EBM臨床問題討論

In patients with cirrhosis and bleeding esophageal varices, is a combination of endoscopic and drug therapy more effective than either therapy alone?

單位:藥劑科
時間:2010.3.25
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提出Background question

- Patients with cirrhosis who have recovered from acute variceal hemorrhage
  - Rebleeding rate：60% within 1-2 years
  - Mortality rate：33%

- Prevention and management
  - Endoscopic therapy
    - Endodcopic injection
    - Endoscopic varieal ligation (EVL)
  - Pharmacological therapy
    - β-blockers
    - β-blockers＋nitrates
  - Surgery
    - Transjugular Intrahepatic Portosystemic Shunt (TIPS)

Garcia-Ysao et al. Am J Gastroenterol 2007; 102: 2086-2102

AASLD Guideline

- Combination of nonselective beta blockers plus EVL is the best option for secondary prophylaxis of variceal hemorrhage.
  - Lo GH et al. Endoscopic variceal ligation plus nadolol and sucralfate compared with ligation alone for the prevention of variceal rebleeding: a prospective, randomized trial. Hepatology 2000;32:461–465.
    - EVL plus nadolol:23%
    - EVL:47%
  - De la Pena J et al. Variceal ligation plus nadolol compared with ligation for prophylaxis of variceal rebleeding: a multicenter trial. Hepatology 2005;41:572–578.
    - EVL plus nadolol:14%
    - EVL:38%

Garcia-Tsao et al. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology 2007; 46:922.

Problem description(臨床問題敘述)

預防肝硬化病人之食道靜脈曲張再出血，合併使用藥物治療及內視鏡結紮術是否會比單獨使用藥物治療或者內視鏡結紮術效果較佳?

將問題寫成PICO

問題類型	■治療性 □診斷性 □預後性 □併發性
Patient	Oesophageal variceal rebleeding in patients with liver cirrhosis
Intervention	Endoscopic band ligation plus pharmacotherapy
Comparison	Endoscopic band ligation or pharmacotherapy
Outcome	mortality or rebleeding

Key words(關鍵字)設定

P	oesophageal variceal bleeding；liver cirrhosis
I	Endoscopic band ligation；nonselective beta-blockers；nadolol；propranolol；isosorbide mononitrate；combination therapy
C	
O	mortality；rebleeding；secondary prevention

尋找最有用的資料

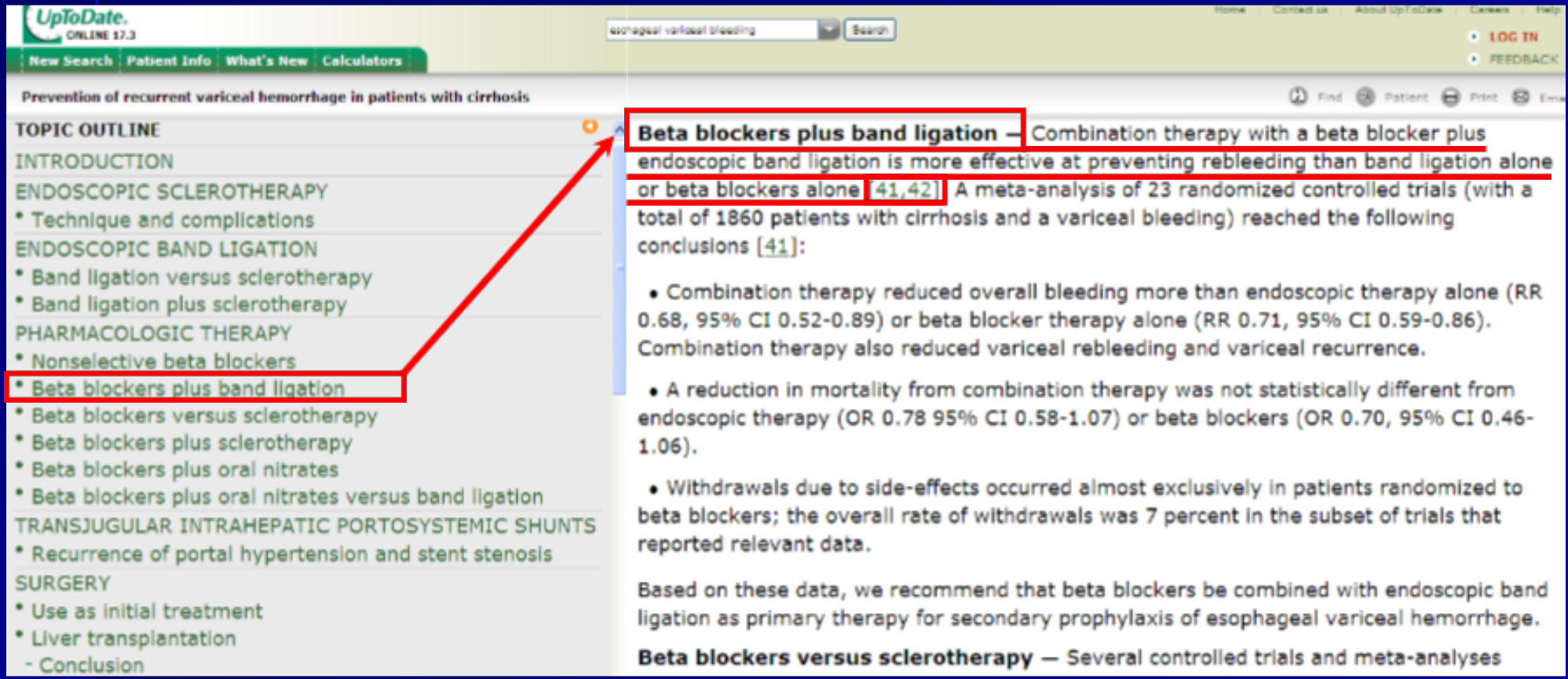
- 先從已經過評讀的Database開始找起，最後再找尚未經過嚴格評讀的Study
  - Cochrane
  - UpToDate
  - PubMed
  - 中文電子期刊

