Variceal Bleeding: To Band, Block, or TIPS?

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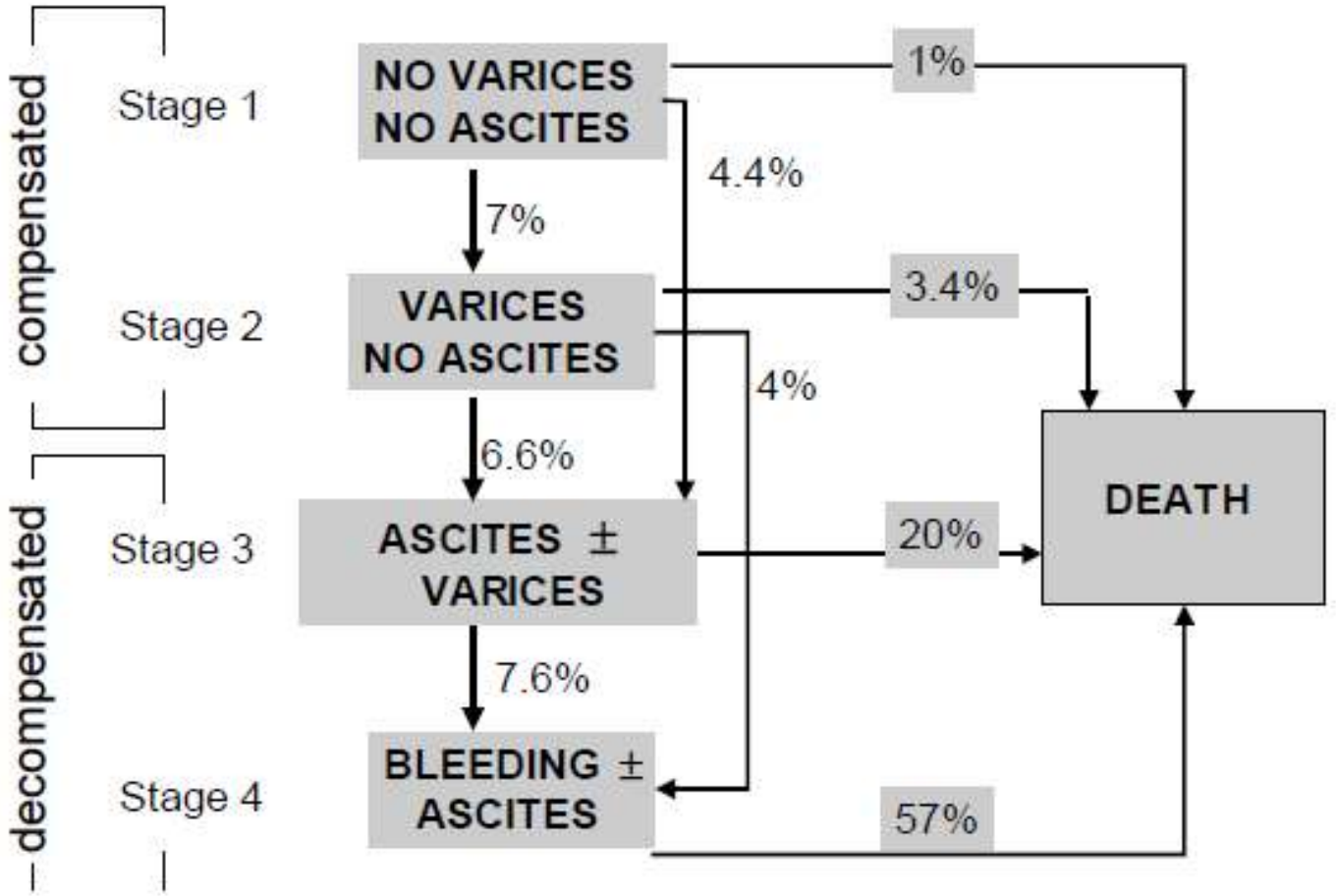


Fig. 4. Clinical course of cirrhosis: 1-year outcome probabilities according to clinical stages.

D'Amico G, Garcia-Tsao G, Pagliaro L. J Hepatol. 2006

Natural History of Esophageal Varices

- 7% - development and growth per year
- 12% - first variceal bleed per year (5% for small varices, 15% for large varices)
- 60% - recurrent variceal bleeding per year
- 15-20% - 6-week mortality (0% for Childs A, 30% for Childs C)

Groszmann RJ, Garcia-Tsao, Bosch J et al. NEJM 2005
Merli M, Nicolini G, Angeloni S et al. J Hepatol 2003
D'Amico G, Pagliaro L, Bosch J. Semin Liver Dis 1999
Bosch J, Garcia-Pagan JC. Lancet 2003

Natural History of Esophageal Varices

- Portal Hypertension (HVPG) > 5 mm Hg
- Clinically significant (development of esophageal varices) > 10 mm Hg
- Variceal bleeding > 12 mm Hg
- Poor outcome > 20 mm Hg

Groszmann RJ, Garcia-Tsao, Bosch J et al. NEJM 2005
Ripoll C, Groszmann R, Garcia-Tsao et al. Gastroenterol ogy 2007
Moitinho E, Escorsell A, Bandi JC et al. Gastroenterology 1999
Burroughs AK , Triantos CK. J Hepatol 2008

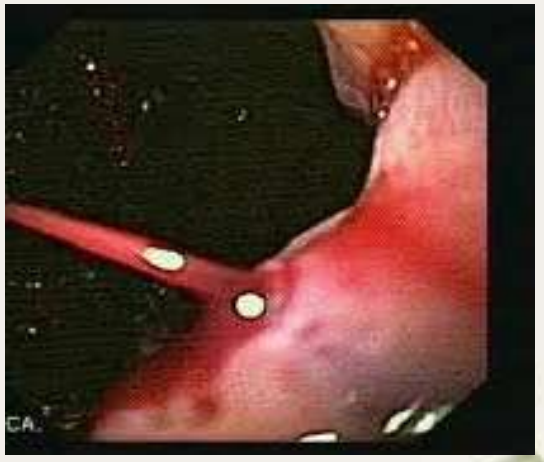
Clinical Scenarios

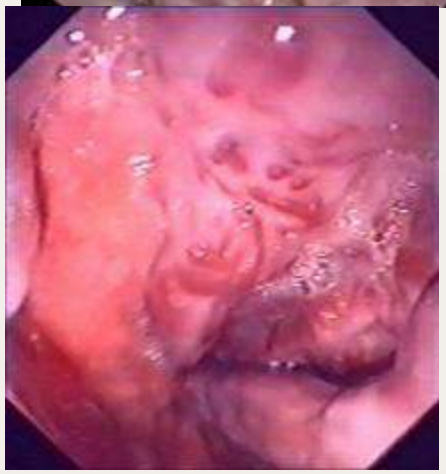
- Primary prophylaxis – prevention of first variceal bleeding
- Acute variceal bleeding
- Secondary prophylaxis – prevention of recurrent variceal bleeding

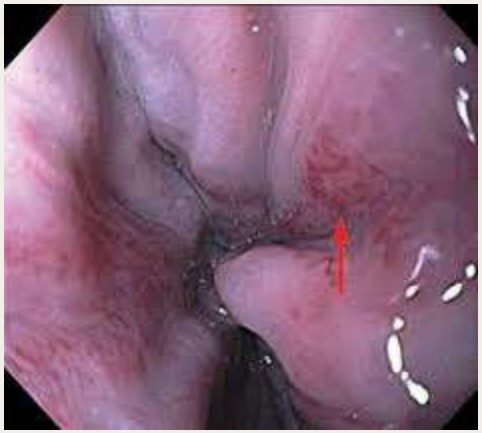
High-risk Varices

- Large size
- Presence of red color signs
- Severity of liver disease (Child-Pugh, MELD)
- High HVPG > 12 mm Hg

North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices. NEJM 1988
Groszmann RJ et al. Gastroenterology 1990
Reverter E et al. Gastroenterology 2013







Clinical Scenarios

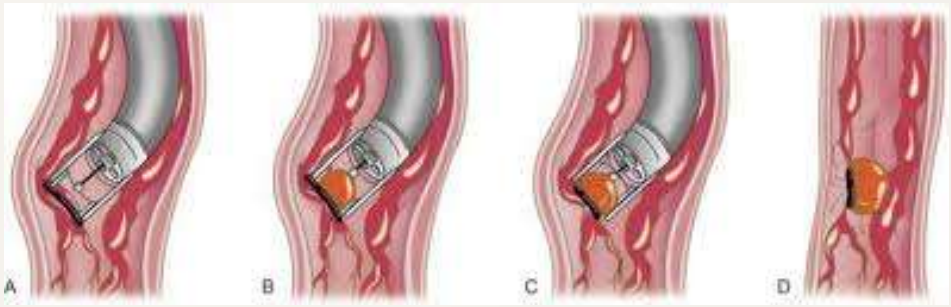
- Primary prophylaxis – prevention of first variceal bleeding
- Acute variceal bleeding
- Secondary prophylaxis – prevention of recurrent variceal bleeding

Baveno V Consensus in Portal Hypertension

- Patients with small varices with red wale marks or Child C class should be treated with NSBB (5,D).
- For large varices, either NSBB or EBL is recommended for prevention of the first variceal bleeding(1a,A).

