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## Role of band ligation for secondary prophylaxis of variceal bleeding

Ioanna Aggeletopoulou, Christos Konstantakis, Spilios Manolakopoulos, Christos Triantos

Ioanna Aggeletopoulou, Christos Konstantakis, Christos Triantos, Department of Gastroenterology, University Hospital of Patras, Patras 26504, Greece

Spilios Manolakopoulos, 2<sup>nd</sup> Department of Internal Medicine, Hippokraton General Hospital of Athens, Athens 11527, Greece

ORCID number: Ioanna Aggeletopoulou (0000-0003-4489-1485); Christos Konstantakis (0000-0001-5834-9182); Spilios Manolakopoulos (0000-0003-3130-7155); Christos Triantos (0000-0003-3094-8209).

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Correspondence to: Christos Triantos, PhD, Assistant Professor in Internal Medicine and Gastroenterology, Department of Gastroenterology, University Hospital of Patras, D. Stamatopoulou 4, Rio, Patras 26504, Greece. [chtriantos@hotmail.com](mailto:chtriantos@hotmail.com)  
Telephone: +30-69-72894651  
Fax: +30-26-10625382

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### Abstract

#### AIM

To summarize and critically examine the role of band ligation in secondary prophylaxis of variceal bleeding in patients with cirrhosis.

#### METHODS

A literature review was performed using the MEDLINE and PubMed databases. The search terms consisted of the words "endoscopic band ligation" OR "variceal band ligation" OR "ligation" AND "secondary prophylaxis" OR "secondary prevention" AND "variceal bleeding" OR "variceal hemorrhage" AND "liver cirrhosis". The data collected from relevant meta-analyses and from the most recent randomized studies that were not included in these meta-analyses were used to evaluate the role of endoscopic band ligation in an effort to demonstrate the most recent advances in the treatment of esophageal varices.

#### RESULTS

This study included 11 meta-analyses published from 2002 to 2017 and 10 randomized trials published from 2010 to 2017 that evaluated the efficacy of band ligation

in the secondary prophylaxis of variceal bleeding. Overall, the results proved that band ligation was superior to endoscopic sclerotherapy. Moreover, the use of  $\beta$ -blockers in combination with band ligation increased the treatment effectiveness, supporting the current recommendations for secondary prophylaxis of variceal bleeding. The use of transjugular intrahepatic portosystemic shunt was superior to combination therapy regarding rebleeding prophylaxis, with no difference in the survival rates; however, the results concerning the hepatic encephalopathy incidence were conflicting. Recent advances in the management of secondary prophylaxis of variceal bleeding have targeted a decrease in portal pressure based on the pathophysiological mechanisms of portal hypertension.

### CONCLUSION

This review suggests that future research should be conducted to enhance current interventions and/or to develop innovative treatment options with improved clinical endpoints.

**Key words:** Band ligation; Variceal bleeding; Rebleeding; Liver cirrhosis; Endoscopic therapy; Variceal eradication; Secondary prophylaxis; Esophageal varices

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**Core tip:** Variceal bleeding is a life-threatening complication of liver cirrhosis. The current guidelines recommend the use of band ligation together with  $\beta$ -blockers in the setting of secondary prophylaxis for variceal bleeding in patients with cirrhosis. This review summarizes data from meta-analyses and randomized trials to demonstrate the most recent advances in the management of variceal rebleeding. The current evidence suggests that the efficacy of band ligation is increased by adding  $\beta$ -blockers in accordance with the current guidelines. However, combination therapy does not procure a survival advantage. Innovative interventions and more effective novel strategies aiming to improve clinical outcomes should be developed.

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### INTRODUCTION

Approximately half of liver cirrhosis patients have developed gastroesophageal varices at diagnosis<sup>[1]</sup>. In the absence of proper treatment, approximately 30% of patients with varices will suffer a bleeding episode within the first 2 years following the cirrhosis diagnosis<sup>[2]</sup>.

Variceal bleeding is considered one of the most severe complications of portal hypertension and constitutes a life-threatening condition for the cirrhosis patient. Patients surviving this first attack have an increased risk for rebleeding, especially during the first 6 weeks following the initial event. Overall, a second episode of variceal bleeding occurs in approximately 60% of this group of patients within 2 years<sup>[3,4]</sup>. The most common risk factors for variceal bleeding are the sizes of the varices<sup>[2,5,6]</sup>, the severity of the liver disease<sup>[2]</sup> and the presence of red color signs on the variceal wall<sup>[2,7]</sup>. Patients with small varices have a low bleeding risk (approximately 5% per year), whereas patients with large varices have a higher bleeding rate of approximately 15% per year<sup>[1,8,9]</sup>. The 1-year bleeding probability in Child-Pugh class A cirrhosis patients with large varices and red signs is 24% compared with a 20% probability for Child-Pugh C patients with small varices and no red signs, indicating that variceal size constitutes the most useful predictor for variceal bleeding<sup>[2,6]</sup>. The aforementioned predictive factors have been combined in the North Italian Endoscopic Club index to classify patients according to the risk of a first variceal bleeding episode<sup>[2]</sup>. Variceal bleeding is associated with an increased hepatic venous pressure gradient (HVPG) (exceeding the threshold value of 12 mmHg). In contrast, a HVPG beneath 12 mmHg or a decrease in the HVPG gradient of more than 20% from the baseline level is related to a considerable reduction in the risk of variceal hemorrhage.

Patients who survive a first bleeding episode have a high risk of recurrence<sup>[8]</sup>. Therefore, these patients should receive appropriate treatment<sup>[10,11]</sup>. The primary aim of secondary prophylaxis is the prevention of further episodes of variceal hemorrhage and a reduction of associated mortality in cirrhosis patients. Available management options for secondary prophylaxis of variceal bleeding include pharmacotherapy, endoscopic treatment, transjugular intrahepatic portosystemic shunt (TIPS) and surgical shunting<sup>[8,12]</sup>. According to the Baveno VI guidelines and the practice guidance of the American Association for the Study of Liver Diseases (AASLD), the combination of non-selective  $\beta$ -blockers (propranolol or nadolol) and endoscopic band ligation constitutes the preferred treatment option for secondary prophylaxis in patients with liver cirrhosis<sup>[10,11]</sup>. Endoscopic band ligation should not be used alone unless the patient cannot tolerate  $\beta$ -blockers or there is a contraindication for non-selective  $\beta$ -blocker administration<sup>[10]</sup>. Patients who have not responded to the combination therapy should undergo covered TIPS insertion<sup>[10]</sup>.

