NCGC National Clinical Guideline Centre

Acute upper gastrointestinal bleeding

Management

Appendices

June 2012

Commissioned by the National Institute for Health and Clinical Excellence

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Appendices

Appendix A: Scope

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SCOPE

1 Guideline title

Gastrointestinal bleeding: the management of acute upper gastrointestinal bleeding

1.1 Short title

Acute upper GI bleeding

2 The remit

The Department of Health has asked NICE: 'To prepare a clinical guideline on the management of acute upper gastrointestinal bleeding'.

3 Clinical need for the guideline

3.1 Epidemiology

a) Upper gastrointestinal bleeding is defined as haemorrhage occurring at any point between the mouth and the duodenum; it is the most common emergency managed by gastroenterologists in the UK. Peptic ulcer disease is the most common pathology underlying upper gastrointestinal bleeding, occurring in 35–50% of cases. Variceal bleeding, accounting for 5–10% of cases, should be considered separately because of the special considerations required in its management. In approximately a fifth of cases no cause is found.

b) The overall incidence of acute upper gastrointestinal bleeding in the UK ranges from 50–150 per 100,000 of the population per year. Men are more commonly affected than women. Those in lower socioeconomic groups are more commonly affected than those in higher groups. Incidence rises

sharply with age, which is especially significant in the context of an ageing population. Increasing use of aspirin, clopidogrel and warfarin (particularly in older people who have vascular disease) poses particular problems. Non-steroidal anti-inflammatory drug (NSAID) usage is a well-recognised risk factor.

c) Upper gastrointestinal tract bleeding is estimated to account for 5000 deaths per year in the UK. In 1995 a major audit described a mortality of 11% in patients admitted to hospital with upper gastrointestinal bleeding, rising to 33% for patients already admitted to hospital who subsequently developed the problem. A similar audit in 2007 reported that the respective figures were 7% and 26% in the 6750 cases that they analysed.

3.2 Current practice

a) Patients on systemic non-steroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase-2 (COX-2) inhibitors, and acutely unwell patients in intensive care units, are at increased risk of developing acute upper gastrointestinal bleeding. Interventions exist that provide both primary and secondary prophylaxis. The current NICE guidance on osteoarthritis recommends that whenever systemic NSAIDs or COX-2 inhibitors are used, they should be co-prescribed with a proton pump inhibitor (PPI). However, in some settings (such as in an intensive care unit) the issue of prophylaxis is more contentious and guidance is needed. In addition, offering prophylactic strategies in intensive care units across the NHS might have economic implications.

b) Patients with suspected upper gastrointestinal bleeding are currently referred to secondary care services for further clinical assessment and investigation. Patients with cardiovascular compromise are resuscitated and stabilised before investigation. Blood products for resuscitation and the correction of coagulopathy are not used in a standard way. For those with suspected chronic liver disease and upper gastrointestinal bleeding there may be a role for terlipressin acetate and intravenous antibiotic therapy before endoscopy.

c) Upper gastrointestinal endoscopy is the widely accepted diagnostic investigation of choice, but the optimal timing for this investigation is unclear. Service provisions for out-of-hours endoscopy are highly variable, and offering 24-hour endoscopy across the NHS would have serious economic implications. Appropriate indications for some therapeutic endoscopic interventions are well established and there has recently been increasing consensus regarding when and how the various methods for controlling bleeding should be deployed.

d) Major advances in therapy have occurred since the British Society of Gastroenterology issued the last national guidance in 2002 and there is significant opportunity to reinforce and build upon the SIGN guidance published in 2008. A recent UK-wide audit showed that compliance with standards of care (the use of blood products, deployment of investigations and management) for acute upper gastrointestinal bleeding is variable at best. A national guideline is needed on the prevention and management of acute upper gastrointestinal bleeding to address the uncertainties and variability in practice in primary and secondary care.

4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, ‘Further information’).

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

a) Adults and young people (16 years and older) with acute variceal and non-variceal upper gastrointestinal bleeding.

b) Adults and young people in high dependency and intensive care units who are at high risk of acute upper gastrointestinal bleeding.

4.1.2 Groups that will not be covered

a) Adults with chronic upper gastrointestinal bleeding.

b) Children (15 years and below).

c) Patients with a bleeding point lower than the duodenum.

4.2 Healthcare setting

a) Primary, secondary and tertiary care.

4.3 Clinical management

4.3.1 Key clinical issues that will be covered

a) Primary prophylaxis for acutely ill patients in high dependency and intensive care units.

b) Assessment of risks (such as mortality, rebleeding and the need for further intervention), including the use of scoring systems.

c) Initial management and resuscitation including:

- blood products
- proton pump inhibitors for likely non-variceal bleeding (pre- and post-endoscopy)
- terlipressin acetate and antibiotics for patients with likely variceal bleeding.

d) Timing of endoscopy.

e) Management of non-variceal upper GI bleeding including:

- endoscopic therapy (which modalities to use in combination)
- treatment options if a first endoscopic therapy has failed (angiography and embolisation, surgery, repeat endoscopy)

- control of bleeding and prevention of rebleeding in patients on NSAIDs, aspirin or clopidogrel.

f) Management of variceal upper GI bleeding including:

- treatment before endoscopy, including pharmacological therapy (antibiotics and terlipressin acetate, including duration of therapy)
- primary treatment for gastric varices (endoscopic injection of glue or thrombin and/or transjugular intrahepatic portosystemic stent shunt [TIPSS])
- interventions for uncontrolled bleeding (oesophageal or gastric) including balloon tamponade, TIPSS, surgery and repeat endoscopy.

g) Information and support for patients and carers.

h) Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

4.3.2 Clinical issues that will not be covered

a) Treatment for *Helicobacter pylori*.

4.4 Main outcomes

a) Mortality.

b) Re-bleeding.

c) Surgery.

d) Blood transfusion requirements.

e) Length of hospital stay.

f) Health-related quality of life.

4.5 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY). However, in disease areas where the QALY is not ideal, another appropriate unit of effectiveness will be assessed. Furthermore the costs considered will usually only be from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see ‘Further information’).

4.6 Status

4.6.1 Scope

This is the final scope.

4.6.2 Timing

The development of the guideline recommendations will begin in July 2010.

5 Related NICE guidance

5.1 Published guidance

- Unstable angina and NSTEMI. NICE clinical guideline 94 (2010). Available from www.nice.org.uk/guidance/CG94
- Stroke. NICE clinical guideline 68 (2008). Available from www.nice.org.uk/guidance/CG68
- Osteoarthritis. NICE clinical guideline 59 (2008). Available from www.nice.org.uk/guidance/CG59
- Acutely ill patients in hospital. NICE clinical guideline 50 (2007). Available from www.nice.org.uk/guidance/CG50
- MI: secondary prevention. NICE clinical guideline 48 (2007). Available from www.nice.org.uk/guidance/CG48
- Atrial fibrillation. NICE clinical guideline 36 (2006). Available from www.nice.org.uk/guidance/CG36
- Dyspepsia. NICE clinical guideline 17 (2004). Available from www.nice.org.uk/guidance/CG17

- Clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome. NICE technology appraisal guidance 80 (2004). Available from www.nice.org.uk/guidance/TA80
- Wireless capsule endoscopy for investigation of the small bowel. NICE interventional procedure guidance 101 (2004). Available from www.nice.org.uk/guidance/IPG101

5.2 Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website).

- Prevention of cardiovascular disease. NICE public health guidance. Publication expected April 2010.
- Alcohol use disorders: clinical management. NICE clinical guideline. Publication expected May 2010.

6 Further information

Information on the guideline development process is provided in:

- ‘How NICE clinical guidelines are developed: an overview for stakeholders' the public and the NHS’
- ‘The guidelines manual’.

These are available from the NICE website (www.nice.org.uk/GuidelinesManual). Information on the progress of the guideline will also be available from the NICE website (www.nice.org.uk).

Appendix B: Declarations of interest

B.1 Introduction

All members of the GDG and all members of the NCGC staff were required to make formal declarations of interest at the outset of each meeting, and these were updated at every subsequent meeting throughout the development process. No interests were declared that required actions.

B.2 Declarations of interests of the GDG members

Richard Anderson

Stephen Atkinson

Mark Donnelly

Ricky Forbes-Young

Carlos Gomez

Dan Greer

Kenneth Halligan

Markus Hauser

Mimi McCord

Simon McPherson

Mike Murphy

Kelvin Palmer

David Patch

Joseph Varghese

Mark Vaughan

B.2.1 Richard Anderson

GDG meeting	Declaration of Interests
GDG Application	No interests to declare
First GDG meeting (16th July 2010)	N/A
Second GDG meeting (30th July 2010)	N/A
Third GDG meeting (24th September 2010)	N/A
Fourth GDG meeting (29th October 2010)	N/A

Fifth GDG meeting (10th December 2010)	N/A
Sixth GDG meeting (28th January 2011)	N/A
Seventh GDG meeting (11th March 2011)	N/A
Eighth GDG meeting (15th April 2011)	N/A
Ninth GDG meeting (27th May 2011)	N/A
Tenth GDG meeting (8th July 2011)	N/A
Eleventh GDG meeting (2nd September 2011)	N/A
Twelfth GDG meeting (30th September 2011)	N/A
Thirteenth GDG meeting (9th March 2011)	N/A

B.2.2 Stephen Atkinson

GDG meeting	Declaration of Interests
GDG Application	No interests to declare
First GDG meeting (16th July 2010)	No interests to declare
Second GDG meeting (30th July 2010)	No interests to declare
Third GDG meeting (24th September 2010)	No interests to declare
Fourth GDG meeting (29th October 2010)	No interests to declare
Fifth GDG meeting (10th December 2010)	No interests to declare
Sixth GDG meeting (28th January 2011)	No interests to declare
Seventh GDG meeting (11th March 2011)	No interests to declare
Eighth GDG meeting (15th April 2011)	No interests to declare
Ninth GDG meeting (27th May 2011)	No interests to declare

Tenth GDG meeting (8th July 2011)	No interests to declare
Eleventh GDG meeting (2nd September 2011)	No interests to declare
Twelfth GDG meeting (30th September 2011)	No interests to declare
Thirteenth GDG meeting (9th March 2011)	No interests ti declare

B.2.3 Mark Donnelly

GDG meeting	Declaration of Interests
GDG Application	No interests to declare
First GDG meeting (16th July 2010)	No interests to declare
Second GDG meeting (30th July 2010)	No interests to declare
Third GDG meeting (24th September 2010)	No interests to declare
Fourth GDG meeting (29th October 2010)	No interests to declare
Fifth GDG meeting (10th December 2010)	No interests to declare
Sixth GDG meeting (28th January 2011)	No interests to declare
Seventh GDG meeting (11th March 2011)	No interests to declare
Eighth GDG meeting (15th April 2011)	No interests to declare
Ninth GDG meeting (27th May 2011)	N/A
Tenth GDG meeting (8th July 2011)	No interests to declare
Eleventh GDG meeting (2nd September 2011)	No interests to declare
Twelfth GDG meeting (30th September 2011)	N/A
Thirteenth GDG meeting (9th March 2011)	No interests to declare

B.2.4 Ricky Forbes-Young

GDG meeting	Declaration of Interests
GDG Application	No interests to declare
First GDG meeting (16th July 2010)	No interests to declare
Second GDG meeting (30th July 2010)	No interests to declare
Third GDG meeting (24th September 2010)	No interests to declare
Fourth GDG meeting (29th October 2010)	No interests to declare
Fifth GDG meeting (10th December 2010)	N/A
Sixth GDG meeting (28th January 2011)	No interests to declare
Seventh GDG meeting (11th March 2011)	No interests to declare
Eighth GDG meeting (15th April 2011)	No interests to declare
Ninth GDG meeting (27th May 2011)	No interests to declare
Tenth GDG meeting (8th July 2011)	N/A
Eleventh GDG meeting (2nd September 2011)	No interests to declare
Twelfth GDG meeting (30th September 2011)	No interests to declare
Thirteenth GDG meeting (9th March 2011)	N/A

B.2.5 Carlos Gomez

GDG meeting	Declaration of Interests
GDG Application	No interests to declare
First GDG meeting (16th July 2010)	No interests to declare
Second GDG meeting (30th July 2010)	N/A
Third GDG meeting (24th September 2010)	No interests to declare
Fourth GDG meeting (29th October 2010)	No interests to declare
Fifth GDG meeting (10th December 2010)	No interests to declare
Sixth GDG meeting (28th January 2011)	N/A

Seventh GDG meeting (11th March 2011)	No interests to declare
Eighth GDG meeting (15th April 2011)	No interests to declare
Ninth GDG meeting (27th May 2011)	No interests to declare
Tenth GDG meeting (8th July 2011)	No interests to declare
Eleventh GDG meeting (2nd September 2011)	No interests to declare
Twelfth GDG meeting (30th September 2011)	No interests to declare
Thirteenth GDG meeting (9th March 2011)	No interests to declare

B.2.6 Dan Greer

GDG meeting	Declaration of Interests
GDG Application	Published article on peptic ulcer disease that referred in part to Upper GI Bleeding 2006: Greer D. Peptic ulcer disease – Pharmacological treatment. Hospital Phamracist 2006. 13(7):245-250, 2006. Member of UKCPA (United Kingdom Clinical Pharmacy Association)
First GDG meeting (16th July 2010)	No interests to declare
Second GDG meeting (30th July 2010)	No interests to declare
Third GDG meeting (24th September 2010)	No interests to declare
Fourth GDG meeting (29th October 2010)	No interests to declare
Fifth GDG meeting (10th December 2010)	No interests to declare
Sixth GDG meeting (28th January 2011)	No interests to declare
Seventh GDG meeting (11th March 2011)	No interests to declare
Eighth GDG meeting (15th April 2011)	No interests to declare
Ninth GDG meeting (27th May 2011)	No interests to declare
Tenth GDG meeting (8th July 2011)	No interests to declare
Eleventh GDG meeting (2nd September 2011)	No interests to declare
Twelfth GDG meeting	N/A

(30th September 2011)	
Thirteenth GDG meeting (9th March 2011)	No interests to declare

B.2.7 Kenneth Halligan

GDG meeting	Declaration of Interests
GDG Application	No interests to declare
First GDG meeting (16th July 2010)	No interests to declare
Second GDG meeting (30th July 2010)	No interests to declare
Third GDG meeting (24th September 2010)	No interests to declare
Fourth GDG meeting (29th October 2010)	No interests to declare
Fifth GDG meeting (10th December 2010)	No interests to declare
Sixth GDG meeting (28th January 2011)	No interests to declare
Seventh GDG meeting (11th March 2011)	No interests to declare
Eighth GDG meeting (15th April 2011)	No interests to declare
Ninth GDG meeting (27th May 2011)	No interests to declare
Tenth GDG meeting (8th July 2011)	No interests to declare
Eleventh GDG meeting (2nd September 2011)	No interests to declare
Twelfth GDG meeting (30th September 2011)	No interests to declare
Thirteenth GDG meeting (9th March 2011)	No interests to declare

B.2.8 Markus Hauser

GDG meeting	Declaration of Interests
GDG Application	No interests to declare
First GDG meeting (16th July 2010)	No interests to declare
Second GDG meeting (30th July 2010)	No interests to declare
Third GDG meeting (24th September 2010)	No interests to declare

Fourth GDG meeting (29th October 2010)	No interests to declare
Fifth GDG meeting (10th December 2010)	No interests to declare
Sixth GDG meeting (28th January 2011)	No interests to declare
Seventh GDG meeting (11th March 2011)	No interests to declare
Eighth GDG meeting (15th April 2011)	No interests to declare
Ninth GDG meeting (27th May 2011)	No interests to declare
Tenth GDG meeting (8th July 2011)	No interests to declare
Eleventh GDG meeting (2nd September 2011)	No interests to declare
Twelfth GDG meeting (30th September 2011)	No interests to declare
Thirteenth GDG meeting (9th March 2011)	No interests to declare

B.2.9 Mimi McCord

GDG meeting	Declaration of Interests
GDG Application	No interests to declare
First GDG meeting (16th July 2010)	No interests to declare
Second GDG meeting (30th July 2010)	No interests to declare
Third GDG meeting (24th September 2010)	No interests to declare
Fourth GDG meeting (29th October 2010)	No interests to declare
Fifth GDG meeting (10th December 2010)	No interests to declare
Sixth GDG meeting (28th January 2011)	No interests to declare
Seventh GDG meeting (11th March 2011)	No interests to declare
Eighth GDG meeting (15th April 2011)	No interests to declare
Ninth GDG meeting (27th May 2011)	No interests to declare
Tenth GDG meeting (8th July 2011)	No interests to declare
Eleventh GDG meeting	N/A

(2nd September 2011)	
Twelfth GDG meeting (30th September 2011)	No interests to declare
Thirteenth GDG meeting (9th March 2011)	No interests to declare

B.2.10 Simon McPherson

GDG meeting	Declaration of Interests
GDG Application	No interests to declare
First GDG meeting (16th July 2010)	No interests to declare
Second GDG meeting (30th July 2010)	Personal pecuniary interest arising from being a GSK shareholder (owns GSK shares of £2,500 value)
Third GDG meeting (24th September 2010)	No interests to declare
Fourth GDG meeting (29th October 2010)	No interests to declare
Fifth GDG meeting (10th December 2010)	No interests to declare
Sixth GDG meeting (28th January 2011)	No interests to declare
Seventh GDG meeting (11th March 2011)	No interests to declare
Eighth GDG meeting (15th April 2011)	No interests to declare
Ninth GDG meeting (27th May 2011)	No interests to declare
Tenth GDG meeting (8th July 2011)	No interests to declare
Eleventh GDG meeting (2nd September 2011)	N/A
Twelfth GDG meeting (30th September 2011)	No interests to declare
Thirteenth GDG meeting (9th March 2011)	No interests to declare

B.2.11 Mike Murphy

GDG meeting	Declaration of Interests
GDG Application	Fees (<£1000 in 2009/10) for advisory activities for haemostatix. A company developing a platelet substitute and fibrin sealants. Fees (<£1000 in 2009/10) for chairing an advisory board for Glaxo, who are marketing a thrombopoietin receptor agonist for autoimmune thrombocytopenia.