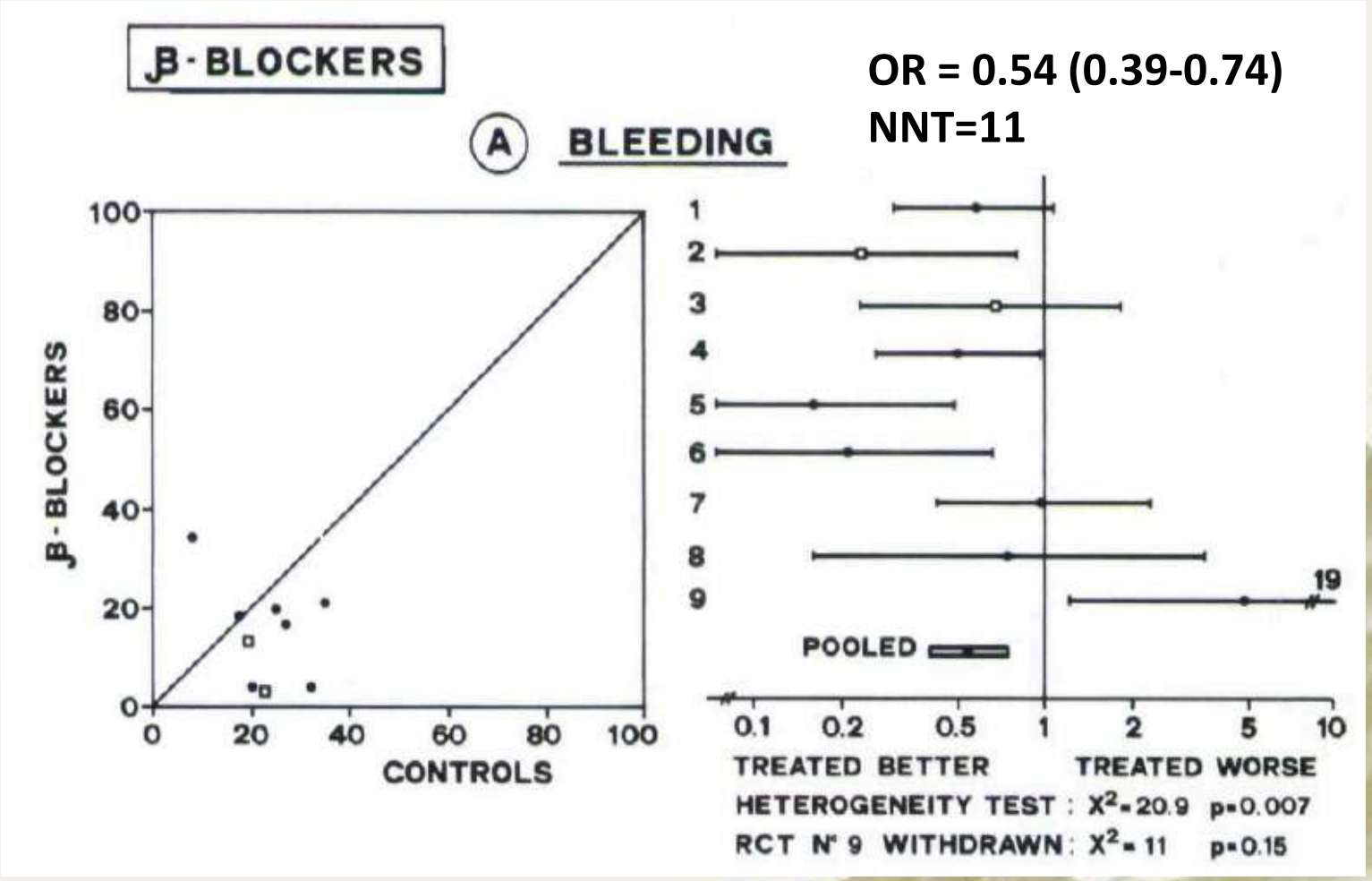
De Francis. Baveno V consensus workshop. J Hepatol . 2010