Cochrane Library

- 關鍵字：oesophageal variceal bleeding＋secondary prevention

UpToDate

- 關鍵字：oesophageal variceal bleeding



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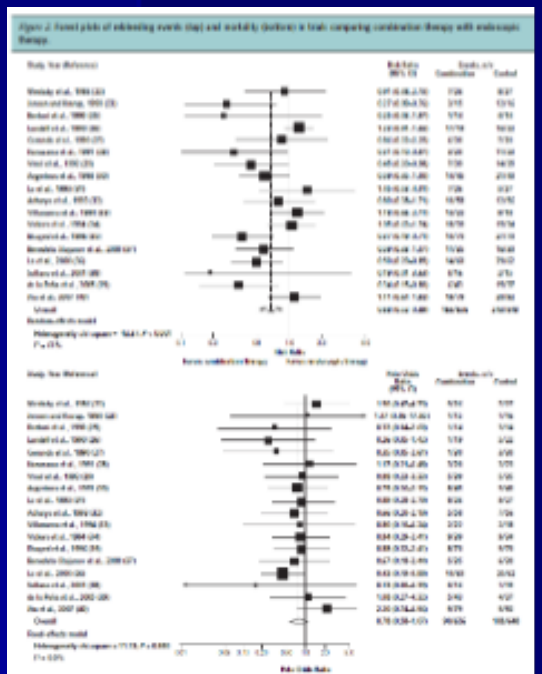
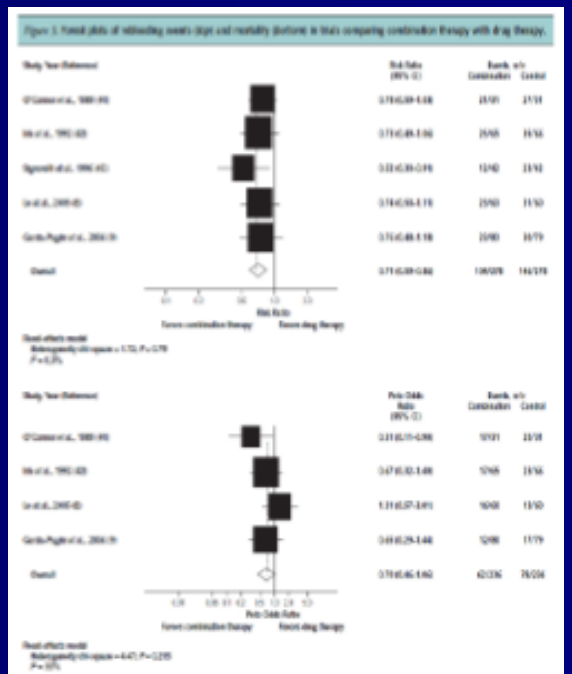
TI Meta-analysis: Combination endoscopic and drug therapy to prevent variceal rebleeding in cirrhosis.

AU Gonzalez R; Zamora J; Gomez-Camarero J; Molinero LM; Banares R; Albillos A

SO Ann Intern Med. 2008 Jul 15;149(2):109-22.

BACKGROUND: Combining endoscopic therapy and beta-blockers may improve outcomes in patients with cirrhosis and bleeding esophageal varices. PURPOSE: To assess whether a combination of endoscopic and drug therapy prevents overal and variceal rebleeding and improves survival better than either therapy alone. DATA SOURCES: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and conference proceedings through 30 December 2007. STUDY SELECTION: Randomized trials comparing endoscopic plus beta-blocker therapy with either therapy alone, without language restrictions. DATA EXTRACTION: Two reviewers independently extracted data on interventions and the primary study outcomes of overall rebleeding and mortality. Metaregression and stratified analysis were used to explore heterogeneity. DATA SYNTHESIS: 23 trials (1860 patients) met inclusion criteria. Combination therapy reduced overall rebleeding more than endoscopic therapy alone (pooled relative risk, 0.68 [95% CI, 0.52 to 0.89]; I(2) = 61%) or beta-blocker therapy alone (pooled relative risk, 0.71 [CI, 0.59 to 0.86]; I(2) = 0%). Combination therapy also reduced variceal rebleeding and variceal recurrence. Reduction in mortality from combination therapy did not statistically significantly differ from that from endoscopic (Peto odds ratio, 0.78 [CI, 0.58 to 1.07) or drug therapy (Peto odds ratio, 0.70 [CI, 0.46 to 1.06]). Effects were independent of the endoscopic procedure (injection sclerotherapy or banding). No trial-level variable associated with the effect was identified through metaregression or stratified analysis. LIMITATION: Statistically significant heterogeneity in trial quality and evidence for selective reporting and publication bias were found. CONCLUSION: A combination of endoscopic and drug therapy reduces overall and variceal rebleeding in cirrhosis more than either therapy alone.





- Rebleeding
  - Combination vs endoscopic
    - Relative risk 0.68 (95%CI, 0.52-0.89)
  - Combination vs β-blockers
    - Relative risk 0.68 (95%CI, 0.52-0.89)
- Mortality
  - Combination vs endoscopic
    - Odds ration 0.78 (95%CI, 0.59-1.07)
  - Combination vs β-blockers

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TI Pharmacotherapy plus endoscopic intervention is more effective than pharmacotherapy or endoscopy alone in the secondary prevention of esophageal variceal bleeding: a meta-analysis of randomized, controlled trials.

AU Ravipati M; Katragadda S; Swaminathan PD; Molnar J; Zarling E

SO Gastrointest Endosc. 2009 Oct;70(4):658-664.e5. Epub 2009 Jul 29.

