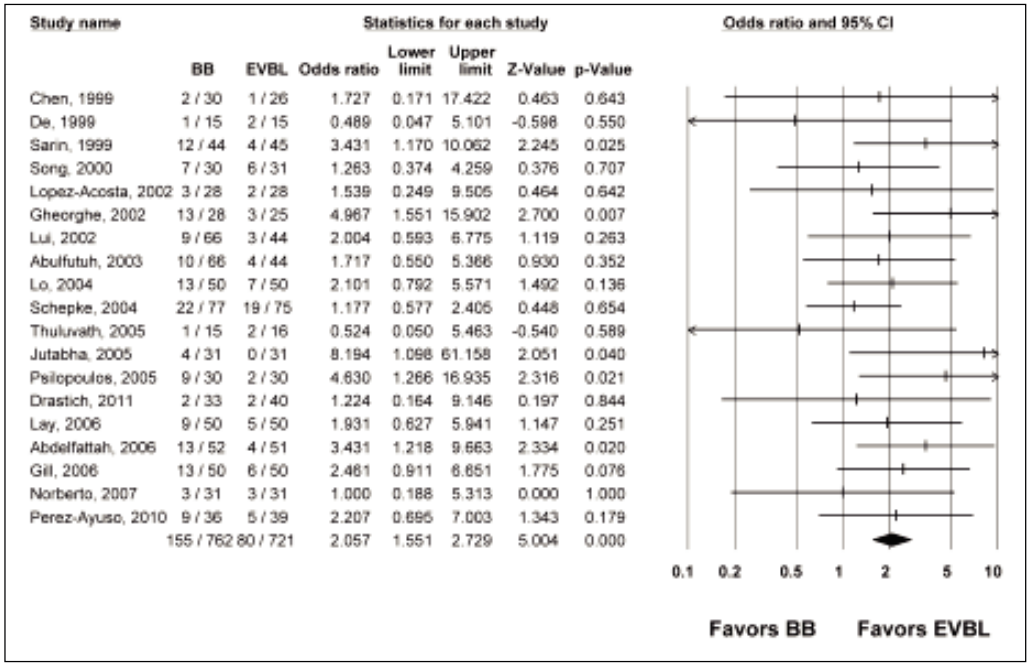


Figure 4. *Forest plot for overall bleeding.*

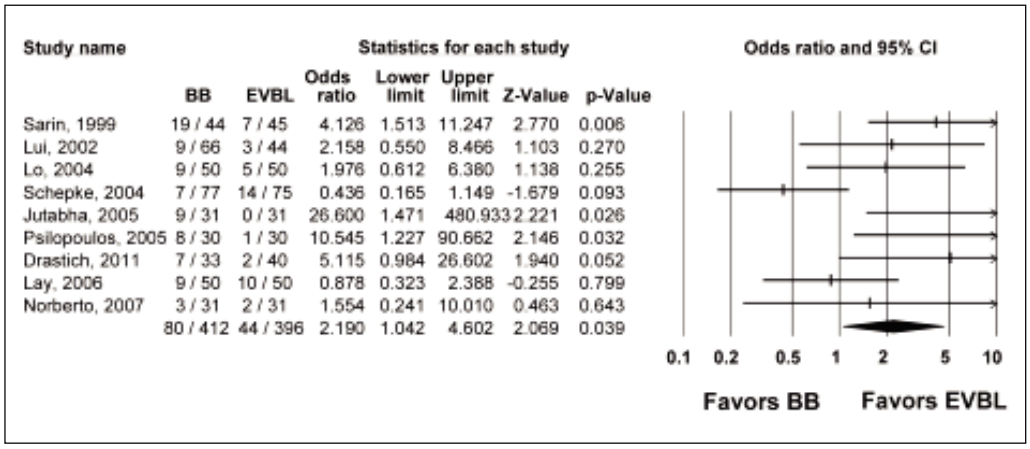


Figure 5. *Forest plot for bleeding at 18 months.*

calculated using Duval and Tweedie's trim and fill method, the adjusted OR was 1.60, 95% CI [0.79-3.50], leading to a loss of significance. The fail safe number was at 1, confirming the lack of robustness of the result.

A subgroup analysis was performed according to the doses of propranolol administered. Studies with mean propranolol doses < 75 mg per day were classified as low dose,[21-22,28-31] whereas studies with mean propranolol doses ≥ 75 mg per day were classified as high dose.[23,25-27,39] Bleeding rates were significantly lower at 6, 12 and 18 months as well as overall in the low dose propranolol group (Table 4). No significant difference in bleeding rates was found either overall or at all time points for the high dose propranolol group.