Primary Prophylaxis



Meta-analysis: Beta-blockers vs no treatment

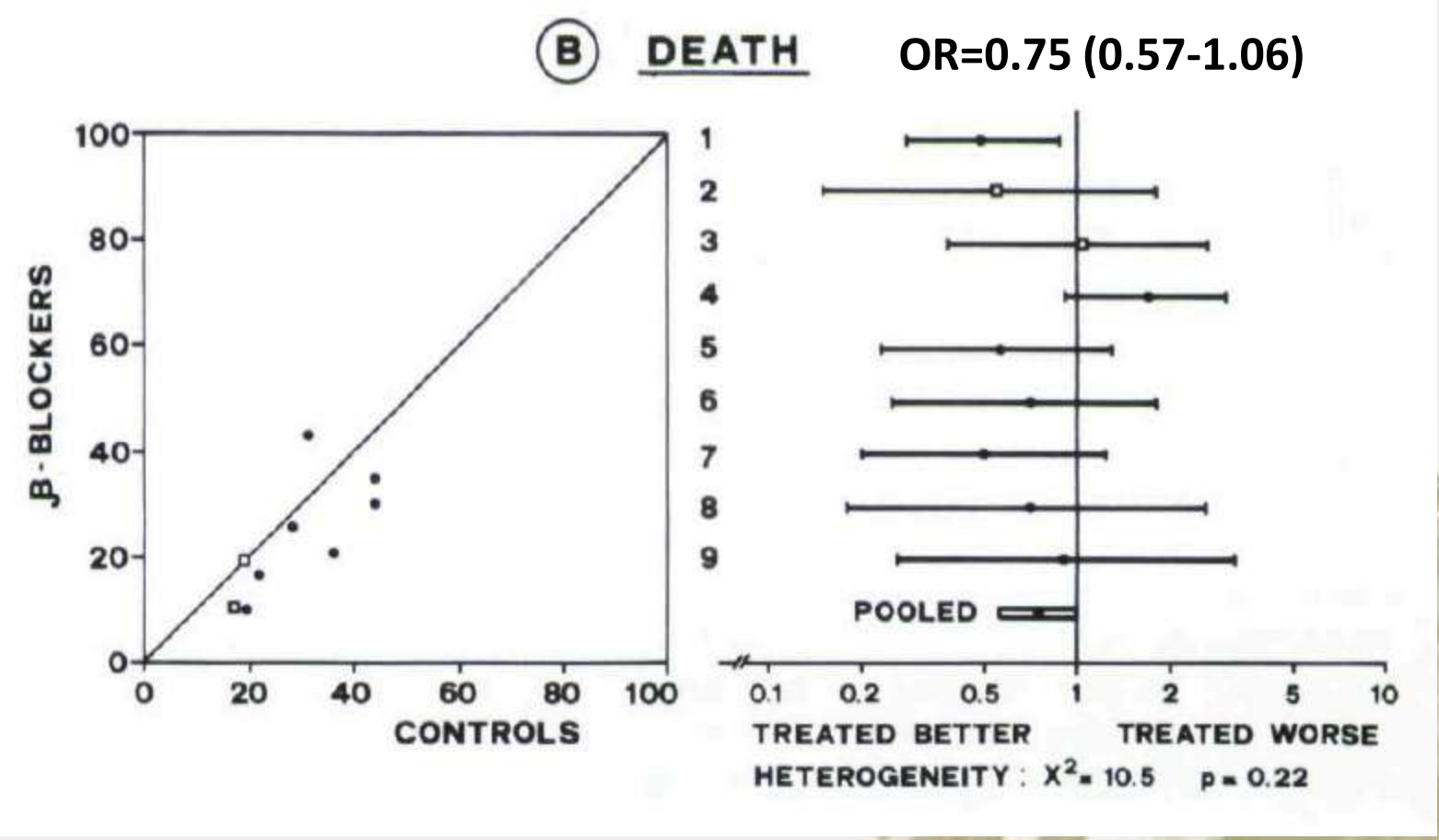
No. of trials=9, No. of patients=996



Pagliaro L et al. Ann Inter Med 1992

Meta-analysis: Beta-blockers vs no treatment

No. of trials=9, No. of patients=996

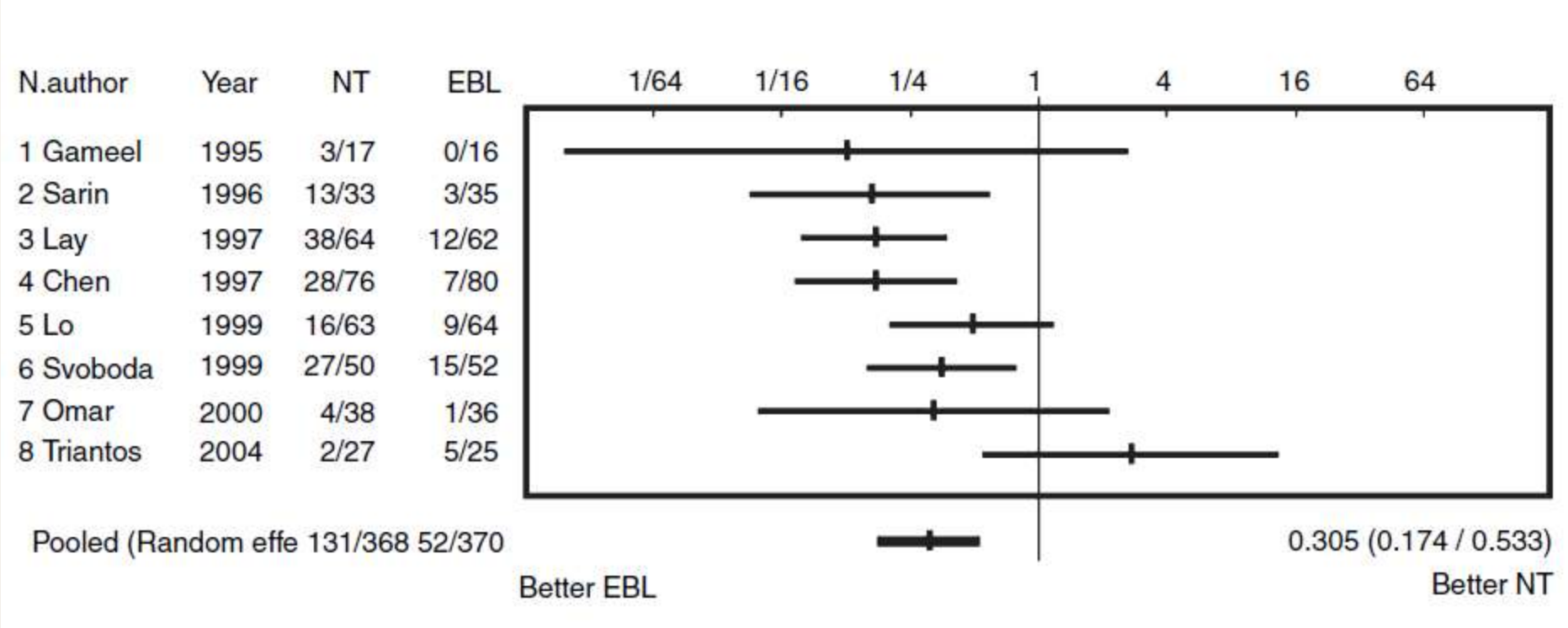


Pagliaro L et al. Ann Inter Med 1992

Meta-analysis: Endoscopic band ligation vs no treatment

No. of trials=8, No. of patients=738

Outcome: Variceal bleeding

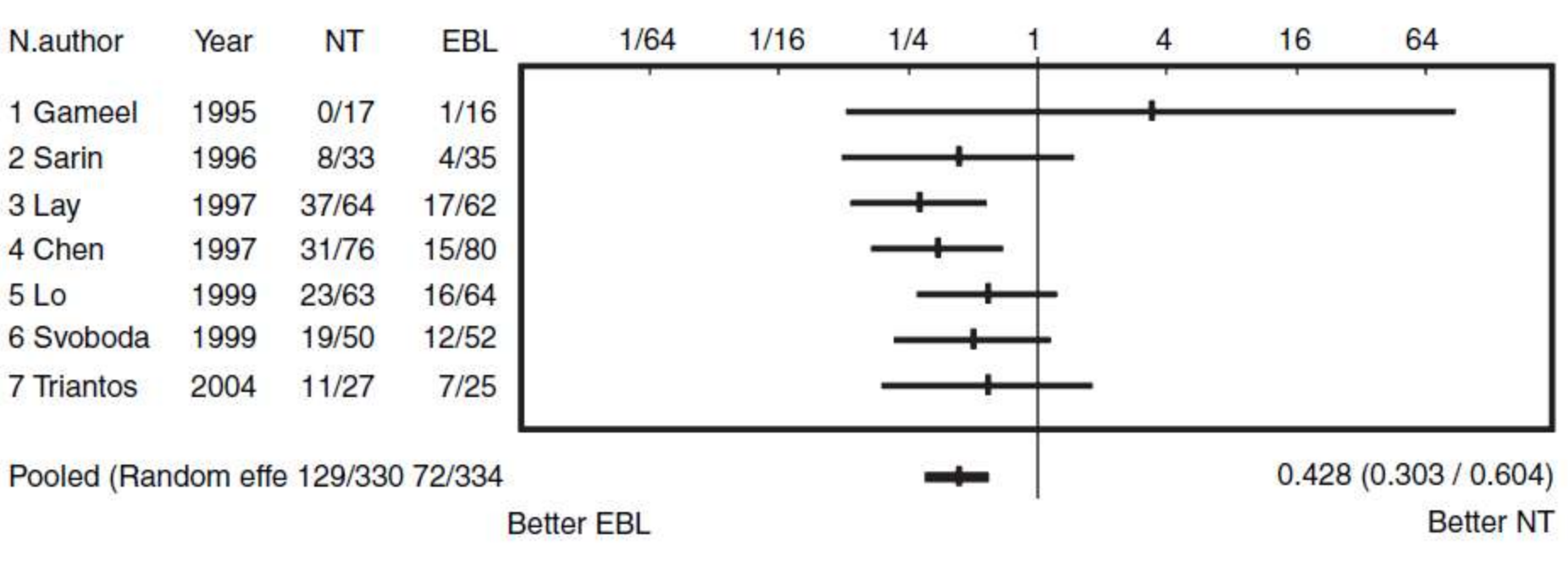


Triantos C et al. Aliment Pharmacol Ther. 2005

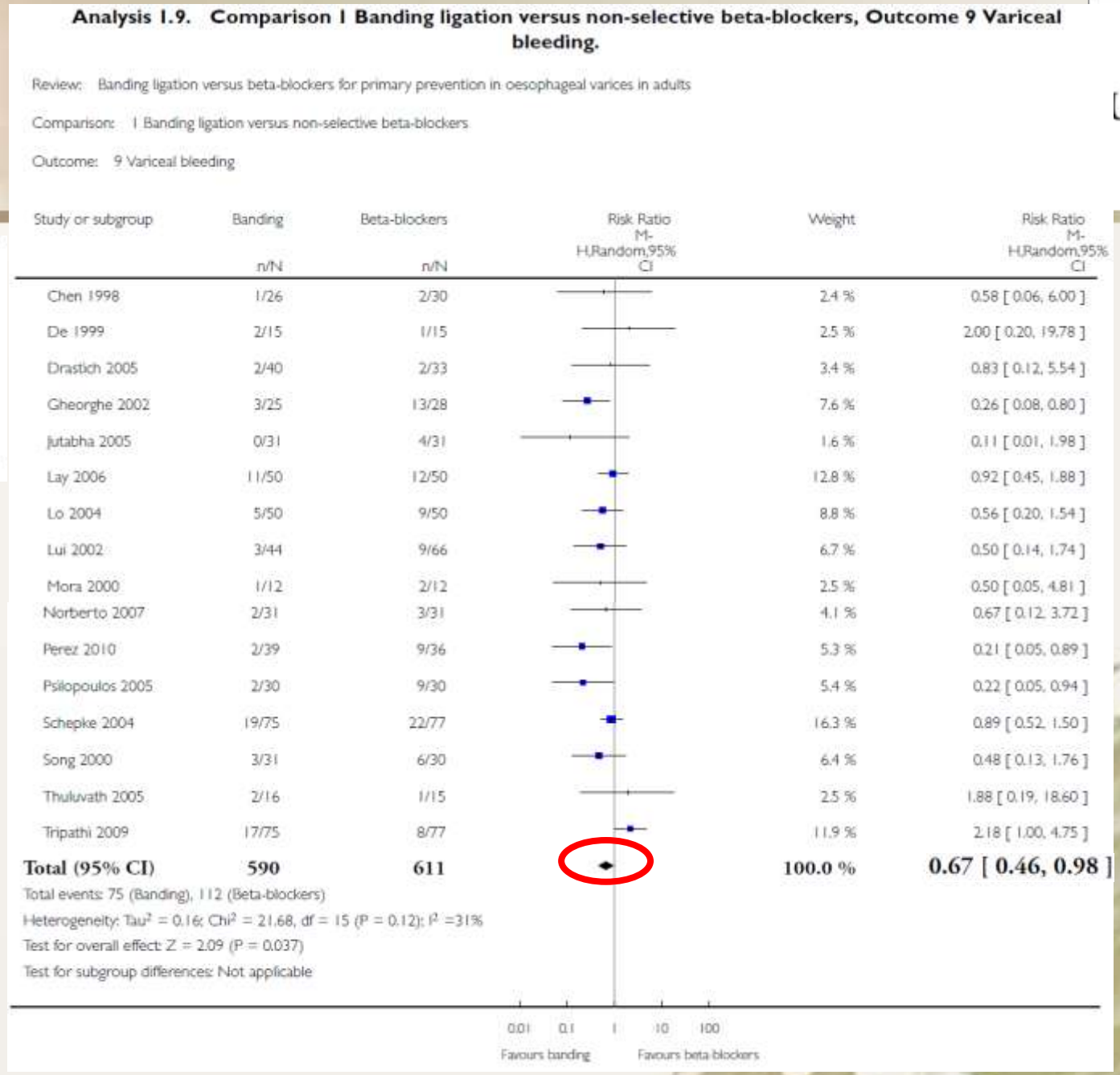
Meta-analysis: Endoscopic band ligation vs no treatment

No. of trials=7, No. of patients=664

Outcome: Mortality



Triantos C et al. Aliment Pharmacol Ther. 2005



Gluud LL, Krag A. Cochrane database of systematic reviews 2012

Analysis 1.1. Comparison 1 Banding ligation versus non-selective beta-blockers, Outcome 1 Mortality.