Systematic reviews and meta-analyses comparing these interventions have highlighted the differences in efficacy between the different modalities. The primary objective of this study is to summarize and critically review the existing data with a focus on the most updated randomized trials of the role of endoscopic band ligation in the secondary prophylaxis of variceal bleeding in liver cirrhosis patients.

## MATERIALS AND METHODS

### Search strategy

We conducted a review of the literature using the MEDLINE and PubMed databases. Data regarding the role of band ligation in secondary prophylaxis of variceal bleeding in liver cirrhosis patients were extracted from the relevant full articles. The search terms consisted of the words "endoscopic band ligation" OR "variceal band ligation" OR "ligation" AND "secondary prophylaxis" OR "secondary prevention" AND "variceal bleeding" OR "variceal hemorrhage" AND "liver cirrhosis".

Two reviewers (Aggeletopoulou I and Konstantakis C) independently reviewed all the titles and abstracts retrieved from the search after applying the inclusion criteria. A third reviewer (Triantos C) made the final decision in cases of disagreement. All manuscripts that compared endoscopic band ligation intervention vs other interventions were evaluated. Data collected from relevant meta-analyses and the most recent randomized studies not included in these meta-analyses were used to evaluate the role of endoscopic band ligation in an effort to demonstrate the most recent advances in the treatment of esophageal varices. All disagreements were resolved after full discussions within the research group.

### Inclusion criteria

The inclusion criteria were as follows: (1) Full articles; (2) meta-analyses or systematic reviews comparing endoscopic band ligation vs other interventions (monotherapy or combination); (3) most recent randomized studies comparing endoscopic band ligation vs other interventions (monotherapy or combination) that were not included in the existing meta-analyses; (4) patients with liver cirrhosis; (5) studies containing the information of interest as subgroup analyses were included; and (6) Criteria 1 and 2 were applied in the setting of secondary prevention.

## RESULTS

### Meta-analyses

The meta-analyses that compared the effectiveness of endoscopic band ligation to that of other treatment options are presented in Table 1. Overall, 11 meta-analyses evaluated the efficacy of band ligation from 2002 to 2017<sup>[13-23]</sup>. Cheung *et al.*<sup>[17]</sup> compared the efficacy of band ligation, pharmacotherapy [ $\beta$ -blockers alone or with isosorbide mononitrate (ISMN)] and their combination for the secondary prevention of variceal bleeding. The authors found no difference in the mortality and complication rates between the different treatment options and concluded that all treatment modalities were equally efficient for the prevention of rebleeding<sup>[17]</sup>. Similar results were found by Ding *et al.*<sup>[13]</sup>, who demonstrated no difference in rebleeding, mortality and complication rates between the band ligation and the  $\beta$ -blockers plus ISMN groups. Band ligation was compared with  $\beta$ -blockers plus ISMN in one additional meta-analysis; the results

showed no significant difference between band ligation and  $\beta$ -blockers with regard to all-cause mortality, bleeding-related mortality and the occurrence of adverse events<sup>[18]</sup>. However, a significant decrease in variceal bleeding was noted in patients who underwent band ligation compared to patients administered  $\beta$ -blockers that was attenuated when the analysis included only studies with adequate randomization and allocation concealment<sup>[18]</sup>. Thiele *et al.*<sup>[19]</sup> assessed the effectiveness of band ligation with medical therapy compared with monotherapy (band ligation or medical therapy) and suggested that the combination treatment decreased the risk of rebleeding but did not influence the mortality rate compared with monotherapy. However, patients treated with combination therapy exhibited an increased trend towards the development of serious adverse events<sup>[19]</sup>. A subgroup analysis was performed in 2 meta-analyses to examine the efficacy of band ligation compared to band ligation plus pharmacotherapy; both meta-analyses agreed that combination therapy decreased the overall and variceal rebleeding rates<sup>[14,15]</sup>. Similar results reported by Ko *et al.*<sup>[21]</sup> indicated that the combination therapy ( $\beta$ -blockers plus band ligation) was superior to pharmacotherapy alone for reduction of variceal rebleeding but not for overall rebleeding and mortality, which exhibited no differences between the two groups<sup>[21]</sup>. Lastly, another meta-analysis compared band ligation plus  $\beta$ -blockers to monotherapy (band ligation or  $\beta$ -blockers) after stratifying the patients according to their cirrhosis severity (Child-Pugh A vs B/C classes)<sup>[23]</sup>. The outcomes showed that the combination therapy was more effective in preventing rebleeding in the compensated patients but had no influence on the mortality rates<sup>[23]</sup>. In the decompensated patients, band ligation alone demonstrated an increased risk of rebleeding and mortality compared to combination therapy<sup>[23]</sup>.

Nonsurgical therapeutic endoscopic approaches (endoscopic sclerotherapy and band ligation) for the control and prevention of bleeding episodes were compared by Dai *et al.*<sup>[20]</sup>, Karsan *et al.*<sup>[22]</sup> and Singh *et al.*<sup>[16]</sup>. Lower rebleeding, adverse event and mortality rates and higher variceal eradication were reported by Dai *et al.*<sup>[20]</sup> in patients treated with band ligation compared to sclerotherapy, suggesting that endoscopic ligation should be the first-choice therapy. Furthermore, comparison of the combination of band ligation plus sclerotherapy with ligation alone failed to demonstrate significant differences in rebleeding prevention and mortality, and the former approach was associated with higher complication rates<sup>[16,22]</sup>. In contrast, a meta-analysis that evaluated the effectiveness of 12 prophylactic modalities for secondary prevention of variceal bleeding using multiple treatments indicated that band ligation combined with sclerotherapy could be used as a first-choice therapy<sup>[24]</sup>. Lastly, comparison of the efficacy of endoscopic procedures to that of pharmacotherapy showed that both methods were equally effective in terms of rebleeding prevention and all-cause mortality<sup>[25]</sup>. However, the combination of these methods was superior compared to endoscopic therapy

**Table 1 Results from meta-analyses comparing band ligation with other interventions in terms of all-cause related rebleeding, variceal rebleeding, all-cause related mortality, bleeding related mortality and complication rates**