The subgroup analysis according to the length of the interval between banding ligation sessions (short interval defined as ≤ 2 weeks;[21-23,25,29-30,34] long interval defined as > 2 weeks[24,26-28,31-32,35,39]) found that bleeding rates were significantly lower at 12, 18 and 24 months for studies with a long interval, which was not the case for short interval studies (Table 4). However, overall bleeding rates were significantly in favor of EVBL for both groups, although *P* was considerably lower for the long interval studies (0.0001 *vs.* 0.04).

An additional subgroup analysis was performed according to the methodological quality of the trials. Trials were considered of higher methodological quality if they were evaluated as low risk for all domains, or if only one domain was evaluated as un-

Table 5. Meta-analysis for bleeding rates and mortality according to trial quality.

	BB, n/N (%)	EVBL, n/N (%)	Number of trials analyzed	OR (OR 95%CI)	P for heterogeneity	I^2 (%)	P-value
Low quality trials							
• First variceal bleed							
6 months	23/237 (9.7)	9/246 (3.7)	6	2.67 [1.30-5.48] *	0.53	0	0.008
12 months	39/267 (14.6)	18/272 (6.6)	7	2.32 [1.34-4.02] *	0.75	0	0.003
18 months	52/207 (25.1)	25/215 (11.6)	5	2.48 [1.51-4.08] *	0.12	45.6	0.0001
24 months	26/130 (20.0)	15/130 (11.5)	3	2.31 [0.49-11.02] †	0.06	64.6	0.29
Overall	108/521 (20.7)	50/501 (10.0)	14	2.31 [1.64-3.26] *	0.77	0	0.0001
• Mortality							
6 months	6/143 (4.2)	7/151 (4.6)	4	0.92 [0.30-2.79] †	0.51	30.8	0.88
12 months	14/173 (8.1)	17/177 (9.6)	5	0.81 [0.39-1.70] †	0.22	17	0.58
18 months	25/187 (13.4)	29/196 (14.8)	5	0.87 [0.49-1.56] †	0.31	55.7	0.63
24 months	15/80 (18.8)	18/80 (22.5)	2	0.79 [0.36-1.70] †	0.13	0	0.54
Overall	92/456 (20.2)	80/436 (18.3)	12	1.08 [0.76-1.52] †	0.88	0	0.68
• Bleeding-related mortality	14/207 (6.8)	10/215 (4.7)	5	1.45 [0.64-3.32] †	0.63	0	0.37
High quality trials							
• First variceal bleed							
6 months	12/205 (5.8)	11/181 (6.1)	4	0.87 [0.28-2.74] *	0.03	65.4	0.81
12 months	20/205 (9.8)	19/181 (10.5)	4	0.88 [0.30-2.59] *	0.001	81.2	0.83
18 months	28/205 (13.7)	19/181 (10.5)	4	1.62 [0.45-5.85] *	0.003	78.2	0.46
24 months	34/174 (19.5)	20/150 (13.3)	3	2.26 [0.51-9.95] *	0.04	69.8	0.28
Overall	47/241 (19.5)	30/220 (13.6)	5	1.61 [0.98-2.66] †	0.41	0	0.06
• Mortality							
6 months	10/241 (4.1)	19/220 (8.6)	5	0.47 [0.22-1.00] †	0.12	45.2	0.05
12 months	24/241 (10.0)	30/220 (13.6)	5	0.65 [0.37-1.16] †	0.25	25.1	0.14
18 months	39/241 (16.2)	44/220 (20.0)	5	0.67 [0.37-1.21] *	0.07	53.1	0.18
24 months	52/210 (24.8)	51/189 (27.0)	4	0.83 [0.53-1.31] †	0.16	41.5	0.44
Overall	70/241 (29.0)	68/220 (30.9)	5	0.92 [0.61-1.41] †	0.15	40	0.71
• Bleeding-related mortality	19/241(7.9)	13/22 (59.1)	5	1.40 [0.68-2.89]	0.59	0	0.36

* Random-effect model, shown when P-heterogeneity is significant with the fixed-effect model. †Fixed-effect model. BB: β-blockers. EVBL: endoscopic variceal banding ligation. OR: odds ratio. An odds ratio < 1 indicates the event is more frequent in the EVBL group.

clear, with the rest of the domains considered low risk. The majority of trials fell into the low quality group,[21-22,24,26,28-29,31-38] whereas five trials were included in the high quality group.[23,25,27,30,39] The analysis concerning low quality studies was strongly in favor of reduced bleeding rates for EVBL, as the difference was significant not only overall and at 18 months (as with the main analysis), but also at 6 and 12 months (Table 5). However, when only high quality studies were considered, the significant difference in bleeding rates in favor of EVBL disappeared both overall and at all time points (Table 5).