Review: Banding ligation versus beta-blockers for primary prevention in oesophageal varices in adults

Comparison: 1 Banding ligation versus non-selective beta-blockers

Outcome: 1 Mortality

Study or subgroup	Banding n/N	Beta-blockers n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Norberto 2007	3/31	3/31		1.3 %	1.00 [0.22, 4.58]
Psilopoulos 2005	12/30	10/30		6.8 %	1.20 [0.61, 2.34]
Lo 2004	12/50	11/50		5.9 %	1.09 [0.53, 2.24]
Perez 2010	20/39	12/36		9.9 %	1.54 [0.88, 2.68]
Lui 2002	14/44	11/66		6.4 %	1.91 [0.96, 3.81]
Jutabha 2005	0/31	4/31		0.4 %	0.11 [0.01, 1.98]
Sarin 1999	5/46	5/44		2.2 %	0.96 [0.30, 3.08]
Tripathi 2009	27/75	26/77		16.1 %	1.07 [0.69, 1.65]
Schepke 2004	34/75	33/77		23.7 %	1.06 [0.74, 1.51]
Song 2000	5/31	8/30		3.1 %	0.60 [0.22, 1.64]
De 1999	1/15	0/15		0.3 %	3.00 [0.13, 68.26]
Drastich 2005	2/40	2/33		0.8 %	0.83 [0.12, 5.54]
Abdelfattah 2006	4/51	5/52		1.9 %	0.82 [0.23, 2.87]
Mora 2000	0/12	1/12		0.3 %	0.33 [0.01, 7.45]
Thuluvath 2005	6/16	3/15		2.1 %	1.88 [0.57, 6.19]
Gheorghe 2002	1/25	5/28		0.7 %	0.22 [0.03, 1.79]
Chen 1998	3/26	3/30		1.3 %	1.15 [0.25, 5.23]
Abulfutuh 2003	13/44	24/66		9.8 %	0.81 [0.47, 1.42]
Lay 2006	14/50	12/50		6.9 %	1.17 [0.60, 2.27]
Total (95% CI)	**731**	**773**		**100.0 %**	**1.09 [0.92, 1.30]**

Total events: 176 (Banding), 178 (Beta-blockers)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 13.44$, df = 18 ($P = 0.76$); $I^2 = 0.0\%$

Test for overall effect: $Z = 1.01$ ($P = 0.31$)

Test for subgroup differences: Not applicable

0.002 0.1 1 10 500

Gluud LL, Krag A. Cochrane database of systematic reviews 2012

Meta-analysis data on primary prevention of variceal bleeding

Study	Treatment	Number of trials	Number of patients	Bleeding OR (95& CI)	Mortality OR (95% CI)
Pagliaro	NSBB vs NT	9	966	0.54 (0.39-0.74)	0.75 (0.57-1.06)
Triantos	EBL vs NT	8	738	0.3 (0.17-0.53)	0.42 (0.3-0.6)
Gluud	NSBB vs EBL	19	1504	0.67 (0.46-0.98)	1.09 (0.92-1.30)

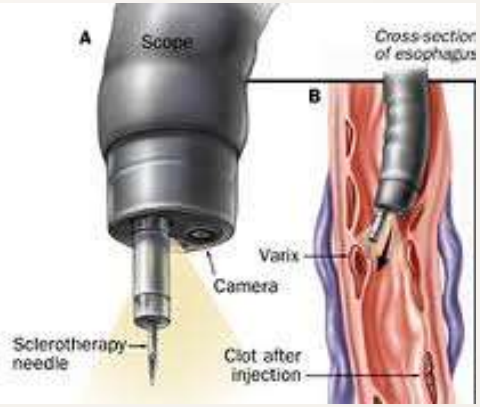
Conclusions:

- NSSB and EBL better than no treatment/placebo.
- EBL better than NSSB for prevention of bleeding but not mortality.

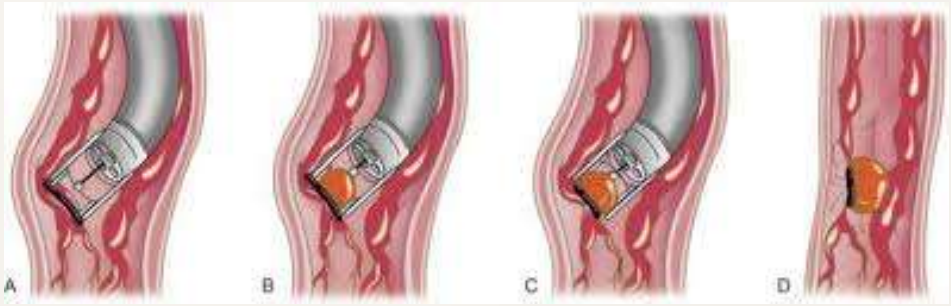
Clinical Scenarios

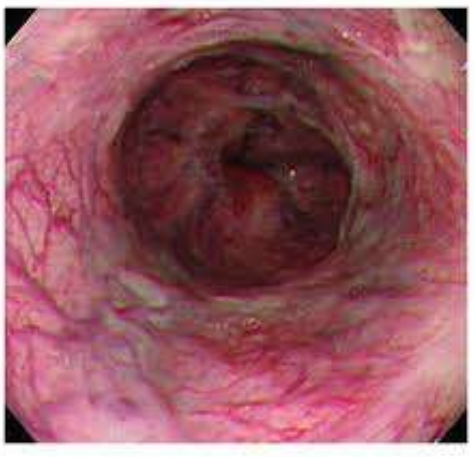
- Primary prophylaxis – prevention of first variceal bleeding
- Acute variceal bleeding
- Secondary prophylaxis – prevention of recurrent variceal bleeding

Endoscopic Variceal Sclerotherapy



Endoscopic Variceal Band Ligation





Baveno V Consensus in Portal Hypertension

- In suspected variceal bleeding, vasoactive drugs should be started as soon as possible, before endoscopy (1b,A).
- Vasoactive drugs should be used in combination with endoscopic therapy and continued for up to 5 days (1a,A).
- Ligation is the recommended form of endoscopic therapy for acute variceal bleeding (1b, A).

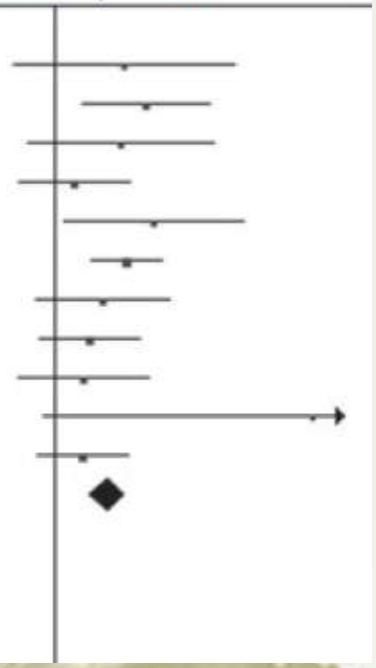
De Francis. Baveno V consensus workshop. J Hepatol . 2010

Vasoactive Drugs in Acute Variceal Bleeding

Study or Subgroup	SSA Events	SSA Total	Control Events	Control Total	Weight	Risk ratio M–H, Random, 95% CI
1.14.1 Octreotide						
Brunati 1996	21	28	16	27	2.8%	1.27 [0.87, 1.85]
El Sayed 1995	45	50	33	50	6.2%	1.36 [1.10, 1.70]
Freitas 2000	32	43	22	37	3.7%	1.25 [0.91, 1.72]
Li 1996	19	20	16	18	7.3%	1.07 [0.88, 1.29]
Shah 2005	37	51	28	54	3.9%	1.40 [1.03, 1.90]
Shiha 1996	89	93	72	96	11.0%	1.28 [1.13, 1.44]
Signorelli 1997	37	44	30	42	5.9%	1.18 [0.93, 1.48]
Silva 2004	33	36	35	43	8.2%	1.13 [0.95, 1.34]
Souza 2003	43	56	39	56	6.0%	1.10 [0.88, 1.38]
Xu 1993	9	10	3	8	0.5%	2.40 [0.96, 6.01]
Zuberi 2000	33	35	30	35	9.0%	1.10 [0.94, 1.29]
Subtotal (95% CI)		466		466	64.5%	1.20 [1.12, 1.27]
Total events	398		324			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 10.06$, df = 10 ($P = 0.44$); $I^2 = 1\%$