First GDG meeting (16th July 2010)	No interests to declare
Second GDG meeting (30th July 2010)	No interests to declare
Third GDG meeting (24th September 2010)	No interests to declare
Fourth GDG meeting (29th October 2010)	No interests to declare
Fifth GDG meeting (10th December 2010)	Applying for research grant to investigate bleed transfusion requirements of patients with Upper GI bleeding
Sixth GDG meeting (28th January 2011)	No interests to declare
Seventh GDG meeting (11th March 2011)	No interests to declare
Eighth GDG meeting (15th April 2011)	No interests to declare
Ninth GDG meeting (27th May 2011)	No interests to declare
Tenth GDG meeting (8th July 2011)	No interests to declare
Eleventh GDG meeting (2nd September 2011)	No interests to declare
Twelfth GDG meeting (30th September 2011)	No interests to declare
Thirteenth GDG meeting (9th March 2011)	N/A

B.2.12 Kelvin Palmer

GDG meeting	Declaration of Interests
GDG Application	• NPSA (National Patient Safety Agency): Participates in projects CROMIES. • National Blood Services projects – participates in project on blood transfusion in GI Bleeding.
First GDG meeting (16th July 2010)	No interests to declare
Second GDG meeting (30th July 2010)	No interests to declare
Third GDG meeting (24th September 2010)	No interests to declare
Fourth GDG meeting (29th October 2010)	No interests to declare
Fifth GDG meeting (10th December 2010)	Applying for research grant to investigate bleed transfusion requirements of patients with Upper GI bleeding
Sixth GDG meeting (28th January 2011)	No interests to declare

Seventh GDG meeting (11th March 2011)	No interests to declare
Eighth GDG meeting (15th April 2011)	No interests to declare
Ninth GDG meeting (27th May 2011)	No interests to declare
Tenth GDG meeting (8th July 2011)	No interests to declare
Eleventh GDG meeting (2nd September 2011)	No interests to declare
Twelfth GDG meeting (30th September 2011)	No interests to declare
Thirteenth GDG meeting (9th March 2011)	No interests to declare

B.2.13 David Patch

GDG meeting	Declaration of Interests
GDG Application	Received payment for speaking at conferences organised by Ferring Pharmaceuticals – the last time was in 2006.
First GDG meeting (16th July 2010)	No interests to declare
Second GDG meeting (30th July 2010)	Personal pecuniary interest arising from receipt of honoraria from Ferring Pharmaceuticals for lecturing
Third GDG meeting (24th September 2010)	No interests to declare
Fourth GDG meeting (29th October 2010)	Personal pecuniary interest arising from receipt of honoraria from Ferring Pharmaceuticals (£500) for a lecture in September
Fifth GDG meeting (10th December 2010)	No interests to declare
Sixth GDG meeting (28th January 2011)	No interests to declare
Seventh GDG meeting (11th March 2011)	No interests to declare
Eighth GDG meeting (15th April 2011)	No interests to declare
Ninth GDG meeting (27th May 2011)	No interests to declare
Tenth GDG meeting (8th July 2011)	No interests to declare
Eleventh GDG meeting (2nd September 2011)	No interests to declare
Twelfth GDG meeting (30th September 2011)	N/A
Thirteenth GDG meeting	No interests to declare

(9th March 2011)	

B.2.14 Joseph Varghese

GDG meeting	Declaration of Interests
GDG Application	No interests to declare
First GDG meeting (16th July 2010)	No interests to declare
Second GDG meeting (30th July 2010)	No interests to declare
Third GDG meeting (24th September 2010)	No interests to declare
Fourth GDG meeting (29th October 2010)	N/A
Fifth GDG meeting (10th December 2010)	No interests to declare
Sixth GDG meeting (28th January 2011)	No interests to declare
Seventh GDG meeting (11th March 2011)	No interests to declare
Eighth GDG meeting (15th April 2011)	No interests to declare
Ninth GDG meeting (27th May 2011)	No interests to declare
Tenth GDG meeting (8th July 2011)	No interests to declare
Eleventh GDG meeting (2nd September 2011)	No interests to declare
Twelfth GDG meeting (30th September 2011)	No interests to declare
Thirteenth GDG meeting (9th March 2011)	No interests to declare

B.2.15 Mark Vaughan

GDG meeting	Declaration of Interests
GDG Application	• Partner: Meddygfa Avenue Villa Surgery, Heol Brynmor, Llanelli, SA4 0ZL • Member Welsh Council RCGP • Chair South West Wales Faculty RCGP • Member Welsh Association of Stroke Physicians
First GDG meeting (16th July 2010)	No interests to declare

Second GDG meeting (30th July 2010)	No interests to declare
Third GDG meeting (24th September 2010)	No interests to declare
Fourth GDG meeting (29th October 2010)	N/A
Fifth GDG meeting (10th December 2010)	No interests to declare
Sixth GDG meeting (28th January 2011)	No interests to declare
Seventh GDG meeting (11th March 2011)	No interests to declare
Eighth GDG meeting (15th April 2011)	No interests to declare
Ninth GDG meeting (27th May 2011)	No interests to declare
Tenth GDG meeting (8th July 2011)	No interests to declare
Eleventh GDG meeting (2nd September 2011)	N/A
Twelfth GDG meeting (30th September 2011)	No interests to declare
Thirteenth GDG meeting (9th March 2011)	No interests to declare

B.2.16 NCGC Members

GDG meeting	Declaration of Interests
GDG Application	No interests to declare
First GDG meeting (16th July 2010)	No interests to declare
Second GDG meeting (30th July 2010)	No interests to declare
Third GDG meeting (24th September 2010)	No interests to declare
Fourth GDG meeting (29th October 2010)	No interests to declare
Fifth GDG meeting (10th December 2010)	No interests to declare
Sixth GDG meeting (28th January 2011)	No interests to declare
Seventh GDG meeting (11th March 2011)	No interests to declare
Eighth GDG meeting (15th April 2011)	No interests to declare

Ninth GDG meeting (27th May 2011)	No interests to declare
Tenth GDG meeting (8th July 2011)	No interests to declare
Eleventh GDG meeting (2nd September 2011)	No interests to declare
Twelfth GDG meeting (30th September 2011)	No interests to declare
Thirteenth GDG meeting (9th March 2011)	No interests to declare

Appendix C: Literature Search Strategies

Search strategies used for the **Upper Gastrointestinal Bleeding** guideline were run in accordance with the NICE Guidelines Manual 2009:
http://www.nice.org.uk/media/5F2/44/The_guidelines_manual_2009_-_All_chapters.pdf

All searches were run up to 23/09/11 unless otherwise stated. Any studies added to the databases after this date were not included unless specifically stated in the text.

Clinical searches

Searches for **clinical evidence** were run in Medline (OVID), Embase (OVID), the Cochrane Library (Wiley), and Cinahl (EBSCO). Typically, searches were constructed in the following way:

- A PICO format was used for intervention searches. **Population** (P) terms were combined with **Intervention** (I) and sometimes **Comparison** (C) terms (as indicated in the tables under each question in Section C.3). An intervention can be a drug, a procedure or a diagnostic test. **Outcomes** (O) are rarely used in search strategies for interventions. Study type filters were added where appropriate (see C.1).

In addition to the databases outlined above, one search (C.3.8) was run in PsycINFO (OVID).

Economic searches

Searches for **economic reviews** were run in Medline (Ovid), Embase (Ovid), the NHS Economic Evaluations Database (NHS EED), the Health Technology Assessment (HTA) database and the Health Economic Evaluation Database (HEED). NHS EED and HTA were searched via the Centre for Reviews and Dissemination (CRD) interface. For Medline and Embase an economic filter (C.1.5) and a Quality of Life filter (C.1.6) were combined with the standard population (C.2). All other searches were conducted using only population terms. Economic searches were run up to 20/7/11.

Section C.1	**Study filter terms**
C.1.1	Systematic reviews (SR)
C.1.2	Randomized controlled trials (RCT)
C.1.3	Observational studies
C.1.4	Patient views
C.1.5	Health economics
C.1.6	Quality of life
Section C.2	**Standard population search strategy** This population was used for all search questions unless stated.
Section C.3	**Searches for specific questions with intervention** (and population where different from A.2)
C.3.1	Initial management and resuscitation
C.3.2	Assessment of risks
C.3.3	Timing of endoscopy
C.3.4	Management of non-variceal bleeding
C.3.5	Control of bleeding

C.3.6	Primary prophylaxis
C.3.7	Management of variceal upper GI bleeding
C.3.8	Information for patients and carers
Section C.4	**Economic searches**
C.4.1	Economic reviews
C.4.2	Quality of life reviews

C.1 Study filter search terms

C.1.1 Systematic reviews (SR)

Medline search terms

1.	meta-analysis.pt.
2.	Meta-analysis/
3.	exp Meta-Analysis as topic/
4.	(meta-analy* or metanaly* or metaanaly* or meta analy*).mp.
5.	((systematic* or evidence* or methodol* or quantitativ*) adj5 (review* or survey* or overview*)).ti,ab,sh.
6.	((pool* or combined or combining) adj (data or trials or studies or results)).ti,ab.
7.	meta-analysis.pt.
8.	or/1-7

Embase search terms

1.	"Review"/ or review.pt. or review.ti.
2.	(systematic or evidence* or methodol* or quantitativ* or analys* or assessment*).ti,sh,ab.
3.	1 and 2
4.	Meta-analysis/
5.	"Systematic review"/
6.	(meta-analy* or metanaly* or metaanaly* or meta analy*).mp.
7.	((systematic* or evidence* or methodol* or quantitativ*) adj5 (review* or survey* or overview*)).ti,ab,sh.
8.	((pool* or combined or combining) adj (data or trials or studies or results)).ti,ab.
9.	"Review"/ or review.pt. or review.ti.
10.	or/3-9

C.1.2 Randomised controlled trials (RCT)

Medline search terms

1.	randomized controlled trial*.pt,sh.
2.	controlled clinical trial*.pt,sh.
3.	Double-blind method/ or Random allocation/ or Single-blind method/
4.	exp Clinical trial/
5.	exp Clinical trials as topic/
6.	clinical trial.pt.
7.	random*.ti,ab.
8.	((clin* or control*) adj5 trial*).ti,ab.
9.	((singl* or doubl* or trebl* or tripl*) adj25 (blind* or mask*)).ti,ab.

10.	Placebos/ or placebo*.ti,ab.
11.	(volunteer* or control group or controls or prospectiv*).ti,ab.
12.	Cross-over studies/
13.	((crossover or cross-over or cross over) adj2 (design* or stud* or procedure* or trial*)).ti,ab.
14.	or/1-13

Embase Search terms

1.	Controlled study/ or Randomized controlled trial/
2.	Clinical trial/
3.	Clinical study/ or Major clinical study/ or Clinical trial/ or Phase 1 clinical trial/ or Phase 2 clinical trial/ or Phase 3 clinical trial/ or Phase 4 clinical trial/
4.	Placebo/
5.	"Double blind procedure"/
6.	((clinical* or control* or compar*) adj3 (trial*or study or studies)).mp.
7.	"Clinical article"/
8.	Randomization/
9.	placebo.tw.
10.	randomi*.tw.
11.	((singl* or double* or triple* or treble*) adj5 (blind* or mask*)).tw.
12.	Crossover procedure/
13.	((crossover or cross over) adj2 (design* or stud* or procedure* or trial*)).ti,ab.
14.	or/1-13
15.	compar*.tw.
16.	control*.tw.
17.	15 and 16
18.	14 or 17

C.1.3 Observational studies

Medline search terms

1.	Epidemiologic studies/
2.	exp Case control studies/
3.	exp Cohort studies/
4.	case control.tw.
5.	(cohort adj (study or studies)).tw.
6.	cohort analy*.tw.
7.	(follow up adj (study or studies)).tw.
8.	(observational adj (study or studies)).tw.
9.	longitudinal.tw.
10.	retrospective.tw.
11.	prospective.tw.
12.	or/1-11

Embase search terms

1.	Clinical study/
2.	Case control study/
3.	Family study/

4.	Longitudinal study/
5.	Retrospective study/
6.	Prospective study/
7.	Randomized controlled trials/
8.	6 not 7
9.	Cohort analysis/
10.	(cohort adj (study or studies)).mp.
11.	(case control adj (study or studies)).tw.
12.	(follow up adj (study or studies)).tw.
13.	(observational adj (study or studies)).tw.
14.	(epidemiologic* adj (study or studies)).tw.
15.	or/1-5,8-14

C.1.4 Patient views

Medline search terms

1.	*Stress, Psychological/
2.	*Anxiety/
3.	exp Attitude to health/
4.	exp Patient acceptance of health care/
5.	Patient satisfaction/ or Patient care management/ or *Comprehensive health care/ or "Delivery of health care"/ or Patient-centered care/ or *"Quality of health care"/
6.	((client* or patient* or user* or carer* or consumer* or customer*) adj3 (view* or opinion* or awareness or tolerance or persistenc* or attitude* or compliance or concern* or belief* or feeling* or idea* or choice* or priorit* or perception* or preferen* or expectation* or perspective* or satisfact* or inform* or experience* or feedback or belief* or co?operation or participat* or involve* or buy?in or prepar*)).ti,ab.
7.	(discomfort or comfort or inconvenience or bother*4 or trouble or fear* or anxiety or anxious or worr*3).ti,ab.
8.	Interview/
9.	exp Interviews as topic/
10.	interview*.tw.
11.	grounded theory.tw.
12.	exp Nursing methodology research/
13.	phenomenology.tw.
14.	Qualitative research/
15.	qualitative.tw.
16.	or/1-15

Embase search terms

1.	*Stress, Psychological/
2.	*Anxiety/
3.	exp Attitude to health/
4.	exp Patient acceptance of health care/
5.	Patient satisfaction/ or Patient care management/ or *Comprehensive health care/ or "Delivery of health care"/ or Patient-centered care/ or *"Quality of health care"/
6.	((client* or patient* or user* or carer* or consumer* or customer*) adj3 (view* or opinion* or awareness or tolerance or persistenc* or attitude* or compliance or concern* or belief* or

	feeling* or idea* or choice* or priorit* or perception* or preferen* or expectation* or perspective* or satisfact* or inform* or experience* or feedback or belief* or co?operation or participat* or involve* or buy?in or prepar*)).ti,ab.
7.	(discomfort or comfort or inconvenience or bother*4 or trouble or fear* or anxiety or anxious or worr*3).ti,ab.
8.	Interview/
9.	exp Interviews as topic/
10.	interview*.tw.
11.	grounded theory.tw.
12.	exp Nursing methodology research/
13.	phenomenology.tw.
14.	Qualitative research/
15.	qualitative.tw.
16.	or/1-15

C.1.5 Health economics

Medline search terms

1.	Economics/
2.	exp "Costs and cost analysis"/
3.	exp Economics, hospital/
4.	exp Economics, medical/
5.	Economics, nursing/
6.	Economics, pharmaceutical/
7.	exp Models, economic/
8.	exp "Fees and charges"/
9.	exp Budgets/
10.	(economic* adj2 evaluation*).ti,ab.
11.	(cost or costs or costed or costly or costin*).ti,ab.
12.	(economic* or pharmacoeconomic* or price* or pricing).ti,ab.
13.	(budget* or (cost* adj2 (benefit* or utilit* or effective* or model*))).ti,ab.
14.	(value adj2 money).ti,ab.
15.	or/1-14

Embase search terms

1.	exp Economic aspect/
2.	exp Cost/
3.	exp "Costs and cost analysis"/
4.	exp Economics, hospital/
5.	Economics, nursing/
6.	Economics, pharmaceutical/
7.	exp Models, economic/
8.	exp "Fees and charges"/
9.	exp Budgets/
10.	(economic* or pharmacoeconomic* or price* or pricing).ti,ab.
11.	(cost or costs or costed or costly or costin*).ti,ab.
12.	exp Economic evaluation/

13.	(budget* or (cost* adj2 (benefit* or utilit* or effective* or model*))).ti,ab.
14.	(value adj2 money).ti,ab.
15.	or/1-14

C.1.6 Quality of life

Medline search terms

1.	Value of life/
2.	exp "Quality of life"/
3.	quality of life.ti,ab.
4.	life quality.ti,ab.
5.	Quality-adjusted life years/
6.	Health status indicators/
7.	quality adjusted life.ti,ab.
8.	(qal* or qtime*).ti,ab.
9.	(euroqol or eq5d* or eq 5d*).ti,ab.
10.	(qol or hql or hqol or h qol or hrqol or hr qol).ti,ab.
11.	(health utility* or utility score*).ti,ab.
12.	(hui or hui1 or hui2 or hui3).ti,ab.
13.	quality of well being.ti,ab.
14.	qwb*.ti,ab.
15.	(sf36* or sf 36* or short form 36 or shortform 36).ti,ab.
16.	(sf20 or sf 20 or short form 20 or shortform20).ti,ab.
17.	(sf12 or sf 12 or short form 12 or shortform12).ti,ab.
18.	(sf8 or sf 8 or short form 8 or shortform8).ti,ab.
19.	or/1-18

Embase search terms

1.	exp "Quality of life"/
2.	quality of life.ti,ab.
3.	life quality.ti,ab.
4.	Quality-adjusted life years/
5.	quality adjusted life.ti,ab.
6.	(qal* or qtime*).ti,ab.
7.	(euroqol or eq5d* or eq 5d*).ti,ab.
8.	(qol or hql or hqol or h qol or hrqol or hr qol).ti,ab.
9.	(health utility* or utility score*).ti,ab.
10.	(hui or hui1 or hui2 or hui3).ti,ab.
11.	quality of well being.ti,ab.
12.	qwb*.ti,ab.
13.	(sf36* or sf 36* or short form 36 or shortform 36).ti,ab.
14.	(sf20 or sf 20 or short form 20 or shortform20).ti,ab.
15.	(sf12 or sf 12 or short form 12 or shortform12).ti,ab.
16.	(sf8 or sf 8 or short form 8 or shortform8).ti,ab.
17.	or/1-16

C.2 Population search strategies

Medline search terms

1.	exp Gastrointestinal hemorrhage/
2.	exp "Esophageal and gastric varices"/
3.	(hemateme* or haemateme*).ti,ab.
4.	((oesophag* or esophag* or gastric) adj3 (varic* or varix)).ti,ab.
5.	((GI or stomach or gastric or gastrointest* or gastro-intest* or varic* or varix or ulcer* or duod* or oesoph* or esophag*) adj3 (bleed* or blood* or lesion* or haemorrhag* or hemorrhag* or rebleed*)).ti,ab.
6.	((haemorrhag* or hemorrhag*) adj3 (gastric or ulcer or duodenitis)).ti,ab.
7.	or/1-6

