



Terlipressin:

kajian efektivitas dan keamanan terapi pada kasus *acute variceal bleeding*

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Dipresentasikan dalam:

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OUTLINE

INTRODUCTION

PLACE IN THERAPY

EVIDENCE

AVAILABILITY

CONCLUSION



Mechanism of
action

Chemical structure
and approval
information

PK profile

**EASL Clinical
Practice
Guidelines**

(acute
gastrointestinal
bleeding and
portal
hypertension)

Terlipressin
VS
other vasoactive
drug / procedure

Indonesia?
Prices?

Terlipressin as a
new vasoactive
drug in the
treatment of
acute
gastrointestinal
bleeding

INTRODUCTION

Informasi mengenai perijinan

	Australia - Therapeutics Goods Administration (TGA)
Approval year	2012 - Glypressin®
Bentuk sediaan	Ampul berisi cairan yang mengandung 0,85 mg terlipressin (setara dengan 1 mg terlipressin acetate) dalam 8,5 ml pelarut. Konsentrasi terlipressin 0,1 mg/ml (setara dengan 0,12 mg/ml terlipressin acetate)
Indikasi	Terapi <i>bleeding oesophageal varices</i>
Dosis	Dewasa: <ul style="list-style-type: none">• 1,7 mg terlipressin (setara 2 mg terlipressin acetate) diberikan setiap 4 jam.• Dosis dapat diturunkan menjadi 0,85 mg terlipressin (setara 1 mg terlipressin acetate) bila pendarahan telah terkontrol.• Dosis dapat diturunkan setelah pemberian dosis awal (terlipressin acetate 2 mg) menjadi 1 mg terlipressin acetate setiap 4 jam pada pasien dengan BB <50 kg atau jika terjadi ROTD Anak dan lansia: tidak ada data.
Durasi	Maksimal 48 jam → bila diberikan terlipressin acetate 2 mg Maksimal 5 hari → bila diberikan terlipressin acetate 1 mg

INTRODUCTION

Farmakokinetika-Farmakodinamika

Keterangan:

1. Saner et al, 2007; 2. Drugbank; 3. Drug Information Handbook (DIH)

Parameter	Terlipressin ¹	Somatostatin ²	Octreotide ³
Absorpsi	Tmax: 60-120 menit	<i>No information</i>	Sc: cepat dan sempurna IM: lepas lambat (via <i>microsphere degradation in the muscle</i>) BA: 100% (Sc), 60-63% (IM) Tmax: 0,4 jam (Sc), 1 jam (IM)
Distribusi	Vd (<i>healthy volunteers</i>): 15,5 ± 4,5 L	<i>No information</i>	<ul style="list-style-type: none">Vd: 14 LIkt O-P 65% (terutama pada lipoprotein)
Metabolisme	Terlipressin merupakan prodrug yang akan diaktivasi melalui pemecahan struktur 3 glisil oleh enzim peptidase di plasma → lisin vasopresin (aktif)	Dimetabolisme oleh enzim peptidase di plasma dan sel	<i>Extensively hepatic</i>
Ekskresi	Via urin (1%) t ½: 50-80 menit	t ½: 1-3 menit karena degradasi enzim peptidase yang ada di plasma dan jaringan	<ul style="list-style-type: none">t ½ : 1,7-1,9 jam (meningkat pada pasien lansia), pada sirosis: 3,7 jamEkskresi melalui urin (32% dalam bentuk tak berubah)

INTRODUCTION

Farmakokinetika-Farmakodinamika

Table 1. Sites of activity and molecular properties of terlipressin.

Receptor	Tissue	Effects	Action
V ₁ receptor	Smooth muscle cells of blood vessels	Phospholipase C; release of intracellular calcium	Vasoconstriction
V ₂ receptor	Renal collecting duct, endothelial cells	Via G protein, increase cAMP	Vasodilatation
V ₃ receptor	Pituitary gland	Via G protein, increase cAMP	Increase ACTH secretion
Oxytocin receptor	Uterus, breast, aorta, pulmonary artery	Phospholipase C; release of intracellular calcium, NO increase	Vasodilatation

ACTH: Adrenocorticotrophic hormone; NO: Nitric oxide; V₁, V₂, V₃: Vasopressin receptor 1, 2, 3.

Modified from [97].

PLACE IN THERAPY

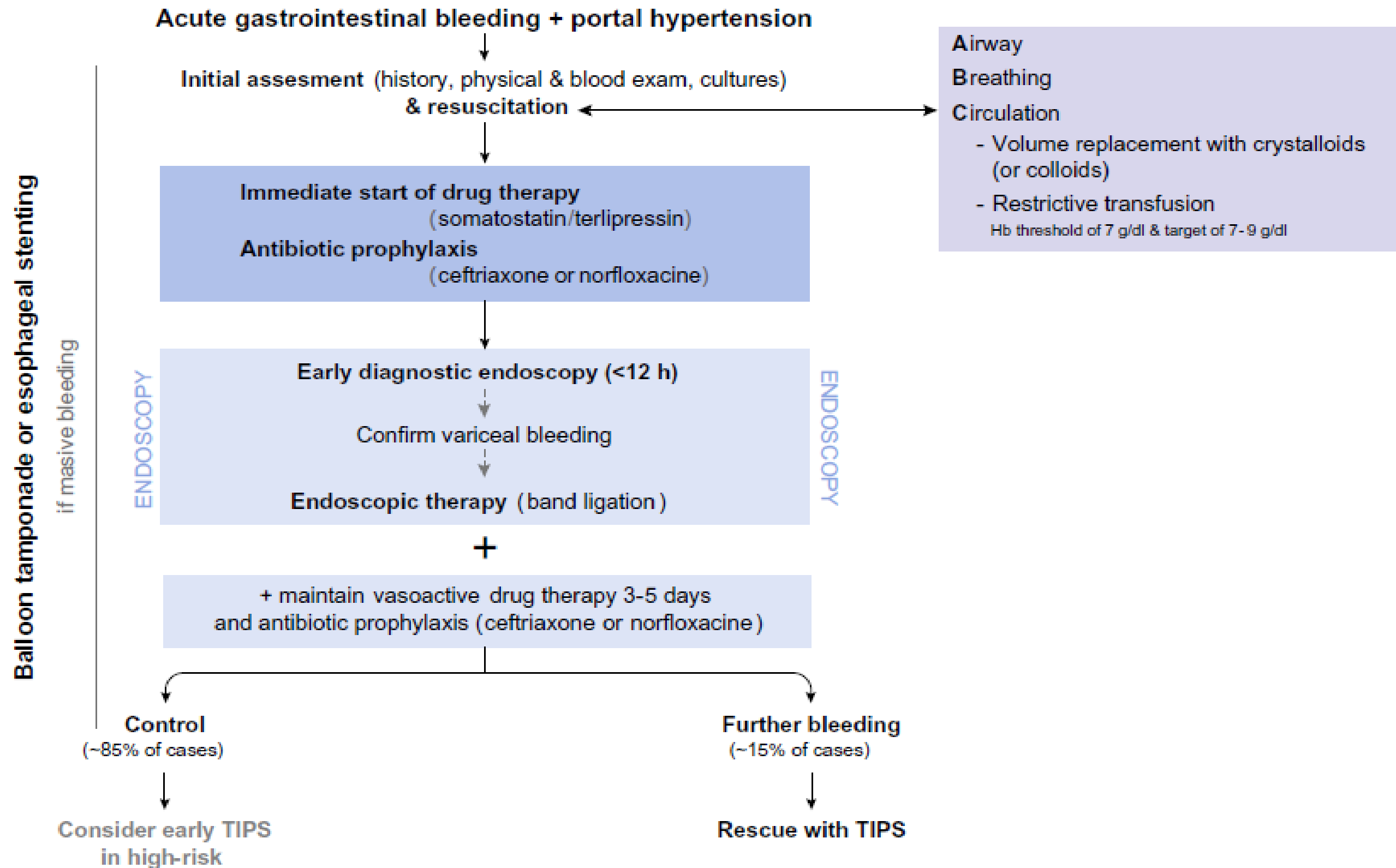


Fig. 2. Algorithm for the management of acute gastrointestinal bleeding in patients with cirrhosis (adapted from Ref. 168). TIPS, transjugular portosystemic shunts.

EVIDENCE (1)



**Cochrane
Library**

Cochrane Database of Systematic Reviews

Terlipressin for acute esophageal variceal hemorrhage (Review)

Ioannou GN, Doust J, Rockey DC

Cochrane Database of Systematic Reviews 2003, Issue 1. Art. No.: CD002147.

DOI: 10.1002/14651858.CD002147.

COMPARISON

Terlipressin	VS	Plasebo
		<i>Balloon tamponade</i>
		<i>Endoscopic treatment</i>
		Octreotide
		Somatostatin
		Vasopressin



OUTCOME

1. Kematian
2. *Number failing initial hemostatis*
3. Jumlah pasien yang mengalami *re-bleeding*
4. Jumlah pasien yang membutuhkan prosedur untuk mengatasi *re-bleeding/bleeding (tamponade, sclerotherapy, surgery, TIPS)*
5. Reaksi merugikan yang menyebabkan kematian
6. Reaksi merugikan yang menyebabkan pasien berhenti menggunakan obat
7. Jumlah pasien yang membutuhkan transfusi darah
8. Lama tinggal di rumah sakit

EVIDENCE (1)

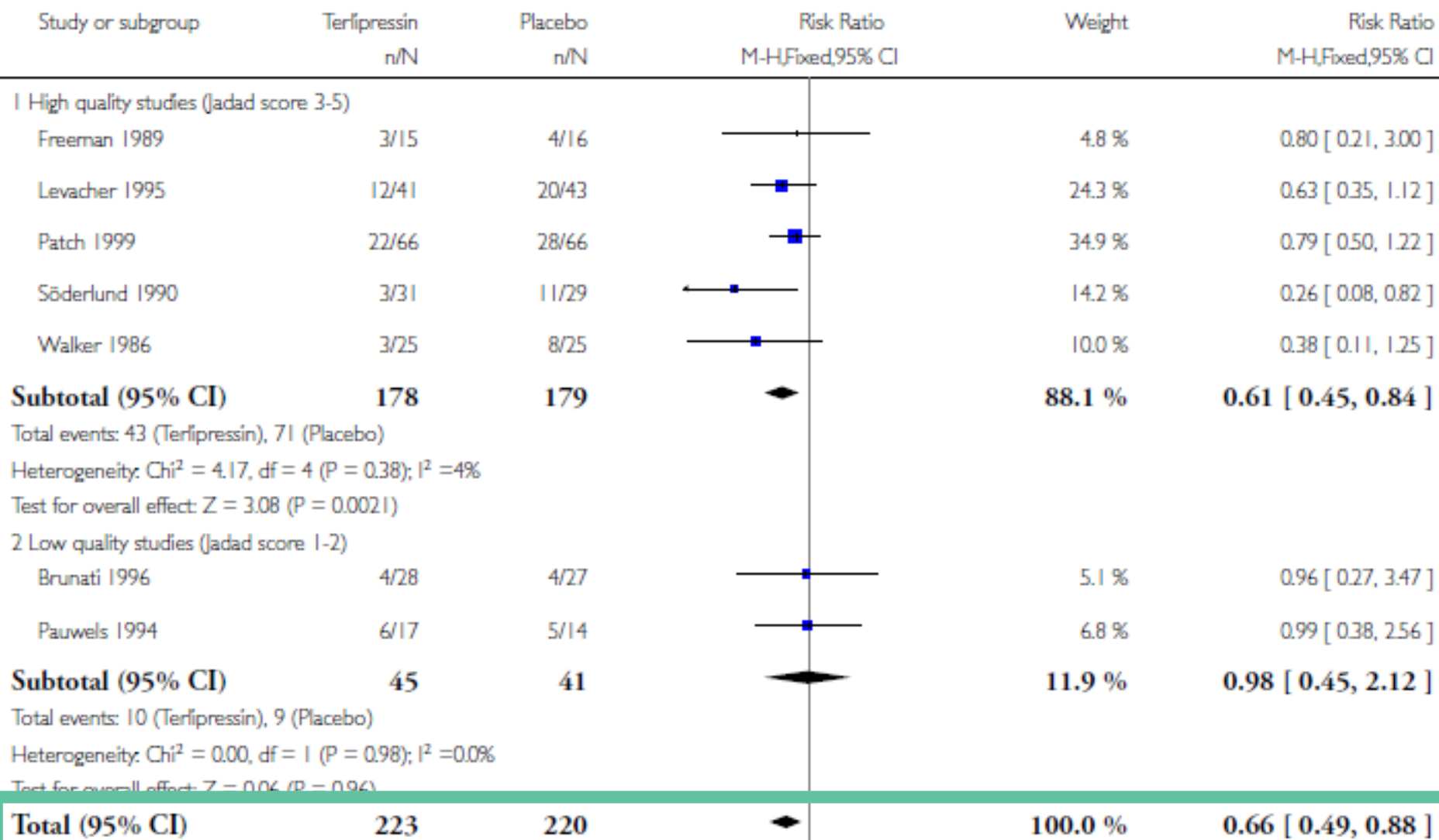
1) Terlipressin vs Placebo

Analysis 1.1. Comparison 1 Terlipressin versus placebo, Outcome 1 Mortality.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 1 Terlipressin versus placebo

Outcome: 1 Mortality



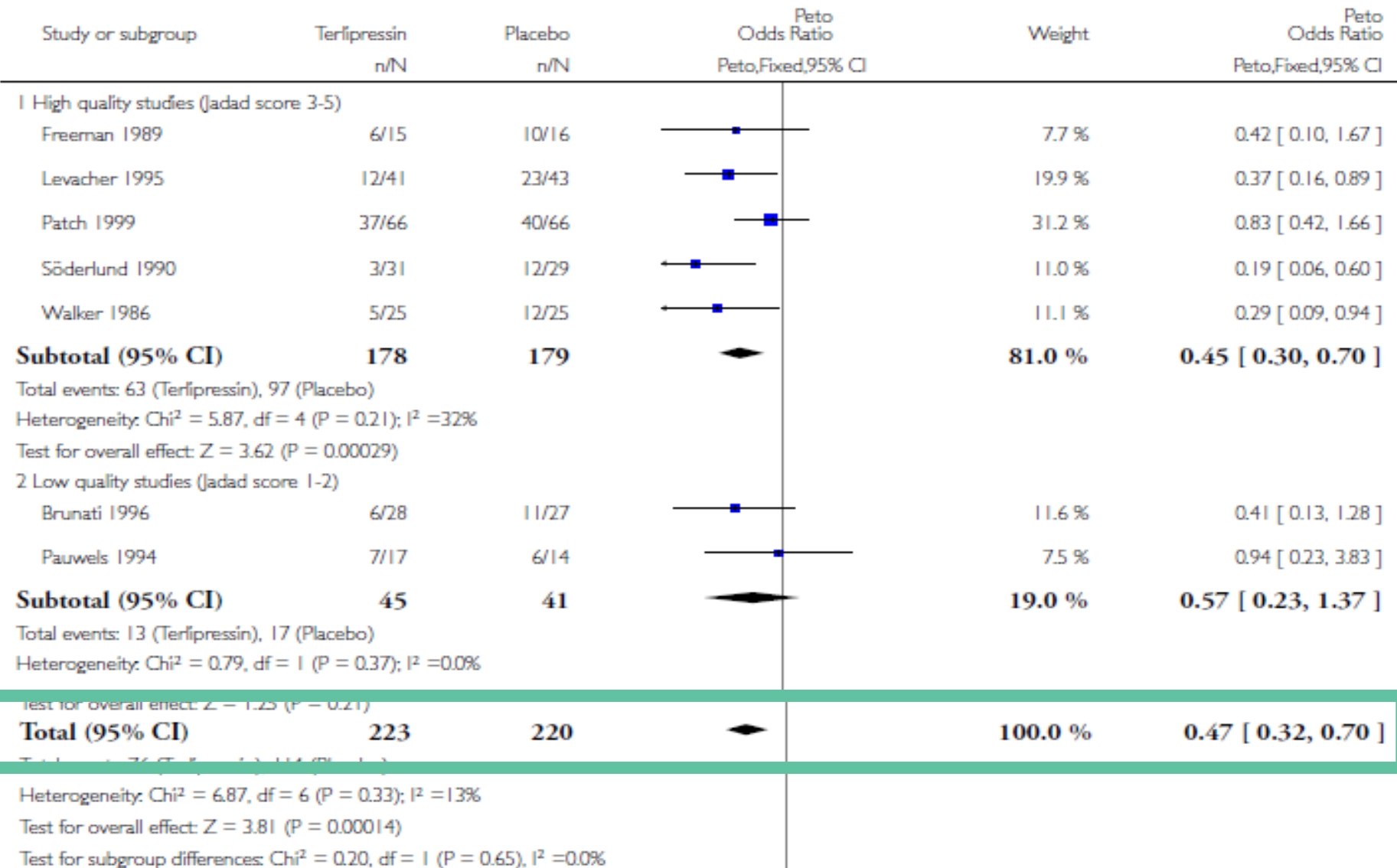
0.1 0.2 0.5 1 2 5 10
Favours terlipressin Favours placebo

Analysis 1.2. Comparison 1 Terlipressin versus placebo, Outcome 2 Number failing initial hemostasis.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 1 Terlipressin versus placebo

Outcome: 2 Number failing initial hemostasis



0.1 0.2 0.5 1 2 5 10
Favours terlipressin Favours placebo

EVIDENCE (1)

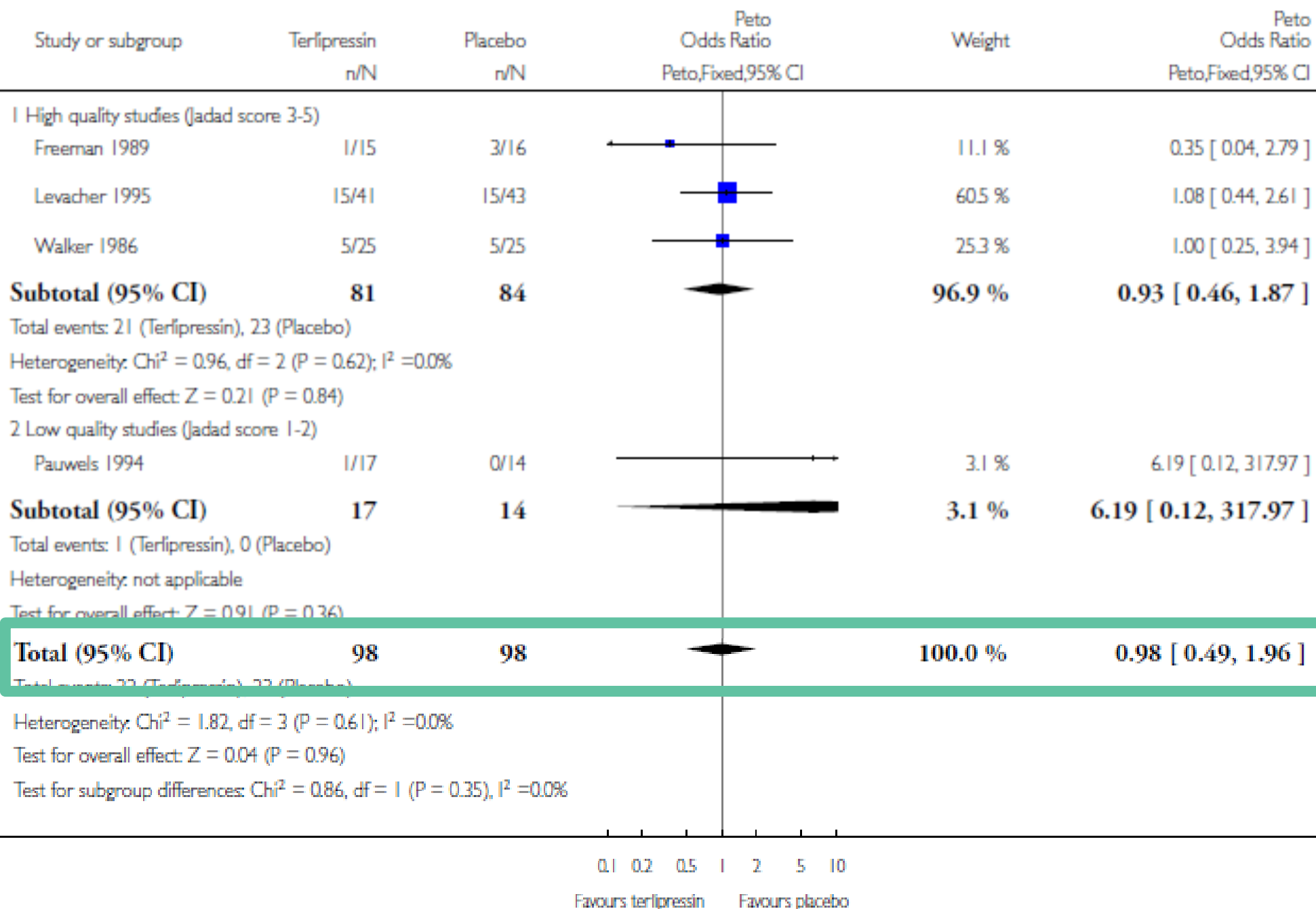
1) Terlipressin vs Placebo

Analysis I.3. Comparison I Terlipressin versus placebo, Outcome 3 Number with rebleeding.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: I Terlipressin versus placebo