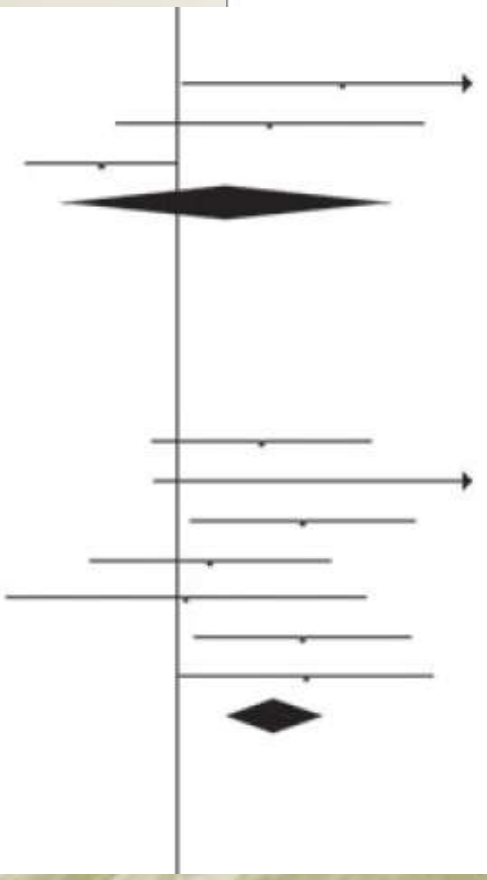
Test for overall effect: $Z = 5.56$ ($P < 0.00001$)



Wells M. et al. Aliment Pharmacol Ther. 2012

Vasoactive Drugs in Acute Variceal Bleeding

1.14.2 Somatostatin						
Moreto 1994	21	33	11	30	1.5%	1.74 [1.02, 2.97]
Pauwels 1994	14	18	8	14	1.6%	1.36 [0.81, 2.28]
Valenzuela 1989	31	48	30	36	5.1%	0.78 [0.60, 1.00]
Subtotal (95% CI)		99		80	8.2%	1.18 [0.67, 2.06]
Total events	66		49			
Heterogeneity: $\tau^2 = 0.19$; $\chi^2 = 10.14$, df = 2 ($P = 0.006$); $I^2 = 80\%$						
Test for overall effect: $Z = 0.58$ ($P = 0.56$)						
1.14.3 Terlipressin						
Brunati 1996	22	28	16	27	2.9%	1.33 [0.92, 1.92]
Freeman 1989	8	15	3	16	0.4%	2.84 [0.92, 8.76]
Levacher 1995	29	41	20	43	2.8%	1.52 [1.04, 2.22]
Patch 1999	29	66	26	66	2.5%	1.12 [0.74, 1.67]
Pauwels 1994	10	17	8	14	1.2%	1.03 [0.56, 1.88]
Soderland 1990	26	31	16	29	3.0%	1.52 [1.06, 2.18]
Walker 1986	20	25	13	25	2.3%	1.54 [1.01, 2.35]
Subtotal (95% CI)		223		220	15.1%	1.39 [1.18, 1.63]
Total events	144		102			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 4.38$, df = 6 ($P = 0.63$); $I^2 = 0\%$						
Test for overall effect: $Z = 3.92$ ($P < 0.0001$)						



Wells M. et al. Aliment Pharmacol Ther. 2012

Vasoactive Drugs in Acute Variceal Bleeding

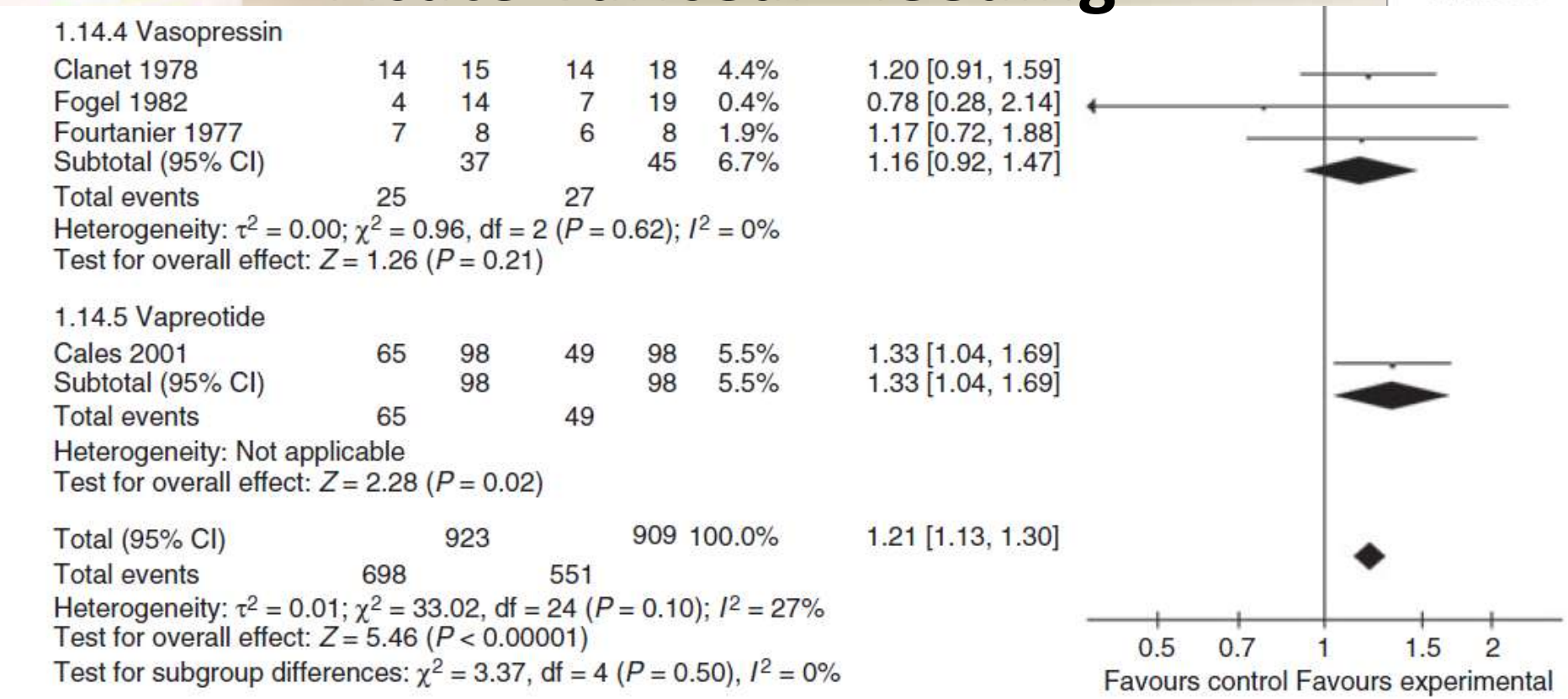


Figure 3 | Forest plot of risk ratio for hemostasis.

Wells M. et al. Aliment Pharmacol Ther. 2012

Meta-analysis : vasoactive drugs for acute variceal bleeding

No. of trials=30, No. of patients=3111

Outcome	Risk Ratio(95%CI)	p value
Mortality	0.74 (0.57-0.95)	0.02
Fail Hemostasis	1.21 (1.13-1.30)	<0.001
Rebleeding	0.68 (0.52-0.90)	0.007
Transfusion req.	-0.7 (-1.01 to -0.38)	<0.001
Hospital stay	-0.71 (-1.23 to -0.19)	0.007

Wells M. et al. Aliment Pharmacol Ther. 2012

Meta-analysis: Vasoactive drugs vs sclerotherapy in acute variceal bleeding

No. of trials=17, No. of patients=1817

Outcome	OR (95% CI)
Failure to control bleeding	-0.02 (-0.06-0.02)
5-d Failure rate	-0.05 (-0.10-0.01)
Mortality rate	-0.02 (-0.06-0.02)
Adverse events	0.08 (0.3 -0.14)