Embase search terms

1.	exp Gastrointestinal hemorrhage/
2.	exp Esophagus hemorrhage/
3.	exp Esophagus varices/
4.	Haematemesis/
5.	(hemateme* or haemateme*).ti,ab.
6.	((oesophag* or esophag* or gastric) adj3 (varic* or varix)).ti,ab.
7.	((GI or stomach or gastric or gastrointest* or gastro-intest* or varic* or varix or ulcer* or duod* or oesoph* or esophag*) adj3 (bleed* or blood* or lesion* or haemorrhag* or hemorrhag* or rebleed*)).ti,ab.
8.	or/1-7

Cinahl search terms

S1.	MH Gastrointestinal Hemorrhage+ or MH (Esophageal and Gastric Varices) or MH Hematemesis
S2.	(hematem* or haemateme*)
S3.	((oesophag* or esophag*) and (varic* or varix*))
S4.	(((stomach* or gastric or gastrointest* or gastro-intest* or varic* or varix or ulcer* or occult* or obscur* or duod* or oesoph* or esophag*)) and ((bleed* or blood* or lesion* or haemorrhag* or hemorrhag* or rebleed*)))
S5.	((haemorrhag* or hemorrhag*) and (gastric or ulcer or duodenitis))
S6.	S1 or S2 or S3 or S4 or S5

Cochrane search terms

1.	MeSH descriptor Gastrointestinal Hemorrhage explode all trees
2.	MeSH descriptor Esophageal and Gastric Varices, this term only
3.	(hemateme* or haemateme*):ti,ab,kw
4.	((oesophag* or esophag* or gastric) NEAR/3 (varic* or varix)):ti,ab,kw
5.	((GI or stomach or gastric or gastrointest* or gastro-intest* or varic* or varix or ulcer* or occult* or obscur* or duod* or oesoph* or esophag*) NEAR/3 (bleed* or blood* or lesion* or haemorrhag* or hemorrhag* or rebleed*)):ti,ab
6.	((haemorrhag* or hemorrhag*) NEAR/3 (gastric or ulcer or duodenitis)):ti,ab,kw
7.	(#1 or #2 or #3 or #4 or #5 or #6)

C.3 Searches by specific questions

C.3.1 Initial management and resuscitation

Q. In patients with upper GI bleeding with low level of haemoglobin, pre-endoscopy, what is the most clinical and cost effective threshold and target level at which red blood cell transfusions should be administered to improve outcome?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
UGIB	Red blood cells OR transfusion		RCTs, Systematic Reviews and Observational studies (Medline and Embase only)	All years – 23/9/11

Medline search terms

1.	exp Blood transfusion/
2.	exp Hemoglobins/
3.	(transfus* or retransfus* or hemotransfus* or haemotransfus*).ti,ab.
4.	(hemoglobin* or haemoglobin*).ti,ab.
5.	((blood adj product*1) or (blood adj2 management) or (blood adj2 administ*5) or (blood adj2 component*1) or (blood adj support)).ti,ab.
6.	Erythrocytes/
7.	(red adj2 cell*).ti,ab.
8.	or/1-7

Embase search terms

1.	exp Blood transfusion/
2.	exp Hemoglobin/
3.	(transfus* or retransfus* or hemotransfus* or haemotransfus*).ti,ab.
4.	(hemoglobin* or haemoglobin*).ti,ab.
5.	((blood adj product*1) or (blood adj2 management) or (blood adj2 administ*5) or (blood adj2 component*1) or (blood adj support)).ti,ab.
6.	Erythrocyte/
7.	(red adj2 cell*).ti,ab.
8.	or/1-7

Cinahl search terms

S1.	(MH "Blood Transfusion+")
S2.	(MH "Hemoglobins+")
S3.	(MH "Erythrocytes")
S4.	transfus* or retransfus* or hemotransfus* or haemotransfus*
S5.	hemoglobin* or haemoglobin*
S6.	red N2 cell*
S7.	((blood and product*) or (blood and management) or (blood and administ*) or (blood and component*) or blood support)
S8.	S1 or S2 or S3 or S4 or S5 or S6 or S7

Cochrane search terms

1.	MeSH descriptor Blood Transfusion explode all trees

2.	MeSH descriptor Hemoglobins explode all trees
3.	MeSH descriptor Erythrocytes explode all trees
4.	(transfus* or retransfus* or hemotransfus* or haemotransfus*):ti,ab,kw
5.	(hemoglobin* or haemoglobin*):ti,ab,kw
6.	(red NEAR/2 cell*):ti,ab,kw
7.	((blood product*) or (blood NEAR/2 management) or (blood NEAR/2 administ*) or (blood NEAR/2 component*) or (blood support)):ti,ab,kw
8.	#1 o r#2 or #3 or #4 or #5 or #6 or #7

Q. In patients with upper GI bleeding with low platelet count and / or abnormal coagulation factors, pre endoscopy, what is the most clinical and cost effective threshold and target level at which platelets and clotting factors should be administered to improve outcome?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
UGIB	Coagulation factors OR platelets		RCTs, Systematic Reviews and Observational studies (Medline and Embase only)	All years – 23/9/11

Medline search terms

1.	exp Blood coagulation factors/
2.	*Anticoagulants/tu [Therapeutic Use]
3.	*Electrocoagulation/
4.	clot* factor*.ti,ab.
5.	"factor VII".ti,ab.
6.	coagulat* factor*.ti,ab.
7.	"factor 7".ti,ab.
8.	procoagulant*.ti,ab.
9.	coagulopathy.ti,ab.
10.	or/1-9
11.	Blood platelets/
12.	platelet*.ti,ab.
13.	thrombocyt*.ti,ab.
14.	exp Plasma/
15.	fresh frozen plasma.ti,ab.
16.	prothrombin complex.ti,ab.
17.	(beriplex or octaplex or NovoSeven).ti,ab.
18.	or/11-17
19.	10 or 18

Embase search terms

1.	exp Blood clotting factor/
2.	Anticoagulant therapy/
3.	*Electrocoagulation/
4.	clot* factor*.ti,ab.
5.	"factor VII".ti,ab.
6.	coagulat* factor*.ti,ab.
7.	"factor 7".ti,ab.

8.	procoagulant*.ti,ab.
9.	coagulopathy.ti,ab.
10.	or/1-9
11.	Thrombocyte/
12.	platelet*.ti,ab.
13.	thrombocyt*.ti,ab.
14.	exp Plasma/
15.	fresh frozen plasma.ti,ab.
16.	prothrombin complex.ti,ab.
17.	(beriplex or octaplex or NovoSeven).ti,ab.
18.	or/11-17
19.	10 or 18

Cinahl search terms

S1.	MH Blood Coagulation Factors or MH anticoagulants or MH Electrocoagulation or clot* factor* or factor VII or coagulat* factor* or factor 7 or procoagulant* or coagulopathy
S2.	MH Blood platelets or platelet* or Thrombocyt* or MH plasma or fresh frozen plasma or Prothrombin complex or beriplex or octaplex or NovoSeven
S3.	S1 or S2

Cochrane search terms

1.	MeSH descriptor Blood Coagulation Factors explode all trees
2.	MeSH descriptor Anticoagulants explode all trees with qualifier: TU
3.	MeSH descriptor Electrocoagulation explode all trees
4.	clot* factor*:ti,ab
5.	factor VII:ti,ab
6.	coagulat* factor*:ti,ab
7.	factor 7:ti,ab
8.	procoagulant*:ti,ab
9.	coagulopathy:ti,ab
10.	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)
11.	MeSH descriptor Blood Platelets explode all trees
12.	platelet*:ti,ab
13.	thrombocyt*:ti,ab
14.	MeSH descriptor Plasma explode all trees
15.	fresh frozen plasma:ti,ab
16.	prothrombin complex:ti,ab
17.	beriplex or octaplex or NovoSeven:ti,ab
18.	(#11 OR #12 OR #13OR #14 OR #15 OR #16 OR #17)
19.	(#10 OR #18)

The following two questions were run as one search:

Q. In patients presenting with likely variceal UGIB at initial management, is terlipressin compared to octreocide, somatostatin or placebo the most clinical / cost effective pharmaceutical strategy?

Q. In patients with confirmed variceal UGIB after endoscopic treatment, how long should pharmacological therapy (terlipressin or octreocide) be administered to improve outcome in terms of clinical and cost effectiveness?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
UGIB	Terlipressin OR octreotide OR somatostatin		RCTs and Systematic Reviews (Medline and Embase only)	All years – 23/9/11

Medline search terms

1.	exp Vasopressins/
2.	(terlipressin* or terlypressin* or vasopressin* or lypressin*).ti,ab.
3.	(haemopressin or variquel or glypressin).ti,ab.
4.	or/1-3
5.	exp Octreotide/
6.	exp Somatostatin/
7.	(octreotide* or somatostatin* or sandostatin*).ti,ab.
8.	somatotropin.ti,ab.
9.	or/5-8
10.	4 or 9

Embase search terms

1.	exp Vasopressins/
2.	(terlipressin* or terlypressin* or vasopressin* or lypressin*).ti,ab.
3.	(haemopressin or variquel or glypressin).ti,ab.
4.	or/1-3
5.	exp Octreotide/
6.	exp Somatostatin/
7.	(octreotide* or somatostatin* or sandostatin*).ti,ab.
8.	somatotropin.ti,ab.
9.	or/5-8
10.	4 or 9

Cinahl search terms

S1.	MH Vasopressins+ or MH Octreotide or MH Somatostatin
S2.	terlipressin* or terlypressin* or vasopressin* or lypressin* or haemopressin or variquel or glypressin
S3.	octreotide* or somatostatin* or sandostatin* or somatotropin
S4.	S1 or S2 or S3

Cochrane search terms

1.	MeSH descriptor Vasopressins explode all trees
2.	(terlipressin* or terlypressin* or vasopressin* or lypressin*):ti,ab,kw or (haemopressin or variquel or glypressin):ti,ab,kw
3.	MeSH descriptor Octreotide explode all trees
4.	MeSH descriptor Somatostatin explode all trees
5.	(octreotide* or somatostatin* or sandostatin* or somatotropin*):ti,ab,kw
6.	(#1 OR #2 OR #3 OR #4 OR #5)

C.3.2 Assessment of risks

Q. In patients with GI bleeding (with or without co-morbidities) is there an accurate scoring system to identify which patients are high risk (of mortality, re-bleeding, need for blood transfusion, surgical intervention) and require immediate intervention and those at low risk who can be safely discharged?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
UGIB	Risk scoring systems		None	All years – 23/9/11

Medline search strategy

1.	(risk adj2 engine*).ti,ab.
2.	(risk adj2 equation*).ti,ab.
3.	(risk adj2 calculation*).ti,ab.
4.	(risk adj2 table*).ti,ab.
5.	scor* system*.ti,ab.
6.	(bleed* adj5 scor*).ti,ab.
7.	(risk adj3 (model* or system* or stratif* or scor*)).ti,ab.
8.	*Risk assessment/
9.	*Factor analysis, Statistical/
10.	*Regression analysis/
11.	*Logistic models/
12.	*Survival analysis/
13.	*Analysis of variance/
14.	*Multivariate analysis/
15.	Severity of illness index/
16.	or/1-15
17.	Rockall.ti,ab,au.
18.	(Blatchford or Glasgow).ti,ab,au.
19.	Addenbrooke.ti,ab,au.
20.	17 or 18 or 19
21.	16 and 20

Embase search terms

1.	(risk adj2 engine*).ti,ab.
2.	(risk adj2 equation*).ti,ab.
3.	(risk adj2 calculation*).ti,ab.
4.	(risk adj2 table*).ti,ab.
5.	scor* system*.ti,ab.
6.	(bleed* adj5 scor*).ti,ab.
7.	(risk adj3 (model* or system* or stratif* or scor*)).ti,ab.
8.	*Risk assessment/
9.	*Factor analysis, Statistical/
10.	exp *Regression analysis/
11.	*Statistical model/
12.	exp *Survival/
13.	*Analysis of variance/

14.	*Multivariate analysis/
15.	*Hospitalization/
16.	or/1-15
17.	Rockall.ti,ab,au.
18.	(Blatchford or Glasgow).ti,ab,au.
19.	Addenbrooke.ti,ab,au.
20.	17 or 18 or 19
21.	16 and 20

Cinahl search terms

S1.	SU risk assessment or TX scor* n1 system* or TX risk n2 engine* or TX risk n2 calculat* or TX risk n2 table* or TX risk n2 scor* or TX risk n2 model*

Cochrane Search terms

1.	(risk NEAR/2 (engine* or calculat* or table* or scor* or model* or straifi*)):ti,ab,kw
2.	(scor* NEXT system*):ti,ab
3.	(#1 OR #2)

C.3.3 Timing of endoscopy

Q. In patients with GI bleeding, does endoscopy carried out within 12 hrs of admission compared to 12-24 hours or longer improve outcome in respect of length of hospital stay, risk of rebleeding or mortality?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
UGIB	Endoscopy (gastrointestinal)		RCTs, Systematic Reviews and Observational studies (Medline and Embase only)	All years – 23/9/11

Medline search terms

1.	Gastrointestinal endoscopy/
2.	Esophagoscopy/
3.	Duodenoscopy/
4.	Gastroscopy/
5.	((GI or stomach* or gastric or gastrointest* or gastro-intest* or varic* or varix or ulcer* or duod* or oesoph* or esophag*) adj3 endoscop*).ti,ab.
6.	(OGD or EGD or UGIE or duodenoscop* or gastroscop* or esophagogastroduodenoscop* or oesophagogastroduodenoscop*).ti,ab,hw.
7.	or/1-6

Embase search terms

1.	Gastrointestinal endoscopy/
2.	Esophagoscopy/
3.	Duodenoscopy/
4.	Gastroscopy/
5.	((GI or stomach* or gastric or gastrointest* or gastro-intest* or varic* or varix or ulcer* or duod* or oesoph* or esophag*) adj3 endoscop*).ti,ab.
6.	(OGD or EGD or UGIE or duodenoscop* or gastroscop* or esophagogastroduodenoscop* or oesophagogastroduodenoscop*).ti,ab,hw.

7.	or/1-6

Cinahl search terms

S1.	(MH "Endoscopy, Gastrointestinal")
S2.	(OGD or EGD or UGIE or duodenoscop* or gastroscop* or esophagogastroduodenoscop* or oesophagogastroduodenoscop*)
S3.	((stomach or gastric or gastrointest* or gastro-intest* or varic* or varix or ulcer* or duod* or oesoph* or esophag*)) and endoscop*
S4.	(MH "Gastroscopy")
S5.	(MH "Esophagoscopy")
S6.	S1 OR S2 OR S3 OR S4 OR S5

Cochrane search strategy

1.	MeSH descriptor Endoscopy, Gastrointestinal, this term only
2.	MeSH descriptor Esophagoscopy, this term only
3.	MeSH descriptor Duodenoscopy, this term only
4.	MeSH descriptor Gastroscopy, this term only
5.	((GI or stomach* or gastric or gastrointest* or gastro-intest* or varic* or varix or ulcer* or duod* or oesoph* or esophag*) NEAR/3 endoscop*):ti,ab
6.	(OGD or EGD or UGIE or duodenoscop* or gastroscop* or esophagogastroduodenoscop* or oesophagogastroduodenoscop*):ti,ab,kw
7.	(#1 OR #2 OR #3 OR #4 OR #5 OR #6)

C.3.4 Management of non-variceal bleeding

Q. In patients with non-variceal UGIB are combinations of endoscopic treatments more clinically/cost effective than adrenaline injection alone?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
UGIB	Endoscopic treatment combinations	Adrenalin injections	RCTs and Systematic Reviews (Medline and Embase only)	All years – 23/9/11

Medline search terms

1.	exp Hemostasis, Endoscopic/
2.	Electrocoagulation/
3.	Hemostatic techniques/
4.	Epinephrine/
5.	or/1-4
6.	Thrombin/
7.	Saline solution, Hypertonic/ or Sodium chloride/
8.	Polyethylene glycols/
9.	exp Sclerosing solutions/
10.	Sclerotherapy/
11.	exp Tissue adhesives/
12.	Laser therapy/
13.	or/6-12
14.	exp Injections/

15.	Endoscopy, digestive system/ or Endoscopy, gastrointestinal/ or Duodenoscopy/ or Esophagoscopy/ or Gastroscopy/
16.	(endoscop* adj2 (intervention* or treatment* or therap*)).ti,ab.
17.	or/14-16
18.	13 and 17
19.	(endoscop* adj2 (clip* or hemostat* or hemostasis)).ti,ab.
20.	epinephrine.ti,ab.
21.	(hemoclip* or haemoclip* or endoclip*).ti,ab.
22.	((polidocanol or adrenalin* or saline or dextrose or sclerosant* or sclerosing or thrombin or adhesive* or glue or thermal or mechanical) adj3 (endoscop* or inject*)).ti,ab.
23.	(heaterprobe* or heater probe*).ti,ab.
24.	argon plasma coagulation.ti,ab.
25.	(electrocoagulation or thermocoagulation or electro-coagulation or thermo-coagulation or thermal coagulation).ti,ab.
26.	(heaterprobe* or heater probe* or contact-probe*).ti,ab.
27.	(thermal adj3 device*).ti,ab.
28.	or/19-27
29.	5 or 18 or 28

Embase search terms

1.	exp Electrocoagulation/
2.	Hemostasis/ and (endoscop* or technique*).ti,ab.
3.	*Adrenalin/
4.	Thermocoagulation/
5.	Clip/
6.	(endoscop* adj2 (clip* or hemostat* or hemostasis)).ti,ab.
7.	epinephrine.ti,ab.
8.	(hemoclip* or haemoclip* or endoclip*).ti,ab.
9.	((polidocanol or saline or dextrose or sclerosant* or sclerosing or thrombin or adhesive* or adrenalin* or thermal or mehanical or glue) adj3 (endoscop* or inject*)).ti,ab.
10.	(heaterprobe* or heater probe*).ti,ab.
11.	argon plasma coagulation.ti,ab.
12.	(electrocoagulation or thermocoagulation or electro-coagulation or thermo-coagulation or thermal coagulation).ti,ab.
13.	(heaterprobe* or heater probe* or contact-probe*).ti,ab.
14.	(thermal adj3 device*).ti,ab.
15.	or/1-14
16.	Polidocanol/ or Sclerosing agent/
17.	*Sodium chloride/
18.	exp Sclerotherapy/
19.	exp Tissue adhesive/
20.	Hemostatic agent/ or Thrombin/ or Thrombin derivative/
21.	Low level laser therapy/
22.	or/16-21
23.	exp Injection/
24.	exp Endoscopic therapy/
25.	Gastrointestinal endoscopy/ or Gastroscopy/