Mortality

All trials except two[21, 38] reported all-cause mortality. 162 patients died in the β-blocker group (23.2%) whereas 148 deaths occurred in the EVBL group (22.5%). Mortality rates for individual trials ranged from 0 to 43% for β-blockers, and from 0 to 51% for EVBL. Only one trial found a significant reduction in mortality in favor of EVBL;[27] a second trial also found a reduction in mortality in the EVBL group without specifying whether it was significant or not.[33] There was no significant difference in mortality between the two groups in fifteen trials,[22-26,28-37,39] whereas two trials[21,38] did not perform statistical analysis for mortality.

There was no significant difference in all-cause mortality rates between the two groups either overall (Figure 6) or at 6, 12, 18 or 24 months, although there was a tendency towards lower mortality rates in the β-blocker group, as shown in table 3. Similarly, the subgroup analysis according to trial quality did not find any significant difference in mortality rates either for low quality or high quality trials (Table 5).

Bleeding-related mortality

Thirteen trials reported bleeding-related mortality.[21-32,39] Three trials reported no bleeding-related deaths in either group.[21,26,32] One trial[35] found a trend towards reduced bleeding-related mortality for patients treated with EVBL, but did not provide figures. A total of 33 patients (7.3%) died from bleeding-related causes in the β-blocker group and 23 (5.3%) died in the EVBL group. We did not perform separate analyses at different time-points as data were insufficient for the majority of trials. Overall analysis using a fixed-effect model did not find any significant difference for bleeding-related mortality between BB and EVBL as shown in figure 7 (OR 1.43, 95% CI [0.83-2.46], p = 0.20). The subgroup analysis according to trial quality did not find any significant difference in bleeding-related mortality.

Adverse events

Twelve trials reported adverse events in both groups.[21-25,27-28,30-31,34,38-39] In the β-blocker group, 154 patients in total (32.5%) experienced adverse events, whereas 49 (13.4%) had severe adverse events. Severe adverse events included hypotension, bradycardia, heart block, renal insufficiency, dyspnea, asthenia, exanthema, vertigo and aggravation of pre-existing peripheral vascular disease. Twelve bleeding episodes following treatment discontinuation were reported. No patients died directly as a result of β-blocker treatment. In the EVBL group, a total of 134 patients presented adverse events (29.8%) with seventeen patients presenting severe adverse events (4.9%), including bleeding from banding ulcers, severe post-ligation pain and esophageal perforation following endoscope insertion. Four fatal adverse events were reported in the EVBL group, all resulting from bleeding from EVBL-induced ulcers.

As shown in table 3, severe adverse events were significantly more frequent in the β-blocker group (OR 2.61, 95% CI [1.60-4.40], $P < 0.0001$, P-Eggers = 0.26) whereas the EVBL group had a significantly higher number of fatal adverse events (OR 0.14, 95% CI [0.02-0.99], $P = 0.05$, P-Eggers = 0.24). No significant difference was shown when considering all adverse events using the random-effect model, although marked heterogeneity was present (P-heterogeneity < 0.0001, $I^2 = 83.9$), which may be due to differences in reporting adverse events between trials.

DISCUSSION

This meta-analysis is the largest to date comparing β-blockers with EVBL in the primary prophylaxis of esophageal variceal bleeding. Nineteen trials published as full articles or abstracts were included; taken individually, the majority of these trials had inadequate statistical power due to insufficient numbers of patients. Four meta-analyses have been published previously: Imperiale, *et al.*,[8] in 2001 included 884 patients (nine trials), Khuroo, *et al.*[9] in 2005 included 596 patients (eight trials), Tripathi, *et al.*,[7] in 2007 included 734 patients (nine trials) and Gluud, *et al.*,[6] in 2007 included 1,167 patients (sixteen trials). Our meta-analysis is

justified by the fact that it included a considerably greater number of patients (1,483), which represents a relative increase in patient numbers of 68, 149, 102 and 27%, respectively compared to the previous meta-analyses. The abstracts of Abulfutuh,[36] Gill[38] and Lopez-Acosta[34] and the articles of Perez-Ayuso[39] and Drastich[31] were included in a meta-analysis for the first time. The abstract of Lopez-Acosta is the definitive results of the trial of De La Mora, *et al.*,[40] which was included in previous meta-analyses,[6,9] whereas the article of Drastich[31] had only been published previously in abstract form. We did not include the trial of Tripathi, *et al.,*[41] as this trial used carvedilol, which is not strictly comparable to standard non-selective β-blockers as it has intrinsic anti-α1-adrenergic activity (equivalent to the association of propanolol with prazosin),[42-43] and the addition of this trial did not modify the overall results for bleeding rates and mortality (data not shown). We also performed analyses excluding the study of Sarin, *et al.*[22] as a small number of patients in this study were not cirrhotic and had portal hypertension due to extrahepatic portal vein obstruction or non-cirrhotic portal fibrosis. However, the exclusion of this trial, which had been included in previous meta-analyses[6-9] did not modify overall results (data not shown). Follow-up duration varied greatly between studies (range 10-55 months), leading to inter-trial heterogeneity which may affect overall outcomes. We therefore decided to analyse results at different time-points in order to determine whether results differ according to follow-up duration, as suggested by Gluud, *et al.*[6] We did not make allowances for multiple comparisons as the analyses at different time points did not always concern the same studies, although a certain proportion of studies were identical. We used the random-effect model when *P*-heterogeneity < 0.10, which meant that certain results calculated with the fixed-effect model became non-significant (data not shown), justifying this conservative approach towards heterogeneity.