D'Amico G et al. Cochrane database of systematic reviews. 2012

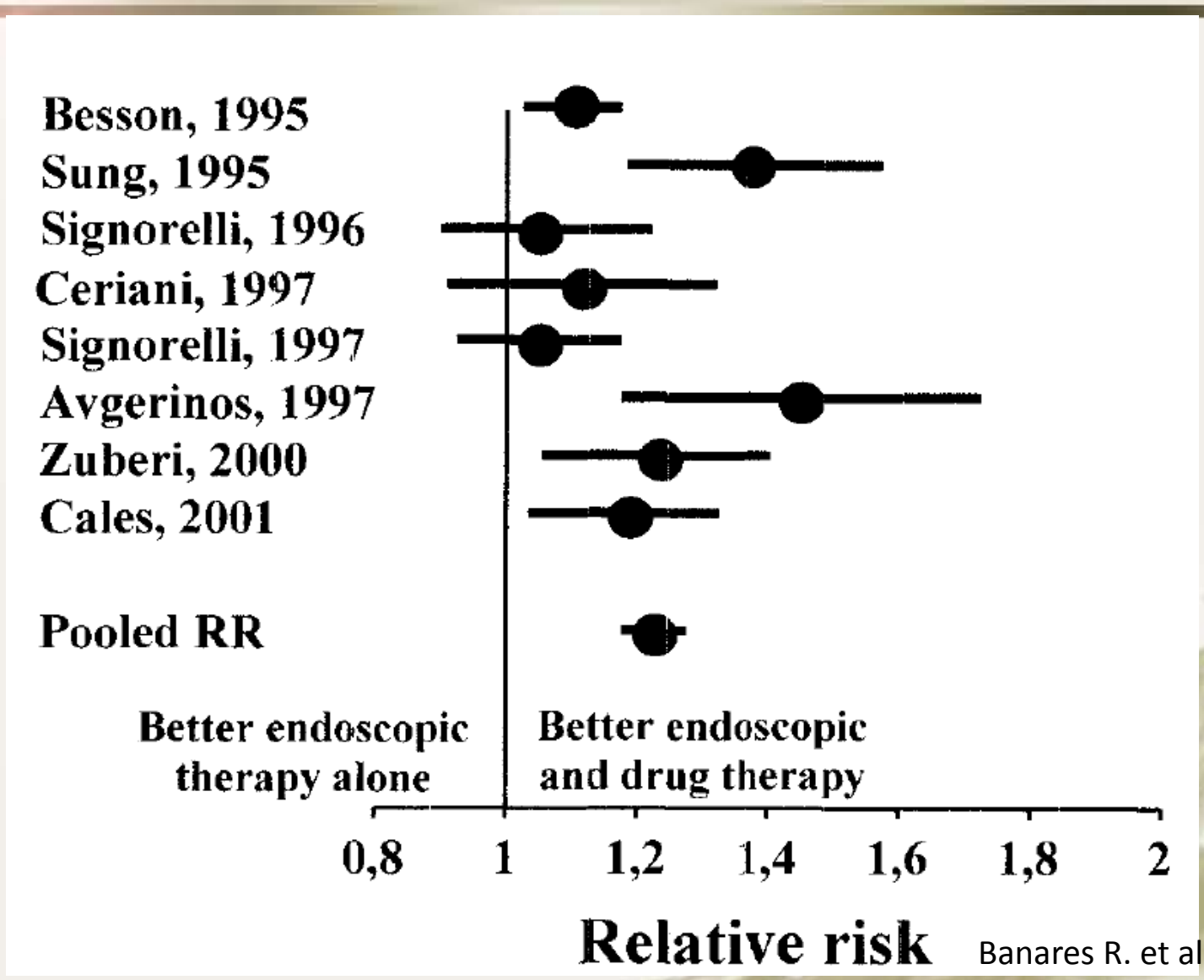
Meta-analysis: Endoscopic Band Ligation vs Sclerotherapy for Acute Variceal Bleeding

No. of trials=12, No. of patients=1309

Outcome	OR (95% CI)
Failure to control bleeding	1.95 (1.27-9.28)
Mortality	1.3 (-2.3-4.9)

Triantos C et al.Evidence-based gastroenterology and hepatology 2010

Meta-analysis: Endoscopic Treatment + Vasoactive Drugs for Acute Variceal Bleeding



Banares R. et al. Hepatology 2002

Meta-analysis: Endoscopic Treatment + Vasoactive Drugs for Acute Variceal Bleeding

No. of trials=8, No. of patients=939

Outcome	Relative risk (95% CI)	NNT
Initial Hemostasis	1.12 (1.02-1.23)	8
5-d Hemostasis	1.28 (1.18-1.39)	5
Mortality	0.73 (0.45-1.18)	

Banares R. et al. Hepatology 2002

Meta-analysis data on acute variceal bleeding

Study	Treatment	Number of trials	Number of patients	Failure to control bleeding OR (95& CI)	Mortality OR (95% CI)
Wells	VAD vs NT	30	3111	1.21 (1.13-1.3)	0.74 (0.57-0.95)
D'Amico	VAD vs Scler	17	1817	-0.02 (-0.06-0.02)	-0.02 (-0.06-0.02)
Triantos	EBL vs Scler	12	1309	1.95 (1.27-2.98)	1.3 (-2.3-4.9)
Banares	VAD + Endo vs Endo	8	939	1.12 (1.02-1.23)	0.73 (0.45-1.18)

Conclusion:

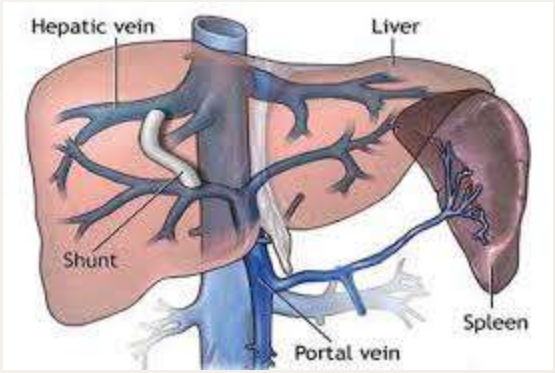
- VAD and Endoscopic therapy are effective in control of acute variceal bleeding.
- EBL better that EVS.

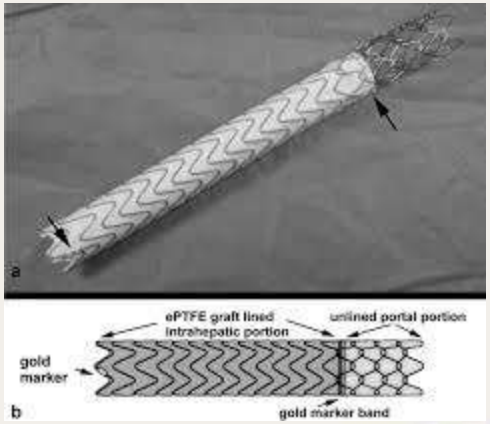
Baveno V Consensus in Portal Hypertension

- Persistent bleeding despite combined pharmacological and endoscopic therapy is best managed by TIPS with PTFE-covered stents (2b,B).
- An early TIPS within 72 h should be considered in patients at high risk of treatment failure (Child C) after initial pharmacologic and endoscopic therapy (1b,A).

De Francis. Baveno V consensus workshop. J Hepatol . 2010

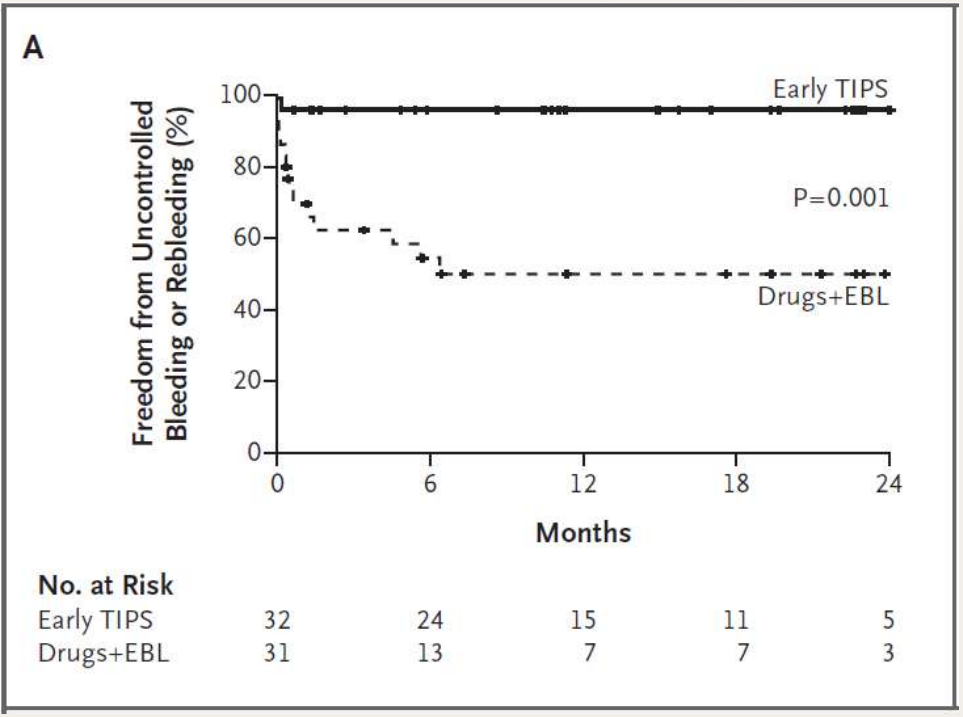
Transjugular intrahepatic portosystemic shunt (TIPS)