26.	Duodenoscopy/
27.	Digestive tract endoscopy/ or Esophagoscopy/
28.	(endoscop* adj2 (intervention* or treatment* or therap*)).ti,ab.
29.	or/23-28
30.	22 and 29
31.	15 or 30

Cinahl search terms

S1.	(MH "Hemostasis, Endoscopic") OR (MH "Electrocoagulation") OR (MH "Hemostatic Techniques") OR (MH "Epinephrine")
S2.	endoscop* N2 hemostat* or endoscop* N2 hemostasis or endoscop* N2 clip* or epinephrine or haemoclip* or hemoclip* or endoclip* or argon plasma coagulation or electrocoagulation or thermocoagulation or electro-coagulation or thermo-coagulation or thermal coagulation or thermal N3 device* or heaterprobe* or heater probe* or contact-probe*
S3.	((polidocanol or saline or dextrose or sclerosant* or sclerosing or thrombin or adhesive* or glue* or adrenalin* or thermal or mechanical) and (endoscop* or inject*))
S4.	S1 or S2 or S3
S5.	(MH "Thrombin") OR (MH "Sclerosing Solutions") OR (MH "sodium chloride") or (MH "Saline Solution, Hypertonic") OR (MH "Polyethylene Glycols") OR (MH "Sclerotherapy") OR (MH "Laser Therapy") OR (MH "Fibrin Tissue Adhesive") OR (MH "Tissue Adhesives")
S6.	(MH "Injections+") OR (MH "Gastroscopy") OR (MH "Esophagoscopy")
S7.	(MH "Endoscopy, Gastrointestinal") OR (MH "Endoscopy, Digestive System")
S8.	endoscop* and (intervention* or treatment* or therap*)
S9.	S6 or S7 or S8
S10.	S5 and S9
S11.	S4 or S10

Cochrane search terms

1.	MeSH descriptor Hemostasis, Endoscopic explode all trees
2.	MeSH descriptor Electrocoagulation, this term only
3.	MeSH descriptor Hemostatic Techniques, this term only
4.	MeSH descriptor Epinephrine, this term only
5.	(endoscop* NEAR/2 (clip* or hemostat* or hemostasis)):ti,ab
6.	(epinephrine or haemoclip* or hemoclip* or endoclip* or "argon plasma coagulation" or heaterprobe* or "heater probe*" or contact-probe* or electrocoagulation or thermocoagulation or electro-coagulation or thermo-coagulation or "thermal coagulation"):ti,ab
7.	(thermal NEXT device*):ti,ab
8.	((polidocanol or saline or dextrose or sclerosant* or sclerosing or thrombin or adrenalin* or thermal or mechanical) NEAR/3 (inject* or endoscop*)):ti,ab
9.	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
10.	MeSH descriptor Thrombin, this term only
11.	MeSH descriptor Sodium Chloride, this term only
12.	MeSH descriptor Polyethylene Glycols, this term only
13.	MeSH descriptor Sclerosing Solutions, this term only
14.	MeSH descriptor Sclerotherapy explode all trees
15.	MeSH descriptor Tissue Adhesives explode all trees
16.	MeSH descriptor Laser Therapy, this term only

17.	(#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)
18.	MeSH descriptor Injections explode all trees
19.	MeSH descriptor Endoscopy, Digestive System, this term only
20.	MeSH descriptor Endoscopy, Gastrointestinal, this term only
21.	MeSH descriptor Duodenoscopy, this term only
22.	MeSH descriptor Esophagoscopy, this term only
23.	MeSH descriptor Gastroscopy, this term only
24.	(endoscop* NEAR/2 (intervention* or therap* or treatment*)):ti,ab
25.	(#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24)
26.	(#17 AND #25)
27.	(#9 OR #26)

The following two questions were run as one search:

Are proton pump inhibitors (PPIs) the most clinical / cost effective pharmaceutical treatment compared to H_2-receptor antagonists (H_2-RAs) or placebo to improve outcome in patients presenting with likely non-variceal Upper Gastrointestinal Bleeding (UGIB) prior and after endoscopic investigation?

Q. Are proton pump inhibitors administered intravenously more clinical / cost effective than administered in tablet form for patients with likely non-variceal UGIB?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
UGIB	Proton pump inhibitors OR H2 receptor-antagonists		RCTs and Systematic Reviews (Medline and Embase only)	All years – 23/9/11

Medline search terms

1.	exp Receptors, histamine H2/
2.	exp Histamine H2 antagonists/
3.	((recept* or histamine*) adj2 H2).ti,ab.
4.	Cimetidine/
5.	(cimetidine or tagamet).ti,ab.
6.	exp Famotidine/
7.	(famotidine or pepcid).ti,ab.
8.	exp Nizatidine/
9.	(nizatidine or axid).ti,ab.
10.	exp Ranitidine/
11.	(ranitidine or zantac).ti,ab.
12.	or/1-11
13.	Proton pump inhibitors/
14.	(proton adj3 pump* adj3 inhibitor*).ti,ab.
15.	Omeprazole/
16.	exp Benzimidazoles/
17.	(omeprazole or benzimidazoles or nexium or esomeprazole or losec or pantoprazole or protium or lansoprazole or zoton or rabeprazole or pariet).ti,ab.
18.	or/13-17
19.	12 or 18

Embase search terms

1.	exp Receptors, histamine H2/
2.	exp Histamine H2 antagonists/
3.	((recept* or histamine*) adj2 H2).ti,ab.
4.	Cimetidine/
5.	(cimetidine or tagamet).ti,ab.
6.	exp Famotidine/
7.	(famotidine or pepcid).ti,ab.
8.	exp Nizatidine/
9.	(nizatidine or axid).ti,ab.
10.	exp Ranitidine/
11.	(ranitidine or zantac).ti,ab.
12.	or/1-11
13.	exp Proton pump inhibitor/
14.	(proton adj5 pump* adj5 inhibitor*).ti,ab.
15.	Esomeprazole/
16.	Omeprazole/
17.	Pantoprazole/
18.	Lansoprazole/
19.	Rabeprazole/
20.	Benzimidazole derivative/
21.	(omeprazole or benzimidazole* or nexium or esomeprazole or losec or pantoprazole or protium or lansoprazole or pariet or rabeprazole or zoton).ti,ab,sh.
22.	or/13-21
23.	12 or 22

Cinahl search terms

S1.	MH "Proton Pump Inhibitors+"
S2.	(proton and pump* and inhibitor*)
S3.	MH "Omeprazole"
S4.	(omeprazole or benzimidazoles or nexium or esomeprazole or losec or pantoprazole or protium or lansoprazole or zoton or rabeprazole or pariet)
S5.	S1 or S2 or S3 or S4
S6.	(recept* or histamine*) and H2
S7.	MH Cimetidine
S8.	MH Famotidine
S9.	(cimetidine or tagamet or Famotidine or pepcid or Nizatidine or axid or Ranitidine or zantac)
S10.	S6 or S7 or S8 or S9
S12.	S5 or S10

Cochrane search terms

1.	MeSH descriptor Proton Pump Inhibitors explode all trees
2.	(proton NEAR/5 pump* NEAR/5 inhibitor*):ti,ab,kw
3.	MeSH descriptor Omeprazole explode all trees
4.	MeSH descriptor Benzimidazoles explode all trees
5.	(omeprazole or benzimidazole or nexium or esomeprazole or losec or pantoprazole or protium or lansoprazole or zoton or rabeprazole or pariet):ti,ab,kw

6.	(#1 OR #2 OR #3 OR #4 OR #5)
7.	MeSH descriptor Receptors, Histamine H2 explode all trees
8.	MeSH descriptor Histamine H2 Antagonists explode all trees
9.	(recept* or histamine*) NEAR H2:ti,ab,kw
10.	MeSH descriptor Cimetidine explode all trees
11.	MeSH descriptor Famotidine explode all trees
12.	MeSH descriptor Nizatidine explode all trees
13.	MeSH descriptor Ranitidine explode all trees
14.	(cimetidine or tagamet):ti,ab,kw or (famotidine or pepcid):ti,ab,kw or (nizatidine or axid):ti,ab,kw or (ranitidine or zantac):ti,ab,kw
15.	(#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)
16.	(#6 OR #15)

The following three questions were run as one search:

Q. In patients with non-variceal UGIB after first endoscopic treatment, is a routine second-look endoscopy more clinically/cost effective than routine clinical follow-up?

Q. In patients with non-variceal UGIB who rebleed after the first endoscopic therapy is repeat endoscopy more clinical / cost effective compared to surgery or embolization/angiography to stop bleeding?

Q. In patients with non-variceal UGIB where endoscopic therapy fails, is angiography/embolization more clinical/cost effective than surgery to stop bleeding?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
UGIB	Gastrointestinal endoscopy OR (endoscopy AND repeat, 2nd look)		RCTs, Systematic Reviews and Observational studies (Medline and Embase only)	All years – 23/9/11

Medline search terms

1.	Gastrointestinal endoscopy/
2.	Esophagoscopy/
3.	Duodenoscopy/
4.	Gastroscopy/
5.	(OGD or EGD or UGIE or duodenoscop* or gastroscop* or esophagogastroduodenoscop* or oesophagogastroduodenoscop*).ti,ab,hw.
6.	or/1-5
7.	endoscop*.ti,ab.
8.	(repeat* or repetition or second look or revisit or retreatment or re-treatment).ti,ab.
9.	7 and 8
10.	6 or 9

Embase search terms

1.	Gastrointestinal endoscopy/
2.	Esophagoscopy/
3.	Duodenoscopy/
4.	Gastroscopy/
5.	(OGD or EGD or UGIE or duodenoscop* or gastroscop* or esophagogastroduodenoscop* or

	oesophagogastroduodenoscop*).ti,ab,hw.
6.	or/1-5
7.	endoscop*.ti,ab.
8.	(repeat* or repetition or second look or revisit or retreatment or re-treatment).ti,ab.
9.	7 and 8
10.	6 or 9

Cinahl search terms

S1.	MH Esophagoscopy or MH Gastroscopy or MH Endoscopy, Gastrointestinal
S2.	OGD or EGD or UGIE or duodenoscop* or gastroscop* or esophagogastroduodenoscop* or oesophagogastroduodenoscop*
S3.	endoscop*
S4.	repeat* or repetition or "second look" or revisit or retreatment or re-treatment
S5.	S3 and S4
S6.	S1 or S2 or S5

Cochrane search terms

1.	MeSH descriptor Endoscopy, Gastrointestinal, this term only
2.	MeSH descriptor Esophagoscopy, this term only
3.	MeSH descriptor Duodenoscopy, this term only
4.	MeSH descriptor Gastroscopy, this term only
5.	(OGD or EGD or UGIE or duodenoscop* or gastroscop* or esophagogastroduodenoscop* or oesophagogastroduodenoscop*):ti,ab
6.	endoscop*:ti,ab.
7.	repeat* or repetition or "second look" or revisit or retreatment or re-treatment:ti,ab.
8.	(#6 AND #7)
9.	(#1 OR #2 OR #3 OR #4 OR #5 OR #8)

C.3.5 Control of bleeding

Q. In patients presenting with UGIB who are already on NSAIDs, clopidogrel, aspirin or dipyridamol (single or combination) what is the evidence that discontinuation compared to continuation of the medication leads to better outcome?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
UGIB	NSAIDs OR clopidogrel OR aspirin OR dipyridamol	Discontinuation	RCTs and Systematic Reviews (Medline and Embase only)	All years – 23/9/11

Medline search terms

1.	exp Anti-Inflammatory agents, Non-Steroidal/
2.	(non-steroidal anti-inflammatory drug* or non-steroidal anti-inflammatory agent* or nonsteroidal anti-inflammatory drug* or nonsteroidal anti-inflammatory agent* or NSAID*).ti,ab.
3.	(aceclofenac or acemetacin or celecoxib or dexibuprofen or dexketoprofen or diclofenac sodium or etodolac or etoricoxib or fenbufen or fenoprofen or flurbiprofen or ibuprofen or indometacin or ketoprofen or mefenamic acid or meloxicam or nabumetone or naproxen or piroxicam or sulindac or tenoxicam or tiaprofenic acid).mp.
4.	(acetylsalicylic acid or aspirin).mp.

5.	(clopidogrel or grepid or plavix).mp.
6.	(dipyridamole or persantin).mp.
7.	or/1-6
8.	(continu* or discontinu* or stop* or halt* or ceas* or cessation).ti,ab.
9.	7 and 8

Embase search terms

1.	exp Nonsteroid antiinflammatory agent/
2.	(non-steroidal anti-inflammatory drug* or non-steroidal anti-inflammatory agent* or nonsteroidal anti-inflammatory drug* or nonsteroidal anti-inflammatory agent* or NSAID*).ti,ab.
3.	(aceclofenac or acemetacin or celecoxib or dexibuprofen or dexketoprofen or diclofenac sodium or etodolac or etoricoxib or fenbufen or fenoprofen or flurbiprofen or ibuprofen or indometacin or ketoprofen or mefenamic acid or meloxicam or nabumetone or naproxen or piroxicam or sulindac or tenoxicam or tiaprofenic acid).mp.
4.	(acetylsalicylic acid or aspirin).mp.
5.	(clopidogrel or grepid or plavix).mp.
6.	(dipyridamole or persantin).mp.
7.	or/1-6
8.	(continu* or discontinu* or stop* or halt* or ceas* or cessation).ti,ab.
9.	7 and 8

Cinahl search terms

S1.	(non-steroidal anti-inflammatory drug* or non-steroidal anti-inflammatory agent* or nonsteroidal anti-inflammatory drug* or nonsteroidal anti-inflammatory agent* or NSAID*)
S2.	(aceclofenac or acemetacin or celecoxib or dexibuprofen or dexketoprofen or diclofenac sodium or etodolac or etoricoxib or fenbufen or fenoprofen or flurbiprofen or ibuprofen or indometacin or ketoprofen or mefenamic acid or meloxicam or nabumetone or naproxen or piroxicam or sulindac or tenoxicam or tiaprofenic acid)
S3.	(acetylsalicylic acid or aspirin)
S4.	(clopidogrel or grepid or plavix)
S5.	(dipyridamole or persantin)
S6.	S1 or S2 or S3 or S4 or S5
S7.	(continu* or discontinu* or stop* or halt* or ceas* or cessation)
S8.	S6 and S7

Cochrane search terms

1.	MeSH descriptor Anti-Inflammatory Agents, Non-Steroidal explode all trees
2.	(non-steroidal anti-inflammatory drug* or non-steroidal anti-inflammatory agent* or nonsteroidal anti-inflammatory drug* or nonsteroidal anti-inflammatory agent* or NSAID*):ti,ab
3.	(aceclofenac or acemetacin or celecoxib or dexibuprofen or dexketoprofen or diclofenac sodium or etodolac or etoricoxib or fenbufen or fenoprofen or flurbiprofen or ibuprofen or indometacin or ketoprofen or mefenamic acid or meloxicam or nabumetone or naproxen or piroxicam or sulindac or tenoxicam or tiaprofenic acid):ti,ab,kw
4.	(acetylsalicylic acid or aspirin):ti,ab,kw
5.	(clopidogrel or grepid or plavix):ti,ab,kw
6.	(dipyridamole or persantin):ti,ab,kw
7.	(#1 OR #2 OR #3 OR #4 OR #5 OR #6)
8.	(continu* or discontinu* or stop* or halt* or ceas* or cessation):ti,ab

9.	(#7 AND #8)

C.3.6 Primary prophylaxis*

Q. For acutely ill patients in high dependency and intensive care units are proton pump inhibitors (PPI) or H_2-receptor antagonists (H_2-RA) more clinically effective compared to placebo (or each other) in the primary prophylaxis of Upper Gastrointestinal Bleeding (UGIB)?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
UGIB	Proton pump inhibitors OR H2 receptor-antagonists		RCTs and Systematic Reviews (Medline and Embase only)	All years – 23/9/11

***Search strategy same as for Management of non-variceal bleeding proton pump inhibitors and H2-receptor agonists**

C.3.7 Management of variceal upper GI bleeding

Searches for the following two questions were run as one search:

Q. IN patients with confirmed gastric varices which primary treatment (endoscopic injection of glue or thrombin and/or transjugular intrahepatic portosystemic shunts [TIPS]) is the most clinical and cost effective to improve outcome?

Q. What is the evidence that TIPS is better than repeat endoscopic therapy or balloon tamponade in patients where the variceal bleed remains uncontrolled?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
UGIB	TIPS OR glue		RCTs and Systematic Reviews (Medline and Embase only)	All years – 23/9/11

Medline search terms

1.	exp Portasystemic shunt, Surgical/ or exp Portasystemic shunt, Transjugular intrahepatic/
2.	((portasystem* or portostystem*) adj3 (anastomosis or shunt*)).ti,ab.
3.	Adhesives/ or exp Tissue adhesives/ or exp Cyanoacrylates/
4.	((gastric adj3 obliteration) or GVO).ti,ab.
5.	cyanoacrylate.ti,ab.
6.	((glue or thrombin) adj3 (endoscop* or inject*)).ti,ab.
7.	tisseel.ti,ab.
8.	Thrombin/
9.	Endoscopy, Gastrointestinal/ and (thrombin or glue*).ti,ab.
10.	or/1-9

Embase search terms

1.	((gastric adj3 obliteration) or GVO).ti,ab.
2.	cyanoacrylate.ti,ab.
3.	((glue or thrombin) adj3 (endoscop* or inject*)).ti,ab.
4.	tisseel.ti,ab.