BACKGROUND: Previous clinical trials on the treatment of esophageal variceal bleeding yielded mixed results regarding the efficacy of endoscopic procedures compared with pharmacotherapy only. OBJECTIVE: To compare the efficacy of endoscopic procedures with that of pharmacotherapy in the prevention of mortality and rebleeding. DESIGN AND SETTING: A systematic literature review was performed to identify randomized, controlled trials of the efficacy of pharmacotherapy and endoscopic therapy. A meta-analysis was performed by using the Comprehensive MetaAnalysis software package. A 2-sided alpha error<.05 was considered statistically significant (P<.05). PATIENTS: Twenty-five clinical trials with a total of 2159 patients were eligible for meta-analysis. OUTCOME MEASUREMENTS: Relative risk (RR) with 95% confidence interval (CI) was computed for all-cause mortality, mortality from rebleeding all-cause rebleeding, and rebleeding caused by varices. RESULTS: Pharmacotherapy was as effective as endoscopic procedures in preventing rebleeding (RR 1.067; 95% CI, 0.865-1.316; P = .546), variceal rebleeding (RR 1.143; 95% CI, 0.791-1.651; P = .476), all-cause mortality (RR 0.997; 95% CI, 0.827-1.202, P = .978), and mortality from rebleeding (RR 1.171; 95% CI, 0.816-1.679; P = .39). Pharmacotherapy combined with endoscopic procedures did not reduce all-cause mortality (RR 0.787; 95% CI, 0.587-1.054; P = .108) or mortality caused by rebleeding (RR 0.786; 95% CI, 0.445-1.387; P = .405) compared with endoscopic procedures. However, combination therapy (endoscopic procedure plus pharmacotherapy) significantly reduced the incidence of all rebleeding (RR 0.623; 95% CI, 0.523-0.741; P<.001) and variceal rebleeding (RR 0.601; 95% CI, 0.440-0.820; P<.001). LIMITATIONS: Heterogeneity of patient population and different treatment protocols may have affected our meta-analysis. CONCLUSION: Pharmacotherapy may be as effective as endoscopic therapy in reducing rebleeding rates and all-cause mortality. Pharmacotherapy plus endoscopic intervention is more effective than endoscopic intervention alone.

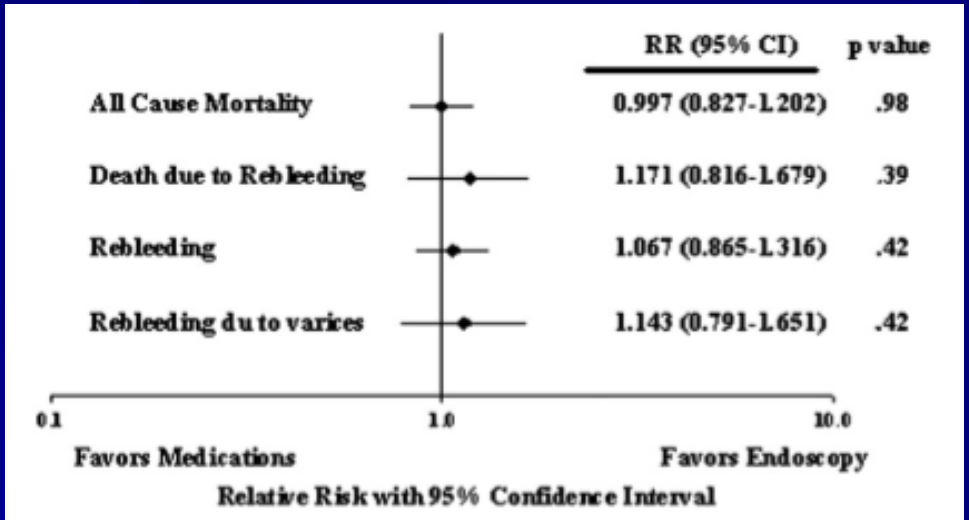
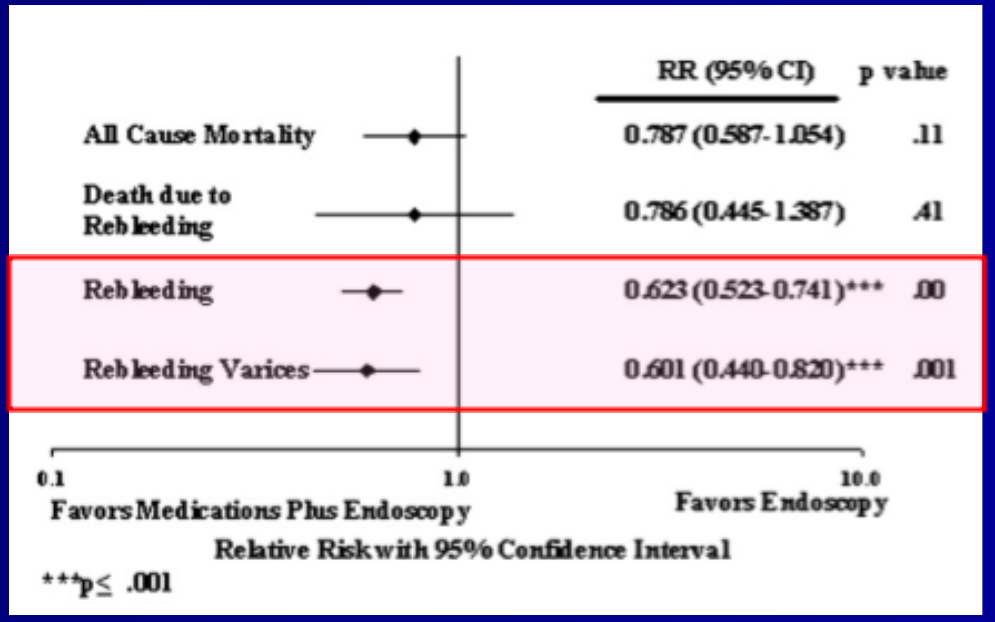
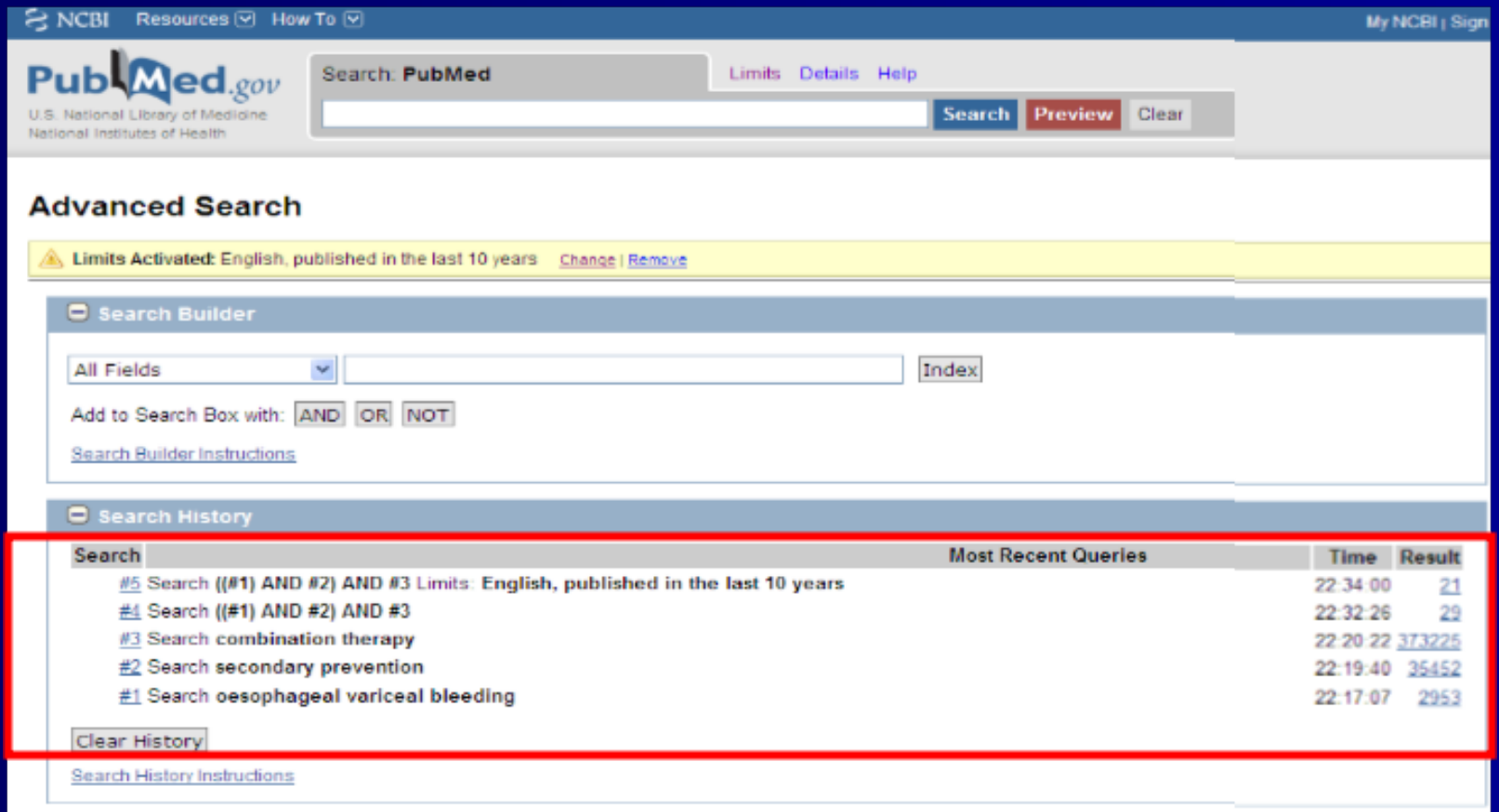