Outcome: 3 Number with rebleeding

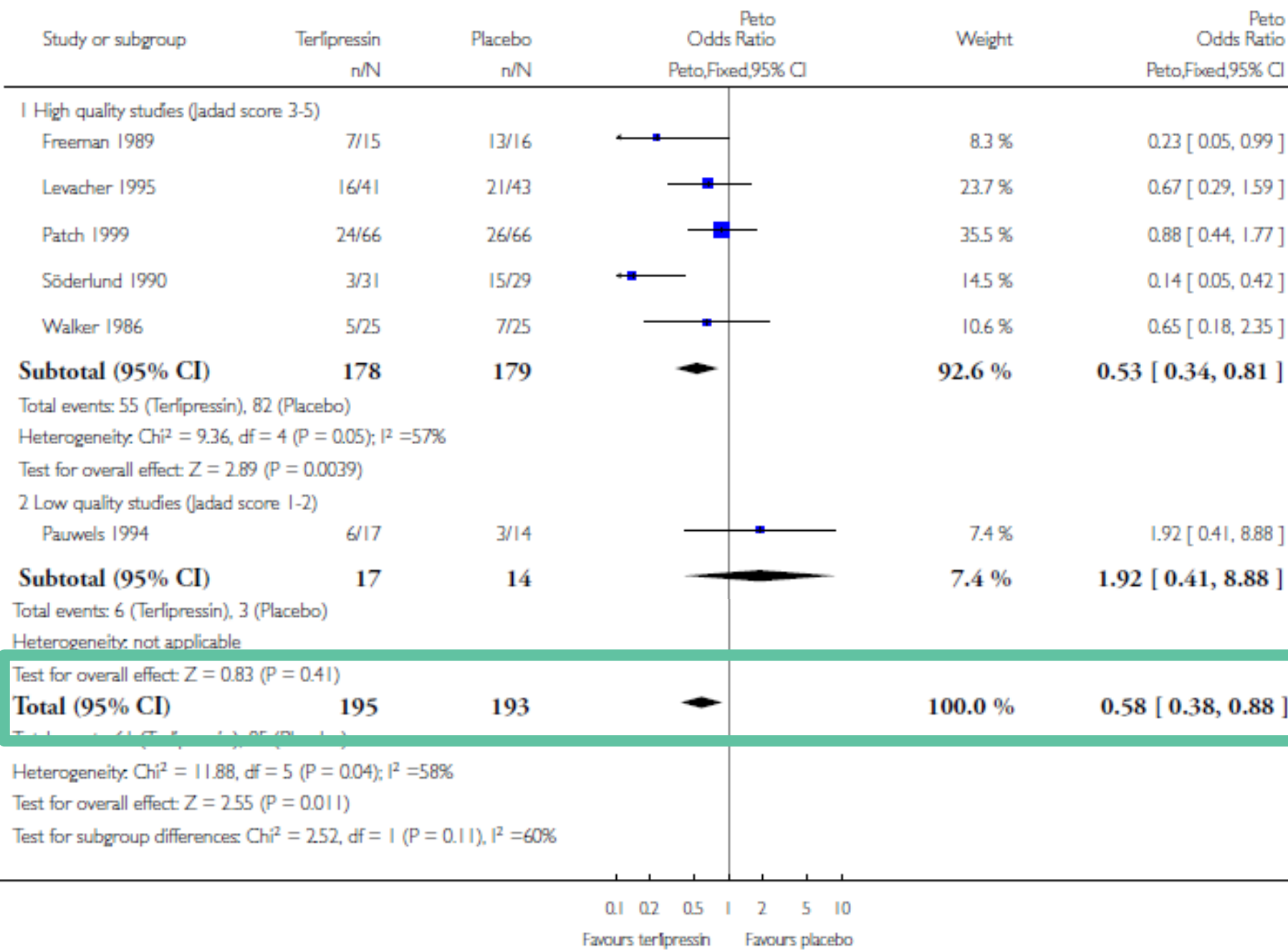


Analysis I.4. Comparison I Terlipressin versus placebo, Outcome 4 Number of procedures (tamponade, sclerotherapy, surgery or TIPS) required for uncontrolled bleeding/rebleeding.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: I Terlipressin versus placebo

Outcome: 4 Number of procedures (tamponade, sclerotherapy, surgery or TIPS) required for uncontrolled bleeding/rebleeding



EVIDENCE (1)

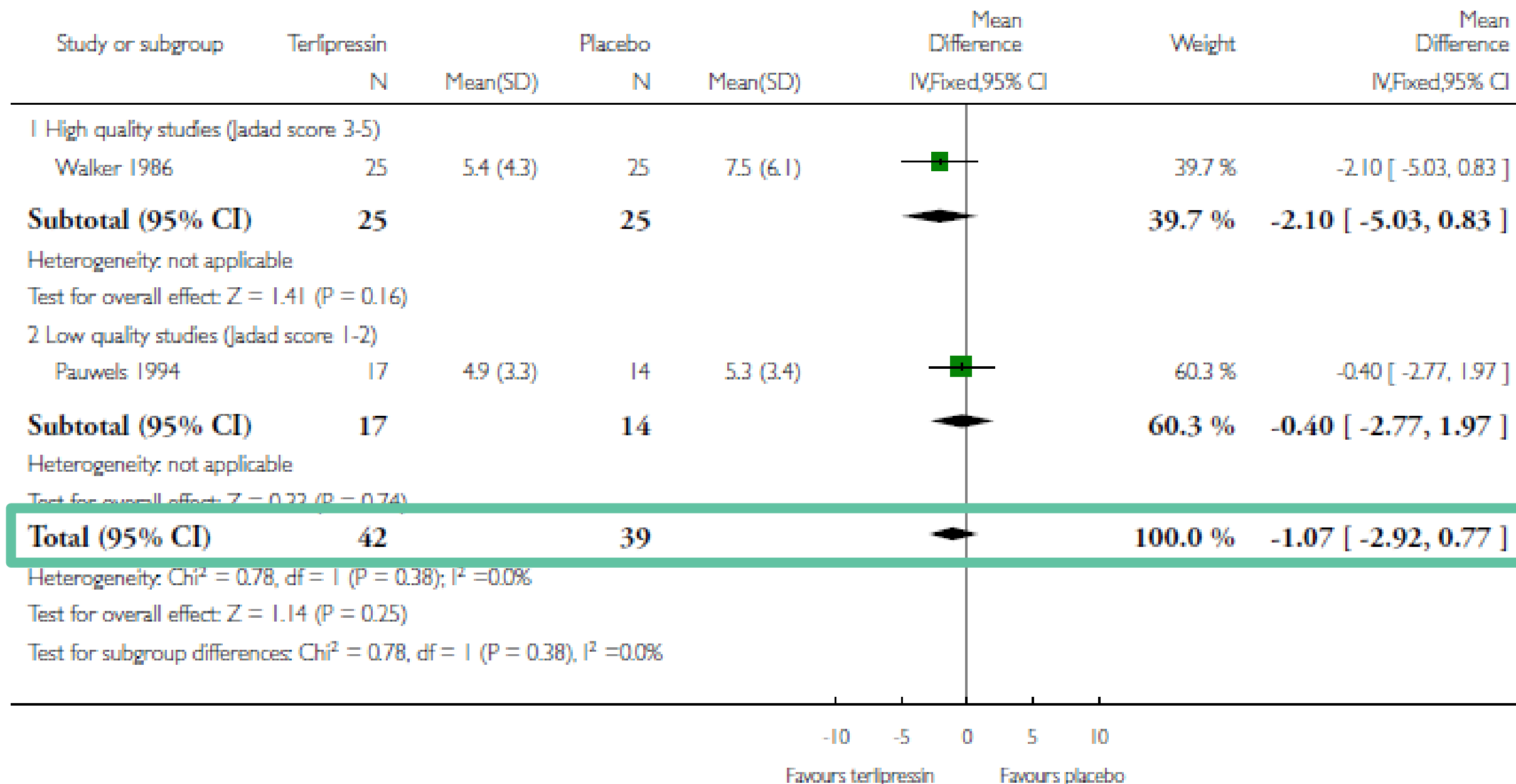
1) Terlipressin vs Placebo

Analysis 1.5. Comparison 1 Terlipressin versus placebo, Outcome 5 Number of blood transfusions.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 1 Terlipressin versus placebo

Outcome: 5 Number of blood transfusions



EVIDENCE (1)

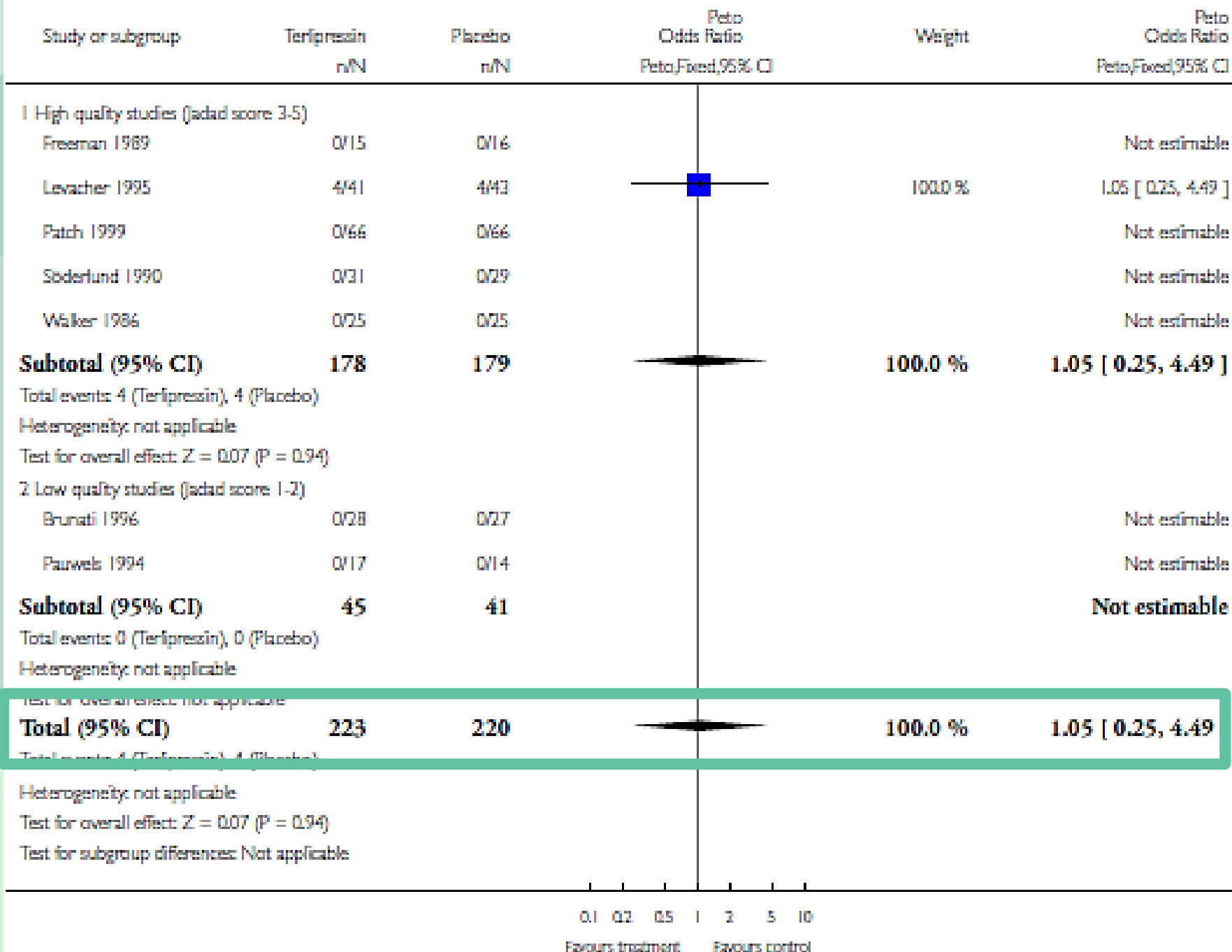
1) Terlipressin vs Plasebo

Analysis 1.6. Comparison 1 Terlipressin versus placebo, Outcome 6 Adverse events causing death.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 1 Terlipressin versus placebo

Outcome: 6 Adverse events causing death

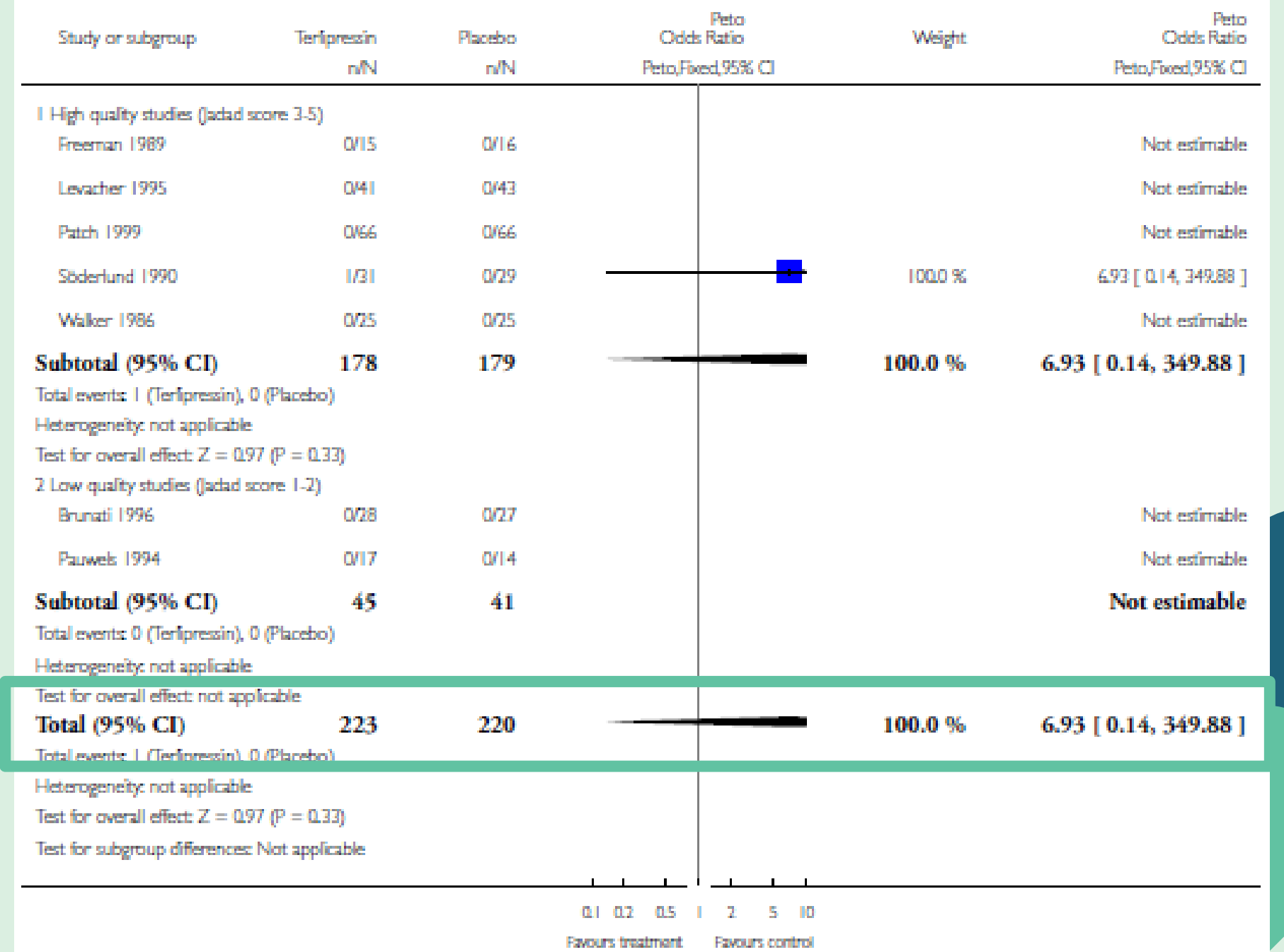


Analysis 1.7. Comparison 1 Terlipressin versus placebo, Outcome 7 Adverse events causing withdrawal of treatment.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 1 Terlipressin versus placebo

Outcome: 7 Adverse events causing withdrawal of treatment



EVIDENCE (1)

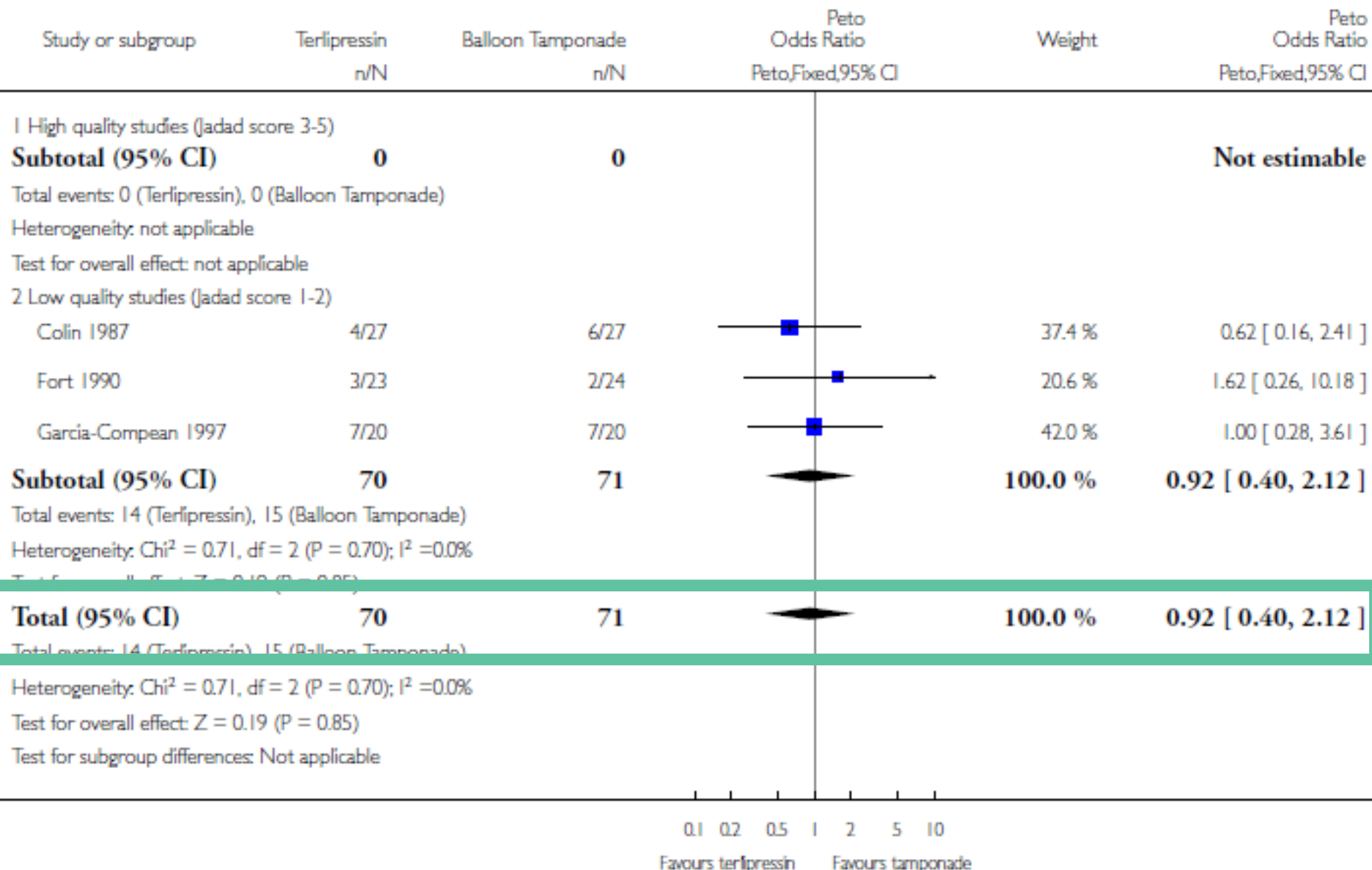
2) Terlipressin vs *Balloon Tamponade*

Analysis 2.1. Comparison 2 Terlipressin versus balloon tamponade, Outcome 1 Mortality.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 2 Terlipressin versus balloon tamponade

Outcome: 1 Mortality

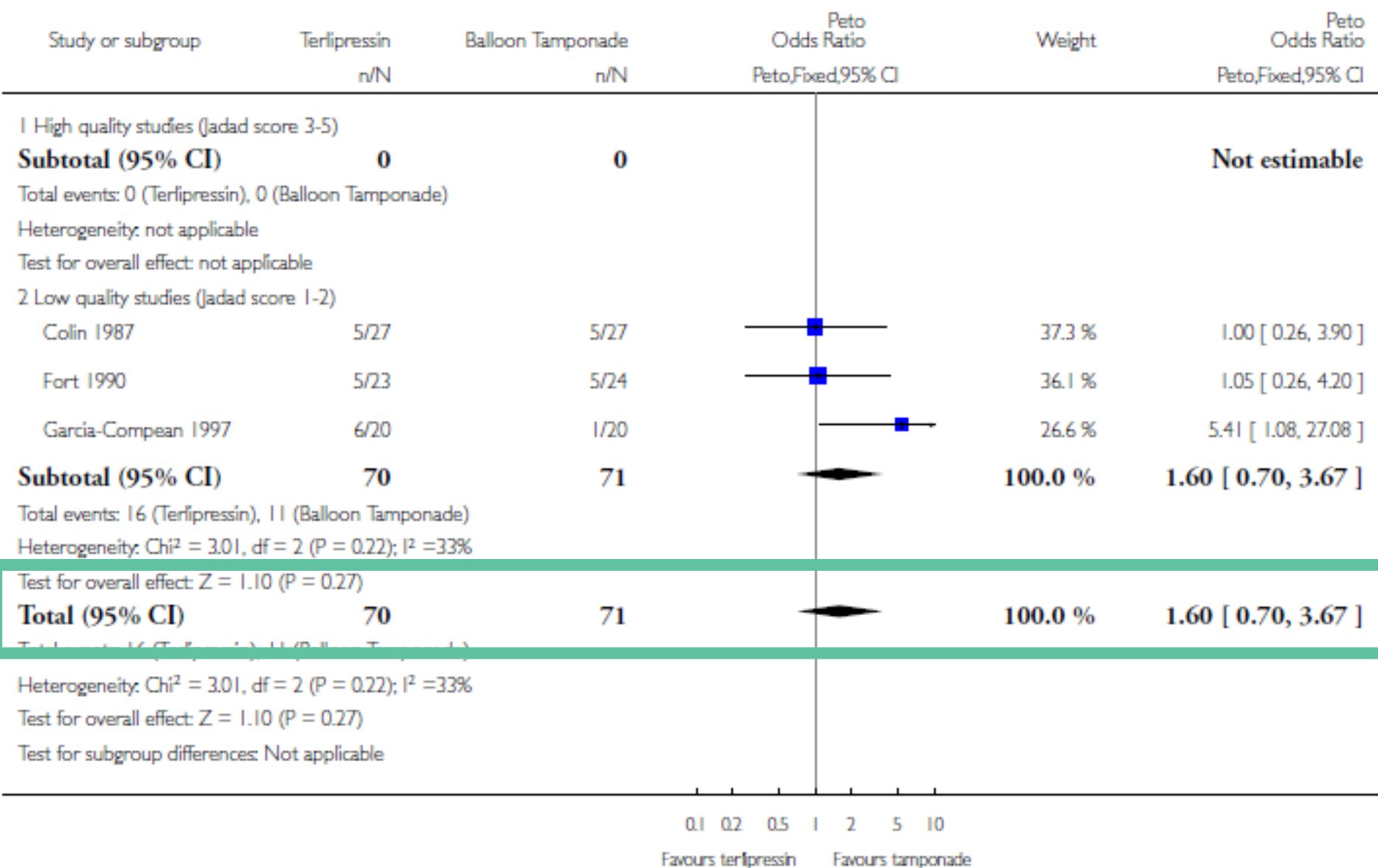


Analysis 2.2. Comparison 2 Terlipressin versus balloon tamponade, Outcome 2 Number failing initial hemostasis.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 2 Terlipressin versus balloon tamponade