5.	exp Tissue adhesive/
6.	Thrombin/
7.	Glue/
8.	exp *Endoscopic therapy/ and (thrombin or glue*).ti,ab.
9.	((portasystem* or portosystem*) adj3 anastomosis).ti,ab.
10.	Portosystemic anastomosis/ or Transjugular intrahepatic portosystemic shunt/
11.	((portasystem* or portosystem*) adj3 shunt*).ti,ab.
12.	or/1-11

Cinahl search terms

S1.	gastric N2 obliteration or (GVO or cyanacrylate or tisseel) or ((glue or thrombin) and (inject* or endoscop*))
S2.	(portasystem* or portosystem*) and (anastomosis or shunt*)
S3.	(MH "Endoscopy, Gastrointestinal") and (thrombin or glue or cyanoacrylate or adhesive)
S4.	(MH "Portasystemic Shunt, Surgical"# OR #MH "Tissue Adhesives"# OR #MH "Fibrin Tissue Adhesive"# OR #MH "Adhesives"# OR #MH "Thrombin"#
S5.	S1 or S2 or S3 or S4

Cochrane search terms

1.	MeSH descriptor Portasystemic Shunt, Surgical, this term only
2.	MeSH descriptor Portasystemic Shunt, Transjugular Intrahepatic, this term only
3.	MeSH descriptor Portasystemic Shunt, Transjugular Intrahepatic, this term only
4.	((portasystem* or portosystem*) NEAR/3 (shunt* or anastomosis)):ti,ab
5.	MeSH descriptor Adhesives, this term only
6.	MeSH descriptor Tissue Adhesives explode all trees
7.	(gastric NEAR/3 obliteration):ti,ab
8.	(GVO or cyanoacrylate or tisseel):ti,ab
9.	((glue or thrombin) NEAR/3 (endoscop* or inject*)):ti,ab
10.	MeSH descriptor Thrombin, this term only
11.	MeSH descriptor Endoscopy, Gastrointestinal, this term only
12.	(adhesive* or glue or thrombin or cyanoacrylate):ti,ab
13.	(#11 AND #12)
14.	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #13)

Q. In patients with likely variceal bleeding at initial management are antibiotics better than placebo to improve outcome (mortality, rebleeding, length of hospital stay, rates of infection)?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
UGIB (expanded)	Antibiotics		RCTs and Systematic Reviews (Medline and Embase only)	All years – 23/9/11

***Population was expanded to deal with underlying condition (cirrhosis AND various treatments e.g. TIPS)**

Medline search terms population expansion

1.	exp Liver cirrhosis/
2.	(cirrhos* or cirrhot*).ti,ab.

3.	1 or 2
4.	Portasystemic shunt, Surgical/ or Portasystemic shunt, transjugular intrahepatic/
5.	((portosystemic or portasystemic) adj3 shunt).ti,ab.
6.	(endoscop* adj3 (therap* or inject* or surg*)).ti,ab.
7.	(TIPS or banding or ligation or sclerotherap* or BORTO or GVO or cyanoacrylate* or balloon tamponade or distal splenorenal shunt).ti,ab.
8.	4 or 5 or 6 or 7
9.	3 and 8

Embase search terms population expansion

1.	exp Liver cirrhosis/
2.	(cirrhos* or cirrhot*).ti,ab.
3.	1 or 2
4.	Endoscopic therapy/ or Endoscopic sclerotherapy/
5.	Portosystemic anastomosis/ or Splenorenal shunt/ or Transjugular intrahepatic portosystemic shunt/
6.	((portosystemic or portasystemic) adj3 shunt).ti,ab.
7.	(endoscop* adj3 (therap* or inject* or surg*)).ti,ab.
8.	(TIPS or banding or ligation or sclerotherap* or BORTO or GVO or cyanoacrylate* or balloon tamponade or distal splenorenal shunt).ti,ab.
9.	or/4-8
10.	3 and 9

Cinahl search terms population expansion

S1.	((TIPS or banding or ligation or sclerotherap* or BORTO or GVO or cyanoacrylate* or ballon tamponade or distal splenorenal shunt)) or (portosystemic N3 shunt or portasystemic N3 shunt or endoscop* N3 therap* or endoscop* N3 inject* or endoscop N3 surg*)
S2.	(MH "Liver Cirrhosis+") or ((cirrhos* or cirrhot*))
S3.	S1 AND S2

Cochrane search terms population expansion

1.	MeSH descriptor Liver Cirrhosis explode all trees
2.	(cirrhos* or cirrhot*):ti,ab
3.	(#1 OR #2)
4.	((portosystemic or portasystemic) NEAR/3 shunt):ti,ab
5.	(endoscop* NEAR/3 (therap* or inject* or surg*)):ti,ab
6.	(TIPS or banding or ligation or sclerotherap* or BORTO or GVO or cyanoacrylate* or "balloon tamponade" or "distal splenorenal shunt"):ti,ab
7.	(#4 OR #5 OR #6)
8.	(#3 AND #7)

Intervention terms

Medline search terms

1.	Antibiotic prophylaxis/
2.	((antibiotic* or antibacteri*) adj5 (prophyl* or prevent* or pre-treat* or pretreat* or pre treat* or pre medic* or treat* or therap* or premedic* or pre-medic*)).ti,ab.
3.	exp Cephalosporins/
4.	exp Quinolones/

5.	(cephalosporin* or quinolone* or ceftriaxone or ciprofloxacin or ciproxin or norfloxacin or cefotaxime or ofloxacin or co-amoyclav or co-amoxiclav or augmentin).ti,ab.
6.	or/1-5

Embase search terms

1.	Antibiotic prophylaxis/
2.	((antibiotic* or antibacteri*) adj5 (prophyl* or prevent* or pretreat* or pre-treat* or pre treat* or treat* or therap* or pre medic* or premedic* or pre-medic*)).ti,ab.
3.	exp Cephalosporin derivative/
4.	exp Quinolone derivative/
5.	(cephalosporin* or quinolone* or ceftriaxone or ciprofloxacin or ciproxin or norfloxacin or cefotaxime or ofloxacin or co-amoyclav or co-amoxiclav or augmentin).ti,ab.
6.	or/1-5

Cinahl search terms

S1.	((antibiotic* or antibacteria*) and (prevent* or prophyl* or pre treat* or pre-treat* or pretreat* or treat* or pre-medic* or premedic* or pre medic* or therap*)) or ((cephalosporin* or quinolone* or ceftriaxone or ciprofloxacin or ciproxin or norfloxacin or cefotaxime or ofloxacin or co-amoxyclav or co-amoxiclav or augmentin))
S2.	(MH "Antibiotic Prophylaxis") OR (MH "Cephalosporins+") OR (MH "Antiinfective Agents, Quinolone+")
S3.	S1 OR S2

Cochrane search terms

1.	MeSH descriptor Antibiotic Prophylaxis explode all trees
2.	(antibiotic* NEAR (prophyl* or treat* or pre-treat* or "pre treat*" or pretreat* or therap* or "pre medic*" or premedic* or pre-medic* or prevent*)):ti,ab
3.	(antibacteri* NEAR (agent* or prophyl* or pretreat* or "pre treat*" or pre-treat* or treat* or therap* or premedic* or pre-medic* or "pre medic*" prevent*)):ti,ab
4.	MeSH descriptor Cephalosporins explode all trees
5.	MeSH descriptor Quinolones explode all trees
6.	(cephalosporin* or quinolone* or ceftriaxone or ciprofloxacin or ciproxin or norfloxacin or cefotaxime or ofloxacin or co-amoxyclav or co-amoxiclav or augmentin):ti,ab
7.	(#1 OR #2 OR #3 OR #4 OR #5 OR #6)

Q. In patients with confirmed oesophageal varices is band ligation superior to injection sclerotherapy in terms of re-bleeding and death?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
UGIB	Sclerotherapy	Band ligation	None	All years – 23/9/11

Medline search terms

1.	exp Sclerotherapy/
2.	exp Sclerosing solutions/
3.	exp Hemostasis, Endoscopic/
4.	(sclerotherap* or scleroligat* or sclerosant*).ti,ab.
5.	or/1-4
6.	exp Ligation/
7.	(ligation adj3 (variceal or endoscop* or band)).ti,ab.
8.	6 or 7

9.	5 and 8

Embase search terms

1.	exp Sclerotherapy/
2.	exp Sclerosing agent/
3.	(hemostas* adj2 endoscop*).ti,ab.
4.	(sclerotherap* or sclerolig* or sclerosant*).ti,ab.
5.	or/1-4
6.	exp Ligation/
7.	exp Experimental ligation/
8.	exp Pylorus ligation/
9.	(ligation adj3 (variceal or endoscop* or band)).ti,ab.
10.	or/6-9
11.	5 and 10

Cinahl search terms

S1.	(sclerotherap* or scleroligat* or sclerosant*)
S2.	(sclerosing and (agent* or solution*))
S3.	(endoscop* n2 hemostas*)
S4.	S1 or S2 or S3
S5.	ligation
S6.	S4 and S5

Cochrane search terms

1.	MeSH descriptor Sclerotherapy explode all trees
2.	MeSH descriptor Sclerosing Solutions explode all trees
3.	MeSH descriptor Hemostasis, Endoscopic explode all trees
4.	(sclerotherap* or sclerolig* or sclerosant*):ti,ab
5.	(#1 OR #2 OR #3 OR #4)
6.	MeSH descriptor Ligation explode all trees
7.	(ligation NEAR/3 (variceal or endoscop* or band)):ti,ab
8.	(#6 OR #7)
9.	(#5 AND #8)

C.3.8 Information for patients and carers

Q. What information is needed for patients with acute upper gastrointestinal bleeding and their carers (including information at presentation, prophylaxis and information for carers)?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Study filter used	Date parameters
Hematemesis OR melena*	Patient experience (Medline and Embase only)	All years – 23/9/11

***Search constructed using a non-standard UGIB population (below).**

Medline population search terms

1.	exp Hematemesis/
2.	(hemateme* or haemateme*).ti,ab.

3.	Melena/
4.	(melen* or melaen*).ti,ab.
5.	or/1-4

Embase population search terms

1.	exp Hematemesis/
2.	(hemateme* or haemateme*).ti,ab.
3.	Melena/
4.	(melen* or melaen*).ti,ab.
5.	or/1-4

PsycINFO population search terms

1.	(hemateme* or haemateme*).ti,ab.
2.	(melen* or melaen*).ti,ab.
3.	Melena/
4.	or/1-3

Cochrane population search terms

1.	MeSH descriptor Hematemesis explode all trees
2.	(hemateme*):ti,ab,kw or (haemateme*):ti,ab,kw
3.	MeSH descriptor Melena explode all trees
4.	(melen*):ti,ab,kw or (melaen*):ti,ab,kw
5.	(#1 OR #2 OR #3 OR #4)

Cinahl population terms

S1.	MH Melena OR melen* OR melaen*
S2.	MH Hematemesis OR Hemateme* OR haemateme*
S3.	(S1 or S2)

C.4 Economics search

C.4.1 Economic reviews

Economic searches were conducted in Medline and Embase by combining the standard population with the economics filter (A.1.5) and limiting by date range (see table below). For, HEED and for NHS EED and HTA (on CRD) a standard population was run without a date limitation. Search terms for CRD and HEED are given below.

Population	Study filter used	Date parameters
UGIB	Economic (Medline and Embase only)	• Medline and Embase: 2009-20/7/11 • CRD EED and HTA: All years-20/7/11 • HEED: All years-20/7/11

CRD search terms

1.	(GI OR stomach OR gastric OR gastrointest* OR gastro-intest* OR varic* OR varix OR ulcer* OR duod* OR oesoph* OR esophag*) AND (bleed* OR blood* OR lesion* OR haemorrhag* OR hemorrhag* OR rebleed*)

HEED search terms

1.	AB=(GI OR stomach OR gastric OR gastrointest* OR gastro-intest* OR varic* OR varix OR ulcer* OR duod* OR oesoph* OR esophag*) AND (bleed* OR blood* OR lesion* OR haemorrhag* OR hemorrhag* OR rebleed*)
2.	TI=(GI OR stomach OR gastric OR gastrointest* OR gastro-intest* OR varic* OR varix OR ulcer* OR duod* OR oesoph* OR esophag*) AND (bleed* OR blood* OR lesion* OR haemorrhag* OR hemorrhag* OR rebleed*)
3.	CS=1 or 2

C.4.2 Quality of life reviews

Quality of life (QOL) searches were conducted in Medline and Embase by combining the standard population with the QOL filter (A.1.6) without a date limitation.

Population	Study filter used	Date parameters
UGIB	Quality of life	• Medline and Embase: All years-20/7/11

Appendix D: Review Protocols

D.1 Initial management

D.1.1 Resuscition – red blood cells

Review Protocol – Blood products (red cells)	
Component	Description Initial administration of red blood cells in the resuscitation of patients with upper GI bleeding.
Review question	In patients with upper GI bleeding with low level of haemoglobin, pre-endoscopy, what is the most clinical and cost effective threshold and target level at which red blood cell transfusions should be administered to improve outcome?
Population	Patients with upper GI bleeding with low levels of haemoglobin No particular subgroups from the outset (see analysis details for other subgroups to assess heterogeneity of results)
Intervention	Red blood cells – any level
Comparison	Red blood cells – no transfusions, low level, high level
Outcomes	Mortality (short and longer follow-up if reported – i.e. 24 hrs, within 30 days and >30 days) Rebleeding Length of hospital stay (days in ICU, total days in hospital) Adverse events (any major events, particularly myocardial infarction etc)
Exclusion	Any exclusion criteria?
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL Randomised controlled trials (RCTs) and observational studies will be considered (no particular year or sample size restrictions), SRs Studies will be restricted to English language only
Search terms	Red blood cells – see search strategy in the Appendix
The review strategy	RCTs (including small scale studies) and observational studies?
Analysis	In case of heterogeneity of result subgroup for follow-up length, variceal / non-variceal bleeding, in-hospital bleeding

Review Protocol – Blood products (red cells)	
Key papers	Key papers for this question: None specified by GDG members during protocol development

D.1.2 Resuscitation – platelets and / or coagulation factors

Review Protocol – Blood products (platelets and coagulation factors)	
Component	Description Initial administration of platelets and / or clotting factors in the resuscitation of patients with upper GI bleeding.
Review question	In patients with upper GI bleeding with low platelet count and / or abnormal coagulation factors, pre endoscopy, what is the most clinical and cost effective threshold and target level at which platelets and clotting factors should be administered to improve outcome?
Population	Patients with upper GI bleeding with low platelet count and / or abnormal coagulation factors No particular subgroups from the outset (see analysis details for other subgroups)
Intervention	Platelets / coagulation factors (any)
Comparison	Platelets / coagulation factors – none, low level or high level
Outcomes	Mortality (short and longer follow-up if reported – i.e. 24 hrs, within 30 days and >30 days) Failure to control bleeding Emergency procedures Rebleeding (short, i.e. within 24 hrs and long term – see mortality) Length of hospital stay (days in ICU, total days in hospital) Major adverse events (related to thromboembolic events) Fatal adverse events (related to bleeding, infection or liver desease)
Exclusion	Any exclusion criteria?
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL Randomised controlled trials (RCTs) and observational studies will be considered (no particular year or sample size restrictions), SRs Studies will be restricted to English language only
Search terms	Platelets / coagulation factors
The review strategy	RCTs (including small scale studies) and observational studies?
Analysis	In case of heterogeneity subgroups according to length of follow-up, variceal / non-variceal bleeding, in hospital bleeding or co-morbidities will be

Review Protocol – Blood products (platelets and coagulation factors)	
	considered as well as severity of cirrhosis for patient groups with variceal bleeding (i.e. number of patients with Child-Pugh GRADE C or percentage of patients), level of administered platelet / coagulation factor if applicable
Key papers	Key papers for this question: None specified by GDG members

D.1.3 Terlipressin compared to placebo, octreotide or somatostatin

Review Protocol – Pharmacological initial treatment	
Component	Description What is the best pharmacological treatment for likely variceal bleeding at the initial stage of management?
Review question	In patients presenting with likely variceal UGIB at initial management, is terlipressin (glypressin) compared to octreotide, somatostatin or placebo the most clinical / cost effective pharmaceutical strategy?
Population	Adults with stigmata of chronic liver disease or previous variceal bleeding with symptoms of UGIB No particular subgroups from the outset (see analysis details for other subgroups)
Intervention	Terlipressin (Glypressin)
Comparison	Octreotide / Placebo/Somatostatin
Outcomes	Mortality Failure to achieve initial haemostasis Rebleeding need for transfusion (plasma, red cells etc) need for additional procedures / treatments (tamponade, sclerotherapy or TIPS) Length of hospital stay Adverse events (adverse events causing death and adverse events causing withdrawal from treatment)
Exclusion	Patients with variceal bleeding due to schistosomiasis
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL Only randomised controlled trials (RCTs) will be considered (no particular year or sample size restrictions), SRs Studies will be restricted to English language only
Search terms	Terlipressin (glypressin) Octreotide Somatostatin

Review Protocol – Pharmacological initial treatment	
	TIPS UGIB population
The review strategy	RCTs (including small scale studies) Outcomes are usually reported ccording to BAVENO criteria and should therefore be comparable across studies
Analysis	Subgroups according to length of follow-up or with cirrhosis severity (if not reported as a subgroup in the study according to proportion of patients classified as Child-Pugh Grade C)
Key papers	Key papers for this question: Cochrane review

D.1.4 Terlipressin treatment duration

Review Protocol – Duration of Pharmacological Treatment	
Component	Description What is the best duration for pharmacological treatment for patients with confirmed variceal bleeding?
Review question	In patients with confirmed variceal UGIB after endoscopic treatment, how long should pharmacological therapy (terlipressin or octreocide) be administered to improve outcome in terms of clinical and cost effectiveness?
Population	Adults with stigmata of chronic liver disease or previous variceal bleeding with symptoms of UGIB No particular subgroups from the outset (see analysis details for other subgroups)
Intervention	Terlipressin according to duration length
Comparison	Terlipressin with a different comparison treatment duration
Outcomes	Mortality Failure to achieve initial haemostasis Rebleeding need for transfusion (plasma, red cells etc) need for additional procedures / treatments (tamponade, sclerotherapy or TIPS) Length of hospital stay Adverse events (adverse events causing death and adverse events causing withdrawal from treatment)
Exclusion	Any exclusion criteria?
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL Only randomised controlled trials (RCTs) will be considered (no particular year or sample size restrictions), SRs

Review Protocol – Duration of Pharmacological Treatment	
	Studies will be restricted to English language only
Search terms	Terlipressin Octreotide TIPS UGIB population
The review strategy	RCTs (including small scale studies)
Analysis	Subgroups according to length of follow-up or with cirrhosis severity (according to proportion of patients classified as Child-Pugh Grade C)
Key papers	Key papers for this question:

D.2 Assessment of risk

Review Protocol – Upper GI bleeding risk scoring	
Component	Description To assess the evidence for different risk stratification scoring systems in upper GI bleeding
Review question	In patients with GI bleeding (with or without comorbidities) is there an accurate scoring system (Rockall, Blatchford [aka Glasgow], Addenbrooke) to identify which patients are high risk (of mortality, rebleeding, need for blood transfusion, surgical intervention) and require immediate intervention and those at low risk who can be safely discharged?
Population	Any patients with upper GI bleeding
Risk score	Rockall (pre and post endoscopy)
Comparison risk score	Blatchford, Addenbrooke
Outcomes	Sensitivity, specificity and other diagnostic accuracy measures for: rebleeding mortality blood transfusion surgical / endoscopic intervention
Search strategy	The databases to be searched are, Medline, Embase, The Cochrane Library,

Review Protocol – Upper GI bleeding risk scoring	
	CINAHL, Registry databases. RCT's Cohort studies will be considered if no RCT evidence available Retrospective reviews of records Case controls studies Studies will be restricted to English language only No date restriction will be applied. Databases will be searched from their date of origin
Search terms	Upper GI population Rockall, Blatchford or Addenbrooke
The review strategy	Due to the nature of the question the evidence base from RCTs would be small. Therefore all other types of study designs are included
Analysis	Area under the curve analysis for various population based studies Comparison and validation in other countries
Key papers	Rockall et al. Risk assessment after acute upper gastrointestinal haemorrhage. Gut, 1996, 38, 316-21. Blatchford et al. A risk score to predict need for treatment for upper gastrointestinal haemorrhage. Lancet, 2000, 356, 1318-21. Cameron et al. Three-year prospective validation of a pre-endoscopic risk stratification in patients with acute upper gastronintestinal haemorrhage. Eurp. J Gastroent & Hepat, 2002, 14(5), 497-501.