We found a significant decrease in bleeding rates for EVBL compared to BB when overall bleeding rates were taken into account. Recalculation with the trim and fill method and estimation of the fail safe number revealed that this result is particularly robust. Despite possible inter-trial variability including variations in follow-up duration, the overall result for bleeding rates was not associated with significant heterogeneity ($I^2 = 0\%$, *P*-heterogeneity = 0.70). Results at 6, 12, 18 and 24 months also showed a tendency towards reduced bleeding rates, although the significant result at 18 months should be interpreted with caution due to possible publication biases. The lack of significance at these different time points may have been due to insufficient patient numbers on analysis, as not all studies provided outcomes at 6, 12, 18 and 24 months. Treatment discontinuation and poor compliance should also be taken into account, as it is probable that patients who did not tolerate b-blockers would have discontinued treatment within the first 6 months, exposing patients to a rebound effect:[44] a total of 12 patients were reported to have bled after stopping treatment. We performed a subgroup analysis according to β-blocker doses in order to determine whether higher doses decrease bleeding rates in the β-blocker group. Results were significantly lower for EVBL in the low dose group, whereas in the high dose group there was no significant difference between the two treatment groups. Higher doses of β-blockers may have minimized differences in bleeding rates between the two groups, indicating that the effect of β-blockers on bleeding rates may be dose dependent. When a subgroup analysis of trials with long intervals between banding sessions was performed, bleeding rates were significantly in favor of EVBL at 12, 18 and 24 months, as well as overall, whereas only the overall bleeding rate was significant in trials with short intervals. This may indicate that better outcomes are obtained with longer intervals between banding sessions, as suggested by Harewood *et al.*,[20] perhaps due to less frequent bleeding from post-banding ulcers. In the subgroup analysis of high quality trials, the significant difference in favor of EVBL for bleeding rates disappears. This suggests that the beneficial effect of EVBL on bleeding rates may have been influenced by inadequate bias control. The results of the main analysis concerning bleeding rates should therefore be interpreted with caution, and additional high quality studies are needed to confirm these results.

Although there is a non-significant decrease in bleeding-related mortality in the EVBL group, reduced bleeding rates did not affect all-cause mortality as no significant difference in mortality rates between the two treatment groups was present. It is interesting to note that there is a trend towards reduced mortality in the β-blocker group particularly at 6 months (OR 0.58), which seems to decrease over time. It has been suggested that b-blockers may have a beneficial effect on survival independent of their preventative effect on variceal bleeding. β-blockers act globally by reducing portal hypertension, as

opposed to EVBL, which acts focally on the esophagus. The decrease in portal hypertension induced by β-blockers may help prevent additional complications of cirrhosis, such ascites, hepato-renal syndrome and portal hypertensive gastropathy.[45-46] β-blockers may also prevent spontaneous bacterial peritonitis[47] by reducing bacterial translocation[48] and endotoxinemia, which are known to trigger variceal bleeding.[49] However, the absence of a significant decrease in mortality for β-blockers as compared to EVBL may due to several factors. Compliance to b-blocker therapy may decrease over time, and discontinuation of treatment may lead to a rebound effect, with increased risk of variceal bleeding. Patients having discontinued β-blocker therapy no longer experience its beneficial effects, leading ultimately to an increase in mortality in the long term. The effect of β-blockers may also be minimized by the natural history of cirrhosis, where mortality without transplantation in decompensated patients may be as high as 85% at 5 years.[50] In the long term, the positive effect of β-blockers may be negated by spontaneously high mortality rates, as many cirrhotics risk death in the absence of liver transplantation. Finally, it is possible that the number of patients analyzed was insufficient to reveal any significant difference in mortality between the two groups.