Outcome: 2 Number failing initial hemostasis



EVIDENCE (1)

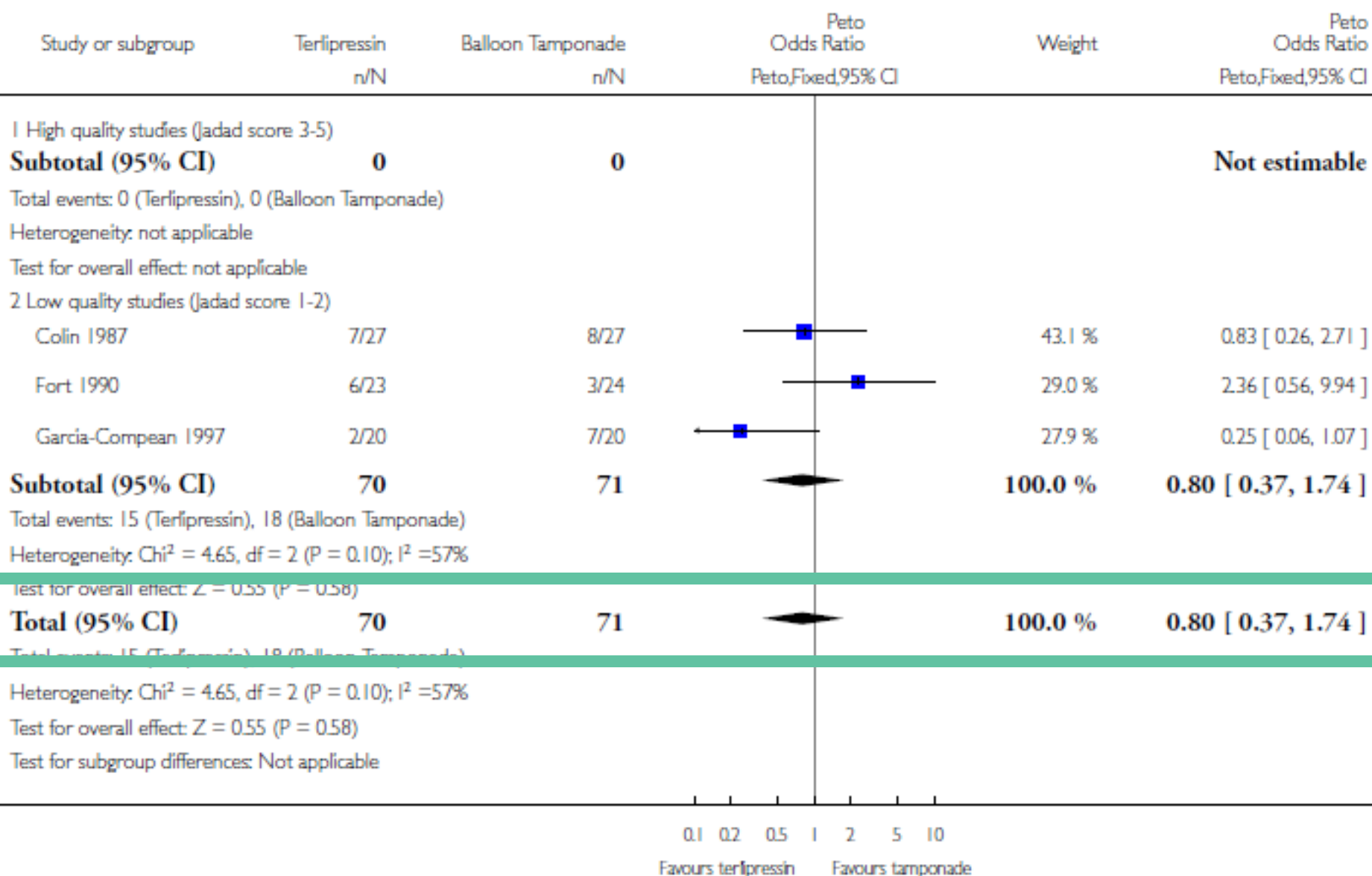
2) Terlipressin vs *Balloon Tamponade*

Analysis 2.3. Comparison 2 Terlipressin versus balloon tamponade, Outcome 3 Number with rebleeding

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 2 Terlipressin versus balloon tamponade

Outcome: 3 Number with rebleeding

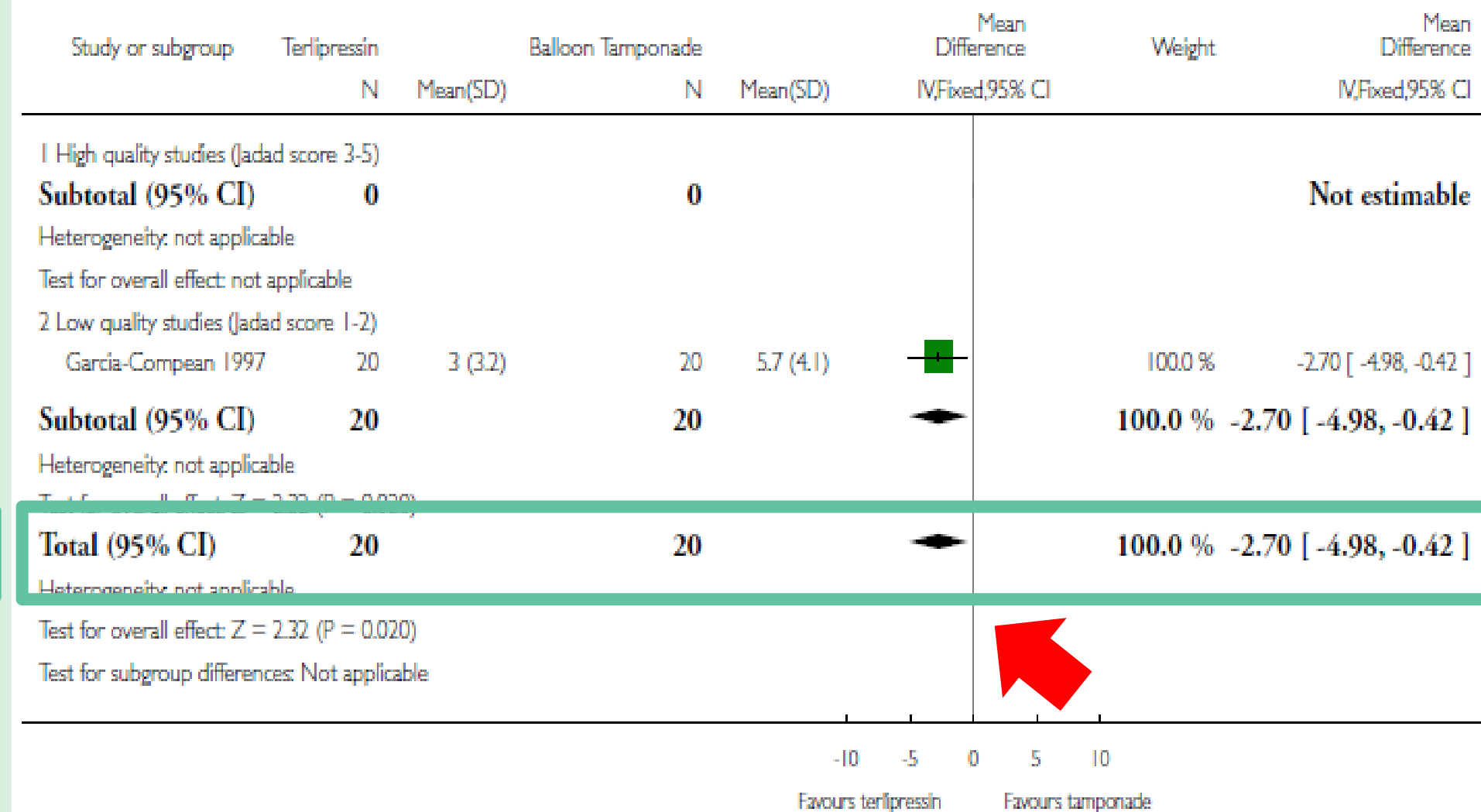


Analysis 2.4. Comparison 2 Terlipressin versus balloon tamponade, Outcome 4 Number of blood transfusions

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 2 Terlipressin versus balloon tamponade

Outcome: 4 Number of blood transfusions



EVIDENCE (1)

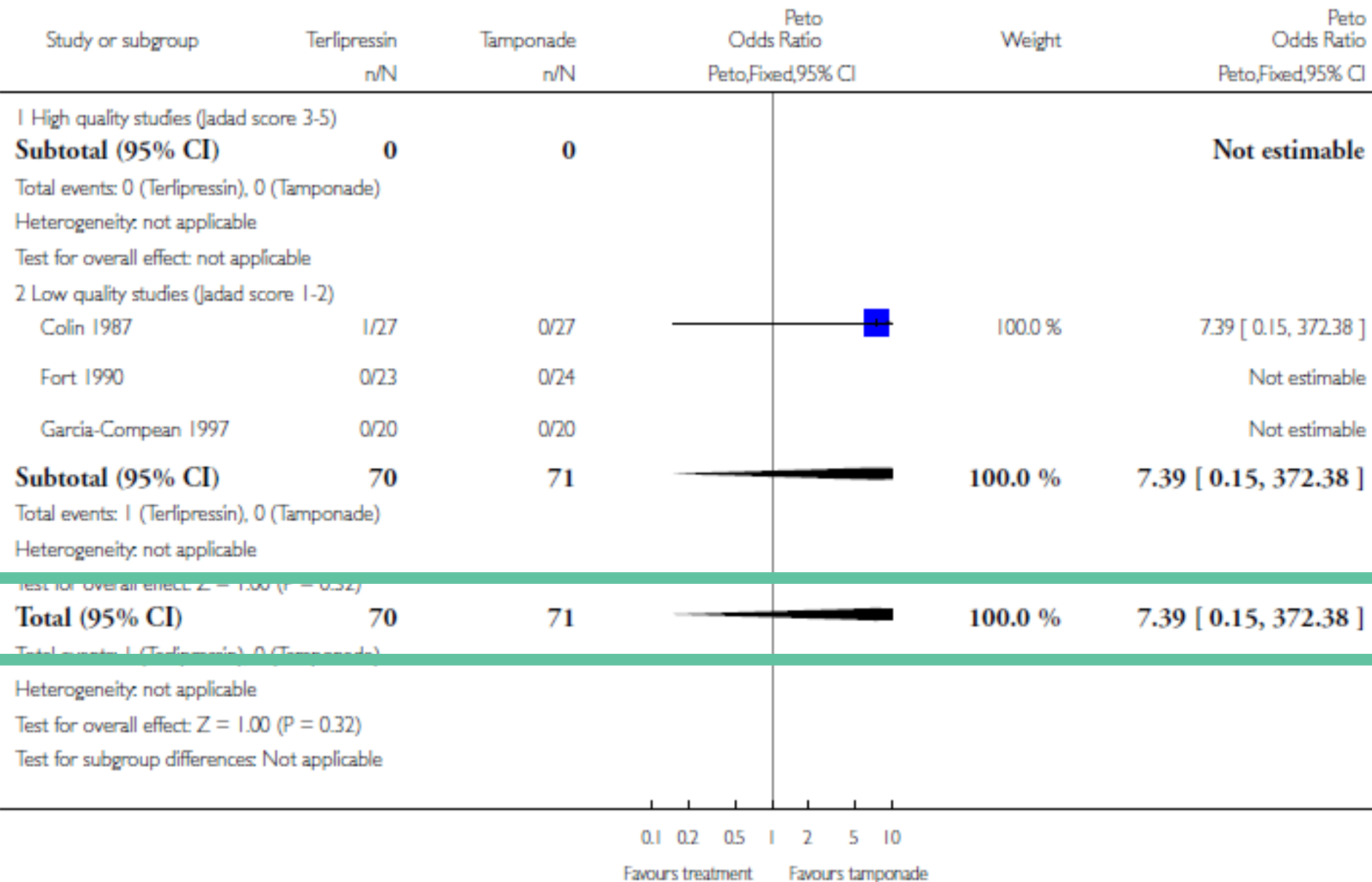
2) Terlipressin vs *Balloon Tamponade*

Analysis 2.5. Comparison 2 Terlipressin versus balloon tamponade, Outcome 5 Adverse events causing death.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 2 Terlipressin versus balloon tamponade

Outcome: 5 Adverse events causing death

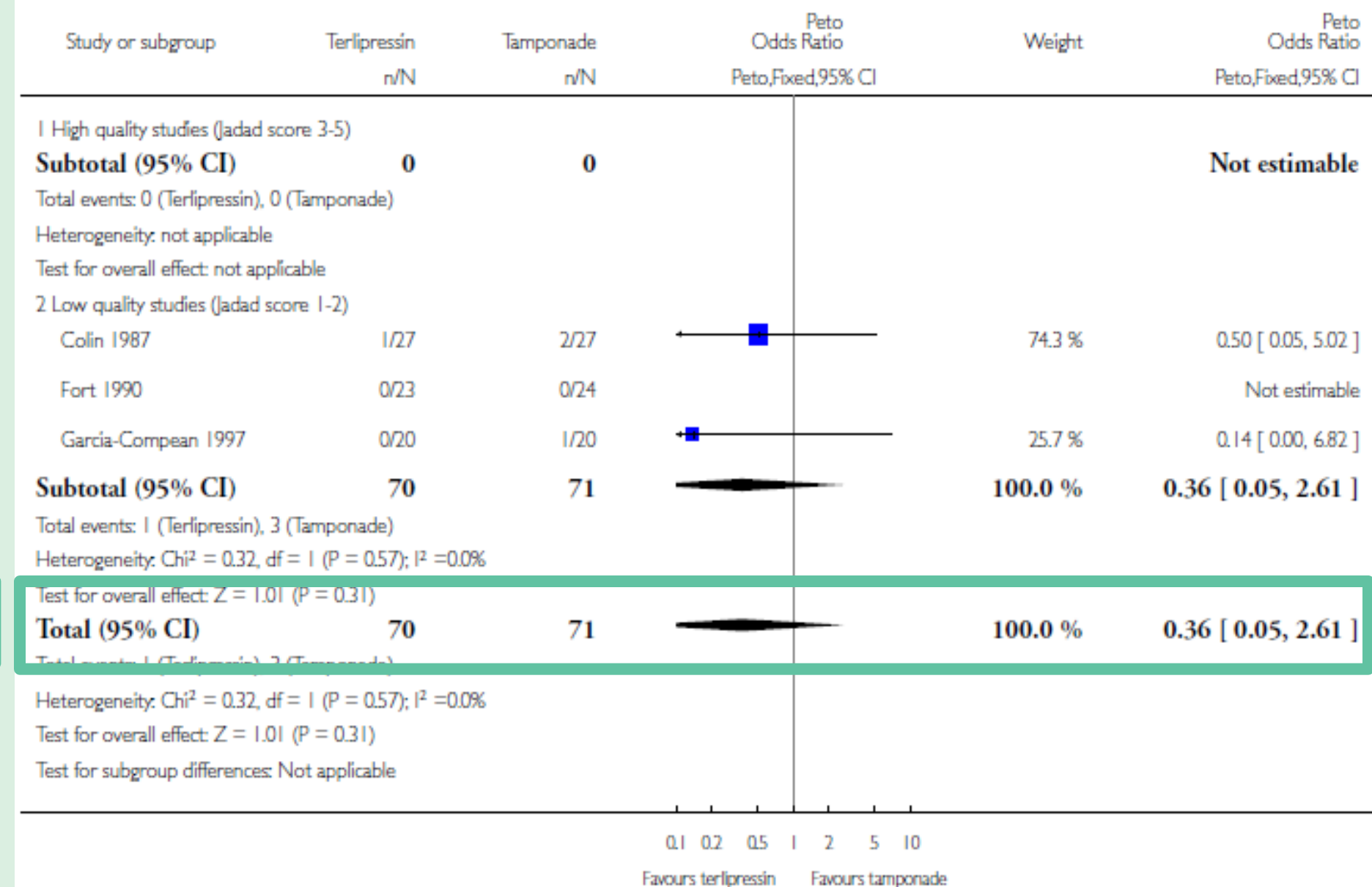


Analysis 2.6. Comparison 2 Terlipressin versus balloon tamponade, Outcome 6 Adverse events causing withdrawal of treatment.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 2 Terlipressin versus balloon tamponade

Outcome: 6 Adverse events causing withdrawal of treatment



EVIDENCE (1)

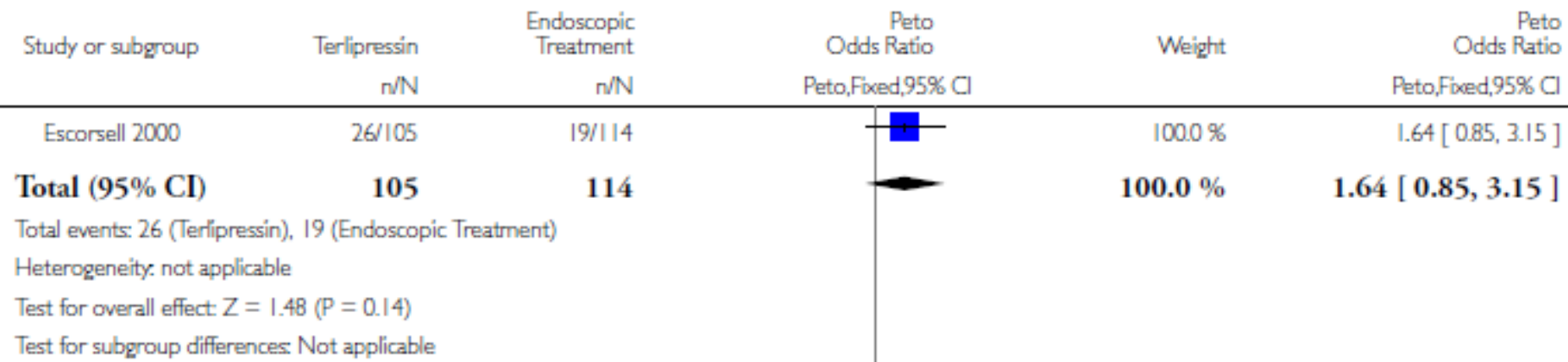
3) Terlipressin vs Endoscopic Treatment

Analysis 3.1. Comparison 3 Terlipressin versus endoscopic treatment, Outcome 1 Mortality.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 3 Terlipressin versus endoscopic treatment

Outcome: 1 Mortality

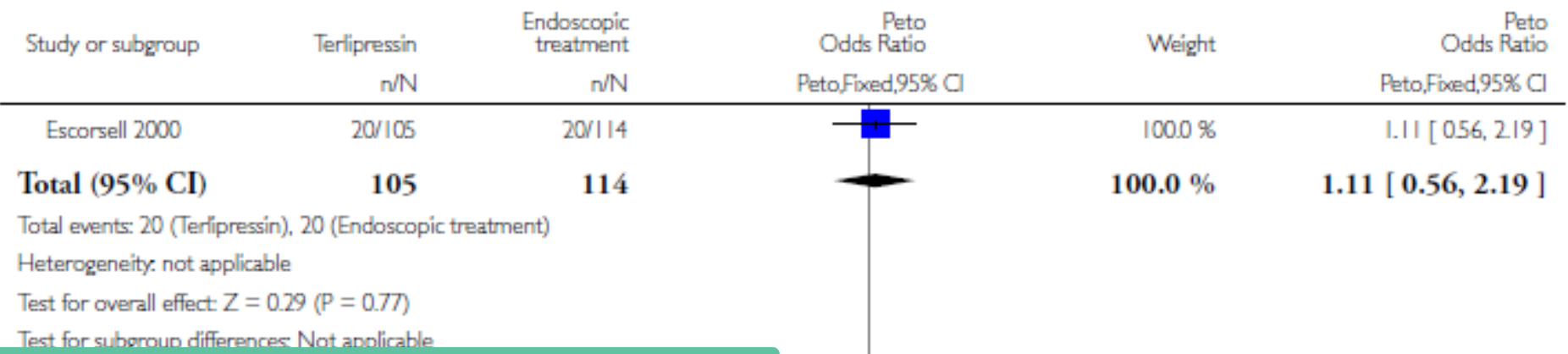


Analysis 3.2. Comparison 3 Terlipressin versus endoscopic treatment, Outcome 2 Number failing initial hemostasis.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 3 Terlipressin versus endoscopic treatment

Outcome: 2 Number failing initial hemostasis

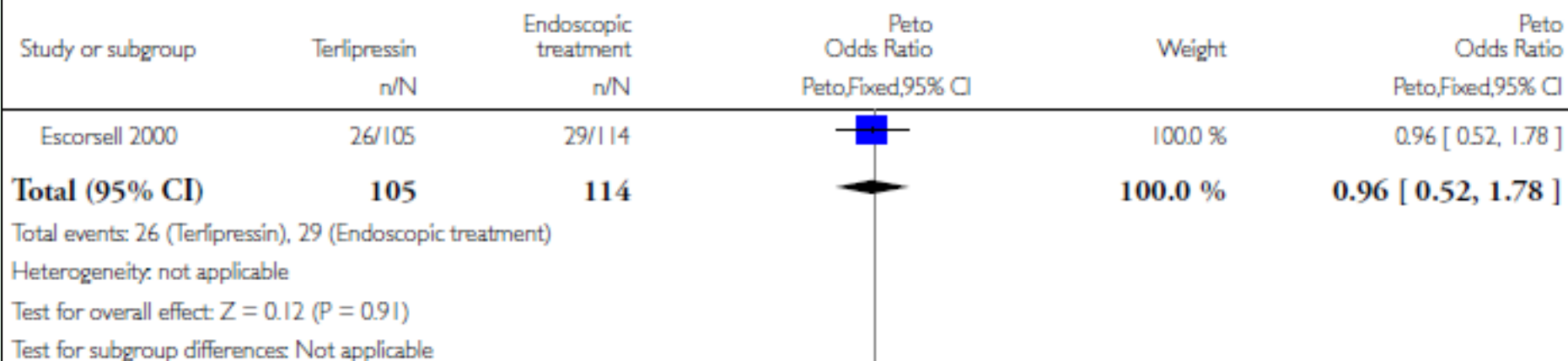


Analysis 3.3. Comparison 3 Terlipressin versus endoscopic treatment, Outcome 3 Number with rebleeding.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 3 Terlipressin versus endoscopic treatment