Figure 1. Summary of RRs: pharmacotherapy versus endoscopic therapy.



PubMed

- 關鍵字：oesophageal variceal bleeding＋secondary prevention＋combination therapy
- 限制：10年內、English 、Humans



PubMed

Results: 1 to 20 of 21

<< First < Prev Page 1 Next > Last >>

1. Combination of pharmacologic and endoscopic therapy for the secondary prevention of esophageal variceal bleeding.
   Ayoub WS, Nguyen MH.
   Gastrointest Endosc. 2009 Oct;70(4):665-7. No abstract available.
   PMID: 19788982 [PubMed - indexed for MEDLINE]
   Related articles

2. Pharmacotherapy plus endoscopic intervention is more effective than pharmacotherapy or endoscopy alone in the secondary prevention of esophageal variceal bleeding: a meta-analysis of randomized, controlled trials.
   Ravipati M, Katragadda S, Swaminathan PD, Molnar J, Zarling E.
   Gastrointest Endosc. 2009 Oct;70(4):658-664.e5. Epub 2009 Jul 29.
   PMID: 19643407 [PubMed - indexed for MEDLINE]
   Related articles

3. Systematic review: secondary prevention with band ligation, pharmacotherapy or combination therapy after bleeding from oesophageal varices.
   Cheung J, Zeman M, van Zanten SV, Tandon P.
   Aliment Pharmacol Ther. 2009 Sep 15;30(6):577-88. Epub 2009 Jun 25.
   PMID: 19558563 [PubMed - in process]
   Related articles

4. Addition of propranolol and isosorbide mononitrate to endoscopic variceal ligation does not reduce variceal rebleeding incidence.
   Kumar A, Jha SK, Sharma P, Dubey S, Tyagi P, Sharma BC, Sarin SK.
   Gastroenterology. 2009 Sep;137(3):892-901, 901.e1. Epub 2009 May 27.
   PMID: 19481079 [PubMed - indexed for MEDLINE]

資料庫搜尋結果

資料庫種類	文章篇數	符合	不符合
PubMed	**21**	**2**	**20**
Cochrane	**8**	**0**	**8**
UpToDate	**2**	**0**	**2**
中文電子期刊	**0**	**0**	**0**

文獻評讀

Alimentary Pharmacology & Therapeutics

Systematic review: secondary prevention with band ligation, pharmacotherapy or combination therapy after bleeding from oesophageal varices

J. CHEUNG*,†, M. ZEMAN*,†, S. V. VAN ZANTEN*,† & P. TANDON*,†

- Aim:
  - to compare band ligation (BL), pharmacotherapy (PT) for EVB secondary prevention
- Inclusion criteria:
  - Randomized trials comparing band ligation vs. β-blockers (±nitrates), or combination therapy with β-blockers (±nitrates) plus band ligation vs. either band ligation or β-blockers (±nitrates)
  - Age±18 years
  - Previous oesophageal variceal bleeding
  - Liver cirrhosis
- Search strategy:
  - 1945~April 2008
- Data extraction:
  - Study population
  - Intervention
  - Outcomes:
    - all-cause mortality, UGI bleeding, variceal rebleeding adverse events
  - Study risk of bias