Study (reference)	Publication year	Country	Method	Number of studies	Number of patients	All-cause related rebleeding RR or OR/CI/ <i>I</i> <sup>2</sup>	Variceal rebleeding RR or OR/CI/ <i>I</i> <sup>2</sup>	All-cause related mortality RR or OR/CI/ <i>I</i> <sup>2</sup>	Bleeding related mortality RR or OR/CI/ <i>I</i> <sup>2</sup>	Complications RR or OR/CI/ <i>I</i> <sup>2</sup>
Singh <i>et al</i> <sup>[16]</sup>	2002	United States	EBL vs EST + EBL	7	453	NR	1.12/ 0.69-1.81/ NR	NR	1.1/ 0.70-1.74/ NR	0.37/ 0.21-0.62/ NR
Karsan <i>et al</i> <sup>[22]</sup>	2005	United States	EBL vs EST + EBL	8	520	NR	1.05/ 0.67-1.64/ NS	0.99/ 0.68-1.44/ NS	NR	NR
<sup>1</sup> Gonzalez <i>et al</i> <sup>[15]</sup>	2008	Spain	<sup>2</sup> Combination therapy vs EBL	4	404	0.62/ 0.44-0.87/ 40%	NR	0.79/ 0.44-1.43/ 54%	NR	NR
Cheung <i>et al</i> <sup>[17]</sup>	2009	Canada	EBL vs PT	6	698	0.96/ 0.73-1.30/ 62%	NR/ NR/ 79%	1.20/ 0.92-1.57/ 0	NR	0.90/ 0.70-1.15/ 0
			EBL+PT vs EBL	4	404	0.57/ 0.31-1.08/ 60%	0.38/ 0.19-0.76/ 0	0.90/ 0.41-1.98/ 45%	NR	3.4/ 1.4-8.2/ 74%
			EBL+PT vs PT	2	279	0.76/ 0.56-1.03/ 0	0.58/ 0.40-0.85/ 0	0.94/ 0.54-1.63/ 31%	NR	NR
Ding <i>et al</i> <sup>[13]</sup>	2009	China	β-blockers + ISMN vs EBL	4	476	0.94/ 0.64-1.38 71.50%	NR	0.81/ 0.61-1.08/ 0	0.76/ 0.31-1.42/ 38.90%	1.26/ 0.93-1.70/ 42.70%
<sup>1</sup> Funakoshi <i>et al</i> <sup>[14]</sup>	2010	France	EBL vs EBL + β-blockers	3	252	3.16/ 1.76-5.34/ 0	NR	1.78/ 0.92-3.43/ 0	NR	NR
Li <i>et al</i> <sup>[18]</sup>	2011	China	EBL vs β-blockers + ISMN	6	687	0.95/ 0.65-1.40/ NR	0.89/ 0.53-1.49/ NR	1.25/ 1.01-1.55/ NR	1.16/ 0.68-1.97/ NR	NR
Thiele <i>et al</i> <sup>[19]</sup>	2012	Denmark	3EBL+PT vs monotherapy	9	955	0.68/ 0.54-0.85/ 1%	0.67/ 0.54-0.84/0	0.89/ 0.65-1.21/ 0	0.52/ 0.27-0.99/ NR	1.42/ 0.94-2.13/ 69%
Ko <i>et al</i> <sup>[21]</sup>	2012	South Korea	EBL + β-blockers vs β-blockers	4	409	0.78/ 0.58-1.04/ NR	0.60/ 0.41-0.88/ NR	1.21/ 0.88-1.65/ NR	NR	NR
Dai <i>et al</i> <sup>[20]</sup>	2015	China	EBL vs EST	14	1236	0.68/ 0.57-0.81/ 9.00%	NR	0.95/ 0.77-1.17/ 32.80%	NR	0.28/ 0.13-0.58/ 86.50%
Albillos <i>et al</i> <sup>[23]</sup>	2017	Spain	EBL + β-blockers vs EBL	4	416	0.36/ 0.21-0.59/ NR	0.52/ 0.25-1.11/ NR	0.50/ 0.28-0.89/ NR	NR	NR
			EBL + β-blockers vs β-blockers	3	389	1.0/ 0.68-1.47/ NR	0.81/ 0.53-1.23/ NR	1.19/ 0.76-1.87/ NR	NR	NR

<sup>1</sup>These results represent a subgroup analysis of the examined meta-analysis; <sup>2</sup>The term combination therapy includes endoscopic therapy combined with injection sclerotherapy or band ligation combined with drug therapy (β-blockers); <sup>3</sup>The term monotherapy includes endoscopic band ligation alone or medical therapy alone (β-blockers alone or combined with ISMN). RR: Risk ratio; OR: Odds ratio; CI: Confidence interval; *I*<sup>2</sup>: Study heterogeneity; EBL: Endoscopic band ligation; EST: Endoscopic sclerotherapy; NR: Not reported; NS: Nonsignificant; PT: Pharmacotherapy; ISMN: Isosorbide mononitrate.

alone<sup>[25]</sup>.

**Randomized trials**

The most recent randomized studies evaluating the role of band ligation in secondary prophylaxis (vs other interventions) that were not included in the existing meta-analyses were reviewed. Ten trials on secondary variceal bleeding prophylaxis in 770 patients with liver cirrhosis from 2010 to 2017 were included in this study (Table 2). The characteristics and clinical profiles of the

patients are summarized in Table 3.

Three trials compared the efficacy of band ligation vs endoscopic sclerotherapy<sup>[26-28]</sup>, 3 trials compared band ligation vs pharmacotherapy<sup>[29-31]</sup>, 2 trials compared band ligation vs TIPS<sup>[32,33]</sup>, one trial compared band ligation vs cyanoacrylate injection<sup>[34]</sup> and one trial compared band ligation combined with sclerotherapy vs band ligation combined with microwave coagulation<sup>[35]</sup>. The results of these studies in terms of variceal obliteration, rebleeding and variceal recurrence are summarized in Table 4, and

**Table 2 Characteristics of the included randomized trials**

Study (reference)	Publication year	Country	Number of subjects
Monici <i>et al</i> <sup>[35]</sup>	2010	Brazil	70
Luz <i>et al</i> <sup>[26]</sup>	2011	Brazil	83
Santos <i>et al</i> <sup>[34]</sup>	2011	Brazil	38
Lo <i>et al</i> <sup>[31]</sup>	2013	Taiwan	118
Stanley <i>et al</i> <sup>[30]</sup>	2014	United Kingdom	64
Chen <i>et al</i> <sup>[28]</sup>	2016	China	96
Holster <i>et al</i> <sup>[32]</sup>	2016	Netherlands	72
Mansour <i>et al</i> <sup>[27]</sup>	2017	Egypt	120
Lv <i>et al</i> <sup>[33]</sup>	2017	China	49
Hanif <i>et al</i> <sup>[29]</sup>	2017	Pakistan	60

the results regarding mortality are summarized in Table 5.