D.3 Timing of endoscopy

Review Protocol – Timing of endoscopy	
Component	Description To estimate the medical and cost effectiveness early compared to late endoscopy
Review question	In patients with GI bleeding, does endoscopy carried out within 12 hrs of admission compared to 12-24 hours or longer improve outcome in respect of length of hospital stay, risk of rebleeding or mortality?
Population	Patients with upper GI bleeding
Intervention	Early endoscopy
Comparison	Late endoscopy

Review Protocol – Timing of endoscopy	
Outcomes	Mortality Rebleeding Surgery Blood transfusion requirements Length of hospital stay
Search strategy	The databases to be searched are, Medline, Embase, The Cochrane Library, CINAHL, Registry databases. RCT's Cohort studies, retrospective reviews of records, ase controls studies and other non-RCT studies will be considered if no RCT evidence available Studies will be restricted to English language only No date restriction will be applied. Databases will be searched from their date of origin
Search terms	Endoscopy, Gastrointestinal/ (MED) Gastrointestinal Endoscopy/ (EMB) Esophagoscopy/ (MED + EMB) Duodenoscopy/ (MED + EMB)) Gastroscopy/ (MED + EMB)) ((GI or stomach* or gastric or gastrointest* or gastro-intest* or varic* or varix or ulcer* or duod* or oesoph* or esophag*) adj3 endoscop*).ti,ab. (OGD or EGD or UGIE or duodenoscop* or gastroscop* or esophagogastroduodenoscop* or oesophagogastroduodenoscop*).ti,ab,hw.
The review strategy	Due to the nature of the question the evidence base from RCTs would be small. Therefore all other types of study designs are considered according to the search strategy section which specifies how study types will be selected (i.e. non-RCT data to be considered only if no RCT studies are available).
Analysis	According to the time frame of endoscopy (below and above 12 hours) According to risk stratification (haemodynamically stable, low or high Rockall score)
Key papers	Spiegel BMR, Vakil NB, Ofman JJ. Endoscopy for acute nonvariceal upper gastrointestinal tract hemorrhage: Is sooner better? A systematic review. Arch Intern Med. 2001; 161(11):1393-1404. Tsoi KKF, Ma TKW, Sung JJY. Endoscopy for upper gastrointestinal bleeding: How urgent is it? Nature Reviews Gastroenterology and Hepatology. 2009; 6(8):463-469.

D.4 Management of non-variceal upper GI bleeding

D.4.1 Combination treatments

Review Protocol – Combination treatments for non-variceal bleeding	
Component	Description Combinations of thermal / mechanical and adrenalin / thrombin injections compared to injection of adrenaline alone for non-variceal UGIB
Review question	In patients with non-variceal UGIB are combinations of endoscopic treatments more clinically / cost effective than adrenaline injection alone and if so is a particular combination more effective than another?
Population	Patients with non-variceal UGIB
Intervention	Combinations of thermal / mechanical and adrenalin / thrombin injections
Comparison	Adrenaline injection alone
Outcomes	Mortality (in ICU / in hospital) Failure to achieve haemostasis Rebleeding Emergency additional treatment Blood transfusions Adverse events (discontinuation, prolongation of ICU stay)
Exclusion	Any particular exclusions?
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL Only randomised controlled trials (RCTs) will be considered (year restriction from 1990 onwards – endoscopic procedures were not the same prior to this), SRs Studies will be restricted to English language only
Search terms	
The review strategy	RCTs (including small scale studies)
Analysis	Subgroup by type of combination
Key papers	Cochrane review

D.4.2 Proton pump inhibitors

Review Protocol – Proton Pump Inhibitors

Review Protocol – Proton Pump Inhibitors	
Component	Description How effective are Proton pump inhibitors as initial and post endoscopic?
Review question	What is the most clinical / cost effective pharmaceutical treatment (Proton Pump Inhibitors compared to H2 receptor antagonists or placebo) to improve outcome in patients presenting with likely non-variceal UGIB pre- and post endoscopic investigation?
Population	Adults with a symptoms of non-variceal upper GI bleeding Subgroups: Pre and post endoscopy patients
Intervention	Proton Pump Inhibitors (intravenous or oral)
Comparison	Placebo or H2-receptor antagonists
Outcomes	Mortality Short and longer follow up Rebleeding Short and longer follow up need for transfusion surgery for continued bleeding Length of hospital stay
Exclusion	Excluded outcome: Stigmata of recent haemorrhage
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL Only randomised controlled trials (RCTs) will be considered (no particular year or sample size restrictions) Studies will be restricted to English language only
Search terms	proton pump inhibitors/ (MED) proton pump inhibitor/ (EMB) (proton adj3 pump*).ti,ab. esomeprazole/ (EMB) esomeprazole.ti,ab omeprazole/ (EMB) omeprazole.ti,ab nexium.ti,ab (italics indicate brand names) losec.ti,ab pantoprazole/ (EMB) 102625-70-7.mp. (pantoprazole CAS Registry/EC Number (RN) in MED) = supplementary concept in MeSH

Review Protocol – Proton Pump Inhibitors	
	pantoprazole.ti,ab protium.ti,ab Lansoprazole Zoton Rabeprazole sodium Pariet
The review strategy	RCTs (including small scale studies)
Analysis	1. According to pre- or post endoscopy 2. According to length of follow up for rebleeding and mortality
Key papers	Key papers for this question: Sreedharan et al. Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding. The Cochrane Library,2010,1,1-67. Leontiadis et al. Proton Pump inhibitor therapy for peptic ulcer bleeding: Cochrane collaboration meta analysisof randomized controlled trials. Mayo Clin Proc 2007;82(3):286-96.

D.4.2.1 Proton pump inhibitors – route of administration

Review Protocol – Proton Pump Inhibitors (PPIs) mode of administration	
Component	Description Which mode of PPI administration is most effective?
Review question	What is the most clinical / cost effective mode of pharmaceutical treatment (intravenous or oral administration) to improve outcome in patients presenting with likely non-variceal UGIB pre- and post endoscopic investigation?
Population	Adults with a symptoms of upper GI bleeding Subgroups: Pre and post endoscopy patients
Intervention	PPI intravenous
Comparison	PPI oral
Outcomes	Mortality Short and longer follow up Rebleeding Short and longer follow up need for transfusion

Review Protocol – Proton Pump Inhibitors (PPIs) mode of administration	
	surgery for continued bleeding Length of hospital stay
Exclusion	Excluded outcome: Stigmata of recent haemorrhage
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL Only randomised controlled trials (RCTs) will be considered (no particular year or sample size restrictions) Studies will be restricted to English language only
Search terms	Same search terms as general PPI search
The review strategy	RCTs (including small scale studies)
Analysis	1. According to pre- or post endoscopy
Key papers	Key papers for this question: Leontiadis GI, Sreedharan A, Dorward S et al. Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding. Health Technol Assess. 2007; 11(51):iii-126.

D.4.3 Treatment options after first or failed endoscopy

D.4.3.1 Routine second look

Review Protocol – Routine second look endoscopy	
Component	Description Routine second look?
Review question	In patients with UGIB after first endoscopic treatment, is a routine second-look endoscopy more clinically / cost effective than routine clinical follow-up?
Population	Patients with non-variceal UGIB after first endoscopic treatment
Intervention	Routine second look (defined as a scheduled follow-up endoscopy regardless of whether or not further bleeding has occurred)
Comparison	Routine follow-up
Outcomes	Mortality Failure to achieve initial haemostasis Rebleeding need for transfusion

Review Protocol – Routine second look endoscopy	
	need for surgery Length of hospital stay Adverse events (treatment complications)
Exclusion	Any exclusion criteria?
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL Only randomised controlled trials (RCTs) will be considered (no particular year or sample size restrictions), SRs Studies will be restricted to English language only
Search terms	UGIB population
The review strategy	 RCTs (including small scale studies)
Analysis	For mortality subgroup by length of follow-up if stated
Key papers	Key papers for this question: None specified at the protocol GDG meeting

D.4.3.2 Re-treatment

Review Protocol – Repeat endoscopic treatment	
Component	Description Repeat endoscopy
Review question	In patients who rebleed after the first endoscopic therapy is repeat endoscopy more clinical / cost effective compared to surgery or embolisation / angiography to stop bleeding?
Population	Patients with non-variceal UGIB after their first endoscopy
Intervention	Repeat endoscopic treatment
Comparison	Surgery, embolisation, angiography
Outcomes	Mortality Failure to achieve initial haemostasis Rebleeding need for transfusion salvage surgery Length of hospital stay Adverse events (treatment complications)
Exclusion	Any exclusion criteria?
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL

Review Protocol – Repeat endoscopic treatment	
	Only randomised controlled trials (RCTs) will be considered (no particular year or sample size restrictions), SRs Studies will be restricted to English language only
Search terms	UGIB population
The review strategy	RCTs (including small scale studies)
Analysis	In case of heterogeneity subgroup by type of re-treatment, length of follow-up
Key papers	Key papers for this question: None specified by GDG members at the protocol stage

D.4.3.3 Embolisation vs. surgery for uncontrolled bleeding

Review Protocol – Failed first endoscopy	
Component	Description Failed endoscopy
Review question	In patients where endoscopic therapy fails is angiography / embolisation more clinical / cost effective than surgery to stop bleeding?
Population	Patients with non-variceal UGIB where the treatment has failed and bleeding was not controlled
Intervention	Angiography / embolisation
Comparison	Surgery
Outcomes	Mortality Failure to achieve initial haemostasis Rebleeding Need for transfusion Salvage surgery (additional emergency procedures) Length of hospital stay Adverse events (treatment complications)
Exclusion	Any exclusion criteria?
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL Randomised controlled trials (RCTs) will be considered and observational studies (no particular year or sample size restrictions), SRs

Review Protocol – Failed first endoscopy	
	Studies will be restricted to English language only
Search terms	UGIB population
The review strategy	Due to the nature of the patient population it is not likely that there are any RCT studies to review therefore observational studies are also included
Analysis	Data from observational studies will not be pooled
Key papers	Key papers for this question: None specified at GDG meeting

D.5 Control of bleeding and prevention of rebleeding

Review Protocol – Continuation / discontinuation of NSAIDs, Clopidogrel, aspirin, dipyridamol	
Component	Description Continuation / discontinuation of concurrent treatment in UGIB management
Review question	In patients presenting with UGIB who are already on NSAIDs, Clopidogrel, Aspirin or dipyridamol (single or combination) what is the evidence that discontinuation compared to continuation of the medication leads to better outcome?
Population	Adults with upper GI bleeding on any of the medications in the review question
Intervention	Continuation
Comparison	Discontinuation
Outcomes	Mortality Rebleeding Other procedures to control bleeding need for transfusion Length of hospital stay Major adverse events (acute coronary syndrome, stroke)
Exclusion	
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL Only randomised controlled trials (RCTs) will be considered (no particular year or sample size restrictions), SRs Studies will be restricted to English language only

Review Protocol – Continuation / discontinuation of NSAIDs, Clopidogrel, aspirin, dipyridamol	
Search terms	UGIB population on one or more of the named medications
The review strategy	RCTs (including small scale studies), also observational studies
Analysis	Patients on NSAIDs separate to patients on anticoagulants
Key papers	Key papers for this question: Kwok et al., Management of anticoagulation before and after gastrointestinal endoscopy.(2009) Am J Gastoenterol. 104; 3085-3097. Veitch, AM, et al. Guidelines for the management of anticoagulant and antiplatelet therapy in patients undergoing endoscopy procedures. (2008); Gut (57),1322-1329.

D.6 Primary prophylaxis

Review Protocol – PPI for UGIB prophylaxis for high dependency / intensive care patients	
Component	Description PPI treatment in UGIB prophylaxis in intensive care
Review question	For acutely ill patients in high dependency and intensive care units are Proton Pump Inhibitors (PPIs) or H2-receptor antagonists more clinically effective compared to placebo (or each other) in the primary prophylaxis of Upper Gastrointestinal Bleeding (UGIB)?
Population	Patients in high dependency / intensive care units: Patients who require mechanical ventilation Additionally patients with at least 1 of the following (if only exactly 1 patients would be at a lower risk subgroup): Sepsis or hypotension; Hepatic or renal failure; Burns over 35% of total body surface area; Head trauma with Glasgow Coma Scale < 10; Multiple trauma
Intervention	PPI or H2-RA (include patients on sucralfate)
Comparison	Placebo (H2-RA vs. placebo or PPI vs. placebo and PPI vs. H2-RA)
Outcomes	Primary outcome: Upper GI bleeding Secondary outcomes Ventilator associated pneumonia Mortality (in ICU in hospital) Duration of ICU stay Duration of intubation Blood transfusions

Review Protocol – PPI for UGIB prophylaxis for high dependency / intensive care patients	
	Adverse events
Exclusion	People already on ICU for bleeding
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL Only randomised controlled trials (RCTs) will be considered (no particular year or sample size restrictions), SRs Studies will be restricted to English language only
Search terms	
The review strategy	RCTs (including small scale studies)
Analysis	Subgroup by type severity of critical illness for instance according to risk factors
Key papers	Key papers for this question: Lin, et al. The efficacy and safety of proton pump inhibitors vs histamine-2 receptor antagonists for stress ulcer bleeding prophylaxis among critical care patients: a meta-analysis. (2010). Critical Care Medicine, 38 (4) 1197-1205.

D.7 Management of variceal upper GI bleeding

D.7.1 Antibiotics

Review Protocol – Initial antibiotic treatment for likely variceal bleeding	
Component	Description Antibiotic treatment prior to endoscopy for variceal bleeding
Review question	In patients with likely variceal bleeding at initial management are antibiotics better than placebo to improve outcome (mortality, rebleeding, length of hospital stay, rates of sepsis)?'
Population	Patients with likely variceal bleeding
Intervention	Antibiotic treatment (which types?)
Comparison	Other antibiotics and placebo comparisons
Outcomes	Mortality (in ICU in hospital) Infection related mortality Rebleeding Rate of patients with any infections Bacteremia Spontaneous bacterial peretonitis Blood transfusions Length of hospital stay Rate of sepsis

Review Protocol – Initial antibiotic treatment for likely variceal bleeding	
	Adverse events (resistence, c-diff) (will be of particular importance)
Exclusion	Patients with variceal bleeding due to schistosomiasis
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL Only randomised controlled trials (RCTs) will be considered (no particular year or sample size restrictions), SRs Studies will be restricted to English language only
Search terms	Cephalosporin quinolone, comoxyclav ciproxin, nolfloxcecillin and use search strategy for antibiotic prophylaxis from Cochrane below
The review strategy	RCTs (including small scale studies)
Analysis	In case of heterogeneity subgroup by studies with higher or lower proportions of patients with severe cirrhosis as indicated by Child-Pugh C grade
Key papers	Key papers for this question: Cochrane meta-analysis Chavez-Tapia, NC Antibiotic prophylaxis for cirrhotic patients with Upper GI bleeding 2010

D.7.2 Band ligation vs. sclerotherapy

Review Protocol – Band ligation vs. sclerotherapy for oesophageal varices	
Component	Description Treatment of confirmed oesophageal varices.
Review question	In patients with confirmed oesophageal varices is band ligation superior to injection sclerotherapy in terms of rebleeding and death?
Population	Adults with confirmed oesophageal varices and upper GI bleeding
Intervention	Band ligation
Comparison	Injection sclerotherapy
Outcomes	Mortality Rebleeding Treatment failure (no initial hemostasis) Other procedures to control bleeding need for transfusion Length of hospital / ICU stay Number of sessions to eradication of varices Adverse events (major or fatal)

Review Protocol – Band ligation vs. sclerotherapy for oesophageal varices	
	Adverse events - stricture
Exclusion	Patients with variceal bleeding due to schistosomiasis
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL Only randomised controlled trials (RCTs) will be considered (no particular year or sample size restrictions), SRs Studies will be restricted to English language only
Search terms	UGIB population restricted to oesophageal variceal bleeding
The review strategy	RCTs
Analysis	Any particular strategies? Mortality by follow-up length if reported (0-3 mths, 3 mths -1 yr, > 1 yr) In case of heterogeneity analyse by severity of cirrhosis – percentage of patients with Child-Pugh class / grade C
Key papers	Key papers Laine & Cook. Endoscopic Ligation Compared with Sclerotherapy for Treatment of Esophageal Variceal Bleeding A Meta-Analysis (1995). Annals of internal medicine. 123 (4), 280-287.