Results

- 12 trials: 6 BL vs. PT, 4 BL+PT vs. BL, 2 BT+PT vs PT

Table 1. Patient characteristics in the included studies

Study	Group I/II N	Age (years)	Males (%)	Alcoholic (%)	Child-Pugh class A/B/C (%) Group I	Group II	F/U (mo)
Band Ligation (I) vs. pharmacotherapy (II)							
Villanueva 2001	72/72	58/60	65/60	60/60	15/60/25	26/54/19	21
Lo 2002	60/61	52/51	77/77	27/36	22/58/20	21/57/21	25
Patch 2002	51/51	51/52	69/69	63/71	16/37/47	13/36/51	10
Sarin 2005	51/50	36/36	72/68				12
Shiha 2005	61/60	50/50	80/83				7
Romero 2006	57/52	53/51	67/65				12
Combination band ligation + pharmacotherapy (I) vs. ligation alone (II)							
Lo 2000	62/60	51/53	79/75	32/28	19/45/35	18/50/31	21
Sollano 2001	16/15	N/A	N/A			N/A	10
De la Pena 2005	43/37	60/60	77/73			16/54/30	16
Jha 2007	79/92	N/A	N/A	N/A	N/A	N/A	16
Combination band ligation + pharmacotherapy (I) vs. pharmacotherapy alone (II)							
Lo 2005	60/60	N/A	N/A	N/A	N/A	N/A	23
Garcia-pagan 2006	80/79	N/A	N/A	N/A	N/A	N/A	11

F/U, follow-up.

N=698 (25 lost to follow up)

N=404 (4 lost to follow up)

N=279

Intervention features of included studies

↓Heart rate 25%
<55-60 beats/min

Table 2. Intervention features of included studies

Study	Beta-blocker (BB)	BB Dose (mean)	Drug Co-intervention (mean)	Other Co-intervention	Comparison Group
Monotherapy trials					
Villanueva 2001	Nadolol	96 mg	ISMN 60 mg	–	Ligation
Lo 2002	Nadolol	48 mg	ISMN 30 mg	–	Ligation
Patch 2002	Propranolol	80 mg	ISMN 20–40 mg	–	Ligation
Sarin 2005	Propranolol	109 mg	ISMN 34 mg	–	Ligation
Shiha 2005	Propranolol	58 mg	ISMN 34 mg	–	Ligation
Romero 2006	Nadolol	88 mg	ISMN 58 mg	–	Ligation
Combination therapy trials					
Lo 2000	Nadolol	60 mg	Sucralfate 1 g QID	Ligation	Ligation
Sollano 2001	Propranolol	N/A	–	Ligation	Ligation
De la Pena 2005	Nadolol	58 mg	–	Ligation	Ligation
Lo 2005	Nadolol	–	ISMN	Ligation	Nadolol/ISMN
Garcia-Pagan 2006	Nadolol	–	ISMN	Ligation	Nadolol/ISMN
Jha 2007	Propranolol	114 mg	ISMN 27 mg	Ligation	Ligation

ISMN, isosorbide mononitrate.

Study design and risk of bias

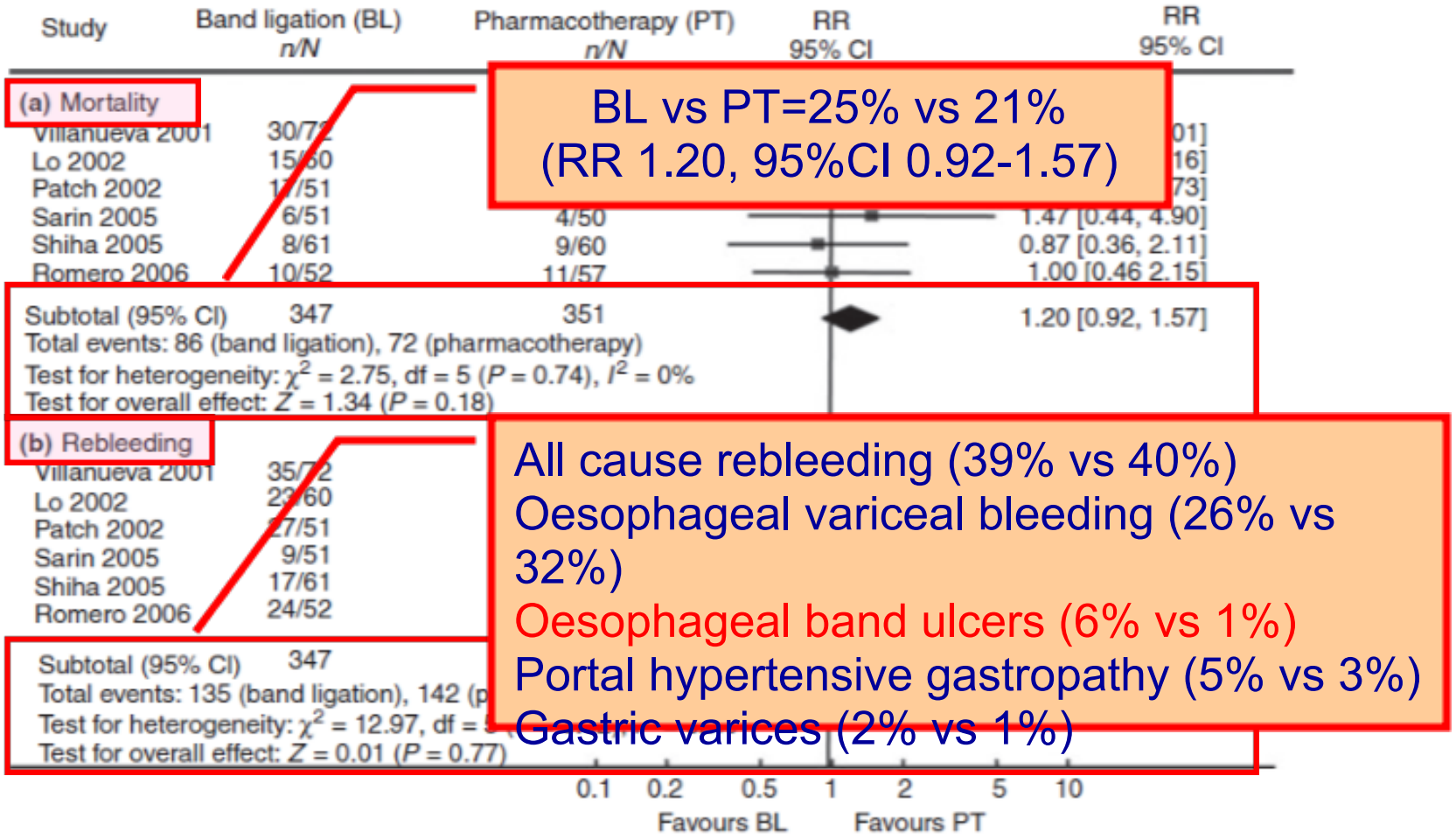
Score ≧3:good quality
Score <3:poor quality