**Band ligation vs endoscopic sclerotherapy:** Three studies evaluated the efficacy of band ligation vs endoscopic sclerotherapy alone<sup>[26]</sup> or in combination<sup>[27,28]</sup>. The comparison of band ligation vs endoscopic sclerotherapy showed no differences in bleeding control or in the early re-bleeding, complication and mortality rates<sup>[26]</sup>. Conflicting results emerged when band ligation was compared to sclerotherapy and band ligation<sup>[27,28]</sup>. Mansour *et al*<sup>[27]</sup> reported that sclerotherapy and band ligation were superior to band ligation for variceal obliteration, whereas Chen *et al*<sup>[28]</sup> showed that band ligation alone was more effective than the combination of ligation and sclerotherapy in terms of rebleeding. However, both studies demonstrated no differences in the adverse event rate and survival<sup>[27,28]</sup>.

**Band ligation vs pharmacotherapy:** Stanley *et al*<sup>[30]</sup> assessed the efficacy of band ligation vs carvedilol and found no difference in the prevention of rebleeding. However, a trend towards an improved survival rate was observed in the patients who received carvedilol<sup>[30]</sup>. The effectiveness of band ligation plus propranolol vs propranolol alone was evaluated by Hanif *et al*<sup>[29]</sup>, who suggested that the combination therapy was superior for secondary prophylaxis compared to the use of propranolol alone. Band ligation combined with proton pump inhibitors (PPIs) was compared to band ligation combined with vasoconstrictors; the results showed that adjuvant therapy with PPIs was similar to vasoconstrictors in relation to initial hemostasis and the very early rebleeding rate, but the combination treatment with PPIs demonstrated a lower rate of adverse events<sup>[31]</sup>.

**Band ligation vs TIPS:** Band ligation plus  $\beta$ -blocker combination treatment was compared to TIPS in 2 trials. Both trials agreed that TIPS was superior to combination therapy for rebleeding prophylaxis; however, no difference was found in the survival rates<sup>[32,33]</sup>.

**Band ligation vs cyanoacrylate injection:** One study evaluated the efficacy of band ligation compared to cyanoacrylate injection<sup>[34]</sup>. The results showed no

significant difference between the two methods in terms of mortality, variceal obliteration and the adverse event rates but reported that patients treated with cyanoacrylate injection presented with more minor complications, earlier variceal recurrence and more bleeding episodes than the ligation group<sup>[34]</sup>.

**Band ligation plus sclerotherapy vs band ligation plus microwave coagulation:** One study evaluated the rate of variceal recurrence in patients who received band ligation combined with either sequential microwave coagulation or endoscopic sclerotherapy in a cohort of Child-Pugh A and B patients<sup>[35]</sup>. The results showed that although the application of thermal therapy after ligation was safe and effective, no difference was found between the two methods in terms of variceal eradication, complications and variceal recurrence<sup>[35]</sup>.

## DISCUSSION

The aim of this review was to evaluate the effectiveness of endoscopic band ligation for secondary prophylaxis of esophageal variceal bleeding in liver cirrhosis patients. In this study, we incorporated data from meta-analyses that evaluated the efficacy of band ligation in comparison to (or in combination with) other interventions as well as the most recent data from randomized clinical trials that were not included in the aforementioned meta-analyses. We collected these data with the intention of identifying conflicting results from previous studies and obtaining precise estimates of treatment outcomes in terms of secondary prevention of variceal hemorrhage. Overall, current data favor the use of band ligation over endoscopic sclerotherapy. In addition, use of  $\beta$ -blockers combined with band ligation increases the treatment efficacy due to the reduced risk of rebleeding from the upper gastrointestinal system and esophageal varices. These findings are in agreement with the current clinical practice recommendations for secondary prophylaxis of variceal bleeding. Despite its proven benefits, the effect of combination therapy on survival remains uncertain. Therefore, further high-quality (and volume) studies and the development of novel treatment options are required.

Esophageal variceal bleeding constitutes a life-threatening complication of portal hypertension with a mortality rate of 12%-16% (depending on the analyzed cohort) and a high incidence of early rebleeding within the first 6 wk of the initial bleeding episode<sup>[36]</sup>. Endoscopic band ligation is a proven therapeutic option for achieving both initial hemostasis and preventing further bleeding episodes. The aim of band ligation is to eradicate varices through their "constriction" with rubber rings that are placed using a device attached to the endoscope tip called a "multiband ligator"<sup>[37]</sup>. The varices are sucked into the cap of the multiband ligator and then ligated through the release of a rubber band, which is responsible for the interruption of blood flow into the ligated varix<sup>[37]</sup>. Application of the bands initiates at