Severe adverse events were significantly higher with β-blockers, whereas fatal adverse events were more frequent with EVBL. Due to their systemic effects, β-blockers are associated with a wide range of side effects. None of these were directly fatal, although three deaths from variceal bleeding were reported for patients having previously discontinued β-blocker treatment.[25,30] Fatalities in the EVBL group were secondary to bleeding from banding ulcers, reported in three trials. All these trials[25,30-31] had particularly aggressive banding protocols, with ligation sessions every one[25] or two weeks,[30-31] with up to ten bands placed at each session,[25-31] which may have increased the likelihood of post-banding complications. It is un-

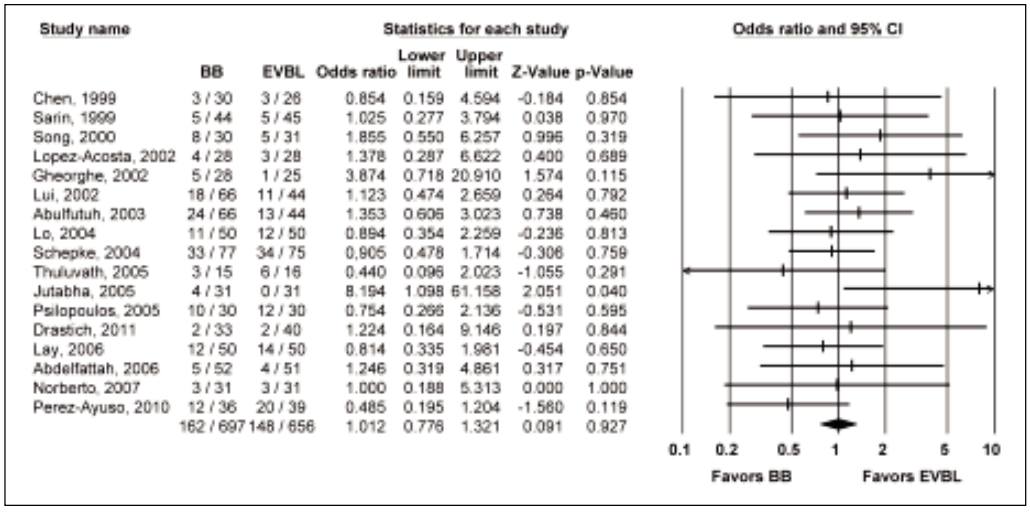


***Figure 6**. Forest plot for overall mortality.*

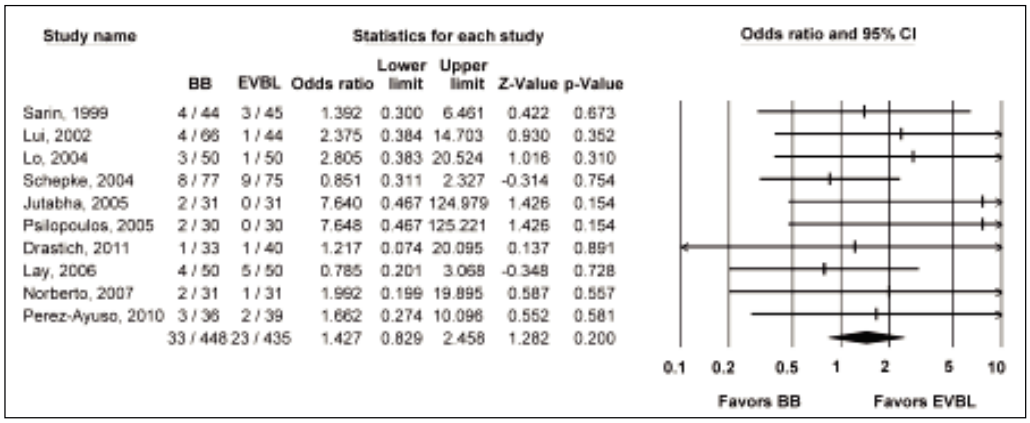


***Figure 7**. Forest plot for bleeding-related mortality.*

likely that these fatalities contributed to increased mortality in the EVBL group, as no difference in bleeding-related mortality was found between the treatment arms. Nonetheless, results concerning adverse events should be interpreted with caution, as the definition of adverse events and severe adverse events varied between trials.

Our meta-analysis was limited by variations in quality of the studies included, and by lack of data concerning eight studies published as abstracts, for which trial and patient characteristics were incomplete. Consequently, subgroup analyses according to criteria such as Child's class, origin of cirrhosis or variceal size were not performed due to insufficient data. Heterogeneity between studies was likely to be present due to variations in baseline characteristics of patient populations, in β-blocker/banding ligation treatment protocols, and in the dates that which studies were undertaken. Not all studies expressed outcome measures according to follow-up time, which limited their input in the meta-analysis. Ideally, a meta-analysis would include individual patient data with updated follow up, but in our case these data were not available and we therefore had to rely on group data provided by each study.

CONCLUSION

In conclusion, this updated meta-analysis suggests that EVBL appears to be superior to β-blockers in preventing the first variceal bleed in cirrhotic patients, although this result was not confirmed when only high quality trials were taken into account. The decrease in bleeding rates does not translate into decreased bleeding-related or overall mortality for patients treated with EVBL, and it must be kept in mind that EVBL has a greater potential for fatal iatrogenic complications. Current evidence is insufficient to recommend EVBL as first-line therapy over β-blockers. β-blockers still remain a valid first-line treatment considering availability and costs, whereas EVBL should be proposed to patients who are non-compliant, have contra-indications or poorly tolerate BB therapy. Further high quality studies are needed in order to confirm the superiority of EVBL over β-blockers concerning bleeding rates.