Table 3. Quality analysis of included trials

Study	RCT	Publication type	Allocation concealment	Intention-to-treat	Jadad Score*
Pharmcotherapy vs. Band Ligation					
Lo 2002	Yes	Article	Adequate	Adequate	3
Patch 2002	Yes	Article	Adequate	Adequate	3
Romero 2006	Yes	Article	Adequate	Adequate	3
Sarin 2005	Yes	Article	Unclear	Adequate	2
Shiha 2005	Yes	Abstract†	Adequate	Adequate	3
Villanueva 2001	Yes	Article	Adequate	Adequate	3
Combination Band Ligation + Pharmacotherapy vs. Band Ligation					
Lo 2000	Yes	Article	Adequate	Adequate	3
Sollano 2001	Yes	Abstract	Unclear	Unclear	2
De la Pena 2005	Yes	Article	Adequate	Adequate	3
Jha 2007	Yes	Abstract	Unclear	Unclear	2
Combination Band Ligation + Pharmacotherapy vs. Pharmacotherapy					
Lo 2005	Yes	Abstract	Unclear	Unclear	2
Garcia-Pagan 2006	Yes	Abstract	Unclear	Adequate	2

* Jadad scale[17]: one point for randomization, adequate method of randomization, and description of withdrawals/dropouts.
† Manuscript obtained.

Outcomes
band ligation vs. pharmacotherapy

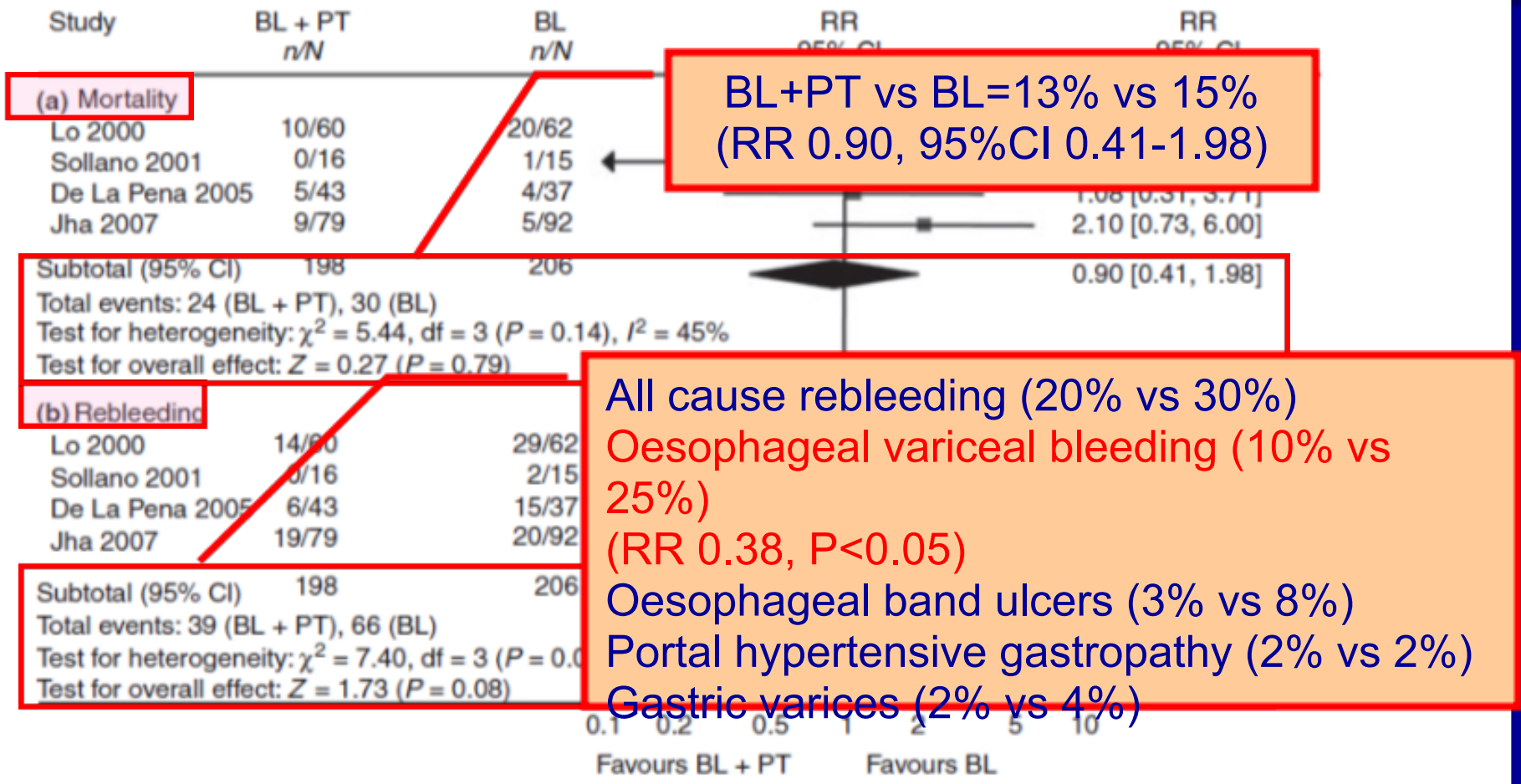


BL vs PT=25% vs 21%
(RR 1.20, 95%CI 0.92-1.57)

All cause rebleeding (39% vs 40%)
Oesophageal variceal bleeding (26% vs 32%)
Oesophageal band ulcers (6% vs 1%)
Portal hypertensive gastropathy (5% vs 3%)
Gastric varices (2% vs 1%)

Figure 1. Pooled meta-analysis for mortality and rebleeding in trials comparing band ligation (BL) with pharmacotherapy (PT) for secondary prophylaxis after oesophageal variceal bleeding.