**Table 3** Baseline characteristics of the patients included in the review

Study (reference)	Patients	Gender (M/F)	Age (range or $\pm$ SD)	CP class (A/B/C)	Cirrhosis etiology (agent %)
Monici <i>et al</i> <sup>[25]</sup>	EBL + EST: 36	25/11	47.8 (30-68)	28/8/0	Alcohol/virus/alcohol+virus/cryptogenic/autoimmune/PSC/PBC 12/13/3/5/2/1
	EBL + MC: 34	26/8	48.5 (22-71)	29/5/0	Alcohol/virus/alcohol+ virus/cryptogenic/autoimmune/PSC/PBC 8/11/3/9/1/2
Luz <i>et al</i> <sup>[26]</sup>	EBL: 44	NR	NR	2/22/20	Alcohol/virus/secondary biliary cirrhosis/cryptogenic/PBC 43.2/43.2/9.1/2.3/2.3
	EST: 39	NR	NR	3/21/15	Alcohol/virus/secondary biliary cirrhosis/cryptogenic/PBC 43.6/38.5/7.7/5.1/5.1
Santos <i>et al</i> <sup>[24]</sup>	EBL: 20	13/7	52 $\pm$ 12.6	0/4/16	Alcohol/HCV/alcohol+HCV/other 30/30/15/25
	CI: 18	14/4	51 $\pm$ 8.2	0/3/15	Alcohol/HCV/alcohol+HCV/other 39/33/6/22
Lo <i>et al</i> <sup>[31]</sup>	EBL+ vasoconstrictors: 60	49/11	52.5 $\pm$ 14.4	18/32/10	Alcohol/HBV/HCV/HBV+HCV/cryptogenic 40/22/30/3/5
	EBL+PPIs: 58	49/9	54.2 $\pm$ 9.7	15/24/19	Alcohol/HBV/HCV/HBV+HCV/cryptogenic 38/29/26/3/2/2
Stanley <i>et al</i> <sup>[30]</sup>	EBL: 31	21/10	49.6 $\pm$ 12.87	11/28/25	Alcohol/NAFLD/PBC/DICLD 91/5/3/2
	Carvedilol: 33	22/11	51.4 $\pm$ 10.8		
Chen <i>et al</i> <sup>[28]</sup>	EBL: 48	32/16	56 $\pm$ 10	19/29/0	HBV/HCV/Alcohol/autoimmune/other 59/4/6/8/23
	EST: 48	31/17	54 $\pm$ 11	20/28/0	HBV/HCV/alcohol/autoimmune/other 75/0/2/10/13
Holster <i>et al</i> <sup>[32]</sup>	EBL+ $\beta$ -blockers: 35	23/12	54 (30-71)	13/18/4	Alcohol/HBV+HCV/alcohol + HBV+HCV/autoimmune liver+biliary disease/other 51/3/8/26/11
	TIPS: 37	18/19	56 (37-75)	13/19/5	Alcohol/HBV+HCV/alcohol + HBV+HCV/autoimmune liver+biliary disease/other 35/19/8/24/14
Mansour <i>et al</i> <sup>[27]</sup>	EBL: 60	34/26	NR	8/20/32	HCV/HBV/HCV+HBV 86.67/6.66/6.66
	EBL + EST: 60	44/16	NR	14/22/24	HCV/HBV/HCV+HBV 86.67/6.66/6.66
Lv <i>et al</i> <sup>[33]</sup>	EBL+propranolol: 25	16/8	46 (38-56)	10/14/1	HBV/HCV/alcohol/AH/HBV+AH/cryptogenic 86.67/13.3/0
	TIPS: 24	13/12	49 (46-62)	9/13/2	HBV/HCV/alcohol/AH/HBV+AH/cryptogenic 83/4/4/4/0/4
Hanif <i>et al</i> <sup>[29]</sup>	EBL+ propranolol: 30	25/5	56.30 $\pm$ 5.80	NR	NR
	Propranolol: 30	13/17	57.63 $\pm$ 5.98	NR	NR

CP: Child Pugh; EBL: Endoscopic band ligation; EST: Endoscopic sclerotherapy; PSC: Primary sclerosing cholangitis; PBC: Primary biliary cirrhosis; MC: Microwave coagulation; NR: Not reported; HCV: Hepatitis C virus; HBV: Hepatitis B virus; CI: Cyanoacrylate injection; AH: Autoimmune hepatitis; NAFLD: Non-alcoholic fatty liver disease; PPIs: Proton pump inhibitors; DICLD: Drug-induced chronic liver disease; TIPS: Transjugular intrahepatic portosystemic shunt; NSBBs: Non-selective  $\beta$ -blockers.

the gastroesophageal junction and moves upwards in a helical manner for approximately 5-8 cm.

After initial control of bleeding, the band ligation sessions should be repeated at 1-wk to 4-wk intervals according to the practice guidelines of the AASLD<sup>[11]</sup> and at 1-wk to 8-wk intervals according to the American Society for Gastrointestinal Endoscopy guidelines<sup>[38]</sup> until the varices are eradicated. The complete eradication process typically requires 2 to 4 ligation sessions<sup>[39]</sup>. Variceal obliteration is achieved in approximately 90% of patients who undergo band ligation<sup>[40]</sup>. Once variceal obliteration has been achieved, a surveillance endoscopy is performed 3 mo to 6 mo after obliteration and every 6 to 12 mo thereafter to evaluate variceal recurrence<sup>[41]</sup>. Episodes of variceal recurrence after obliteration are common, with an incidence range of 20%-75% (within 1 year of therapy)<sup>[37]</sup>.

The most recent consensus guidelines recommend the use of a combination of  $\beta$ -blockers and band ligation as the first-line therapy for the prevention of variceal rebleeding<sup>[10]</sup>. Non-selective adrenergic  $\beta$ -blockers, such as propranolol or nadolol, are preferred. The effect of non-selective adrenergic  $\beta$ -blockers relies on the reduction of portal pressure by decreasing the portal blood flow, because increased portal pressure is the driving force that enhances variceal growth and subsequent rupture, whereas band ligation only has a local effect<sup>[42]</sup>. The beneficial effect of combination treatment on variceal rebleeding was confirmed in 5 meta-analyses that assessed the efficacy of combined endoscopic and  $\beta$ -blocker therapy vs monotherapy in the prevention of variceal hemorrhage in cirrhosis patients<sup>[14,15,19,21,23]</sup>. However, the effect of combination therapy on survival was uncertain, because no significant

**Table 4 Results of individual trials comparing band ligation with other interventions in terms of variceal obliteration, rebleeding and variceal recurrence**