ABBREVIATIONS

- **BB:** beta-blockers.
- **EVBL:** endoscopic variceal banding ligation.
- **OR:** odds ratio.
- **CI:** confidence interval.

DISCLOSURES

The authors did not receive any financial support or grants for this study.

ACKNOWLEDGEMENTS

The authors would like to thank Dr. Rosa Maria Perez-Ayuso for providing the authors with detailed data from her study.

REFERENCES

1. D'Amico G, Luca A. Natural history. Clinical-haemodynamic correlations. Prediction of the risk of bleeding. *Baillieres Clin Gastroenterol* 1997; 11: 243-56.
2. Gunnarsdottir SA, Olsson R, Bjornsson ES. Characteristics, prognosis and outcome of patients with oesophageal varices in a university hospital in Sweden 1994-1999. *Scand J Gastroenterol* 2005; 40: 1462-8.
3. De Franchis R. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol* 2010; 53: 762-8.
4. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology* 2007; 46: 922-38.
5. Garcia-Tsao G, Grace ND, Groszmann RJ, Conn HO, Bermann MM, Patrick MJ, Morse SS, et al. Short-term effects of propranolol on portal venous pressure. *Hepatology* 1986; 6: 101-6.
6. 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: 2842-8; Quiz 41, 49.
7. Tripathi D, Graham C, Hayes PC. Variceal band ligation versus beta-blockers for primary prevention of variceal bleeding: a meta-analysis. *Eur J Gastroenterol Hepatol* 2007; 19: 835-45.
8. Imperiale TF, Chalasani N. A meta-analysis of endoscopic variceal ligation for primary prophylaxis of esophageal variceal bleeding. *Hepatology* 2001; 33: 802-7.
9. Khuroo MS, Khuroo NS, Farahat KL, Khuroo YS, Sofi AA, Dahab ST. Meta-analysis: endoscopic variceal ligation for primary prophylaxis of oesophageal variceal bleeding. *Aliment Pharmacol Ther* 2005; 21: 347-61.
10. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Chichester: Wiley-Blackwell, 2008.
11. Cohen MJ, Sahar T, Benenson S, Elinav E, Brezis M, Soares-Weiser K. Antibiotic prophylaxis for spontaneous bacterial peritonitis in cirrhotic patients with ascites, without gastro-intestinal bleeding. Cochrane Database Syst Rev 2009:CD004791.
12. US Department of Health and Human Services: Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Available from: http://evs.nci.nih.gov/ftp1/CTCAE/About.html 2009.
13. Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *N Engl J Med* 1988; 318: 1162-73.

14. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; 7: 177-88.
15. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21: 1539-58.
16. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315: 629-34.
17. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol* 2001; 54: 1046-55.
18. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000; 56: 455-63.
19. Orwin R. A fail-safe N for effect size in meta-analysis. *J Educational Statistics* 1983; 157-9.
20. Harewood GC, Baron TH, Song LM. Factors predicting success of endoscopic variceal ligation for secondary prophylaxis of esophageal variceal bleeding. *J Gastroenterol Hepatol* 2006; 21: 237-41.
21. De BK, Ghoshal UC, Das T, Santra A, Biswas PK. Endoscopic variceal ligation for primary prophylaxis of oesophageal variceal bleed: preliminary report of a randomized controlled trial. *J Gastroenterol Hepatol* 1999; 14: 220-4.
22. Sarin SK, Lamba GS, Kumar M, Misra A, Murthy NS. Comparison of endoscopic ligation and propranolol for the primary prevention of variceal bleeding. *N Engl J Med* 1999; 340: 988-93.
23. Lui HF, Stanley AJ, Forrest EH, Jalan R, Hislop WS, Mills PR, Finlayson ND, et al. Primary prophylaxis of variceal hemorrhage: a randomized controlled trial comparing band ligation, propranolol, and isosorbide mononitrate. *Gastroenterology* 2002; 123: 735-44.
24. Lo GH, Chen WC, Chen MH, Lin CP, Lo CC, Hsu PI, Cheng JS, et al. Endoscopic ligation vs. nadolol in the prevention of first variceal bleeding in patients with cirrhosis. *Gastrointest Endosc* 2004; 59: 333-8.
25. Schepke M, Kleber G, Nurnberg D, Willert J, Koch L, Veltzke-Schlieker W, Hellerbrand C, et al. Ligation versus propranolol for the primary prophylaxis of variceal bleeding in cirrhosis. *Hepatology* 2004; 40: 65-72.
26. Thuluvath PJ, Maheshwari A, Jagannath S, Arepally A. A randomized controlled trial of beta-blockers versus endoscopic band ligation for primary prophylaxis: a large sample size is required to show a difference in bleeding rates. *Dig Dis Sci* 2005; 50: 407-10.
27. Jutabha R, Jensen DM, Martin P, Savides T, Han SH, Gornbein J. Randomized study comparing banding and propranolol to prevent initial variceal hemorrhage in cirrhotics with high-risk esophageal varices. *Gastroenterology* 2005; 128: 870-81.
28. Psilopoulos D, Galanis P, Goulas S, Papanikolaou IS, Elefsiniotis I, Liatsos C, Sparos L, et al. Endoscopic variceal ligation vs. propranolol for prevention of first variceal bleeding: a randomized controlled trial. *Eur J Gastroenterol Hepatol* 2005; 17: 1111-7.
29. Lay CS, Tsai YT, Lee FY, Lai YL, Yu CJ, Chen CB, Peng CY. Endoscopic variceal ligation versus propranolol in prophylaxis of first variceal bleeding in patients with cirrhosis. *J Gastroenterol Hepatol* 2006; 21: 413-9.
30. Norberto L, Polese L, Cillo U, Grigoletto F, Burroughs AK, Neri D, Zanus G, et al. A randomized study comparing ligation with propranolol for primary prophylaxis of variceal bleeding in candidates for liver transplantation. *Liver Transpl* 2007; 13: 1272-8.
31. Drastich P, Lata J, Petrtyl J, Bruha R, Prochazka V, Vanasek T, Zdenek P, et al. Endoscopic variceal band ligation compared with propranolol for prophylaxis of first variceal bleeding. *Ann Hepatol* 2011; 10: 142-9.
32. Chen C, Sheu M, Su S. Prophylactic endoscopic variceal ligation (EVL) with multiple band ligator for esophageal varices [Abstract]. *Gastroenterology* 1998; 114: A1224.
33. Song I, Shin J, Kim I, Choi J, Lim C, Kim J, Roe I. A prospective randomized trial between the prophylactic endoscopic variceal ligation and propranolol administration for prevention of first bleeding in cirrhotic patients with high-risk esophageal varices [Abstract]. *J Hepatol* 2000; 32: 41.
34. Lopez-Acosta ME, De la Mora-Levy JG, Blancas-Valencia JM, Paz-Flores VM. Primary prophylaxis of variceal bleeding comparing propranolol versus recharging a multiple band ligator: Up to 4 years follow-up [Abstract]. *Gastrointest Endosc* 2002; 55: AB 195.
35. Gheorghe C, Gheorghe L, Vadan R, Hrehoret D, Popescu I. Prophylactic banding ligation of high risk esophageal varices in patients on the waiting list for liver transplantation: an interim report [Abstract]. *J Hepatol* 2002; 36: 38.
36. Abulfutuh A, Morsy M, Solyman A, El Hendawy S, El Desouky M, El Hadad S, Kamel M. Study of variceal band ligation, propranolol and isosorbide mononitrate in the prevention of the first variceal bleeding [Abstract]. *Gastroenterology* 2003;124: A780.
37. Abdelfattah M, Rashed M, Elfakhry A, Soliman M, Shiha G. Endoscopic variceal ligation versus pharmacologic treatment for primary prophylaxis of variceal bleeding: a randomised study [Abstract]. *J Hepatol* 2006; 44: S83.
38. Gill M, Sattar S, Khokar N. Outcomes of endoscopic variceal band ligation versus pharmacological treatment with non selective beta blocker for primary prophylaxis of variceal bleed [Abstract]. *Gut* 2006; 55: A308.
39. Perez-Ayuso RM, Valderrama S, Espinoza M, Rollan A, Sanchez R, Otarola F, Medina B, et al. Endoscopic band ligation versus propranolol for the primary prophylaxis of variceal bleeding in cirrhotic patients with high risk esophageal varices. *Ann Hepatol* 2010; 9: 15-22.
40. De la Mora J, Farca-Belsaguy A, Uribe M, De Hoyos-Garza A. Ligation vs. propranolol for primary prophylaxis of variceal bleeding using a multiple band ligator and objective measurements of treatment adequacy: preliminary results [Abstract]. *Gastroenterology* 2000; 118: A1434-5.
41. Tripathi D, Ferguson JW, Kochar N, Leithead JA, Therapondos G, McAvoy NC, Stanley AJ, et al. Randomized controlled trial of carvedilol versus variceal band ligation for the prevention of the first variceal bleed. *Hepatology* 2009; 50: 825-33.
42. Forrest EH, Bouchier IA, Hayes PC. Acute haemodynamic changes after oral carvedilol, a vasodilating beta-blocker, in patients with cirrhosis. *J Hepatol* 1996; 25: 909-15.
43. Banares R, Moitinho E, Piqueras B, Casado M, Garcia-Pagan JC, de Diego A, Bosch J. Carvedilol, a new nonselective beta-blocker with intrinsic anti- Alpha1-adrenergic activity, has a greater portal hypotensive effect than propranolol in patients with cirrhosis. *Hepatology* 1999; 30: 79-83.
44. Lebrec D, Hillon P, Munoz C, Goldfarb G, Nouel O, Benhamou JP. The effect of propranolol on portal hypertension in patients with cirrhosis: a hemodynamic study. *Hepatology* 1982; 2: 523-7.
45. Abraldes JG, Tarantino I, Turnes J, Garcia-Pagan JC, Rodes J, Bosch J. Hemodynamic response to pharmacological treatment of portal hypertension and long-term prognosis of cirrhosis. *Hepatology* 2003; 37: 902-8.