Outcomes
combination BL and PT vs. BL

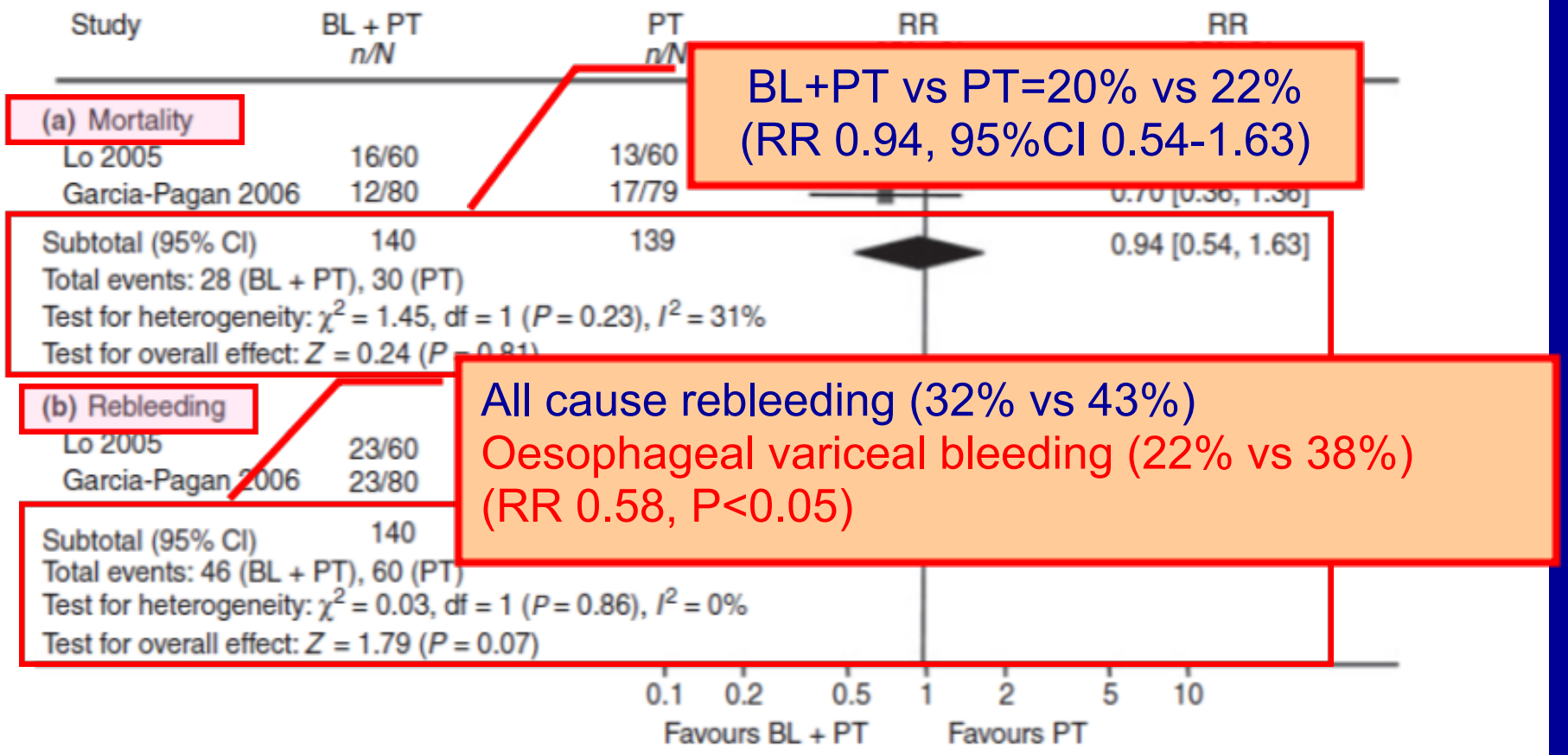


BL+PT vs BL=13% vs 15%
(RR 0.90, 95%CI 0.41-1.98)

All cause rebleeding (20% vs 30%)
Oesophageal variceal bleeding (10% vs 25%)
(RR 0.38, P<0.05)
Oesophageal band ulcers (3% vs 8%)
Portal hypertensive gastropathy (2% vs 2%)
Gastric varices (2% vs 4%)

Figure 2. Pooled meta-analysis for mortality and rebleeding in trials comparing combination band ligation and pharmacotherapy (BL+PT) with band ligation (BL) for secondary prophylaxis after oesophageal variceal bleeding.

Outcomes
combination BL and PT vs. PT



BL+PT vs PT=20% vs 22%
(RR 0.94, 95%CI 0.54-1.63)

All cause rebleeding (32% vs 43%)
Oesophageal variceal bleeding (22% vs 38%)
(RR 0.58, P<0.05)

Figure 3. Pooled meta-analysis for mortality and rebleeding in trials comparing combination band ligation and pharmacotherapy (BL+PT) with pharmacotherapy (PT) for secondary prophylaxis after oesophageal variceal bleeding.

Outcomes
adverse events

- Adverse events rate
  - BL vs PT (27% vs 31%)
  - Combination therapy vs BL (21% vs 6%)
    - RR 3.4 (P=0.006)
    - Dizziness (4%), sexual dysfunction (3%), fatigue (2%), crrhythmia (2%), chest discomfort (2%)
- Withdrawal rate
  - BL vs PT (1% vs 11%)
  - Combination therapy:5%
- Noncompliance rate
  - BL vs PT (2% vs 4%)

Subgroup analyses

Variable	BL (%)	PT (%)	Relative risk	95% CI	*P* value
Mortality					
CP A	5/57 (9)	5/69 (7)	1.46	0.47–4.52	0.51
CP B-C	56/178 (31)	40/171 (23)	1.28	0.91–1.79	0.12
Rebleeding					
CP A	17/57 (30)	21/69 (30)	1.01	0.41–2.49	0.99
CP B-C	74/178 (42)	77/171 (45)	0.92	0.72–1.17	0.49
Variceal rebleeding					
CP A	13/57 (23)	17/69 (25)	0.89	0.28–2.80	0.84
CP B-C	52/178 (29)	62/171 (36)	0.75	0.42–1.32	0.44

BL, band ligation; PT, pharmacotherapy; CP, Child-Pugh.