Study (reference)	Treatment	Mean sessions to obliterate	Rate of obliteration /time to obliterate (%)	Rebleeding rate (%)	Variceal recurrence rate
Endoscopic band ligation <i>vs</i> endoscopic sclerotherapy					
Luz <i>et al</i> <sup>[26]</sup>	EBL	NR	75 at 5 d	25 at 5 d	NR
	EST		84.6 at 5 d	15.4 at 5 d	
Mansour <i>et al</i> <sup>[27]</sup>	EBL	3.43 ± 0.67	100 at 15.6 wk	16.70	26.7 at 3 mo 10 at 6 mo
	EBL + EST	2.22 ± 0.92	100 at 8.64 wk	13.30	20 at 3 mo 10 at 6 mo
Chen <i>et al</i> <sup>[28]</sup>	EBL	3 ± 0.5	25	14.60	NR
	EBL + EST	3 ± 0.6	16.30	35.40	
Endoscopic band ligation <i>vs</i> β-blockers					
Stanley <i>et al</i> <sup>[30]</sup>	EBL	NR	65	35.50	NR
	Carvedilol		68	36.40	
Endoscopic band ligation + β-blockers <i>vs</i> β-blockers					
Hanif <i>et al</i> <sup>[29]</sup>	EBL + propranolol	NR	NR	10	NR
	Propranolol			40	
Endoscopic band ligation + PPIs <i>vs</i> endoscopic band ligation + vasoconstrictors					
Lo <i>et al</i> <sup>[31]</sup>	EBL + vasoconstrictors	NR	NR	1.7 at 6 d 8.3 at 6-42 d	NR
	EBL + PPIs			1.7 at 6 d 8.6 at 6-42 d	
Endoscopic band ligation + β-blockers <i>vs</i> TIPS					
Holster <i>et al</i> <sup>[32]</sup>	EBL + β-blockers	NR	71 at 2 yr	26 at 2 yr	NR
	TIPS		73 at 2 yr	0 at 2 yr	
Lv <i>et al</i> <sup>[33]</sup>	EBL + propranolol	NR	NR	37 at 6 mo 45 at 12 mo 45 at 24 mo 52 at 30.4 mo	NR
	TIPS			5 at 6 mo 15 at 12 mo 20 at 24 mo 17 at 30.9 mo	
Santos <i>et al</i> <sup>[34]</sup>	EBL	3.17 ± 1.15	90 at 75.4 d	0	33 at 14.6 mo
	CI	3 ± 1.36	78 at 55.4 d	10	57 at 7.9 mo
Endoscopic band ligation + endoscopic sclerotherapy <i>vs</i> endoscopic band ligation + microwave coagulation					
Monici <i>et al</i> <sup>[35]</sup>	EBL + EST	2.75 ± 1.92	97.30	8.30	27.7 at 9.5 mo 19.5 at 12 mo
	EBL + MC	2.38 ± 1.63	97.10	0	17.6 at 9.16 mo 17.5 at 12 mo

EBL: Endoscopic band ligation; EST: Endoscopic sclerotherapy; NR: Not reported; PPIs: Proton pump inhibitors; TIPS: Transjugular intrahepatic portosystemic shunt; CI: Cyanoacrylate injection; MC: Microwave coagulation.

difference was observed<sup>[14,15,19,21,23]</sup>. This result could be explained by a possible link between band ligation and the development of new or the exacerbation of previous complications, such as a ligation-related ulcer, portal hypertensive gastropathy, or the development of fundal varices<sup>[43-45]</sup>. The meta-analysis by Albillos *et al*<sup>[23]</sup> reported that the addition of band ligation with β-blockers resulted in a higher but not significant risk of mortality [incidence rate ratio (IRR) = 1.40; 95%CI: 0.87-2.27], all-source rebleeding (IRR = 1.36; 95%CI: 0.87-2.14) and variceal rebleeding (IRR = 1.24; 95%CI: 0.75-2.05) in patients with Child-Pugh class B/C, suggesting a potential deleterious effect of band ligation in this setting and highlighting the use of β-blockers as a key element of combination therapy<sup>[23]</sup>. The use of β-blockers enhances nonhemodynamic effects, such as a decrease in the drive of the sympathetic nervous system, and hemodynamic effects, such as a reduction

in the splanchnic or gastroesophageal collateral blood flow and portal pressure<sup>[46,47]</sup>. Moreover, β-blockers may have a favorable effect on overall mortality, because they reduce the frequency of complications of cirrhosis, such as ascites, hepatorenal syndrome, portal hypertensive gastropathy<sup>[9,48]</sup> and spontaneous bacterial peritonitis<sup>[49-51]</sup>. A recent study described the “window hypothesis”, which proposed that β-blockers had a beneficial impact on survival during the early phase of decompensated liver cirrhosis<sup>[46]</sup>. However, this benefit seems to diminish/disappear in well-compensated and end-stage cirrhosis patients<sup>[46,52]</sup>. Over the past few decades, variceal bleeding-related mortality has decreased. Conversely, deaths related other causes that are not associated with endoscopic treatment or pharmacotherapy, such as hepatocellular carcinoma, have demonstrated an increasing trend. Other studies, including a meta-analysis and four studies comparing

**Table 5 Results of individual trials comparing band ligation with other interventions in terms of mortality**

Study (reference)	Treatment	Mean hospitalization days (range or ± SD)	Mortality rate (%)	Follow up (range or ± SD)
Luz <i>et al</i> <sup>[26]</sup>	EBL	NR	13.60	5 d
	EST		7.70	5 d
Mansour <i>et al</i> <sup>[27]</sup>	EBL	NR	No difference	6 mo
	EBL + EST			
Chen <i>et al</i> <sup>[28]</sup>	EBL	NR	2.10	6 mo
	EBL + EST		6.30	
Stanley <i>et al</i> <sup>[30]</sup>	EBL	NR	51.60	26.3 mo
	Carvedilol		27.30	
Hanif <i>et al</i> <sup>[29]</sup>	EBL + propranolol	NR	NR	6 mo
	Propranolol			
Lo <i>et al</i> <sup>[31]</sup>	EBL + vasoconstrictors	9.4 ± 2.3	6.7 at 42 d	42 d
	EBL + PPIs	8.8 ± 3.8	5.2 at 42 d	
Holster <i>et al</i> <sup>[32]</sup>	EBL + β-blockers	8.8 ± 5.4	20 at 2 yr	23.4 mo
	TIPS	12.4 ± 11.2	22 at 2 yr	
Lv <i>et al</i> <sup>[33]</sup>	EBL + propranolol	NR	12 at 6 mo	30.4 mo
			12 at 12 mo	
			16 at 24 mo	
	TIPS	NR	33 at 30.4 mo	30.9 mo
			16 at 6 mo	
			17 at 12 mo	
Santos <i>et al</i> <sup>[34]</sup>	EBL	NR	55	338 ± 189 d
	CI		56	
Monici <i>et al</i> <sup>[35]</sup>	EBL + EST	NR	5.50	36.1 (15-53) mo
	EBL + MC		5.88	33.6 (14-54) mo

EBL: Endoscopic band ligation; EST: Endoscopic sclerotherapy; NR: Not reported; PPIs: Proton pump inhibitors; TIPS: Transjugular intrahepatic portosystemic shunt; CI: Cyanoacrylate injection; MC: Microwave coagulation.

band ligation vs combined ligation and β-blockers, found no significant differences in the rebleeding and mortality rates<sup>[17]</sup>. Several studies have compared the effectiveness of band ligation vs β-blockers with or without nitrates. Their results are compiled in 3 meta-analyses, which demonstrated comparable results for both the rebleeding and mortality rates<sup>[13,17,18]</sup>.