D.7.3 TIPS

Review Protocol – Primary treatment for confirmed gastric varices - TIPS	
Component	Description Endoscopic injections of glue or thrombin and / or transjugular intrahepatic protosystemic shunts for gastric varices
Review question	In patients with confirmed gastric varices which primary treatment (endoscopic injection of glue or thrombin and / or transjugular intrahepatic portosystemic shunt [TIPS]) is the most clinical and cost effective to improve outcome?
Population	Patients with confirmed gastric varices
Intervention	Endoscopic injections (glue or thrombin)
Comparison	TIPS
Outcomes	Mortality (in ICU in hospital) Rebleeding Duration of ICU stay

Review Protocol – Primary treatment for confirmed gastric varices - TIPS	
	Blood transfusions Adverse events (sepsis, encephalopathy)
Exclusion	Patients with variceal bleeding due to schistosomiasis
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL Only randomised controlled trials (RCTs) will be considered (no particular year or sample size restrictions), SRs Studies will be restricted to English language only
Search terms	
The review strategy	RCTs (including small scale studies) Include RCTs with mixed patients, i.e. oesophageal or gastric varices as indirect evidence
Analysis	Is there a particular approach to take in case of heterogeneity of results: Subgroup by severity of cirrhosis
Key papers	Key papers for this question: No particular key papers suggested by GDG members

D.7.4 TIPS for uncontrolled varices

Review Protocol – Treatment for uncontrolled variceal bleeding - TIPS	
Component	Description Transjugular intrahepatic protosystemic shunts for uncontrolled varices
Review question	What is the evidence that TIPSs are better than repeat endoscopy or balloon tamponade in patients where the variceal bleed remains uncontrolled?
Population	Patients where the variceal bleeding remains uncontrolled after treatment
Intervention	TIPS
Comparison	Repeat endoscopy or balloon tamponade
Outcomes	Mortality (in ICU in hospital) Rebleeding Duration of ICU stay Blood transfusions Adverse events (sepsis, encephalopathy)
Exclusion	Patients with variceal bleeding due to schistosomiasis
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL Both randomised controlled trials (RCTs) or observational studies will be considered (no particular year or sample size restrictions), SRs

Review Protocol – Treatment for uncontrolled variceal bleeding - TIPS	
	Studies will be restricted to English language only
Search terms	
The review strategy	RCTs (including small scale studies) and observational studies
Analysis	Subgroup by length of follow-up, type of comparison intervention, type of varices (oesophageal or gastric) or severity of cirrhosis
Key papers	Key papers for this question: No particular key papers suggested by GDG members

D.8 Information for patients

Review Protocol – Patient / carer information	
Component	Description Patient
Review question	What information is needed for patients with acute upper gastrointestinal bleeding and their carers (including information at presentation, prophylaxis and information for carers)?
Population	Patients / carers - UGIB population patients and carers
Intervention	Any type of written or verbal information (about treatment or prophylaxis) handed out or recorded
Comparison	
Outcomes	Patient / carer satisfaction Quality of life
Exclusion	Any exclusion criteria?
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL PsychInfo Randomised controlled trials (RCTsno particular year or sample size restrictions), SRs, qualitative studies will be searched Studies will be restricted to English language only
Search terms	UGIB population
The review strategy	Generic filter Medical info for patients Guiding Patient and carers after bleeding ie the f/u
Analysis	Only studies addressing the acute upper GI population will be considered, extrapolation from all patients undergoing endoscopy for any reasons were not seen as appropriate for this question

Review Protocol – Patient / carer information	
Key papers	Key papers for this question: None were identified by the GDG

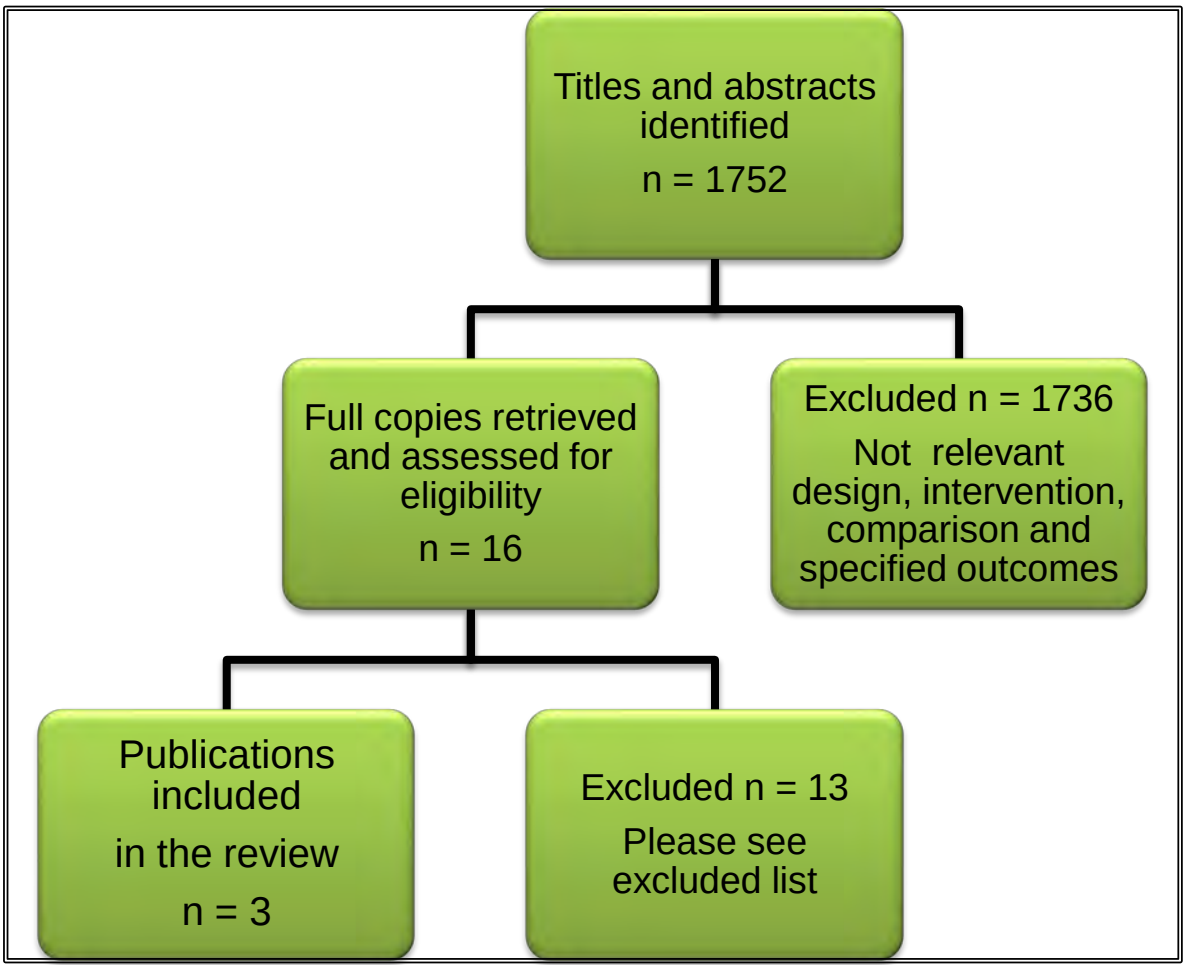
D.9 Health Economic Protocol

Review Protocol – Health Economics	
Objectives	The aim is to identify economic studies relevant to the review questions set out above.
Criteria	Populations, interventions and comparators as specified in the review protocols above. Must be a relevant economic study design (cost-utility analysis, cost-benefit analysis, cost-effectiveness analysis, cost-consequence analysis, comparative cost analysis).
Search strategy	See Appendix C
The review strategy	Each study is assessed using the NICE economic evaluation checklist NICE (2009) Guidelines Manual, Appendix H. Inclusion/exclusion criteria • If a study is rated as both Directly applicable and Minor limitations" (using the NICE economic evaluation checklist) then it should be included in the guideline. An evidence table should be completed and it should be included in the economic profile. • If a study is rated as either Not applicable or Very serious limitations then it should be excluded from the guideline. It should not be included in the economic profile and there is no need to include an evidence table. • If a study is rated as Partially applicable and/or Potentially serious limitations then there is discretion over whether it should be included. The health economist should make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the GDG if required. The ultimate aim being to include studies that are helpful for decision making in the context of the guideline. Where exclusions occur on this basis, this should be noted in the relevant section of the guideline with references. Also exclude: • unpublished reports unless submitted as part of the call for • evidence • abstract-only studies • letters • editorials • reviews of economic evaluations • foreign language articles Where there is discretion The health economist should be guided by the following hierarchies. Setting: 1. UK NHS 2. OECD countries with predominantly public health insurance systems (e.g.

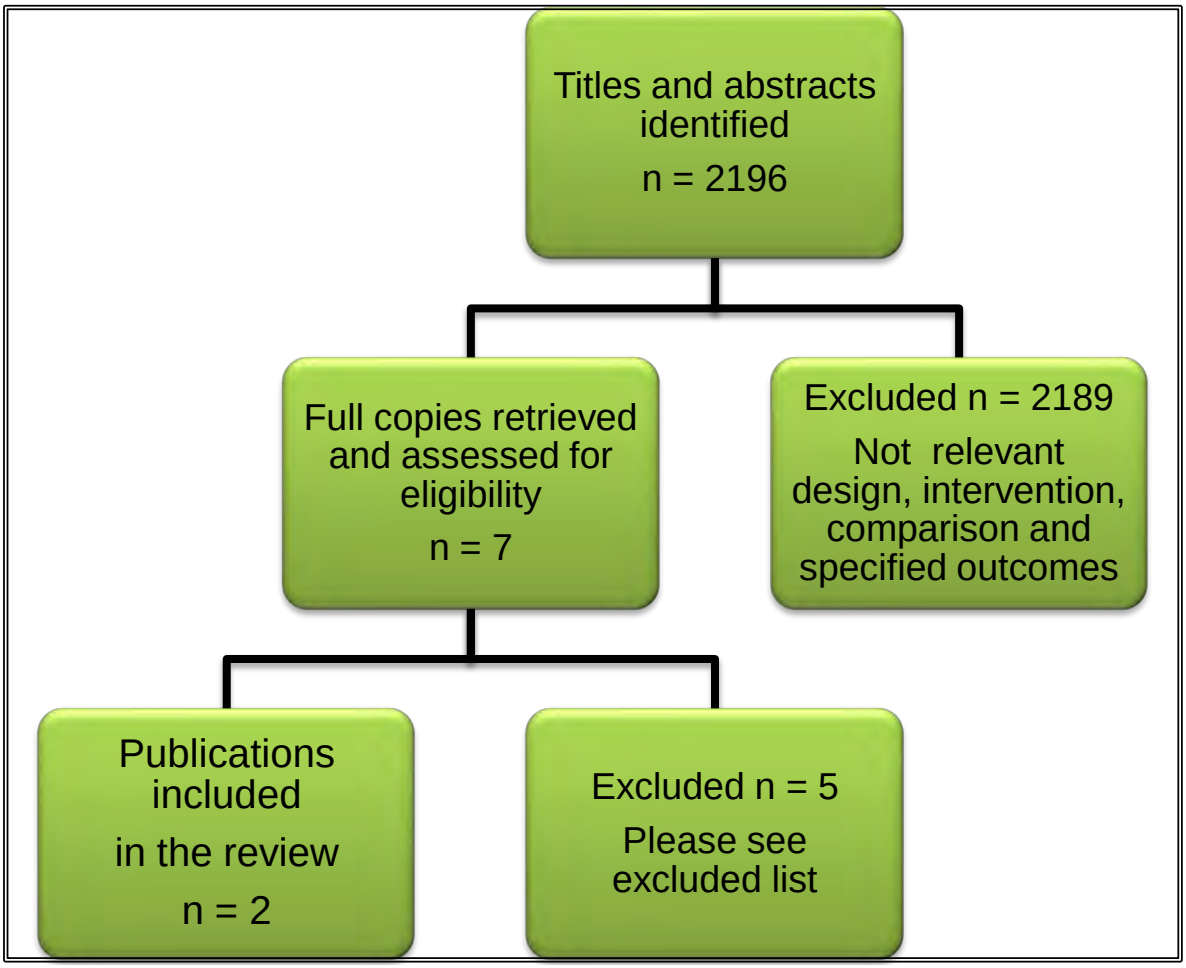
Review Protocol – Health Economics	
	France, Germany, Sweden) 3. OECD countries with predominantly private health insurance systems (e.g. USA, Switzerland) 4. Non-OECD settings (always „Not applicable“) Economic study type: 1. Cost-utility analysis 2. Other type of full economic evaluation (cost-benefit analysis, cost-effectiveness analysis, Cost-consequence analysis) 3. Comparative cost analysis 4. Non-comparative cost analyses including cost of illness studies (always „Not applicable“) Year of analysis: The more recent the study, the more applicable it is Quality of effectiveness data used in the economic analysis: The more closely the effectiveness data used in the economic analysis matches with the studies included for the clinical review the more useful the analysis will be to decision making for the guideline.

Appendix E: Clinical study selection flow charts

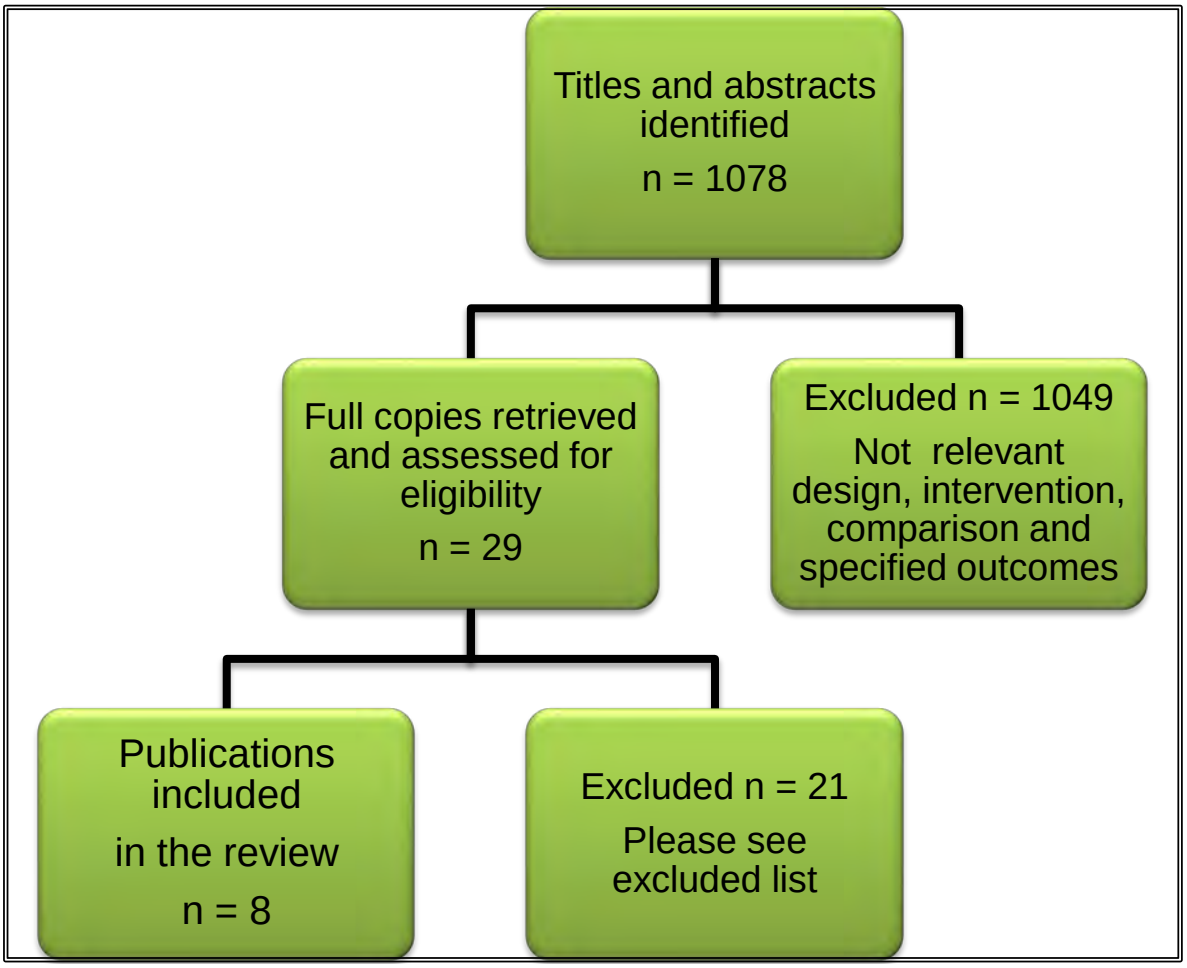
E.1 In patients with upper GI bleeding with low level of haemoglobin, pre-endoscopy, what is the most clinical and cost effective threshold and target level at which red blood cell transfusions should be administered to improve outcome? 3 RCTs were included for this review



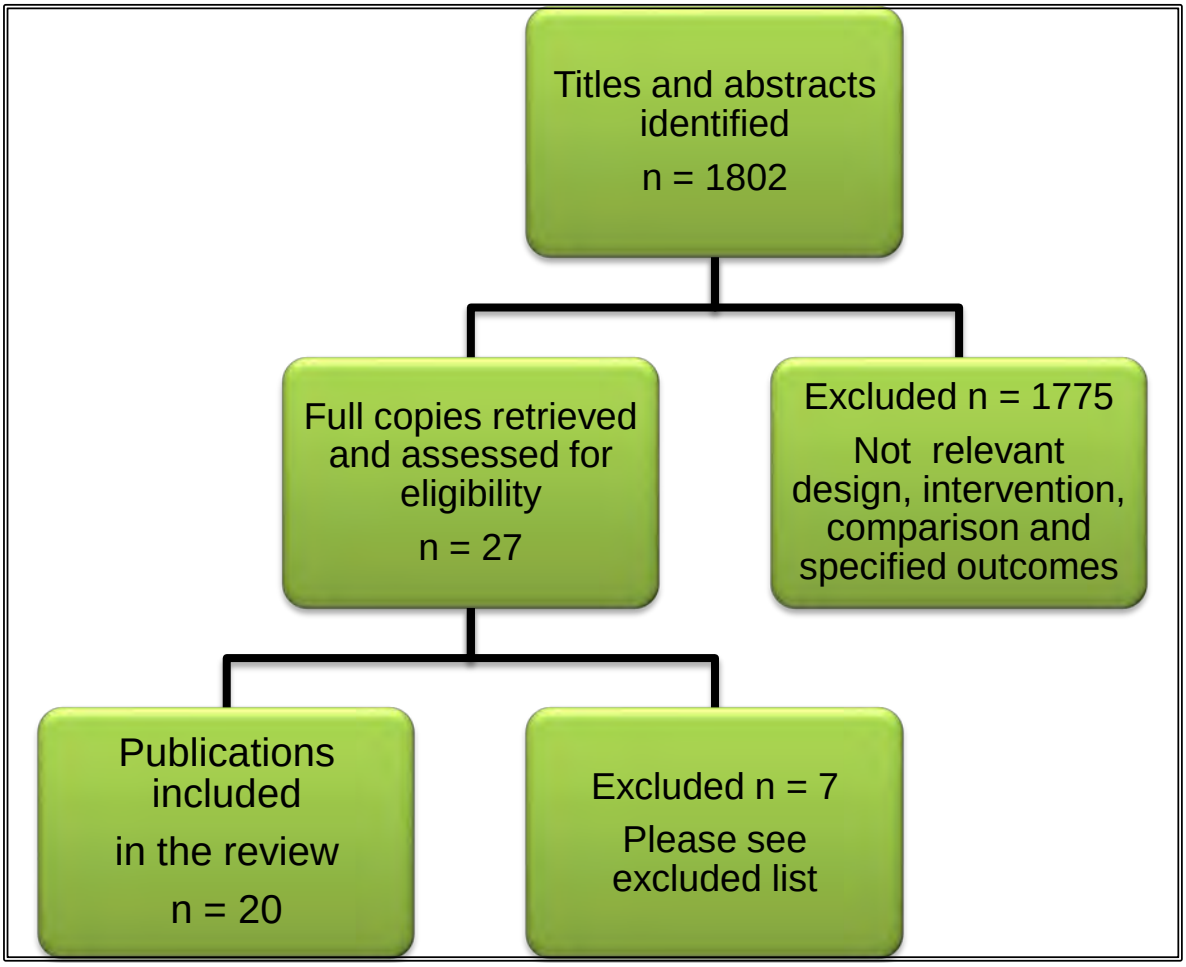
E.2 In patients with upper GI bleeding with low platelet count and / or abnormal coagulation factors, pre endoscopy, what is the most clinical and cost effective threshold and target level at which platelets and / or clotting factors should be administered to improve outcome?