Table 4. Within-study subgroup analysis by Child-Pugh class of patients from four trials comparing band ligation vs. pharmacotherapy (n = 475)

Subgroup analyses

Table 5. Between-study subgroup analyses for trials comparing band ligation with pharmacotherapy by follow-up length, majority of liver disease and mean beta blocker dose

	BL (*n*/*N*)	PT (*n*/*N*)	RR (95% CI)	*P* value	I^2 Statistic (%)
Mortality					
Follow-up < 20 mo.					
Follow-up > 20 mo.					
Majority Alcoholic					
Majority Viral Hepatitis					
Beta Blocker > 80 mg/da					
Beta Blocker < 80 mg/da					
Rebleeding					
Follow-up < 20 mo.					
Follow-up > 20 mo.	58/132	59/133	0.98 (0.46–2.12)	0.97	87
Majority Alcoholic	86/175	70/180	1.26 (0.97–1.63)	0.09	16
Majority Viral Hepatitis	49/172	72/171	0.68 (0.51–0.90)	0.007	0
Beta Blocker > 80 mg/day	95/226	82/230	1.19 (0.90–1.56)	0.22	26
Beta Blocker < 80 mg/day					
Oesophageal variceal rebleed					
Follow-up < 20 mo.					
Follow-up > 20 mo.					
Majority Alcoholic					
Majority Viral Hepatitis					
Beta Blocker > 80 mg/day					
Beta Blocker < 80 mg/day					

BL, band ligation; PT, pharmacotherapy.

Majority viral hepatitis
↓ rebleeding with BL (28%) compared to PT (42%)
RR=0.68, NNT=7
↓oesophageal variceal rebleeding with BL (14%) compared to PT (35%)
RR=0.41, NNT=5

β-blockers<80mg/day
↓ rebleeding with BL (33%) compared to PT (50%)
RR=0.67, NNT=6
↓oesophageal variceal rebleeding with BL (17% compared to PT (39%)
RR=0.43, NNT=5

Conclusion

- No mortality difference among therapies of BL, PT and BL+PT.
- Both BL and PT are equally effective for prevention EVB.
- Combination therapy trials are limited in number, included variable drug regimens and have heterogenous outcomes.

嚴謹地評估證據

- 實證效度
  - 系統性回顧是否針對隨機之研究報告？是，但某些研究是否分組隱匿並不清楚。
  - 是否有方法的段落來描述如何搜尋所有相關的研判及評估各別研究的效度?是。
  - 各研究的結果是否一致?4個研究中有兩個正向及兩個負向結果。
  - 是否針對所有個別案例之資料重新分析?是，subgroup analysis。
- 實證重要性
  - 該治療成效有多大?及準確性?

Outcomes (F/U 15mo)	Number of trials	Weighted event rates		RRR	NNT
		Combination	BL		
Mortality	4 (404)	12.1%	14.6%	17%	Not significant
Rebleeding	4 (404)	19.7%	32.0%	38%	8

證據等級評估

Level		Therapy/Prevention, Aetiology/Harm
1	a	將隨機對照臨床試驗研究(RCT)以系統性評論後(systematic review: SR)的結果
	b	具有嚴格的信賴區間的個別RCT研究
	c	無論使用何種研究方法,但其研究結果為完全正面,完全負面或完全無效的研究報告
2	a	將同質性的世代研究(cohort studies)以系統性評論後的結果
	b	個別世代研究或質量不足的RCT研究(例如低於80%follow-up)
	c	以多數結果為基礎的研究及生態學的研究
3	a	將同質性的個案對照研究(case control studies),以系統性評論後的結果
	b	個別的個案對照研究(individual case control study)
4		病例統計報告,以及質量不足的個案對照研究
5		未經嚴謹評估的專家意見或基礎生理學,一般實驗室研究

英國的Oxford Centre證據應用等級

臨床應用

- 我們研究的病人是否與文獻中病人群有本質上差異而影響套用?約50%為肝硬化病人，平均追蹤15個月。
- 在我們的病人是否能使用該治療?是。
- 我們病人在該治療下之可能利與弊?病人對於治療成效及後果的期待與看法如何?
  - Combination therapy mortality rate:13~20%
  - NNT:8
  - Higher adverse events rate: BL+PT vs BL (21% vs 6%)

評估成果

- 步驟1:在提出臨床問題方面
  - 我提出的問題是否具有臨床重要性？是，可以作為治療參考。
  - 是否知道自己設定的問題類型?是，治療性的問題。
- 步驟2:在搜尋最佳證據方面
  - 我是否從大量的資料庫來搜尋答案？是。
  - 我是否在搜尋上愈來愈熟練了？需要加強。
- 步驟3:在文獻評讀方面
  - 我可以更正確更有效率的使用一些審慎評估度良工具(如:NNT)? 需要加強。
- 步驟4:在整合證據與病患的價值觀方面
  - 我盡力將審慎評估的結果融入治療中嗎?是。
  - 我是否因此搜尋結果而改變了原來的治療策略？沒有，目前證據未改變臨床策略。

結論

- 目前併用EVL及 β -blockers預防EVB的療效並沒有一致性的結論
  - 證據強度:Level Ⅰ
- 目前建議第一線的預防治療方式
  - Endoscopic therapy
    - Endoscopic varieal ligation (EVL)
  - Pharmacological therapy
    - β-blockers＋nitrates
- AASLD Guideline
  - Combination of nonselective beta blockers plus EVL is the best option for secondary prophylaxis of variceal hemorrhage.
- 未來需要進一步的臨床試驗證實合併療法的角色

Thanks for your attention!