Outcome: 3 Number with rebleeding



0.1 0.2
Favours terlipressin

0.5 1 2 5 10
Favours endoscopy

0.1 0.2 0.5 1 2 5 10
Favours terlipressin Favours endoscopy

EVIDENCE (1)

3) Terlipressin vs Endoscopic Treatment

Analysis 3.4. Comparison 3 Terlipressin versus endoscopic treatment, Outcome 4 Number of procedures (tamponade, sclerotherapy, surgery or TIPS) required for uncontrolled bleeding/rebleeding.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 3 Terlipressin versus endoscopic treatment

Outcome: 4 Number of procedures (tamponade, sclerotherapy, surgery or TIPS) required for uncontrolled bleeding/rebleeding

Study or subgroup	Terlipressin n/N	Endoscopic treatment n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Escorsell 2000	17/105	21/114		100.0 %	0.86 [0.43, 1.72]
Total (95% CI)	105	114		100.0 %	0.86 [0.43, 1.72]

Total events: 17 (Terlipressin), 21 (Endoscopic treatment)

Heterogeneity: not applicable

Test for overall effect: Z = 0.43 (P = 0.66)

Test for subgroup differences: Not applicable

0.1 0.2
Favours terlipressin

Analysis 3.6. Comparison 3 Terlipressin versus endoscopic treatment, Outcome 6 Length of hospitalization.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 3 Terlipressin versus endoscopic treatment

Outcome: 6 Length of hospitalization

Study or subgroup	Terlipressin N	Mean(SD)	Endoscopic treatment N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Escorsell 2000	105	17 (10)	114	18 (10)		100.0 %	-1.00 [-3.65, 1.65]
Total (95% CI)	105		114			100.0 %	-1.00 [-3.65, 1.65]

Heterogeneity: not applicable

Test for overall effect: Z = 0.74 (P = 0.46)

Test for subgroup differences: Not applicable

-10 -5 0 5 10
Favours terlipressin Favours endoscopy

Analysis 3.5. Comparison 3 Terlipressin versus endoscopic treatment, Outcome 5 Number of blood transfusions.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 3 Terlipressin versus endoscopic treatment

Outcome: 5 Number of blood transfusions

Study or subgroup	Terlipressin N	Mean(SD)	Endoscopic treatment N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Escorsell 2000	105	4.7 (4.8)	114	4.5 (4.3)		100.0 %	0.20 [-1.01, 1.41]
Total (95% CI)	105		114			100.0 %	0.20 [-1.01, 1.41]

Heterogeneity: not applicable

Test for overall effect: Z = 0.32 (P = 0.75)

-10 -5 0 5 10
Favours terlipressin Favours endoscopy

EVIDENCE (1)

3) Terlipressin vs *Endoscopic Treatment*

Analysis 3.7. Comparison 3 Terlipressin versus endoscopic treatment, Outcome 7 Adverse events causing death.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 3 Terlipressin versus endoscopic treatment

Outcome: 7 Adverse events causing death

Study or subgroup	Terlipressin n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 High quality studies (Jadad score 3-5)					
Escorsell 2000	0/105	0/114			Not estimable
Subtotal (95% CI)	105	114			Not estimable
Total events: 0 (Terlipressin), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Low quality studies (Jadad score 1-2)					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Terlipressin), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	105	114			Not estimable
Total events: 0 (Terlipressin), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: $\text{Chi}^2 = 0.0$, $df = 1$ ($P = 0.0$), $I^2 = 0.0\%$					

0.1 0.2 0.5 1 2 5 10
Favours treatment Favours control

EVIDENCE (1)

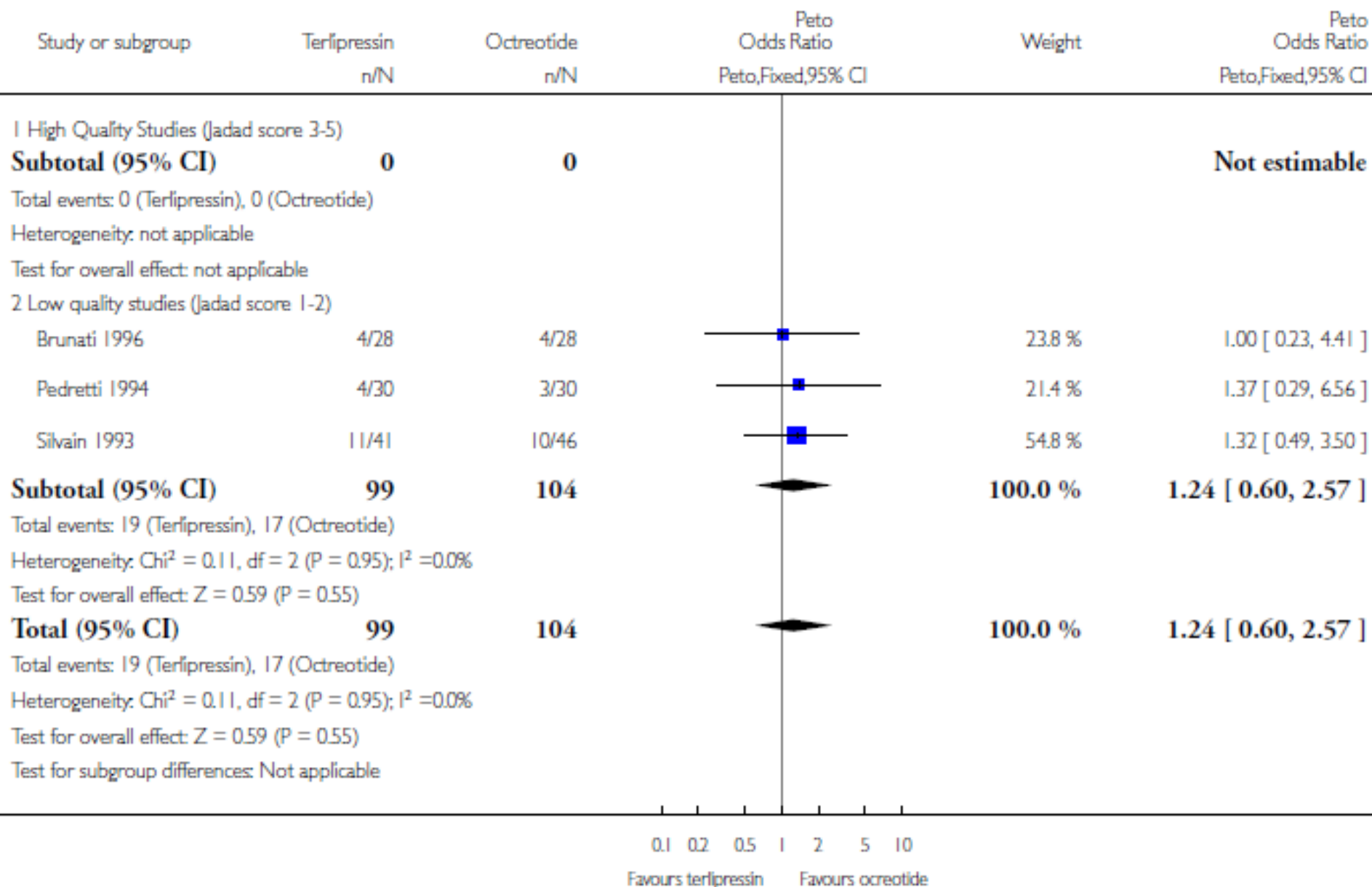
4) Terlipressin vs Octreotide

Analysis 4.1. Comparison 4 Terlipressin versus octreotide, Outcome 1 Mortality.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 4 Terlipressin versus octreotide

Outcome: 1 Mortality

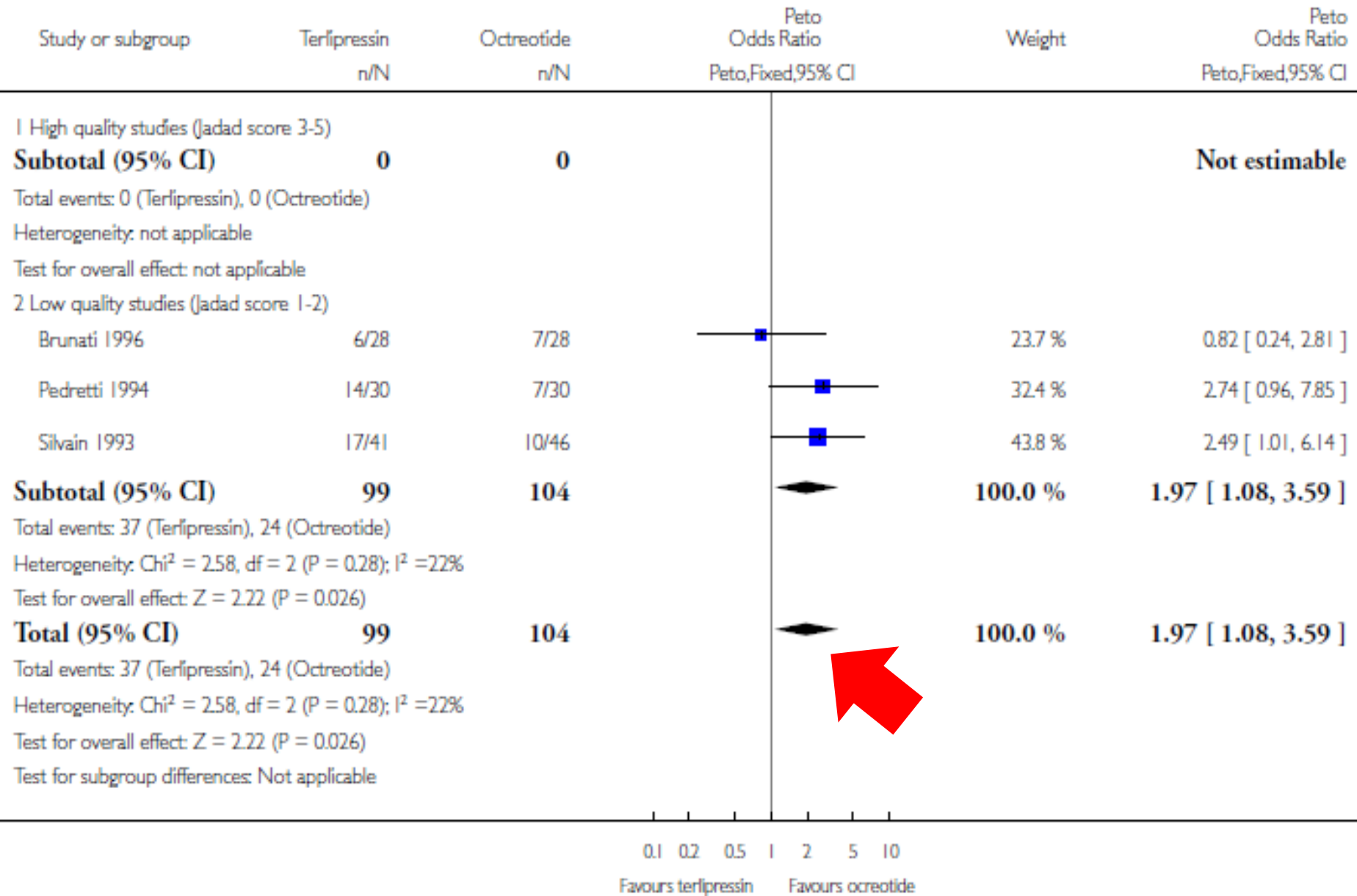


Analysis 4.2. Comparison 4 Terlipressin versus octreotide, Outcome 2 Number failing initial hemostasis.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 4 Terlipressin versus octreotide

Outcome: 2 Number failing initial hemostasis



EVIDENCE (1)

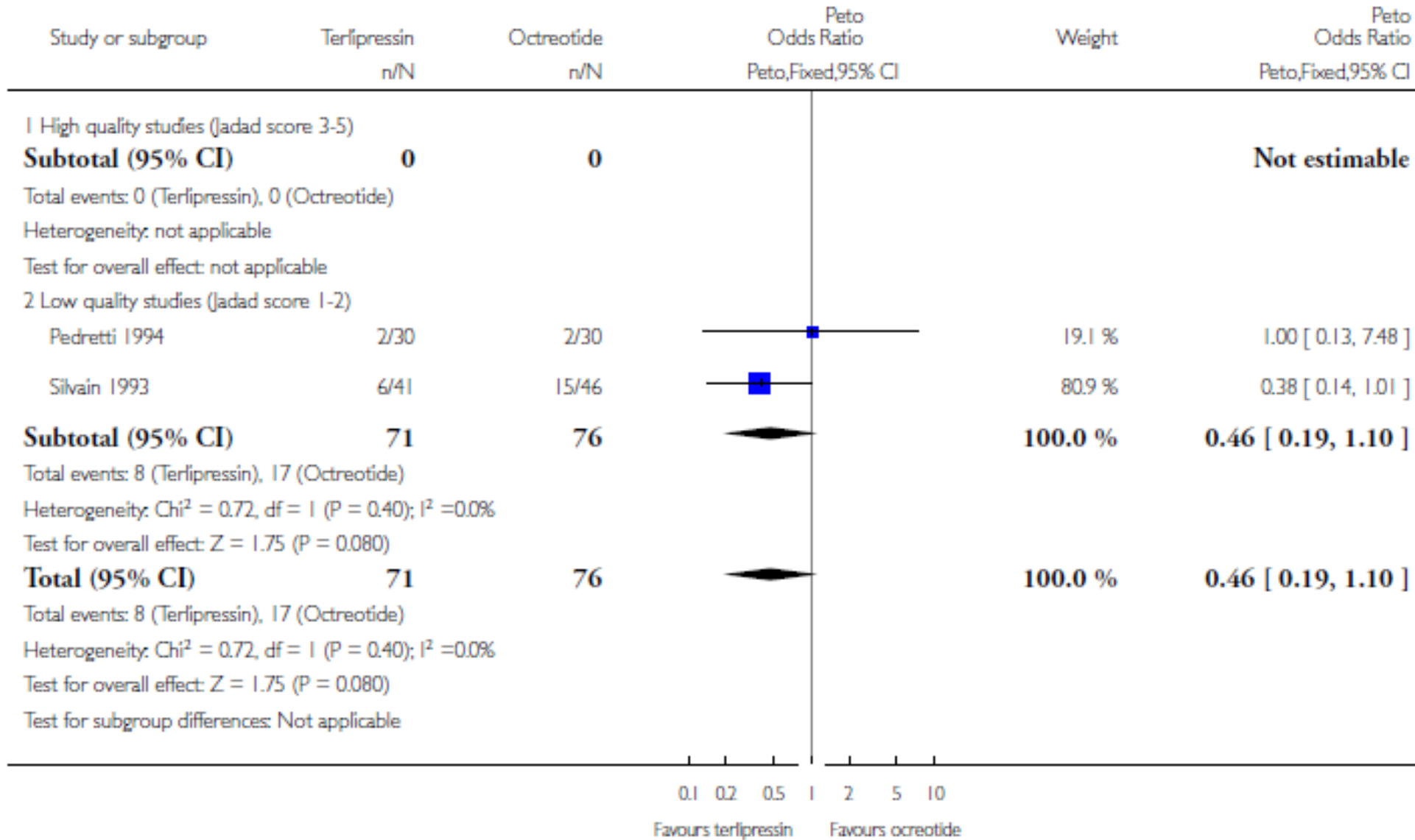
4) Terlipressin vs Octreotide

Analysis 4.3. Comparison 4 Terlipressin versus octreotide, Outcome 3 Number with rebleeding.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 4 Terlipressin versus octreotide

Outcome: 3 Number with rebleeding

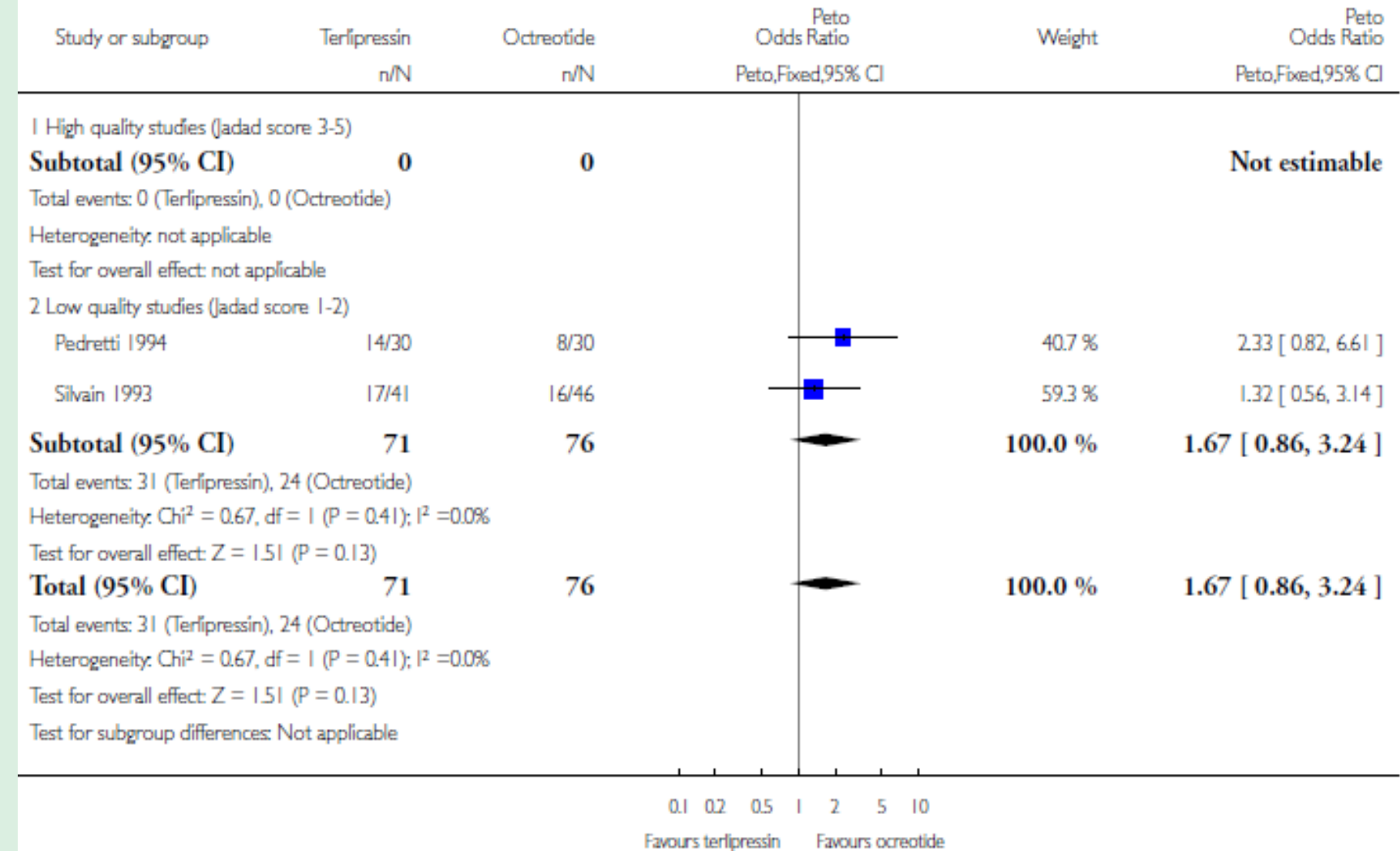


Analysis 4.4. Comparison 4 Terlipressin versus octreotide, Outcome 4 Number of procedures (tamponade, sclerotherapy, surgery or TIPS) required for uncontrolled bleeding/rebleeding.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 4 Terlipressin versus octreotide

Outcome: 4 Number of procedures (tamponade, sclerotherapy, surgery or TIPS) required for uncontrolled bleeding/rebleeding



EVIDENCE (1)