Endoscopic sclerotherapy, which is another therapeutic intervention for variceal obliteration, has proven to be inferior to band ligation due to its higher complication rates and the number of sessions required for variceal obliteration<sup>[37,53]</sup>. However, endoscopic sclerotherapy achieves better results in cases of deeper paraesophageal varices, possibly because sclerotherapy induces fibrosis and eradication of perforating veins in contrast to band ligation, which does not affect collateral vessels in the deeper layers<sup>[54]</sup>. A randomized study that compared the early effects of endoscopic sclerotherapy vs band ligation on the HVPG values during acute bleeding episodes showed a sustained increase in the portal pressure levels after sclerotherapy that was followed by a higher rebleeding rate; in contrast, the HVPG values

in the ligation group returned to the baseline levels within 48 h<sup>[55]</sup>. A recent meta-analysis evaluated these two endoscopic approaches and concluded that band ligation was superior in terms of the rebleeding and mortality rates<sup>[20]</sup>. The combination of band ligation plus sclerotherapy was assessed by Singh *et al*<sup>[16]</sup> and Karsan *et al*<sup>[22]</sup>, who found no advantage over ligation alone in the prevention of rebleeding and reduction of mortality.

Endoscopic band ligation, endoscopic sclerotherapy, drug therapy and TIPS constitute the nonsurgical therapeutic options for control of variceal bleeding and prevention of rebleeding episodes. Band ligation is considered the preferred initial approach, whereas TIPS is recommended in patients who fail endoscopic and pharmacological therapy or coagulation and those who are at high risk of treatment failure<sup>[10,11,56]</sup>. Portal vein thrombosis (PVT) is a frequent complication in patients with liver cirrhosis, with a prevalence rate ranging from 10% to 23%<sup>[57]</sup>. Acute variceal bleeding occurs in patients with PVT under certain circumstances. PVT is related to an increased risk of variceal bleeding and higher failure rates of primary and secondary prophylaxis of variceal

bleeding, resulting in higher mortality rates compared to those of cirrhosis patients without PVT. TIPS insertion has been well established as a safe and effective method for the secondary prophylaxis of variceal bleeding and recanalization of the portomesenteric system in patients with liver cirrhosis and PVT<sup>[58-62]</sup>.

Recent randomized studies assessed the efficacy and safety of covered TIPS vs band ligation with  $\beta$ -blockers in patients with and without PVT<sup>[32,33]</sup>. Both studies suggested that TIPS implementation resulted in decreased variceal rebleeding rates but similar survival rates when compared to patients who received combination treatment<sup>[32,33]</sup>. In patients with PVT, TIPS insertion was also related to a higher rate of portal vein patency<sup>[33]</sup>. However, conflicting results were found regarding the incidence of hepatic encephalopathy. In patients with PVT, both groups demonstrated similar risks of hepatic encephalopathy<sup>[33]</sup>. In contrast, TIPS was associated with higher rates of early hepatic encephalopathy development in patients without PVT<sup>[32]</sup>. A meta-analysis showed a significant reduction in variceal rebleeding episodes and rebleeding-related mortality in patients undergoing TIPS vs endoscopic techniques; although TIPS increased the rate of post-treatment encephalopathy, the overall mortality rate remained the same for both groups<sup>[63]</sup>. Another meta-analysis that evaluated various interventions for secondary prophylaxis of variceal bleeding reported that TIPS,  $\beta$ -blockers combined with sclerotherapy and band ligation combined with sclerotherapy were superior to  $\beta$ -blockers alone in decreasing the rebleeding rates<sup>[24]</sup>. Moreover, TIPS was superior to  $\beta$ -blockers, band ligation, sclerotherapy,  $\beta$ -blockers combined with ISMN and  $\beta$ -blockers combined with sclerotherapy in terms of bleeding-related mortality<sup>[24]</sup>. These results were confirmed by a recent meta-analysis that evaluated the efficacy of TIPS compared to endoscopic treatment (band ligation, endoscopic sclerotherapy and cyanoacrylate injection) for the secondary prevention of variceal bleeding, the incidence of post-treatment hepatic encephalopathy and the survival of cirrhosis patients<sup>[64]</sup>. The results showed that the incidence of bleeding following TIPS was significantly lower than that in the endoscopic treatment group. Moreover, TIPS had a survival benefit in patients with Child-Pugh class C and those who underwent TIPS with a covered stent and did not increase the risk of hepatic encephalopathy. These results suggested that the use of covered TIPS was the preferred choice in patients with severe liver disease<sup>[64]</sup>.

Other approaches that have been proposed to improve the outcome of band ligation, particularly variceal recurrence and rebleeding, include the following. Harras *et al*<sup>[65]</sup> proposed a combination of band ligation and argon plasma coagulation as an effective method to facilitate the rapid obliteration of varices accompanied by a low recurrence rate without obvious adverse events<sup>[65]</sup>. Another approach involves the injection of a monomeric liquid compound [cyanoacrylate (n-butyl-2-cyanoacrylate)], which is quickly polymerized when it

comes into contact with the tissue surface and results in immediate eradication of the vessel<sup>[66]</sup>. Several randomized controlled studies have evaluated the efficacy of cyanoacrylate injection compared to other treatment modalities for esophageal varices<sup>[34,67,68]</sup>. Band ligation was compared with cyanoacrylate injection in two randomized studies, and the results showed no significant differences between the two groups in terms of variceal obliteration, mortality and major complications<sup>[34,67]</sup>. However, Santos *et al*<sup>[34]</sup> reported significantly more frequent minor complications, variceal recurrence and a clear trend towards an increase in bleeding episodes in the cyanoacrylate injection group than in the ligation group. Lastly, microwave coagulation, which is another thermal endoscopic treatment method, has been proposed in conjunction with band ligation for the treatment of esophageal varices<sup>[35]</sup>. Monici *et al*<sup>[35]</sup> evaluated the efficacy of band ligation plus microwave coagulation compared to band ligation plus endoscopic sclerotherapy and found that application of the microwave coagulation method was safe and gave similar results to the sclerotherapy group.