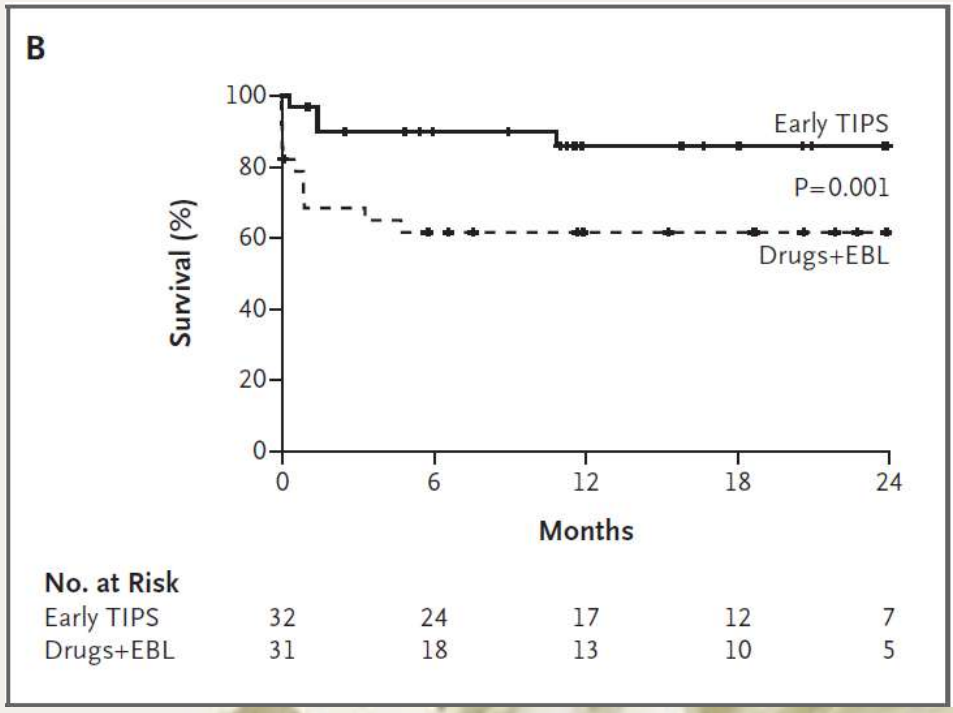


Early TIPS vs VAD + EBL in Acute Variceal Bleeding

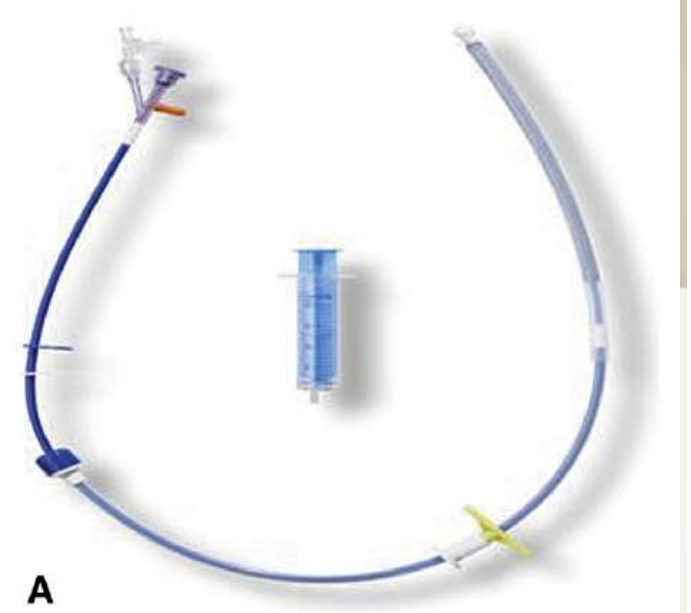
Bleeding: 1/31 vs 14/32

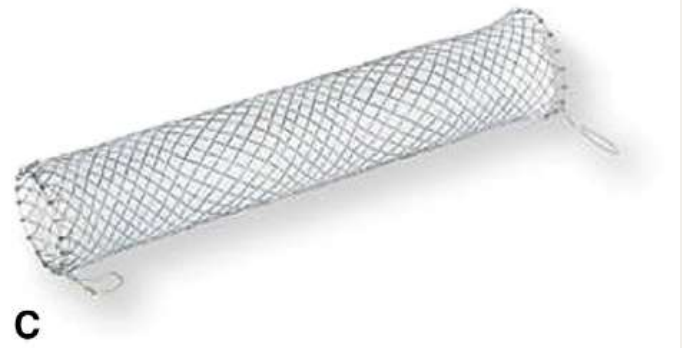


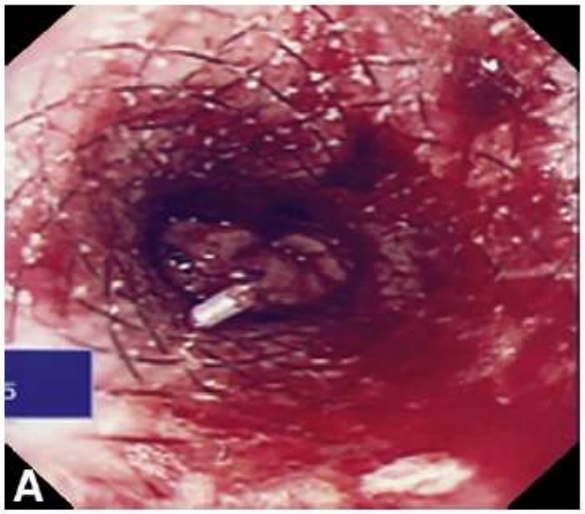
Mortality: 4/31 vs 16/32

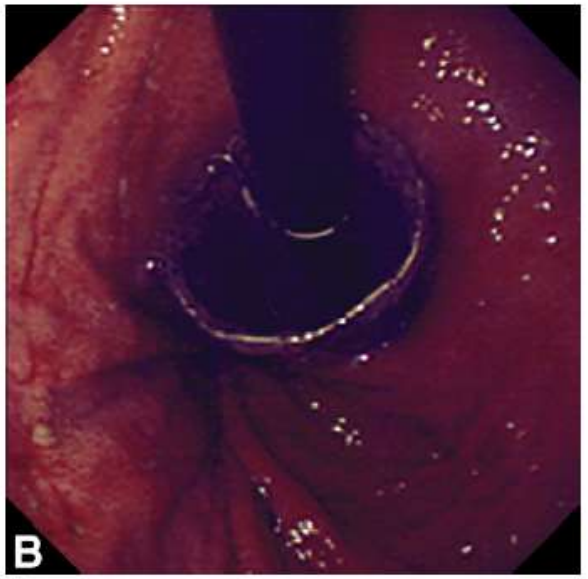


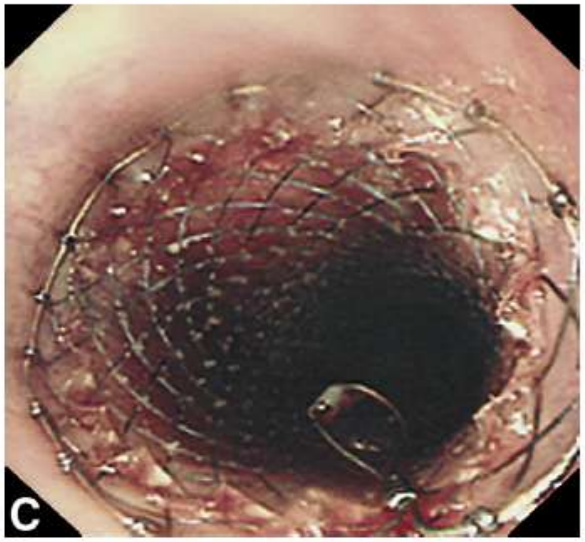
Garcia-Pagan JC et al. N Engl J Med 2010

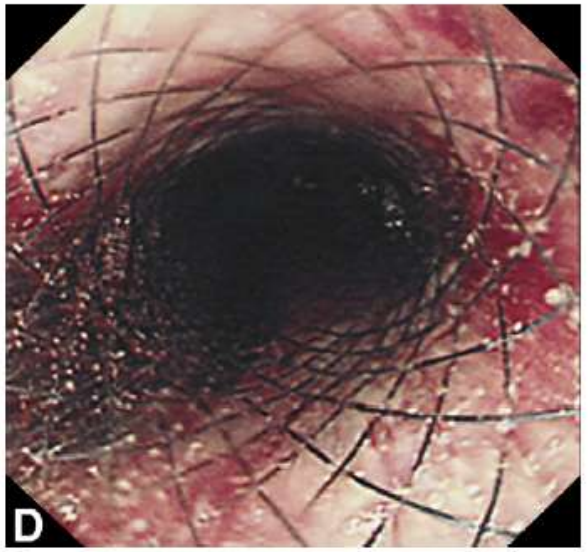












SEMS – SX-Ella DANIS stent

Wright G et al. Gastrointest Endosc 2010

Clinical Scenarios

- Primary prophylaxis – prevention of first variceal bleeding
- Acute variceal bleeding
- Secondary prophylaxis – prevention of recurrent variceal bleeding

Baveno V Consensus in Portal Hypertension

- Combination of beta-blockers and band ligation is the preferred therapy as it results in lower rebleeding compared to either therapy alone (1a,A)
- Secondary prophylaxis should start as soon as possible from day 6 of the index variceal episode (5,D).