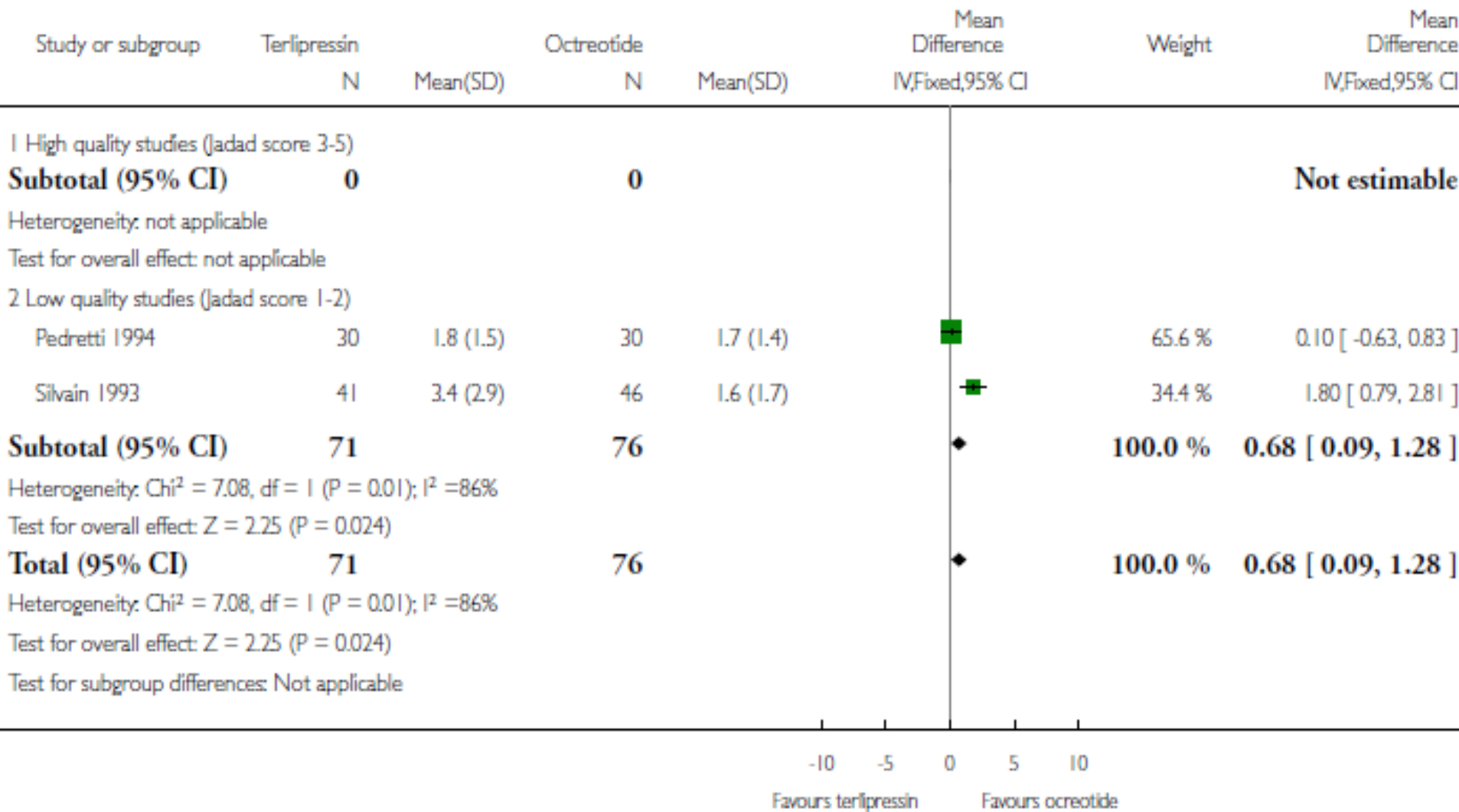
4) Terlipressin vs Octreotide

Analysis 4.5. Comparison 4 Terlipressin versus octreotide, Outcome 5 Number of blood transfusions.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 4 Terlipressin versus octreotide

Outcome: 5 Number of blood transfusions

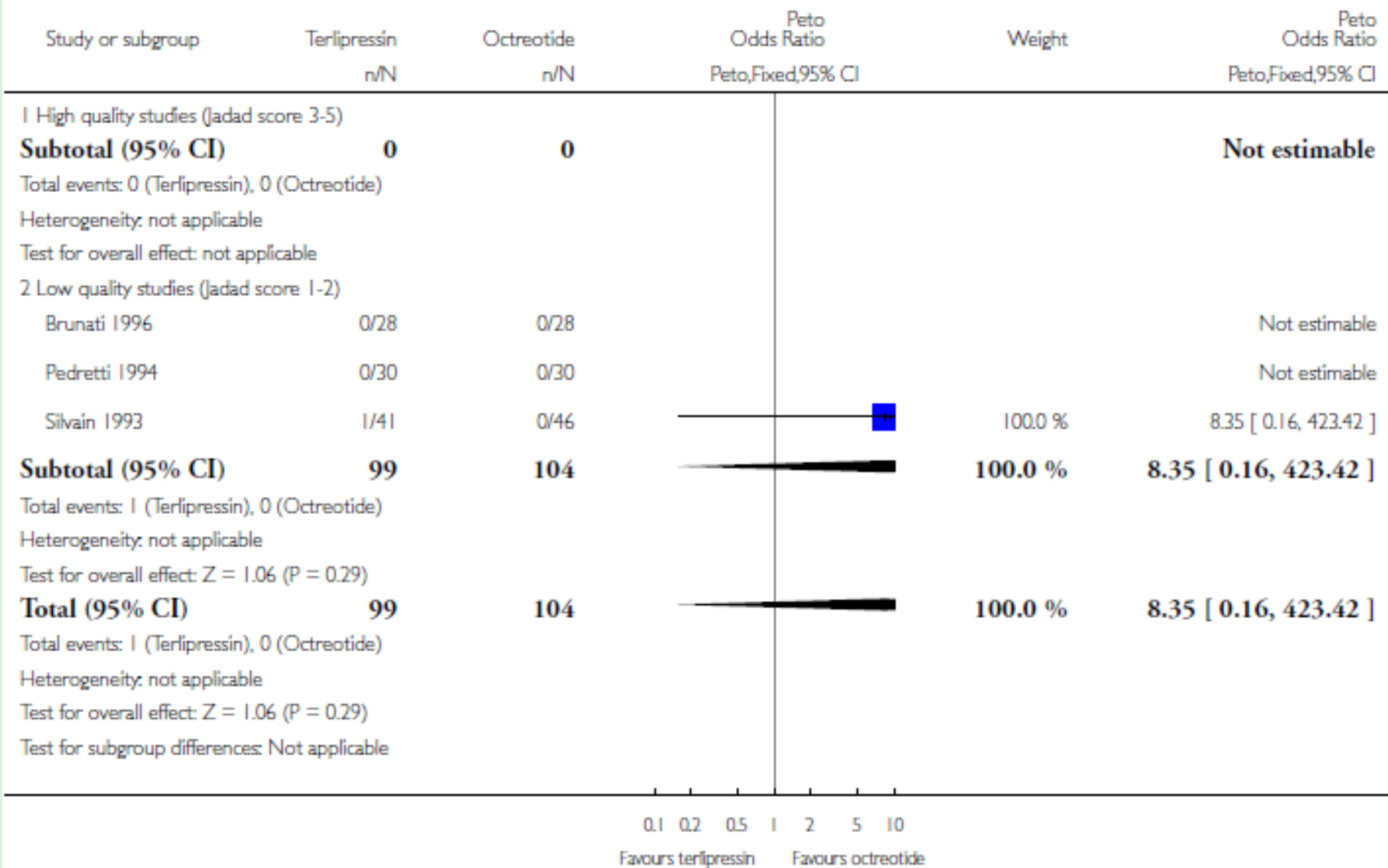


Analysis 4.6. Comparison 4 Terlipressin versus octreotide, Outcome 6 Adverse events causing death.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 4 Terlipressin versus octreotide

Outcome: 6 Adverse events causing death



EVIDENCE (1)

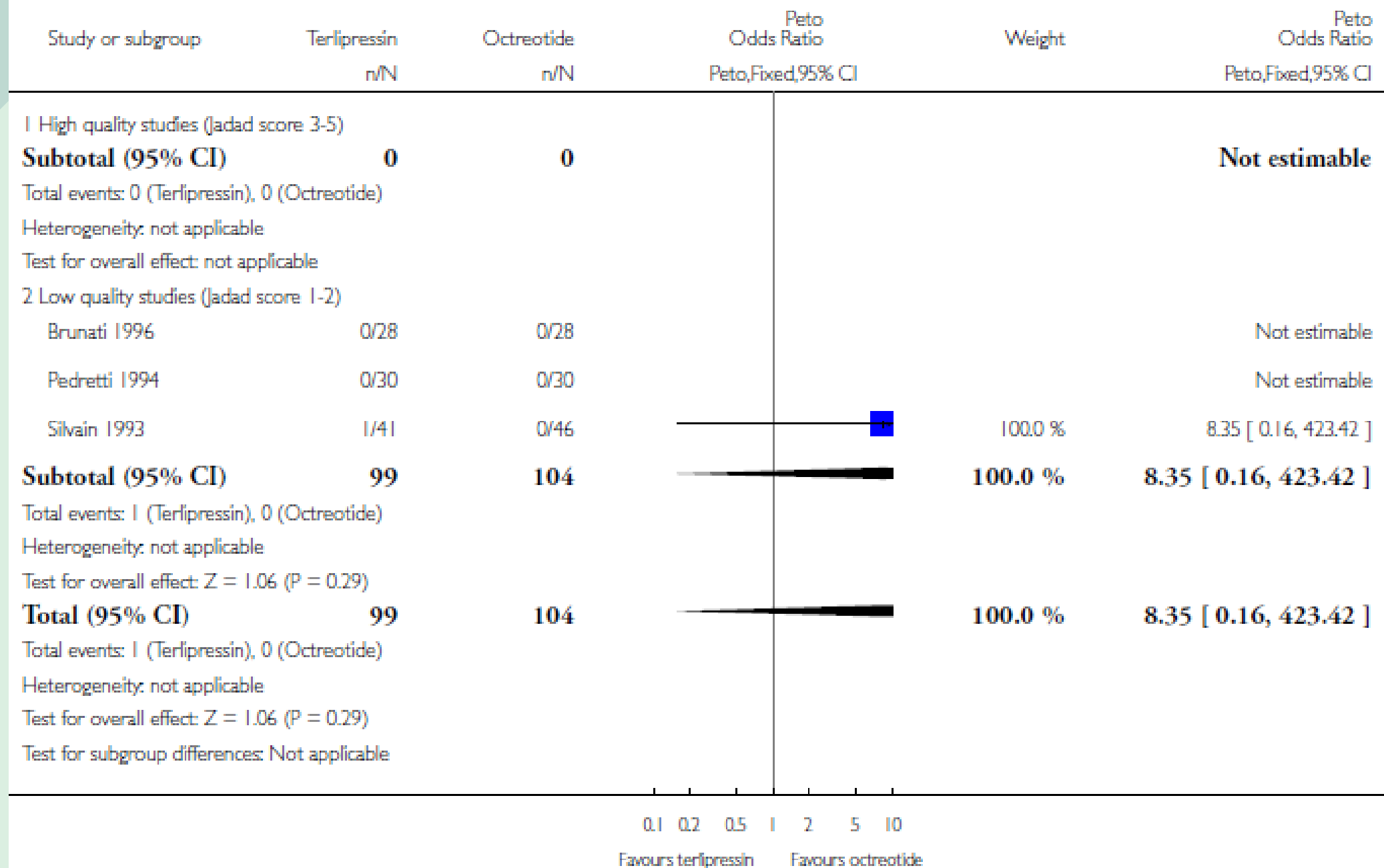
4) Terlipressin vs Octreotide

Analysis 4.7. Comparison 4 Terlipressin versus octreotide, Outcome 7 Adverse events causing withdrawal of treatment.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 4 Terlipressin versus octreotide

Outcome: 7 Adverse events causing withdrawal of treatment



EVIDENCE (1)

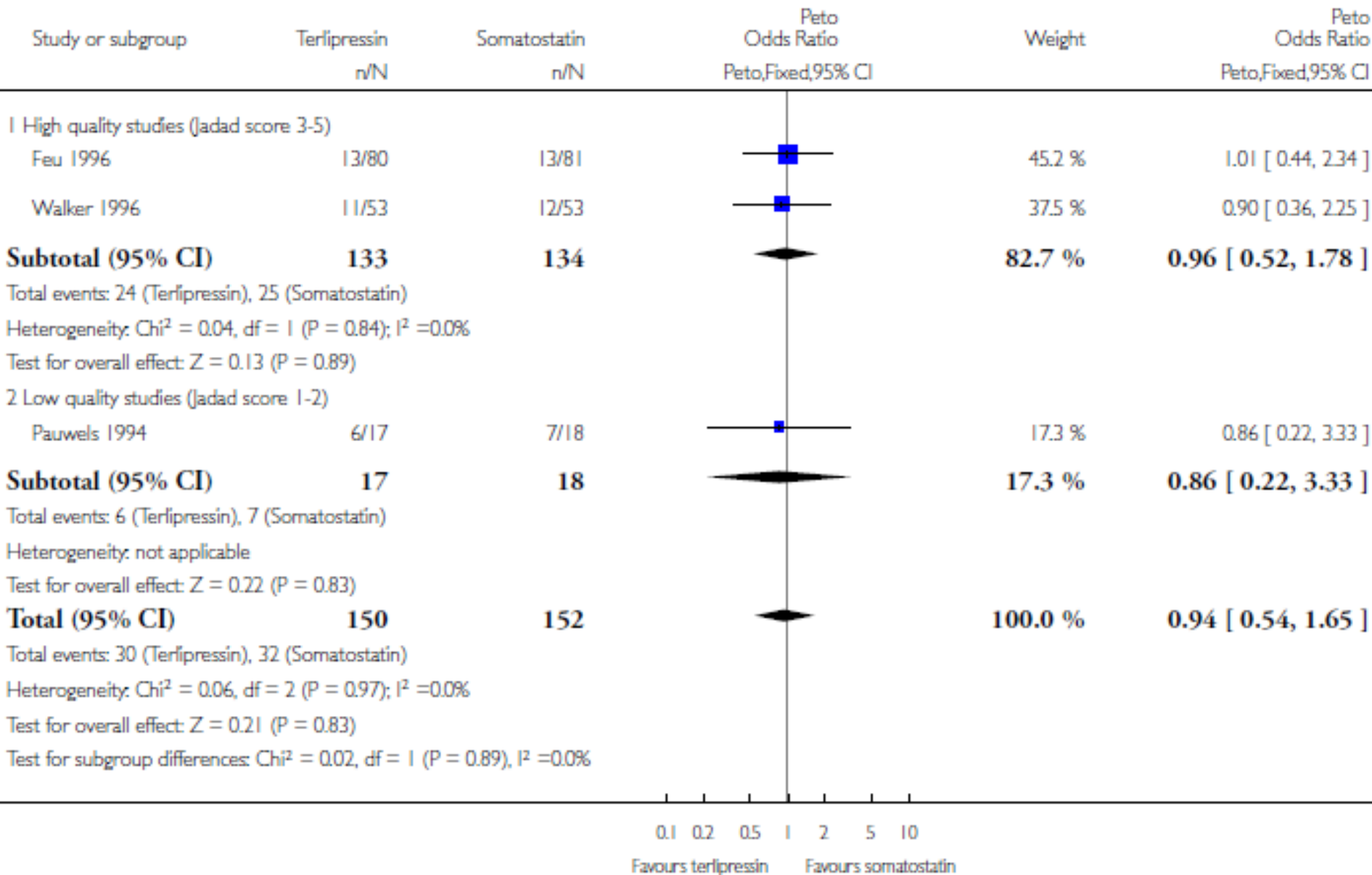
5) Terlipressin vs Somatostatin

Analysis 5.1. Comparison 5 Terlipressin versus somatostatin, Outcome 1 Mortality.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 5 Terlipressin versus somatostatin

Outcome: 1 Mortality

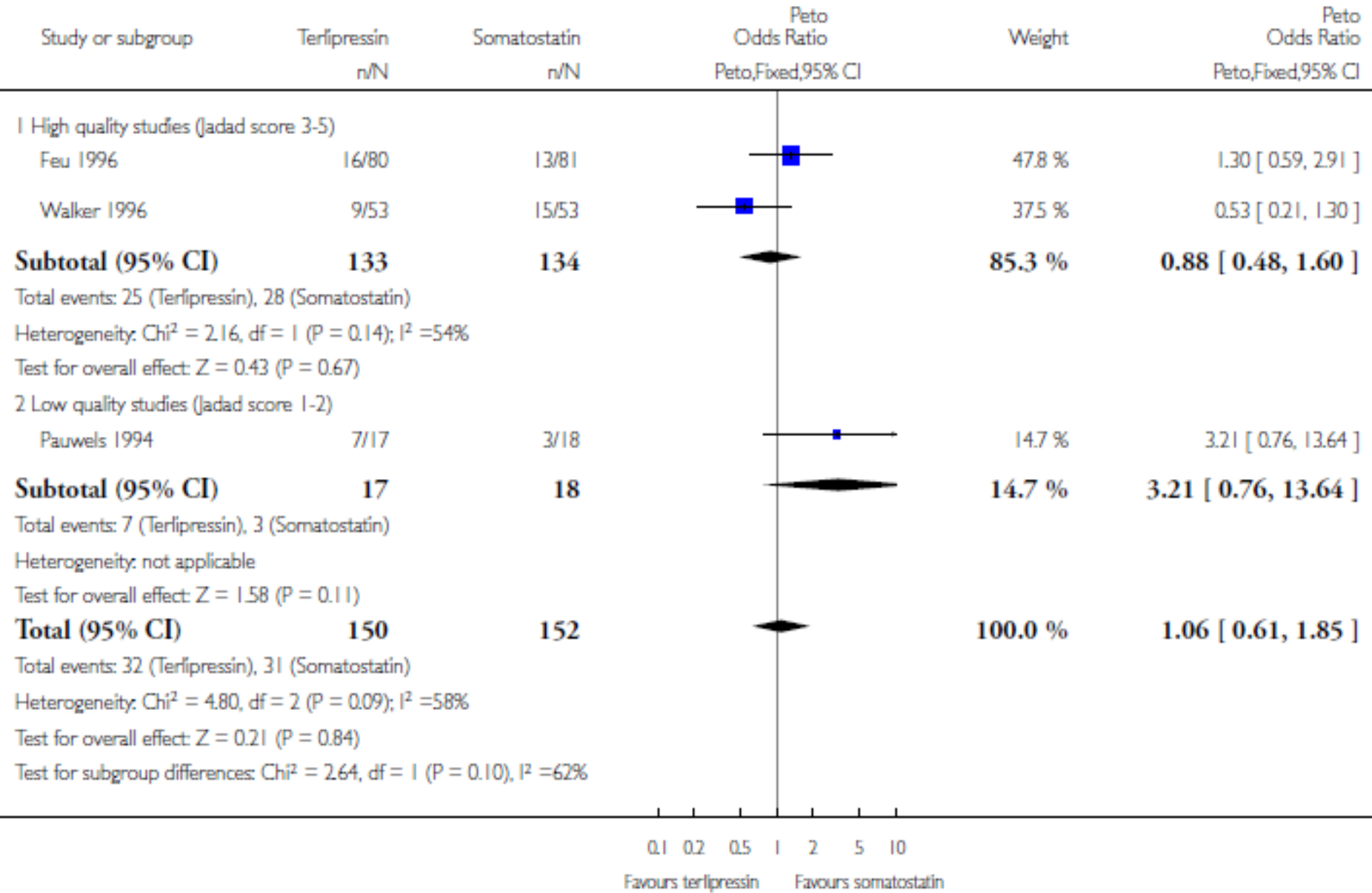


Analysis 5.2. Comparison 5 Terlipressin versus somatostatin, Outcome 2 Number failing initial hemostasis.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 5 Terlipressin versus somatostatin

Outcome: 2 Number failing initial hemostasis



EVIDENCE (1)

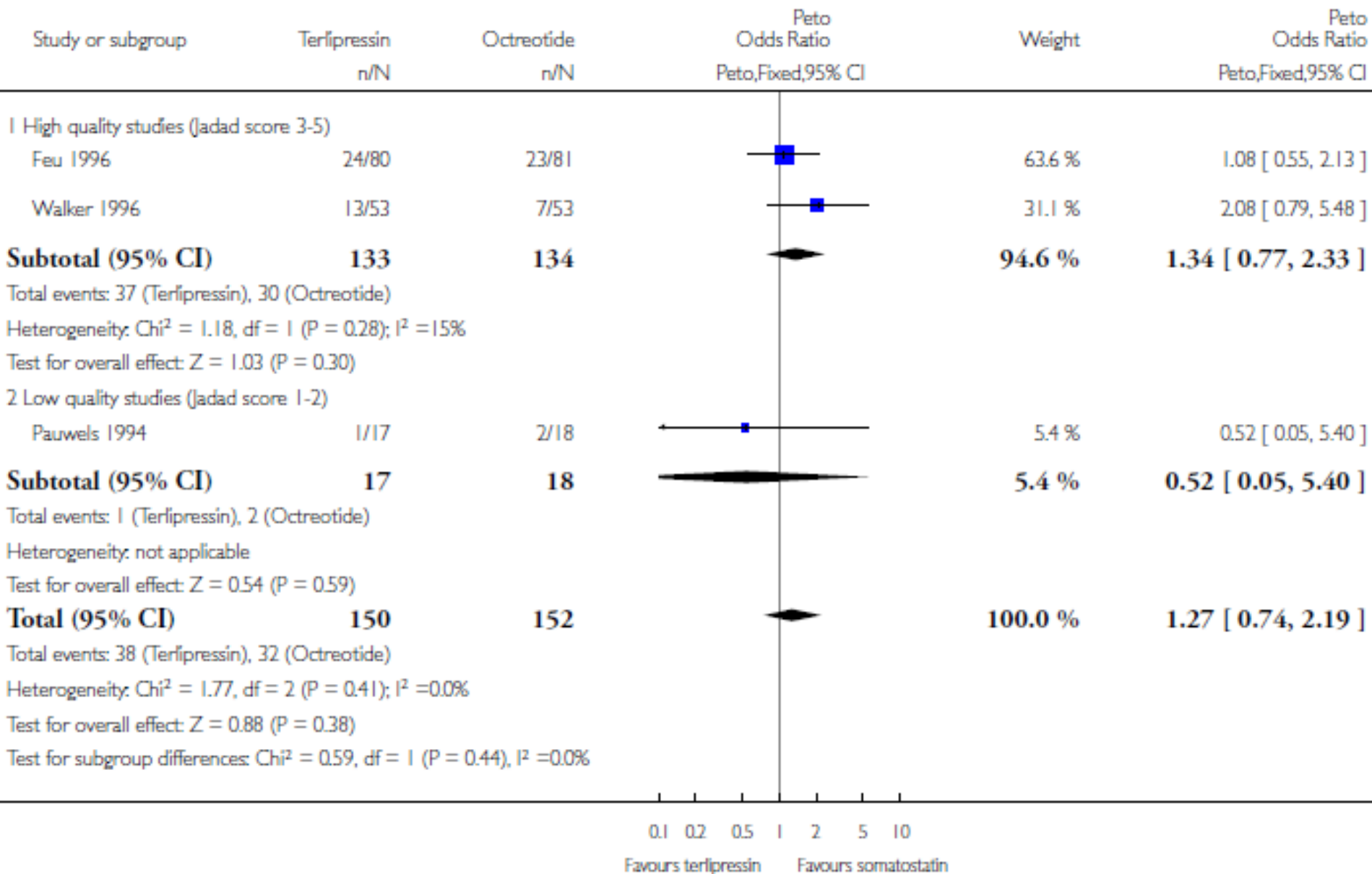
5) Terlipressin vs Somatostatin

Analysis 5.3. Comparison 5 Terlipressin versus somatostatin, Outcome 3 Number with rebleeding.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 5 Terlipressin versus somatostatin