Recent advances in the management of secondary prophylaxis of variceal bleeding have emerged by targeting a decrease in portal pressure through the pathophysiological mechanisms of portal hypertension. First, the lipid-lowering agent simvastatin, which reduces the portal pressure and improves hepatocellular function, has been added to the standard treatment ( $\beta$ -blocker and band ligation) for variceal bleeding in cirrhosis patients. A recent placebo-controlled randomized trial showed that simvastatin administration was related to a significant amelioration of survival in Child-Pugh A and B patients<sup>[69]</sup>. However, no improvement was found in the rebleeding rates compared to those of patients who received the placebo<sup>[69]</sup>. Second, the use of alternative and more powerful  $\beta$ -blockers, which further reduce the HVPG compared to the effects of those used at present. The most recent guidelines recommend the use of propranolol or nadolol with or without ISMN for the prevention of variceal bleeding. However, reduction of HVPG is achieved in approximately 40% of patients, and the variceal bleeding risk is increased in hemodynamic non-responders. Studies have suggested that the use of carvedilol, which is a  $\beta$ -blocker with additional  $\alpha$ -1 adrenoceptor inhibition properties, promotes a better hemodynamic response than propranolol or nadolol, prevents the progression of small esophageal varices and is more potent in reducing HVPG<sup>[70-73]</sup>. Lastly, portal pressure-guided therapy has been used to further improve the prevention of variceal rebleeding episodes. Villanueva *et al*<sup>[74]</sup> showed that the use of HVPG-guided therapy resulted in a significantly lower risk of rebleeding [hazard ratio (HR) = 0.53; 95%CI: 0.29-0.98], a decreased decompensation (HR = 0.68; 95%CI: 0.46-0.99), and mortality rate (HR = 0.59; 95%CI: 0.35-0.99) compared to the control group (combination of nadolol, nitrates and band ligation). Moreover, the hemodynamic responders in the HVPG-guided therapy group received

monotherapy with  $\beta$ -blockers, whereas the non-responders received combination treatment with  $\beta$ -blockers and band ligation. All patients in the control group received the combination treatment<sup>[74]</sup>. These results conclude that the addition of band ligation will not be beneficial for improving the outcomes if there is no hemodynamic response to  $\beta$ -blockers and set the stage for reevaluation of which patients should receive band ligation<sup>[75]</sup>.

In conclusion, recently, management of variceal bleeding has markedly improved. These gains stem mainly from improvement of the overall strategy for secondary variceal prophylaxis of the cirrhosis population resulting from better understanding of the underlying mechanisms of the pathogenesis of portal hypertension, which guides the rationale behind each therapeutic intervention. In light of current evidence, endoscopic band ligation constitutes an effective treatment option for the prevention of recurrent variceal bleeding. However, the efficacy of band ligation is clearly increased by adding  $\beta$ -blocker therapy, and this combination is suggested as the first-line treatment for the prevention of rebleeding. Although the incidence of rebleeding is reduced by combined therapy in most studies, this option does not result in an overall survival advantage. However, other treatment modalities could also be considered in selected clinical scenarios. In the future, innovative endoscopic techniques and more effective treatment strategies or combinations of novel drugs should be developed with an aim of better clinical management of these patients.

## ARTICLE HIGHLIGHTS

### Research background

Variceal bleeding is considered one of the most severe complications of portal hypertension and constitutes a life-threatening condition for cirrhosis patients. Recurrent variceal bleeding occurs in approximately 60% of patients within 2 years, with a six-week mortality rate of approximately 12%-16%. Available treatments for the secondary prophylaxis of variceal bleeding include pharmacotherapy, endoscopic treatment, transjugular intrahepatic portosystemic shunt (TIPS) placement and surgical shunting. The most recent guidelines suggest that the combination of non-selective  $\beta$ -blockers (propranolol or nadolol) and endoscopic band ligation constitutes the preferred treatment option for prevention of rebleeding in liver cirrhosis patients. Endoscopic band ligation should not be used alone unless the patient cannot tolerate  $\beta$ -blockers or there is a contraindication for non-selective  $\beta$ -blocker administration. Covered TIPS insertion is recommended for patients who do not respond to combination treatment.

### Research motivation

Systematic reviews and meta-analyses have compared these interventions and highlighted differences in the efficacy of the different modalities. However, conflicting data are present in the existing literature.

### Research objectives

The authors aimed to summarize and critically examine existing data focusing on the most updated randomized trials of the role of endoscopic band ligation in the secondary prophylaxis of variceal bleeding in liver cirrhosis patients.

### Research methods

A systematic search of the MEDLINE and PubMed databases was performed. All manuscripts comparing the endoscopic band ligation intervention vs other

interventions were studied. Data from the relevant meta-analyses and the most recent randomized studies not included in these meta-analyses were analyzed.

### Research results

The results demonstrated that band ligation was more effective than endoscopic sclerotherapy. The use of  $\beta$ -blockers in combination with band ligation increased the treatment efficacy, supporting the current guidelines regarding secondary prevention of variceal bleeding. TIPS placement was superior to combination therapy in terms of rebleeding prophylaxis, with no difference in the survival rates. However, the data concerning the incidence of hepatic encephalopathy were conflicting.

### Research conclusions

This review demonstrated the most recent advances in the role of endoscopic band ligation for the treatment of esophageal variceal rebleeding. Endoscopic band ligation constitutes an effective treatment option for the prevention of recurrent variceal bleeding. However, the efficacy of band ligation is clearly increased by the addition of  $\beta$ -blocker therapy. Other treatment modalities could also be considered in selected clinical scenarios.

### Research perspectives

Innovative endoscopic techniques and more effective treatment strategies or combinations of novel drugs should be developed in the future, with an aim of better clinical management of these patients.

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