De Francis. Baveno V consensus workshop. J Hepatol . 2010

Meta-analysis: Nonselective Beta-blockers vs No treatment

No. of trials=12, No. of patients=769

Outcome	% Improv (95%CI)	p value	NNT
Variceal Rebleeding	20% (11-28%)	<0.001	5
Overall Mortality	5.4% (0-11%)	0.05	14
Bleeding-related Mortality	7.4% (2-13%)	<0.01	13

Bernard B et al. Hepatology 1997

NSBB + EBL vs NSSB alone or EBL alone

Study or subgroup	MI and EVL Events	MI and EVL Total	MI or EVL Events	MI or EVL Total	Weight	Risk ratio M-H, Random, 95% CI
1.5.1 EVL as control						
De la Pena 2005	6	43	15	37	7.2%	0.34 [0.15, 0.80]
Kumar 2009	14	84	16	83	11.9%	0.86 [0.45, 1.66]
Lo 2000	14	60	29	62	17.9%	0.50 [0.29, 0.85]
Lo 2001	9	37	13	40	9.7%	0.75 [0.36, 1.54]
Subtotal (95% CI)		224		222	46.7%	0.59 [0.41, 0.85]
Total events	43		73			
Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 3.72$, df = 3 ($P = 0.29$); $I^2 = 19\%$						
Test for overall effect: $Z = 2.79$ ($P = 0.005$)						
1.5.2 MI as control						
Garcia-Pagan 2009	22	80	27	78	22.8%	0.79 [0.50, 1.27]
Lo 2009	23	60	31	60	30.5%	0.74 [0.50, 1.11]
Subtotal (95% CI)		140		138	53.3%	0.76 [0.56, 1.04]
Total events	45		58			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.05$, df = 1 ($P = 0.83$); $I^2 = 0\%$						
Test for overall effect: $Z = 1.73$ ($P = 0.08$)						
Total (95% CI)		364		360	100.0%	0.68 [0.54, 0.85]
Total events	88		131			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 5.06$, df = 5 ($P = 0.41$); $I^2 = 1\%$						
Test for overall effect: $Z = 3.39$ ($P = 0.0007$)						
Test for subgroup differences: $\chi^2 = 1.11$, df = 1 ($P = 0.29$), $I^2 = 9.8\%$						

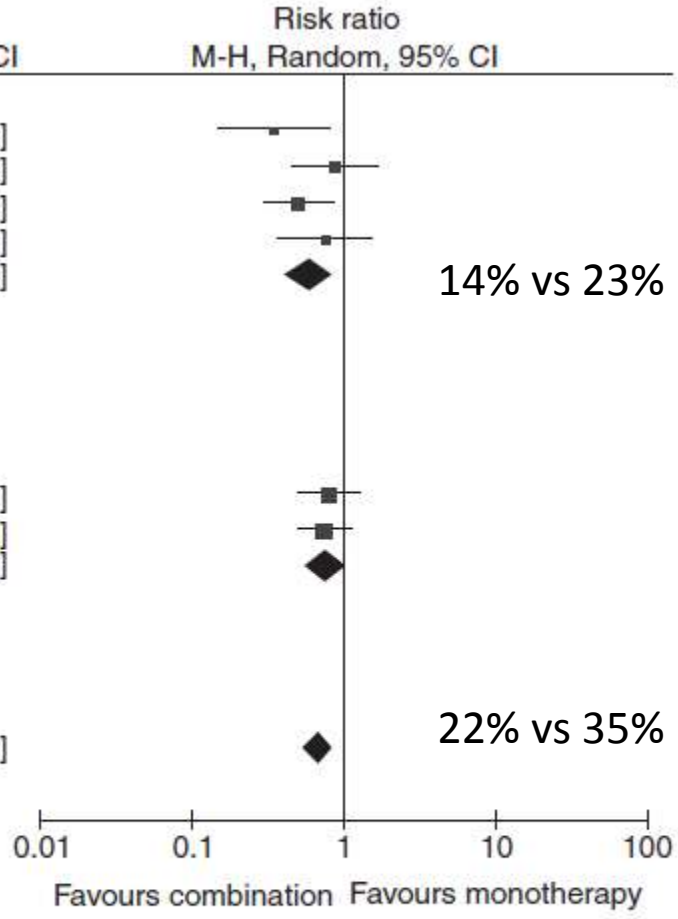


Figure 2 | Random effect meta-analysis of overall rebleeding in randomised trials on combination therapy [medical interventions (MI) and banding ligation (EVL)] vs. monotherapy (MI or EVL) on secondary prevention in oesophageal varices.

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NSBB + EBL vs NSSB alone or EBL alone

Study or subgroup	MI and EVL Events	MI and EVL Total	EVL or MI Events	EVL or MI Total	Weight	Risk ratio M-H, Random, 95% CI
1.8.1 EVL as control						
Abdel-Rahim 2000	2	25	3	25	7.1%	0.67 [0.12, 3.65]
Ahmad 2009	7	37	8	39	24.9%	0.92 [0.37, 2.29]
De la Pena 2005	5	43	4	37	13.4%	1.08 [0.31, 3.71]
Kumar 2009	2	84	3	83	6.6%	0.66 [0.11, 3.84]
Lo 2000	10	60	20	62	45.8%	0.52 [0.26, 1.01]
Sollano 2001	1	16	0	15	2.1%	2.82 [0.12, 64.39]
Subtotal (95% CI)		265		261	100.0%	0.71 [0.45, 1.11]
Total events	27		38			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.38$, df = 5 ($P = 0.80$); $I^2 = 0\%$						
Test for overall effect: $Z = 1.50$ ($P = 0.13$)						
1.8.2 Medical interventions as control						
Ahmad 2009	7	37	15	74	23.7%	0.93 [0.42, 2.09]
Garcia-Pagan 2009	16	80	15	78	38.6%	1.04 [0.55, 1.96]
Lo 2009	16	60	13	60	37.7%	1.23 [0.65, 2.33]
Subtotal (95% CI)		177		212	100.0%	1.08 [0.73, 1.60]
Total events	39		43			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.30$, df = 2 ($P = 0.86$); $I^2 = 0\%$						
Test for overall effect: $Z = 0.39$ ($P = 0.70$)						
Test for subgroup differences: $\chi^2 = 1.92$, df = 1 ($P = 0.17$), $I^2 = 48.0\%$						

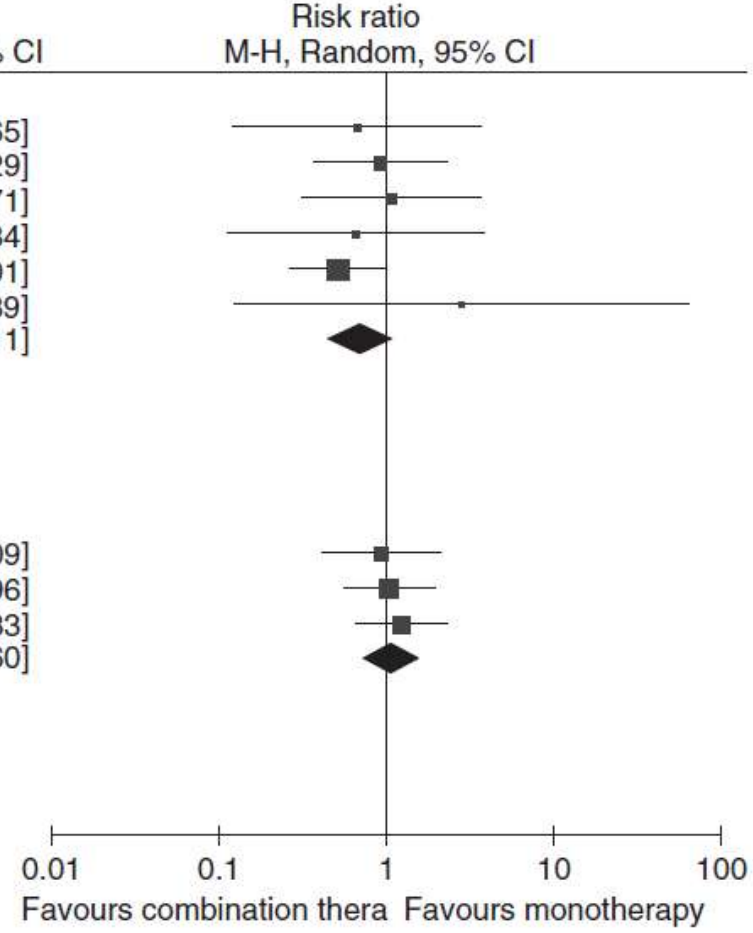

Figure 4 | Random effect meta-analysis of mortality in randomised trials on combination therapy [medical interventions (MI) and banding ligation (EVL)] vs. monotherapy (MI or EVL) on secondary prevention in oesophageal varices. *Overall risk estimate not shown, referred in text.

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Meta-analysis data on secondary prevention of variceal bleeding

Study	Treatment	Number of trials	Number of patients	Rebleeding OR (95& CI)	Mortality OR (95% CI)
Bernard	NSBB vs NT	12	769	1.42 (0.10-0.32)	1.27 (0-0.11)
Thiele	EBL and NSSB vs EBL	6	591	0.59 (0.41-0.85)	0.71 (0.45-1.11)
Thiele	EBL and NSSB vs NSBB	3	471	0.76 (0.56-1.04)	1.08 (0.73-1.6)

Conclusions:

- NSSB better than no treatment/placebo.
- EBL plus NSSB prevents rebleeding better than EBL alone or NSSB alone but not mortality.

Variceal Bleeding: To Band, Block, or TIPS?

Summary

- NSBB and EBL are effective for primary and secondary prophylaxis of variceal bleeding.
- The combination of vasoactive drugs and EBL is the best option for acute variceal bleeding.
- TIPS is reserve for failure to control acute variceal bleeding.