Outcome: 3 Number with rebleeding

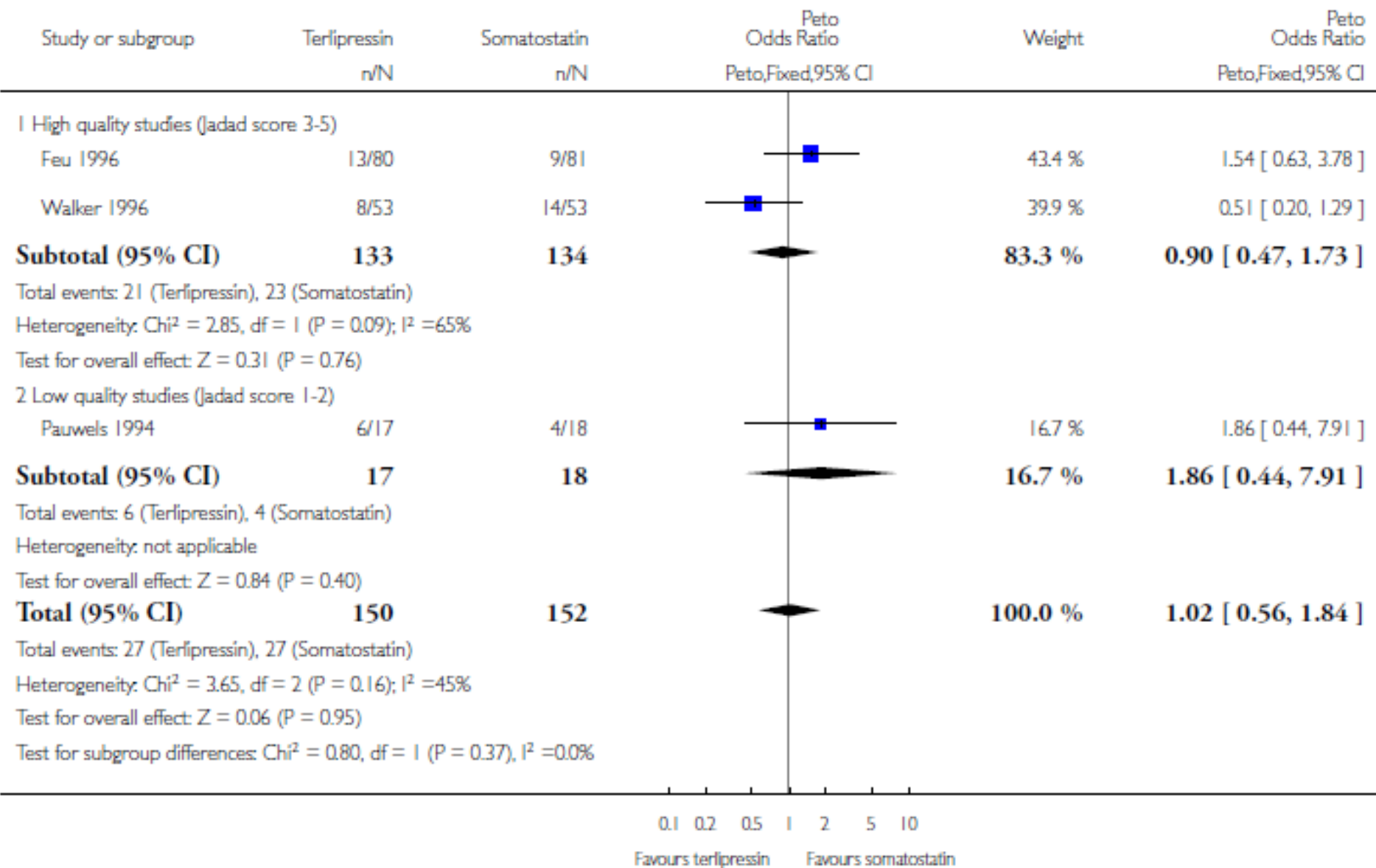


Analysis 5.4. Comparison 5 Terlipressin versus somatostatin, Outcome 4 Number of procedures (tamponade, sclerotherapy, surgery or TIPS) required for uncontrolled bleeding/rebleeding.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 5 Terlipressin versus somatostatin

Outcome: 4 Number of procedures (tamponade, sclerotherapy, surgery or TIPS) required for uncontrolled bleeding/rebleeding



EVIDENCE (1)

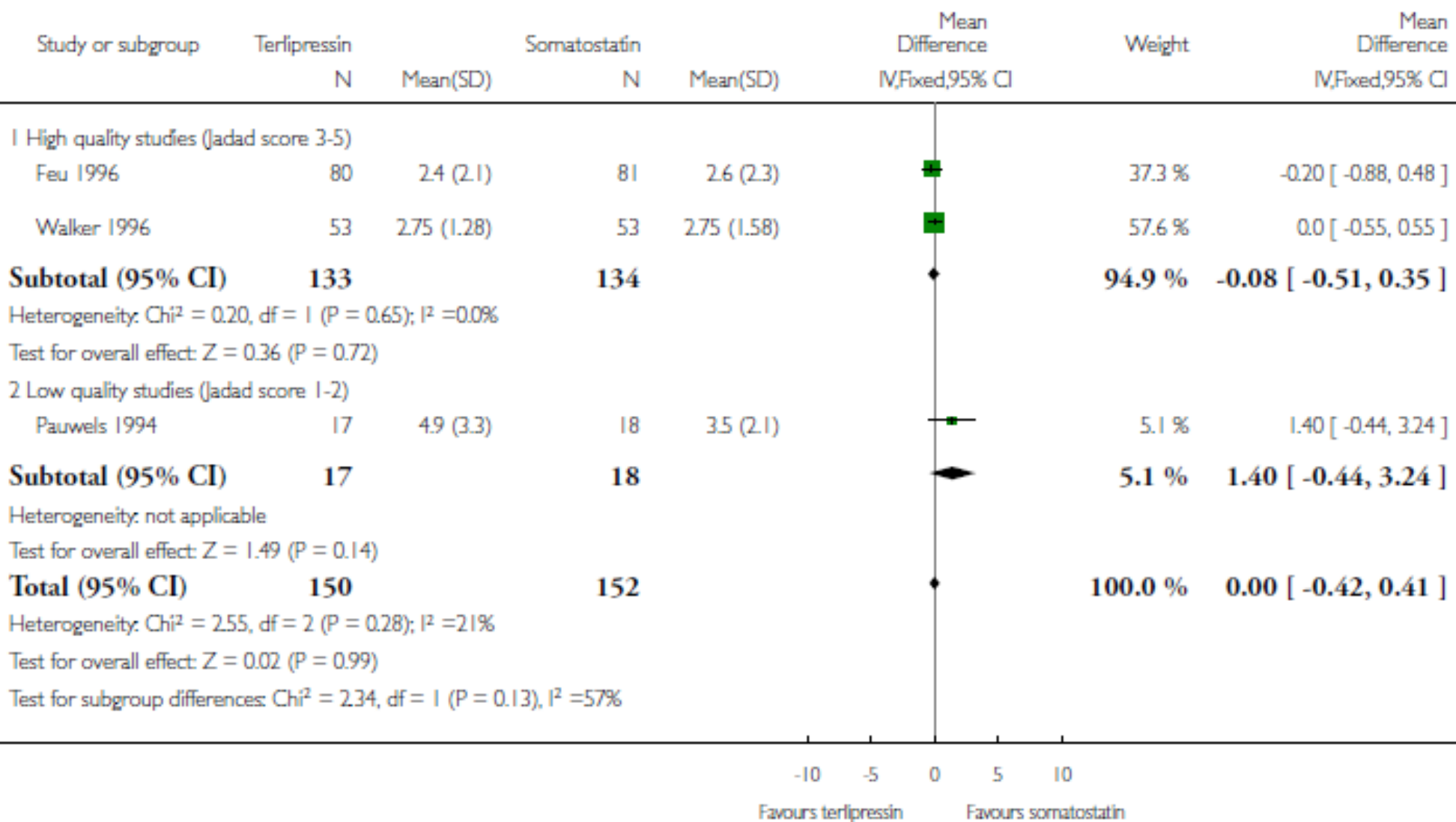
5) Terlipressin vs Somatostatin

Analysis 5.5. Comparison 5 Terlipressin versus somatostatin, Outcome 5 Number of blood transfusions.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 5 Terlipressin versus somatostatin

Outcome: 5 Number of blood transfusions

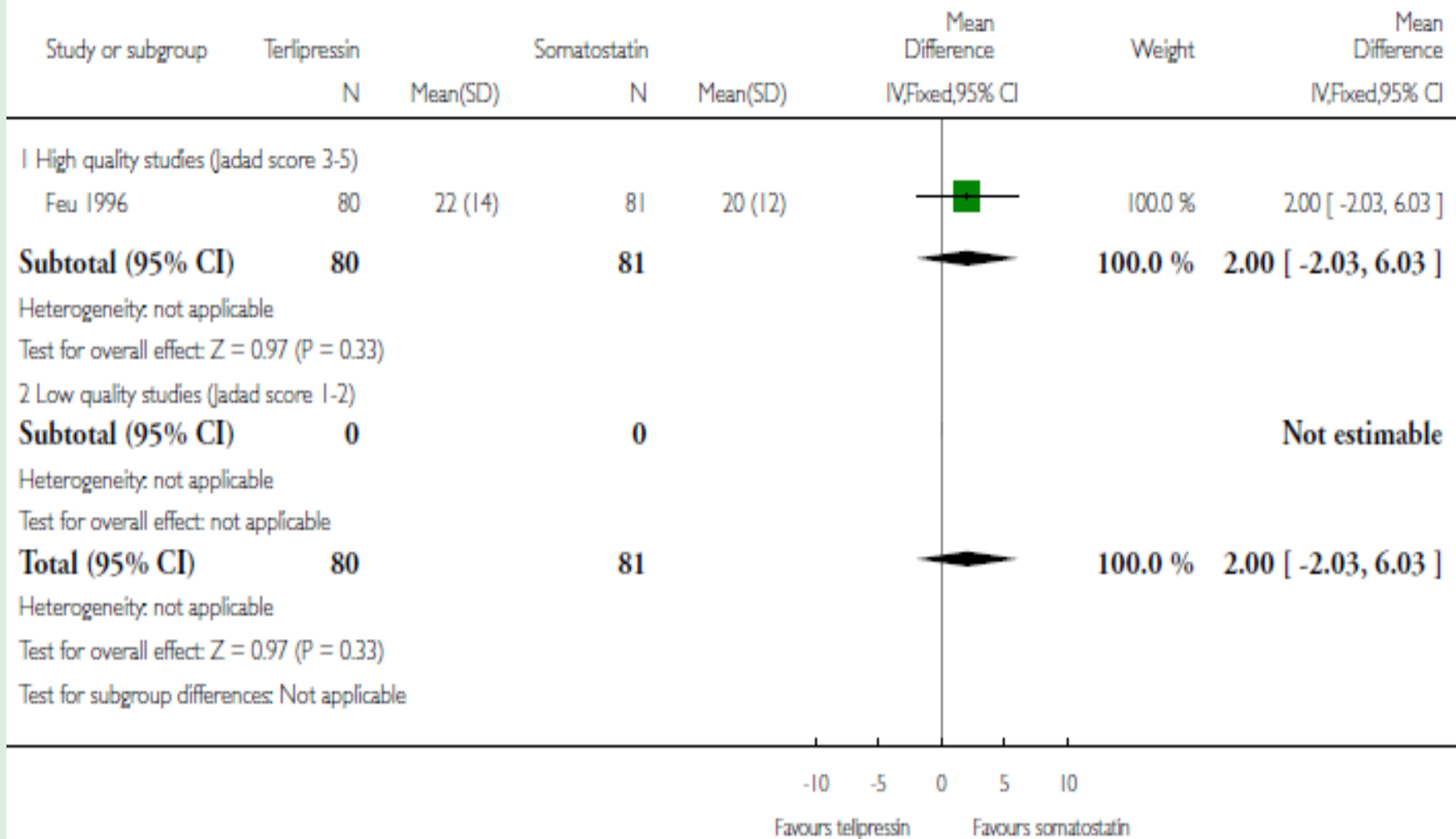


Analysis 5.6. Comparison 5 Terlipressin versus somatostatin, Outcome 6 Length of hospitalization.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 5 Terlipressin versus somatostatin

Outcome: 6 Length of hospitalization



EVIDENCE (1)

5) Terlipressin vs Somatostatin

Analysis 5.7. Comparison 5 Terlipressin versus somatostatin, Outcome 7 Adverse events causing death.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 5 Terlipressin versus somatostatin

Outcome: 7 Adverse events causing death

Study or subgroup	Terlipressin n/N	Somatostatin n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 High quality studies (Jadad score 3-5)					
Feu 1996	0/80	0/81			Not estimable
Walker 1996	0/53	0/53			Not estimable
Subtotal (95% CI)	133	134			Not estimable
Total events: 0 (Terlipressin), 0 (Somatostatin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Low quality studies (Jadad score 1-2)					
Pauwels 1994	0/17	0/18			Not estimable
Subtotal (95% CI)	17	18			Not estimable
Total events: 0 (Terlipressin), 0 (Somatostatin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	150	152			Not estimable
Total events: 0 (Terlipressin), 0 (Somatostatin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Chi ² = 0.0, df = -1 (P = 0.0), I ² = 0.0%					

Analysis 5.8. Comparison 5 Terlipressin versus somatostatin, Outcome 8 Adverse events causing withdrawal of treatment.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 5 Terlipressin versus somatostatin

Outcome: 8 Adverse events causing withdrawal of treatment

Study or subgroup	Terlipressin n/N	Somatostatin n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 High quality studies (Jadad score 3-5)					
Feu 1996	1/80	0/81		100.0 %	7.48 [0.15, 377.10]
Walker 1996	0/53	0/53			Not estimable
Subtotal (95% CI)	133	134		100.0 %	7.48 [0.15, 377.10]
Total events: 1 (Terlipressin), 0 (Somatostatin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.01 (P = 0.31)					
2 Low quality studies (Jadad score 1-2)					
Pauwels 1994	0/17	0/18			Not estimable
Subtotal (95% CI)	17	18			Not estimable
Total events: 0 (Terlipressin), 0 (Somatostatin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	150	152		100.0 %	7.48 [0.15, 377.10]
Total events: 1 (Terlipressin), 0 (Somatostatin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.01 (P = 0.31)					
Test for subgroup differences: Not applicable					

EVIDENCE (1)

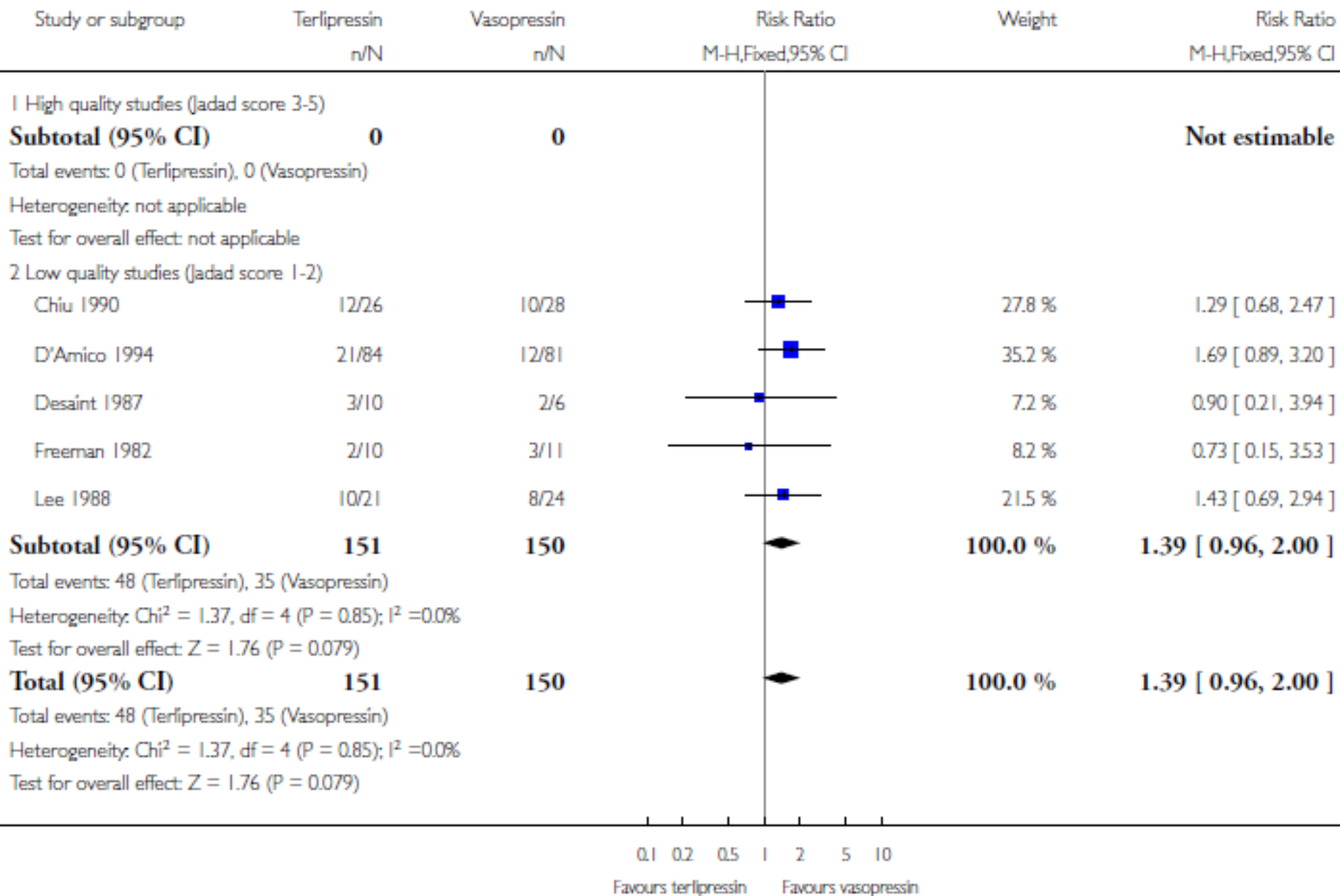
6) Terlipressin vs Vasopressin

Analysis 6.1. Comparison 6 Terlipressin versus vasopressin, Outcome 1 Mortality.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 6 Terlipressin versus vasopressin

Outcome: 1 Mortality

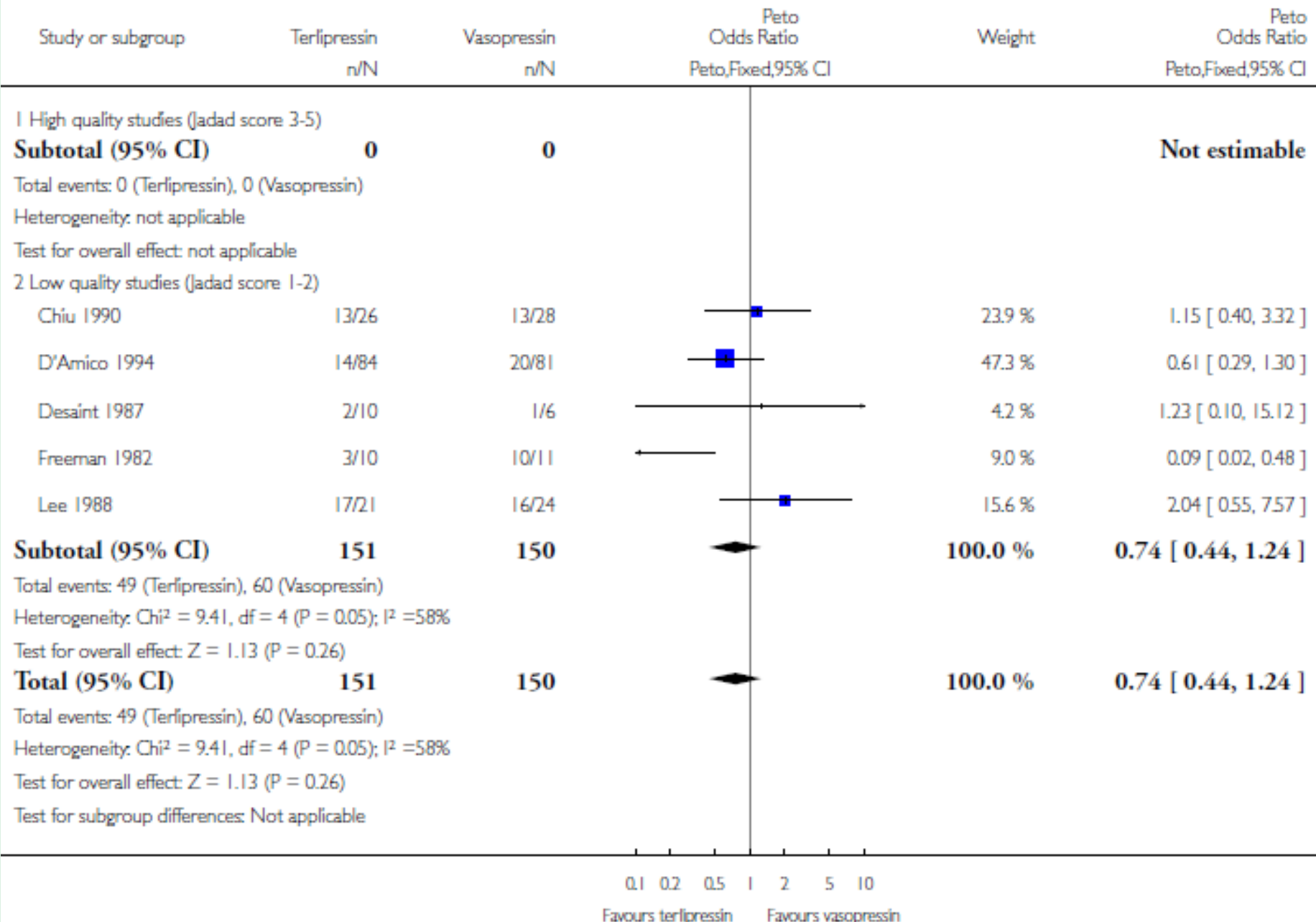


Analysis 6.2. Comparison 6 Terlipressin versus vasopressin, Outcome 2 Number failing initial hemostasis.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 6 Terlipressin versus vasopressin