46. Perez-Ayuso RM, Pique JM, Bosch J, Panes J, Gonzalez A, Perez R, Rigau J, et al. Propranolol in prevention of recurrent bleeding from severe portal hypertensive gastropathy in cirrhosis. *Lancet* 1991; 337: 1431-4.
47. Hoshino S, Shinoura S, Akamine H. Effect of propranolol for the prevention of spontaneous bacterial peritonitis. *Am J Gastroenterol* 2000; 95: A349.
48. Perez-Paramo M, Munoz J, Albillos A, Freile I, Portero F, Santos M, Ortiz-Berrocal J. Effect of propranolol on the factors promoting bacterial translocation in cirrhotic rats with ascites. *Hepatology* 2000; 31: 43-8.
49. Goulis J, Patch D, Burroughs AK. Bacterial infection in the pathogenesis of variceal bleeding. *Lancet* 1999; 353: 139-42.
50. Schuppan D, Afdhal NH. Liver cirrhosis. *Lancet* 2008; 371: 838-51.

Appendix. Search strategy used for identification of studies.

MEDLINE :

- Explode "liver cirrhosis" in MESH.
- Explode "hypertension, portal" in MESH.
- Explode "gastrointestinal hemorrhage" in MESH.
- Explode "esophageal and gastric varices" in MESH.
- 1 or 2 or 3 or 4.
- "Gastrointestinal hemorrhage"and "portal hypertension".
- "Gastrointestinal hemorrhage" and "esophageal varices".
- 6 or 7.
- 5 or 8.
- "Therapy" and 9.
- "Beta blockers" and 9.
- "Banding ligation" and 9.
- 10 or 11 or 12.
- "Prophylaxis" and 9 or 13.
- "Randomized controlled trials" [publication type].
- 15 and 9 or 13 or 14.

EMBASE:

- Explode "liver cirrhosis"/all subheadings.
- Explode "hypertension, portal"/all subheadings.
- Explode "gastrointestinal hemorrhage"/all subheadings.
- Explode "esophageal and gastric varices"/all subheadings.
- 1 or 2 or 3 or 4.
- "Gastrointestinal hemorrhage" and "portal hypertension".
- "Gastrointestinal hemorrhage" and "esophageal varices".
- 6 or 7.
- 5 or 8.
- "Therapy" and 9.
- "Beta blockers" and 9.
- "Banding ligation" and 9.
- 10 or 11 or 12.
- "Prophylaxis" and 9 or 13.
- Explode "randomized controlled trials"/ all subheadings.
- 15 and 9 or 13 or 14.

The Cochrane Register of Controlled Trials:

- Explode "liver cirrhosis" in MESH.
- Explode "hypertension, portal" in MESH.
- Explode "gastrointestinal hemorrhage" in MESH.
- Explode "esophageal and gastric varices" in MESH.
- 1 or 2 or 3 or 4.
- "Gastrointestinal hemorrhage" and portal hypertension".
- "Gastrointestinal hemorrhage" and "esophageal varices".
- 6 or 7.
- 5 or 8.
- "Therapy" and 9.
- "Beta blockers" and 9.
- "Banding ligation" and 9.
- 10 or 11 or 12.
- "Prophylaxis" and 9 or 13.

Web of Science:

- "Gastrointestinal hemorrhage" and "liver cirrhosis" or "portal hypertension" or "esophageal varices".
- "Beta blockers" and "gastrointestinal hemorrhage" or "liver cirrhosis" or "portal hypertension" or "esophageal varices".
- "Banding ligation" and "gastrointestinal hemorrhage" or "liver cirrhosis" or "portal hypertension" or "esophageal varices".
- "Therapy" and "gastrointestinal hemorrhage" or "liver cirrhosis" or "portal hypertension" or "esophageal varices".
- "Prophylaxis" and "gastrointestinal hemorrhage" or "liver cirrhosis" or "portal hypertension" or "esophageal varices".
- These searches were performed in the categories "Topic" and "Title"