Outcome: 2 Number failing initial hemostasis



EVIDENCE (1)

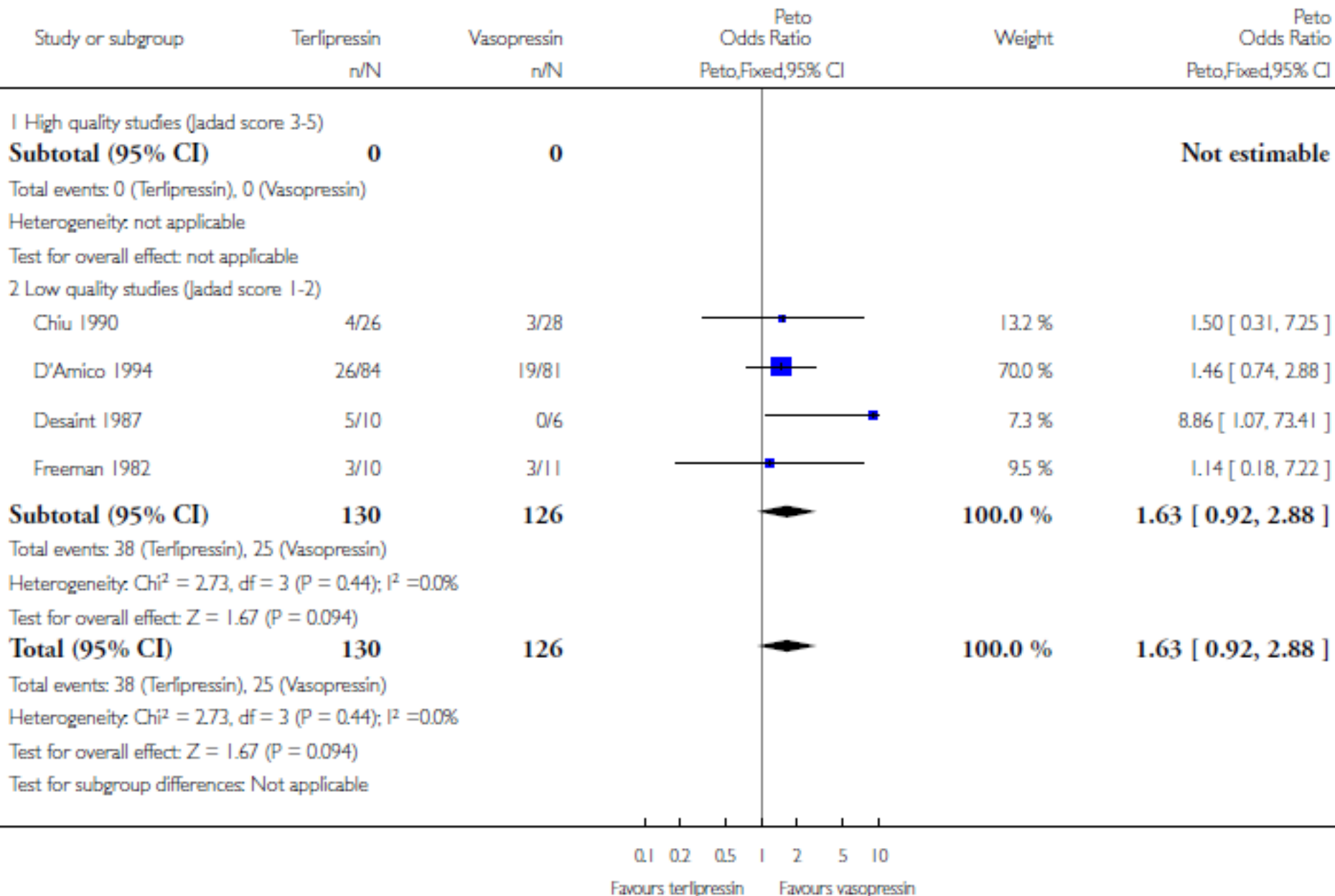
6) Terlipressin vs Vasopressin

Analysis 6.3. Comparison 6 Terlipressin versus vasopressin, Outcome 3 Number with rebleeding.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 6 Terlipressin versus vasopressin

Outcome: 3 Number with rebleeding

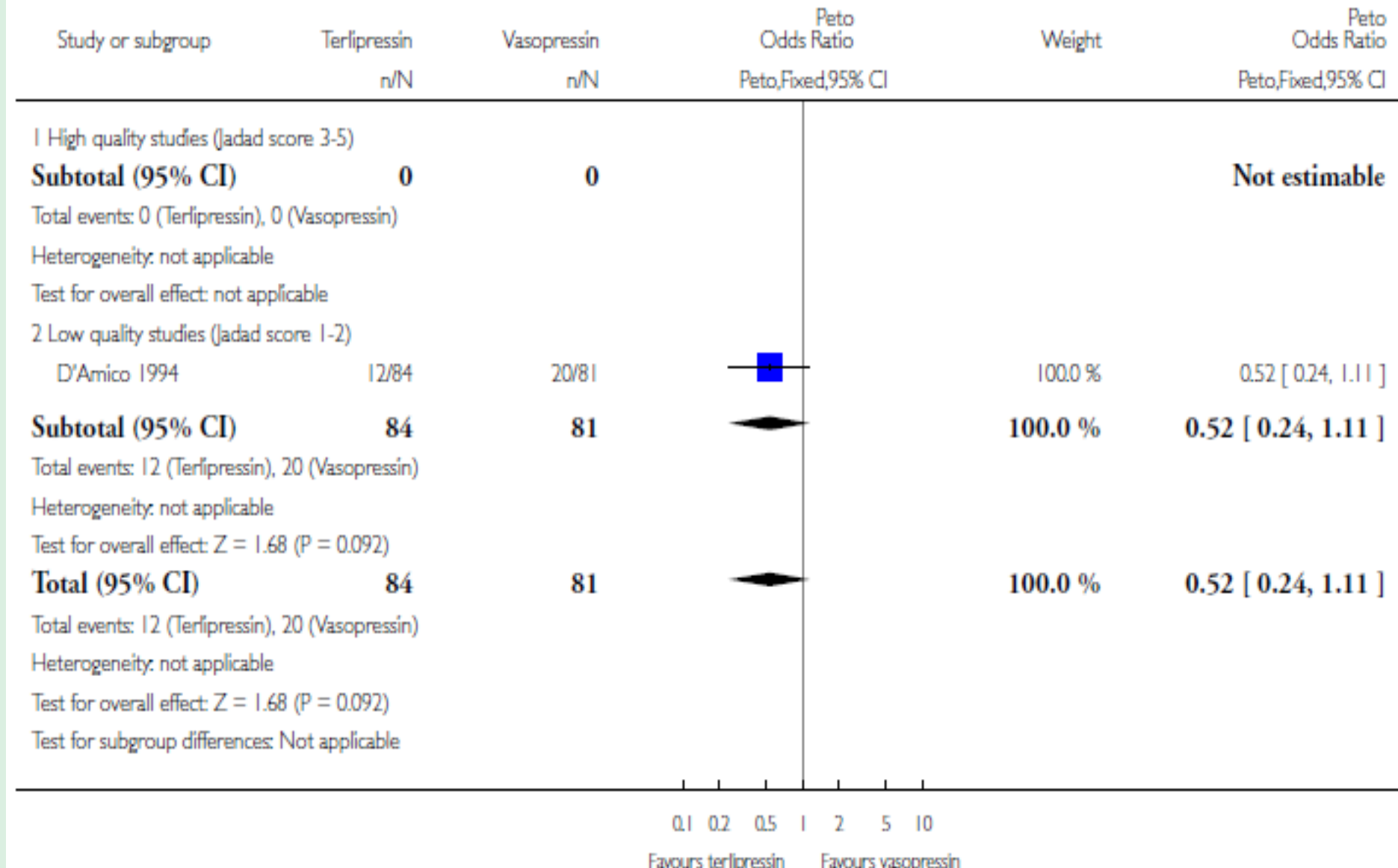


Analysis 6.4. Comparison 6 Terlipressin versus vasopressin, Outcome 4 Number of procedures (tamponade, sclerotherapy, surgery or TIPS) required for uncontrolled bleeding/rebleeding.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 6 Terlipressin versus vasopressin

Outcome: 4 Number of procedures (tamponade, sclerotherapy, surgery or TIPS) required for uncontrolled bleeding/rebleeding



EVIDENCE (1)

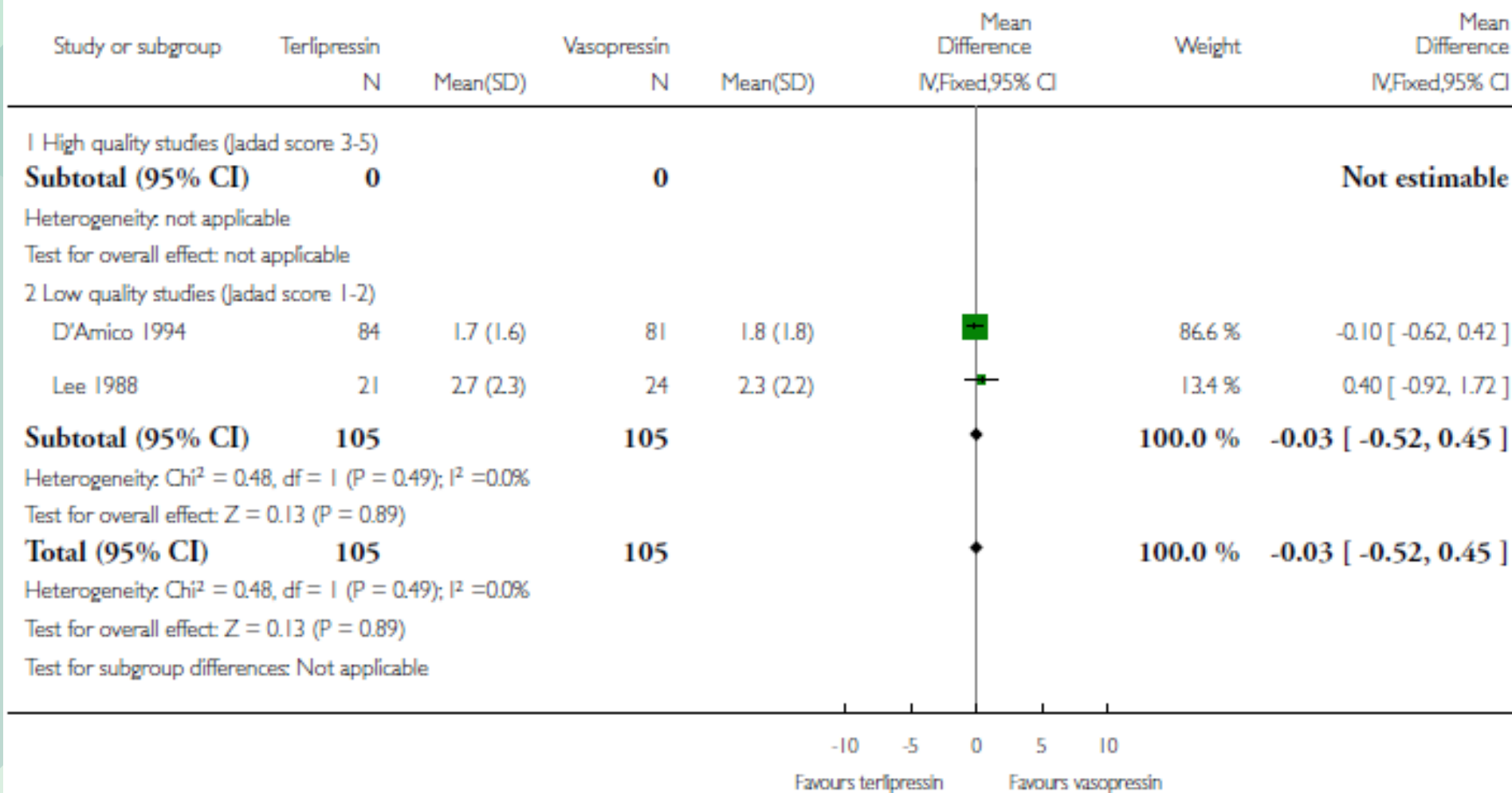
6) Terlipressin vs Vasopressin

Analysis 6.5. Comparison 6 Terlipressin versus vasopressin, Outcome 5 Number of blood transfusions.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 6 Terlipressin versus vasopressin

Outcome: 5 Number of blood transfusions

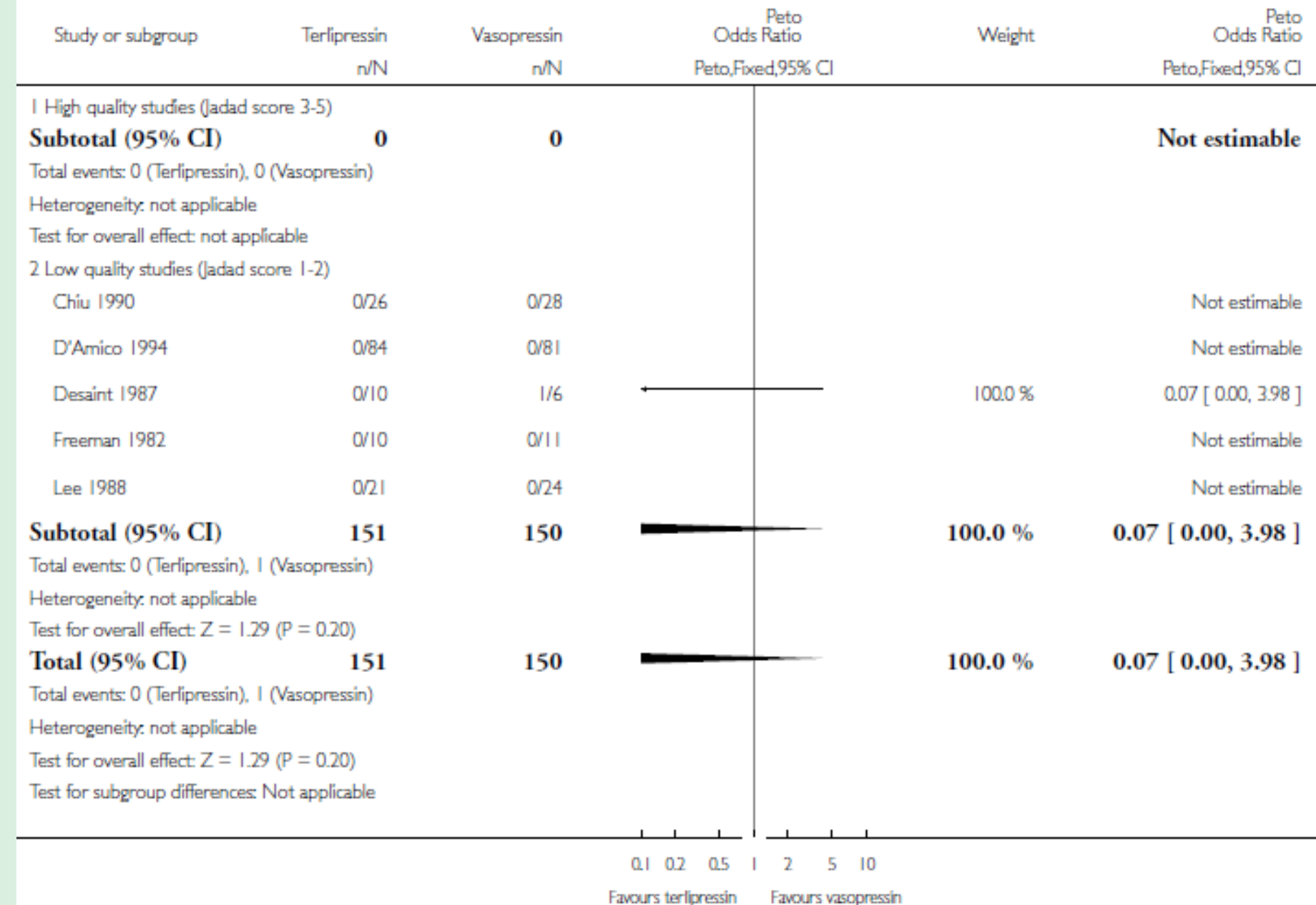


Analysis 6.6. Comparison 6 Terlipressin versus vasopressin, Outcome 6 Adverse events causing death.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 6 Terlipressin versus vasopressin

Outcome: 6 Adverse events causing death



EVIDENCE (1)

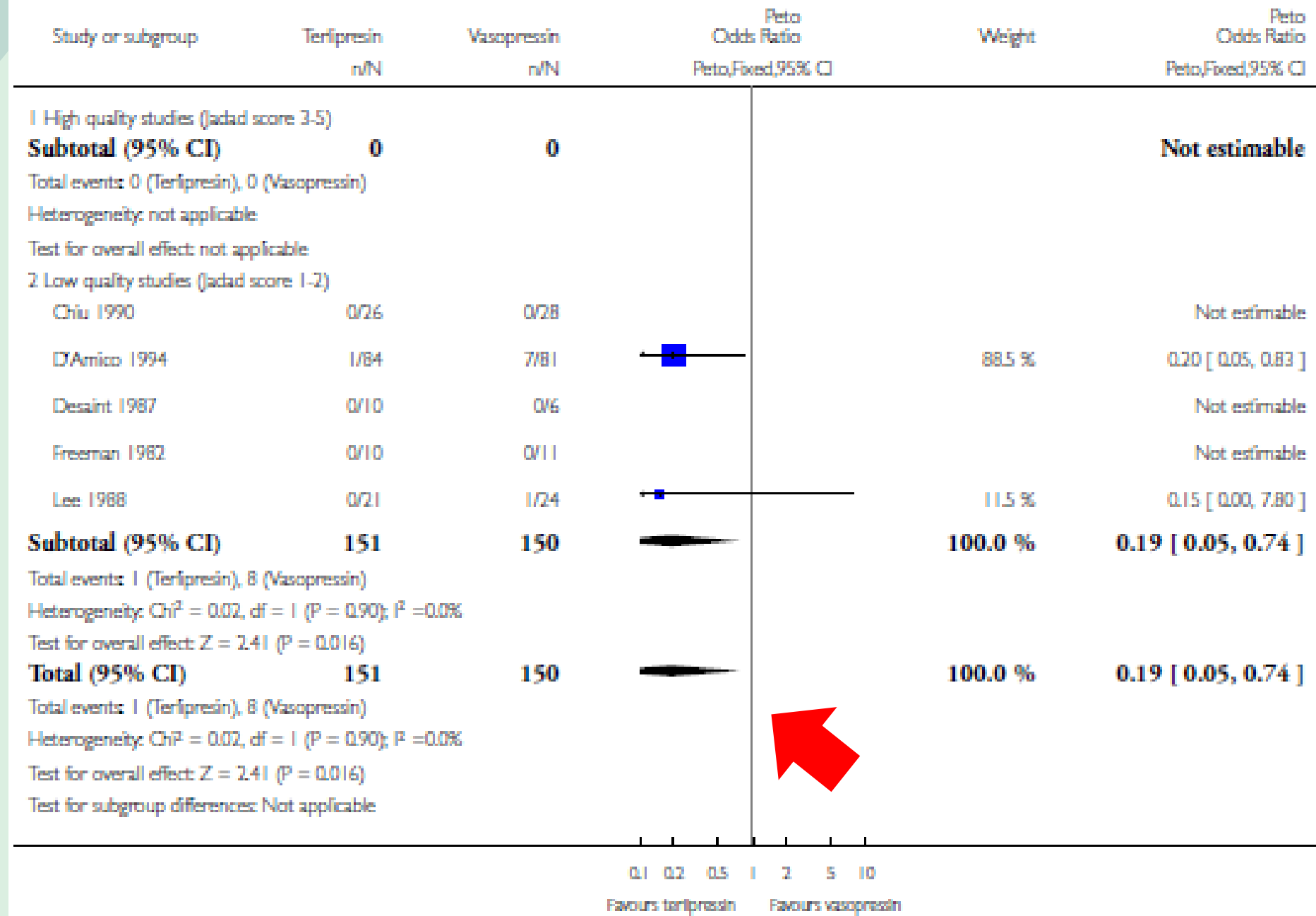
6) Terlipressin vs Vasopressin

Analysis 6.7. Comparison 6 Terlipressin versus vasopressin, Outcome 7 Adverse events causing withdrawal of treatment.

Review: Terlipressin for acute esophageal variceal hemorrhage

Comparison: 6 Terlipressin versus vasopressin

Outcome: 7 Adverse events causing withdrawal of treatment



EVIDENCE (2)

AP&T Alimentary Pharmacology and Therapeutics

Meta-analysis: vasoactive medications for the management of acute variceal bleeds

M. Wells, N. Chande, P. Adams, M. Beaton, M. Levstik, E. Boyce & M. Mrkobrada

Aliment Pharmacol Ther 2012; 35: 1267-1278

EVIDENCE (2)

Table 2 | Summary of findings for the comparative meta-analysis of vasoactive medications

Outcome	Number of trials	Number of patients	Combined RR (95% CI)	P-value
Terlipressin compared with somatostatin				
Mortality	7	635	1.05 (0.74–1.49)	0.78
Haemostasis	7	635	1.01 (0.94–1.07)	0.84
Rebleeding	5	542	1.07 (0.74–1.54)	0.73
Terlipressin compared with vasopressin				
Mortality	5	290	1.36 (0.94–1.96)	0.10
Haemostasis	5	247	1.08 (0.85–1.39)	0.53
Rebleeding	5	262	1.41 (0.92–2.18)	0.12
Octreotide compared with terlipressin				
Mortality	6	752	0.98 (0.63–1.52)	0.91
Haemostasis	7	782	1.00 (0.91–1.10)	0.98
Rebleeding	5	375	1.10 (0.73–1.68)	0.65
Hospital stay	2	412	1.25 (0.54–3.04)	0.17
Transfusion requirement	4	527	–0.49 (–1.52 to 0.55)	0.36
Octreotide compared with somatostatin				
Mortality	2	173	1.51 (0.60–3.79)	0.38
Haemostasis	3	314	0.89 (0.76–1.05)	0.17
Rebleeding	2	173	1.66 (0.91–3.03)	0.10
Octreotide compared with vasopressin				
Mortality	1	48	1.00 (0.54–1.85)	1.00
Haemostasis	2	204	1.31 (1.10–1.56)	0.002 (favours octreotide)
Vasopressin compared with somatostatin				
Mortality	4	207	1.25 (0.69–2.28)	0.47
Haemostasis	6	379	0.75 (0.61–0.92)	0.006 (favours somatostatin)
Rebleeding	3	158	0.60 (0.31–1.14)	0.12

Terlipressin for the treatment of acute variceal bleeding

A systematic review and meta-analysis of randomized controlled trials

Xinmiao Zhou, MS^{a,b,c}, Dhiraj Tripathi, MD^d, Tingxue Song, MS^{a,c}, Lichun Shao, MS^c, Bing Han, MS^{a,b}, Jia Zhu, MS^{a,e}, Dan Han, MS^a, Fufang Liu, MS^{a,b}, Xingshun Qi, MD^{a,*}

Medicine (2018) 97:48(e13437)

Received: 28 May 2018 / Accepted: 4 November 2018

<http://dx.doi.org/10.1097/MD.00000000000013437>

EVIDENCE (3)

1) Terlipressin vs *No Vasoactive Drug*

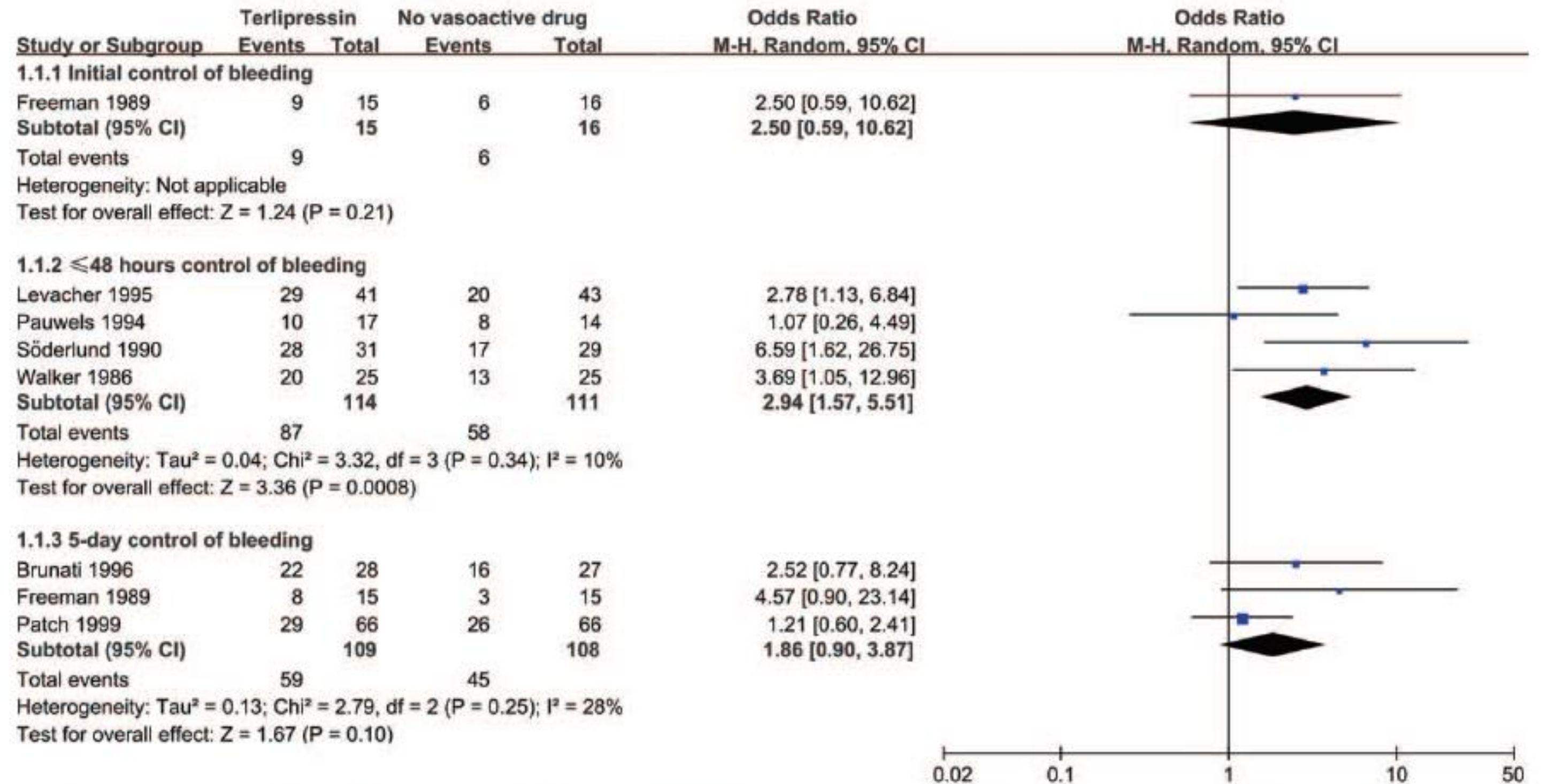


Figure 2. Forest plot showing the difference in the control of bleeding in patients treated with terlipressin compared with no vasoactive drugs.

EVIDENCE (3)

1) Terlipressin vs *No Vasoactive Drug*

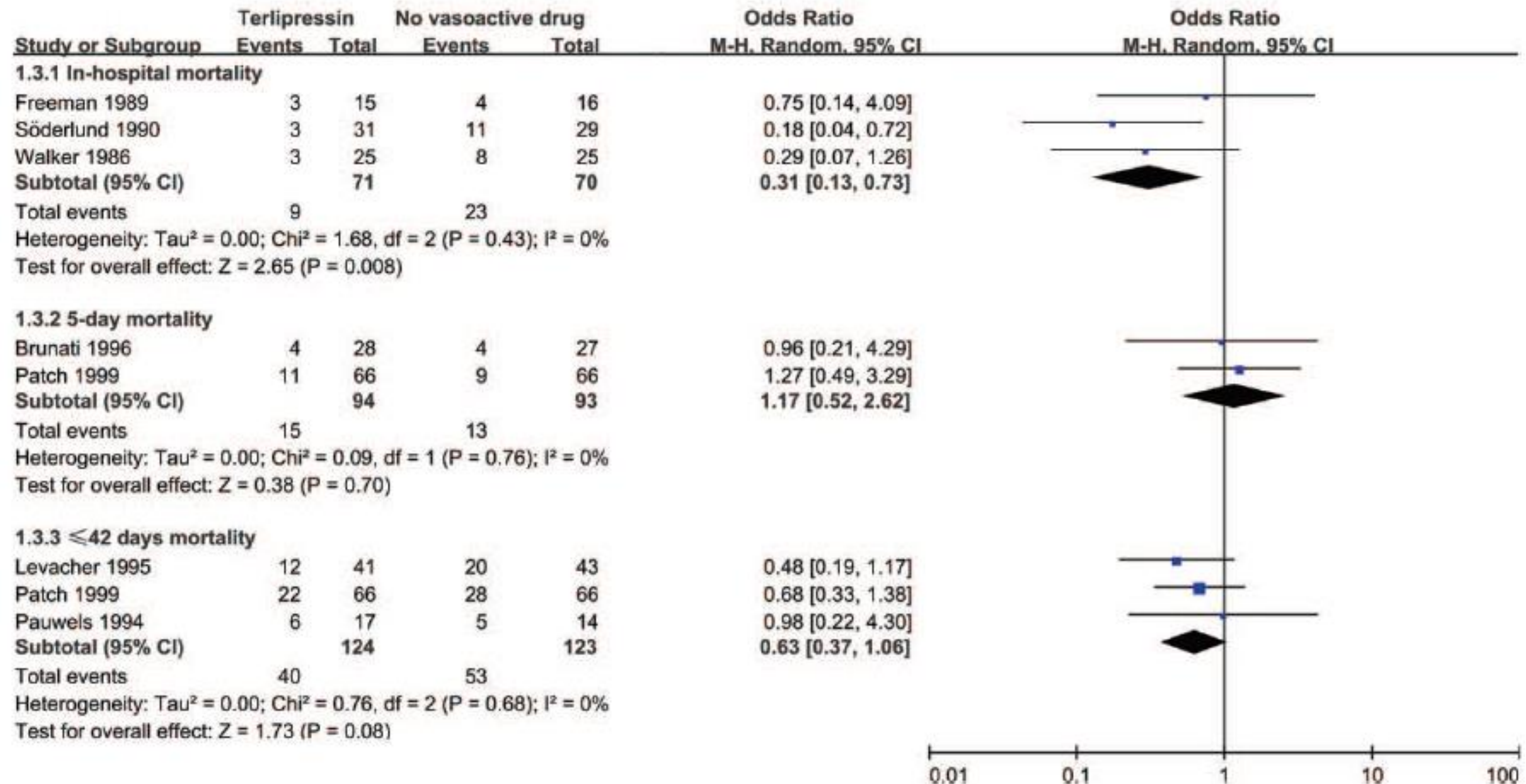


Figure 3. Forest plot showing the difference in the mortality in patients treated with terlipressin compared with no vasoactive drugs.

EVIDENCE (3)

2) Terlipressin vs Somatostatin

Table 2

Results of meta-analyses.

TIDAK SIGNIFIKAN

	No. studies	No. pts	Pooled OR [95% CI]	Pooled WMD [95% CI]	P value	Heterogeneity		Publication bias	
						I ²	χ ² P value	P _{Begg}	P _{Egger}
2. Terlipressin vs somatostatin									
2.1 Control of bleeding									
2.1.1 Initial control of bleeding	3	768	1.35 [0.88, 2.07]	—	.17	0%	.65	.296	.335
2.1.2 48-hour control of bleeding	3	230	0.79 [0.41, 1.50]	—	.47	0%	.38	1.000	.868
2.2 Treatment failure									
2.2.1 24-hour treatment failure	1	106	0.52 [0.20, 1.32]	—	.17	—	—	—	—
2.2.2 5-day treatment failure	3	677	0.92 [0.61, 1.41]	—	.71	2%	.36	.296	.465
2.3 Rebleeding									
2.3.1 In-hospital rebleeding	1	106	1.76 [0.74, 4.15]	—	.20	—	—	—	—
2.3.2 ≤48 hours rebleeding	2	141	0.86 [0.27, 2.74]	—	.80	0%	.63	1.000	—
2.3.3 5-day rebleeding	2	618	1.10 [0.37, 3.26]	—	.87	41%	.19	1.000	—
2.3.4 42-day rebleeding	2	303	0.99 [0.57, 1.71]	—	.97	0%	.66	1.000	—
2.4 Mortality									
2.4.1 In-hospital mortality	2	140	0.85 [0.38, 1.91]	—	.69	0%	.49	1.000	—
2.4.2 5-day mortality	3	677	1.01 [0.59, 1.71]	—	.98	0%	.69	.296	.375
2.4.3 ≤42 days mortality	4	858	1.12 [0.76, 1.66]	—	.57	0%	.94	.734	.737
2.5 Transfusion requirements	6	954	—	0.59 [−0.19, 1.37]	.14	81%	.0001	.260	.144
2.6 Duration of hospital stay	2	204	—	−0.24 [−2.60, 2.12]	.84	0%	.39	1.000	—
2.7 Complications	4	822	2.44 [1.03, 5.80]	—	.04	51%	.11	1.000	.734

EVIDENCE (3)

3) Terlipressin vs Octreotide

Table 2

Results of meta-analyses.

TIDAK SIGNIFIKAN

	No. studies	No. pts	Pooled OR [95% CI]	Pooled WMD [95% CI]	P value	Heterogeneity		Publication bias	
						I ²	χ ² P value	P _{Begg}	P _{Egger}
3. Terlipressin vs octreotide									
3.1 Control of bleeding									
3.1.1 Initial control of bleeding	5	1154	1.26 [0.74, 2.14]	—	.39	26%	.25	.806	.503
3.1.2 ≤24 hours control of bleeding	2	147	0.37 [0.18, 0.76]	—	.007	0%	.87	1.000	—
3.1.3 5-day control of bleeding	1	56	1.22 [0.35, 4.24]	—	.75	—	—	—	—
3.2 5-day treatment failure	1	521	0.83 [0.51, 1.35]	—	.45	—	—	—	—
3.3 Rebleeding									
3.3.1 ≤48 hours rebleeding	1	60	0.68 [0.20, 2.33]	—	.54	—	—	—	—
3.3.2 5-day rebleeding	3	689	0.84 [0.41, 1.71]	—	.63	0%	.65	1.000	.876
3.3.3 ≤42 days rebleeding	4	369	0.96 [0.35, 2.63]	—	.93	68%	.02	.308	.307
3.3.4 60-day rebleeding	1	60	1.00 [0.13, 7.60]	—	1.00	—	—	—	—
3.4. Mortality									
3.4.1 In-hospital mortality	1	324	1.29 [0.47, 3.54]	—	.63	—	—	—	—
3.4.2 5-day mortality	3	657	0.89 [0.51, 1.53]	—	.67	0%	.93	1.000	.705
3.4.3 ≤60 days mortality	6	977	1.03 [0.71, 1.48]	—	.88	0%	.91	1.000	.534
3.5 Transfusion requirements	4	993	—	0.02 [−0.29, 0.34]	.90	0%	.74	.734	.878
3.6 Duration of hospital stay	2	412	—	−1.25 [−3.04, 0.54]	.17	38%	.20	1.000	—
3.7 Complications	3	668	2.50 [0.83, 7.56]	—	.10	74%	.02	.296	.654

EVIDENCE (3)

3) Terlipressin vs Vasopressin

Table 2

Results of meta-analyses.

TIDAK SIGNIFIKAN

	No. studies	No. pts	Pooled OR [95% CI]	Pooled WMD [95% CI]	P value	Heterogeneity		Publication bias	
						I ²	χ ² P value	P _{Begg}	P _{Egger}
4. Terlipressin vs vasopressin									
4.1 24-hour control of bleeding	5	247	1.60 [0.53, 4.88]	—	.41	62%	.03	.806	.638
4.2 Rebleeding									
4.2.1 In-hospital rebleeding	2	34	3.27 [0.24, 45.29]	—	.38	53%	.15	1.000	—
4.2.2 7-day rebleeding	1	28	1.78 [0.32, 10.01]	—	.51	—	—	—	—
4.3 Mortality									
4.3.1 In-hospital mortality	3	91	1.20 [0.50, 2.89]	—	.69	0%	.74	1.000	.186
4.3.2 42-day mortality	1	45	1.82 [0.54, 6.07]	—	.33	—	—	—	—
4.4 Transfusion requirements	1	45	—	0.80 [−1.46, 3.06]	.49	—	—	—	—

EVIDENCE (3)

3) Terlipressin vs Terlipresin+EVL / Sclerotherapy

Table 2

Results of meta-analyses.

TIDAK SIGNIFIKAN

	No. studies	No. pts	Pooled OR [95% CI]	Pooled WMD [95% CI]	P value	Heterogeneity		Publication bias	
						I^2	χ^2 P value	P_{Begg}	P_{Egger}
5. Terlipressin vs terlipressin plus EVL									
5.1 48-hour control of bleeding	1	93	0.23 [0.02, 2.12]	—	.19	—	—	—	—
5.2 5-day treatment failure	1	93	14.46 [1.78, 117.33]	—	.01	—	—	—	—
5.3 48–120 hours rebleeding	1	93	18.04 [1.00, 325.75]	—	.05	—	—	—	—
5.4 42-day mortality	1	93	3.21 [0.32, 32.04]	—	.32	—	—	—	—
5.5 Transfusion requirements									
5.5.1 \leq 48 hours transfusion requirements	1	93	—	0.60 [0.00, 1.20]	.05	—	—	—	—
5.5.2 49–120 hours transfusion requirements	1	93	—	1.20 [0.43, 1.97]	.002	—	—	—	—
5.6 Duration of hospital stay	1	93	—	1.30 [−0.94, 3.54]	.25	—	—	—	—
5.7 Complications	1	93	1.13 [0.50, 2.57]	—	.76	—	—	—	—
6. Terlipressin vs sclerotherapy									
6.1 48-hour control of bleeding	1	219	0.90 [0.46, 1.80]	—	.77	—	—	—	—
6.2 5-day treatment failure	1	219	1.08 [0.61, 1.91]	—	.78	—	—	—	—
6.3 Rebleeding									
6.3.1 5-day rebleeding	1	219	1.02 [0.48, 2.18]	—	.96	—	—	—	—
6.3.2 42-day rebleeding	1	219	0.96 [0.52, 1.78]	—	.91	—	—	—	—
6.4 42-day mortality	1	219	1.65 [0.85, 3.19]	—	.14	—	—	—	—
6.5 Transfusion requirements	1	219	—	0.20 [−1.01, 1.41]	.75	—	—	—	—
6.6 Duration of hospital stay	1	219	—	−1.00 [−3.65, 1.65]	.46	—	—	—	—
6.7 Complications	1	219	0.59 [0.32, 1.10]	—	.10	—	—	—	—

AVAILABILITY

Indikasi: pengobatan pendarahan varises esofagus
Terlipin (terlipressin 0,86 mg ~ terlipressin acetate 1 mg)

NOMOR REGISTRASI	PRODUK	PENDAFTAR	
DKI1952600144A1 Terbit: 11-06-2019	TERLIPIN Merk: - Kemasan: DUS, 1 VIAL @ 1 MG	DEXA MEDICA - Indonesia -	
Nomor Registrasi	DKI1952600144A1	Nama Produk	TERLIPIN
Tanggal Terbit	11-06-2019	Bentuk Sediaan	SERBUK INJEKSI; 0,86 MG
Masa Berlaku s/d	11-06-2024	Komposisi	- TERLIPRESSINE ACETATE
Diterbitkan Oleh	Registrasi Obat Direktorat Registrasi Obat	Merk	-
Produk	Obat	Kemasan	DUS, 1 VIAL @ 1 MG
		Pendaftar	DEXA MEDICA - Indonesia - -
		Diproduksi Oleh	HYBIO PHARMACEUTICAL Co Ltd - China

DKI1951700144A1 Terbit: 02-04-2019	GLYPRESSIN Merk: - Kemasan: Dus, 1 vial @ 1 mg + 1 ampul pelarut @ 5 mL	ABBOTT INDONESIA - Indonesia -	
Nomor Registrasi	DKI1951700144A1	Nama Produk	GLYPRESSIN
Tanggal Terbit	02-04-2019	Bentuk Sediaan	SERBUK INJEKSI; 0.86 MG
Masa Berlaku s/d	02-04-2024	Komposisi	- TERLIPRESSIN
Diterbitkan Oleh	Registrasi Obat Direktorat Registrasi Obat	Merk	-
Produk	Obat	Kemasan	Dus, 1 vial @ 1 mg + 1 ampul pelarut @ 5 mL
		Pendaftar	ABBOTT INDONESIA - Indonesia - -
		Diproduksi Oleh	FERRING GMBH - Federal Republic of Germany

PRICE

TABLE 4. Vasoactive Agents Used in the Management of Acute Variceal Hemorrhage

Drug	Recommended Dose	Duration
Octreotide (SMT analogue)	Initial IV bolus of 50 micrograms (can be repeated in first hour if ongoing bleeding) Continuous IV infusion of 50 µg/hr	2-5 days
Vasopressin	Continuous IV infusion: 0.2-0.4 U/min; can be increased to 0.8 U/min It should always be accompanied by IV nitroglycerin at a starting dose of 40 µg/min, which can be increased to a maximum of 400 µg/min, adjusted to maintain a systolic blood pressure 90 mm Hg.	24 hours
SMT	Initial IV bolus 250 µg (can be repeated in the first hour if ongoing bleeding) Continuous IV infusion of 250-500 µg/h	2-5 days
Terlipressin (VP analogue)	Initial 48 hours: 2 mg IV every 4 hours until control of bleeding Maintenance: 1 mg IV every 4 hours to prevent rebleeding	2-5 days

Only one of these four agents should be used.

Abbreviations: IV, intravenous; SMT, somatostatin; VP, vasopressin.

PRICE

HARGA	OCTREOTIDE	SOMATOSTATIN	TERLIPRESSIN	
			Glypressin	Terlipin
Per ampul	Sandostatin[®] Rp. 356.260 (0,1mg/ml ~ 100 mcg/ml) Octide[®] Rp. 148.500 (0,1mg/ml ~ 100 mcg/ml)	Somatostatin Lyomark[®] Rp. 880.600,- (ampul 3000 mcg)	Rp. 814.000 (ampul 1 mg TA)	Rp. 485.000 (ampul 1 mg TA)
Dosis	50 mcg/jam selama 2-5 hari 1 hari = 50 mcg x 24 = 1200 mcg 12 ampul	250-500 mcg/jam selama 2-5 hari 1 hari = 6000 mcg ~ 2 ampul / 12.000 mcg ~ 4 ampul	Dosis 48 jam (2 hari pertama) 2 mg TA setiap 4 jam = Rp. 19.536.000,- Dosis 3 hari 1 mg setiap 4 jam = Rp. 14.652.000,-	Dosis 48 jam (2 hari pertama) 2 mg TA setiap 4 jam = Rp. 11.640.000,- Dosis 3 hari 1 mg setiap 4 jam = Rp. 8.730.000,-
Total biaya 1 siklus	Sandostatin Rp. 8.550.240 – Rp. 21.375.600 Octide Rp. 3.564.000 – Rp. 8.910.000	250 mcg Rp. 3.522.400 – Rp. 8.806.000,- 500 mcg Rp. 7.044.800 – Rp. 17.612.000	Rp. 34.188.000,-	Rp. 20.370.000,- TA: terlipressin acetate

CONCLUSION

1. *Terlipressin* memiliki kelebihan secara farmakokinetika yang dapat bermanfaat pada praktek klinis, yakni memiliki **waktu paruh yang panjang** sehingga memungkinkan pemberian dengan rute selain infus berkelanjutan
2. Hasil kajian terhadap bukti penelitian menunjukkan efektivitas dan keamanan *Terlipressin* yang **sebanding** dengan vasoaktif lain, termasuk somatostatin.
3. Harga yang **relatif lebih mahal** dibandingkan jenis vasoaktif yang lain dapat menjadi pertimbangan penggunaan *Terlipressin* khususnya di era implementasi JKN.

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- thank you -