E.3 In patients presenting with likely variceal UGIB at initial management, is terlipressin compared to octreotide, somatostatin or placebo the most clinical / cost effective pharmaceutical strategy?



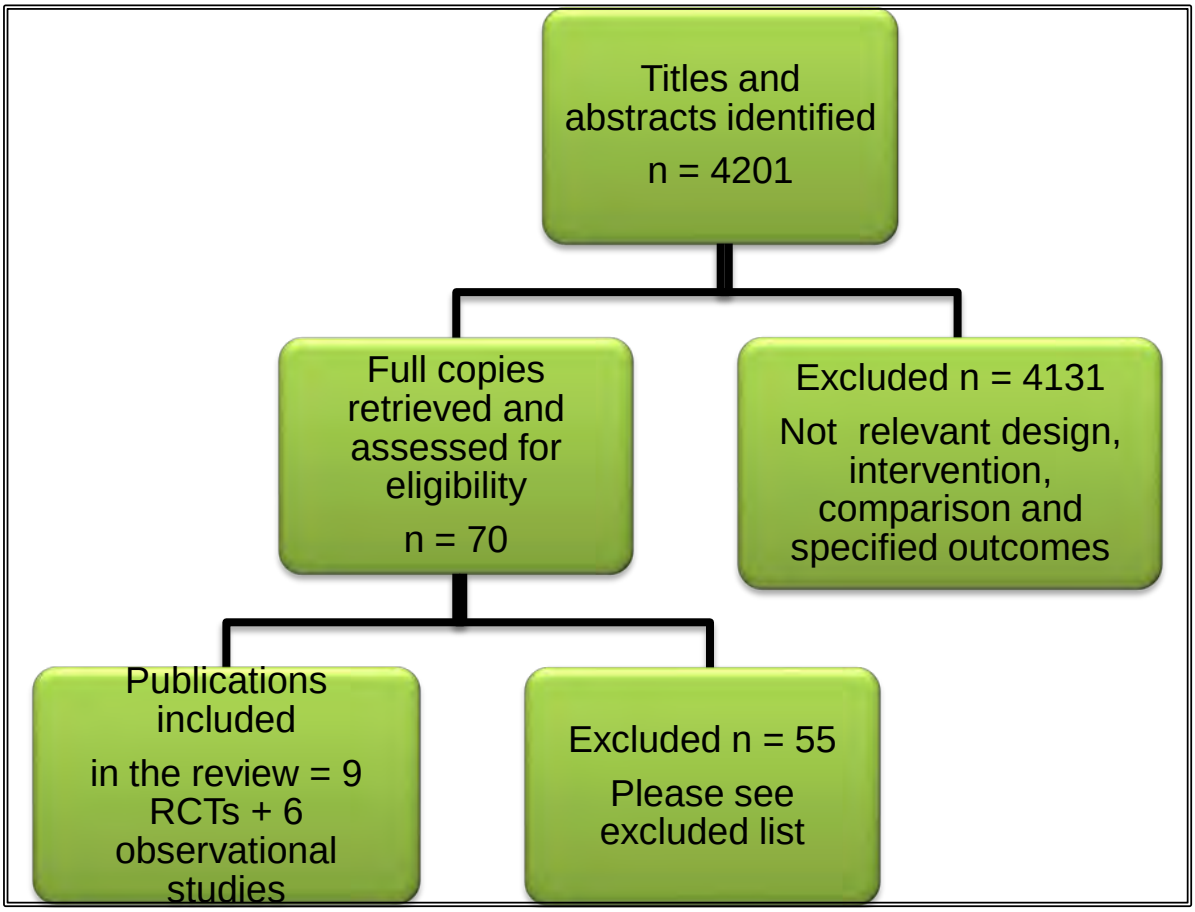
E.4 In patients with GI bleeding (with or without comorbidities) is there an accurate scoring system (Rockall, Blatchford [aka Glasgow], Addenbrooke) to identify which patients are high risk (of mortality, rebleeding, need for blood transfusion, surgical intervention) and require immediate intervention and those at low risk who can be safely discharged?



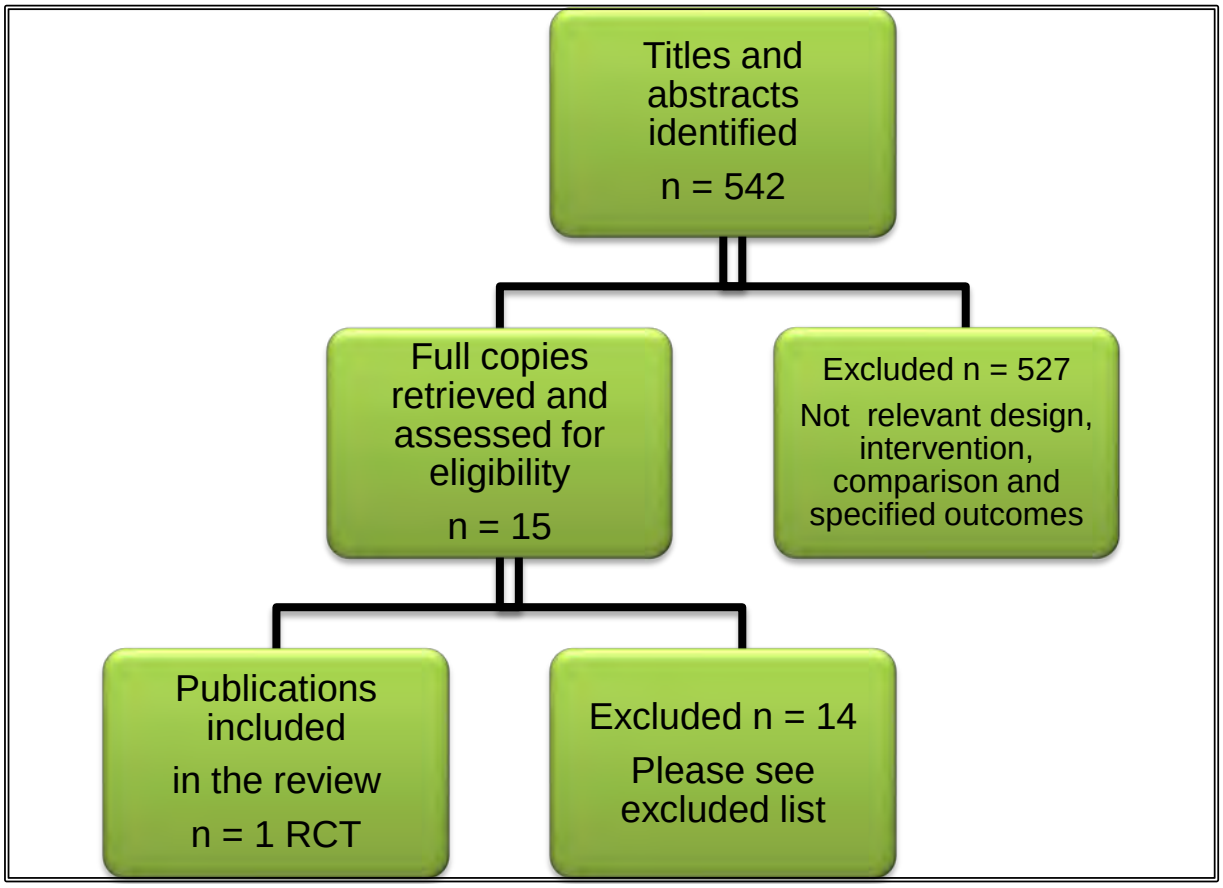
E.5 In patients with GI bleeding, does endoscopy carried out within 12 hrs of admission compared to 12-24 hours or longer improve outcome in respect of length of hospital stay, risk of rebleeding or mortality?

Is routine second look and / or repeat endoscopy most clinically effective to improve outcome and what is the best treatment strategy when endoscopy fails to achieve haemostasis?

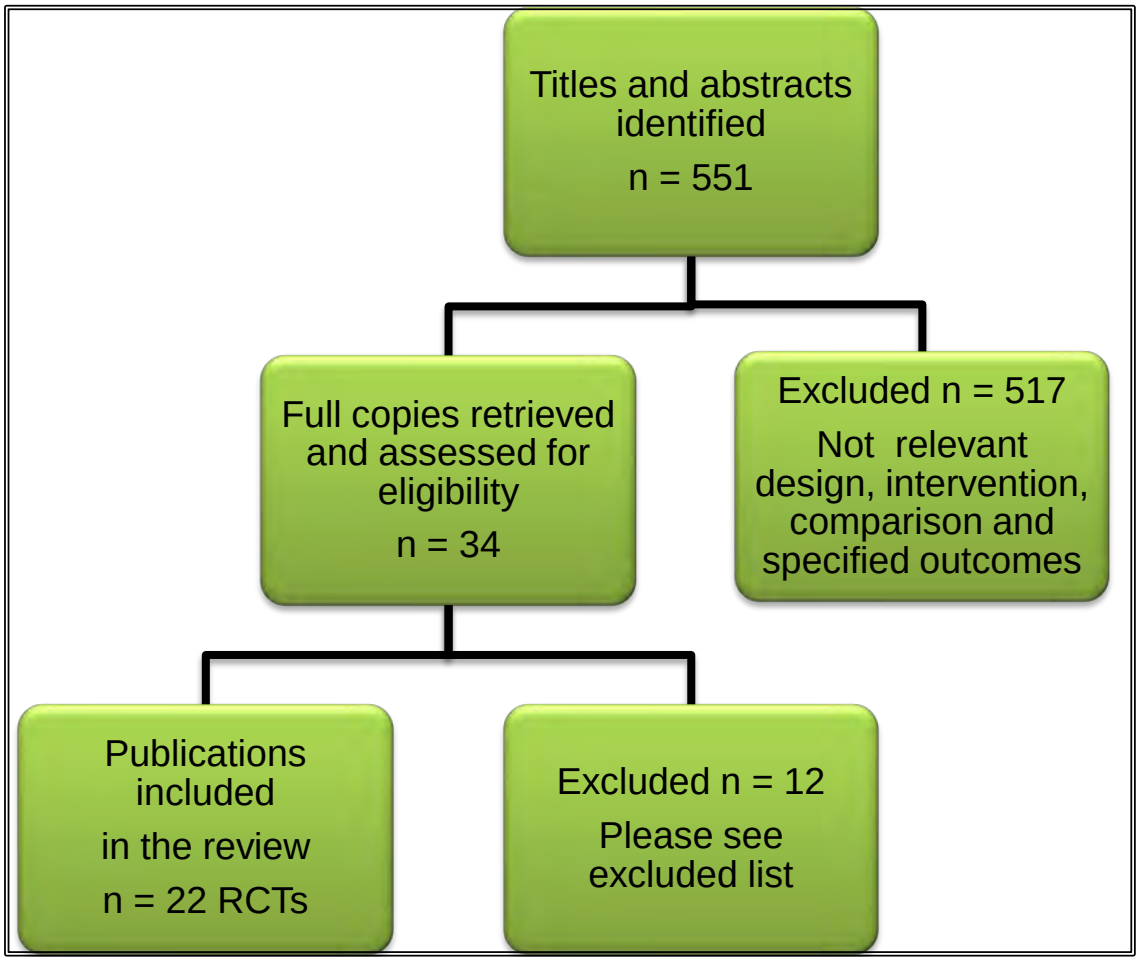
a. **In patients with non-variceal UGIB after first endoscopic treatment, is a routine second-look endoscopy more clinically / cost effective than routine clinical follow-up?**
b. **In patients with non-variceal UGIB who rebleed after the first endoscopic therapy is repeat endoscopy more clinical / cost effective compared to surgery or embolization / angiography to stop bleeding?**
c. **In patients with non-variceal UGIB where endoscopic therapy fails, is angiography / embolization more clinical / cost effective than surgery to stop bleeding? Observational studies were searched for this review question**


Titles and abstracts identified
n = 4201
Full copies retrieved and assessed for eligibility
n = 70
Excluded n = 4131
Not relevant design, intervention, comparison and specified outcomes
Publications included
in the review = 9 RCTs + 6 observational studies
Excluded n = 55
Please see excluded list

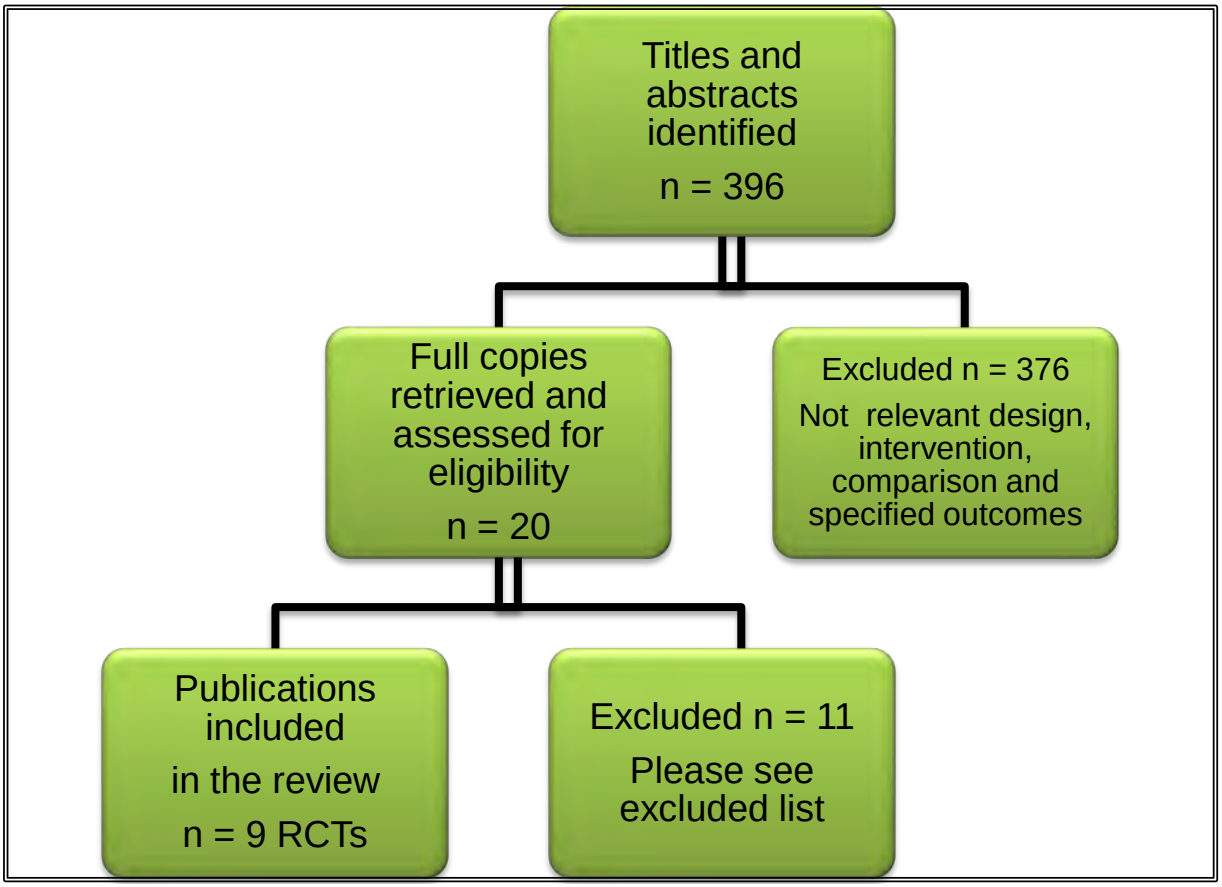
E.6 In patients presenting with UGIB who are already on NSAIDs, Clopidogrel, Aspirin or dipyridamol (single or combination) what is the evidence that discontinuation compared to continuation of the medication leads to better outcome?



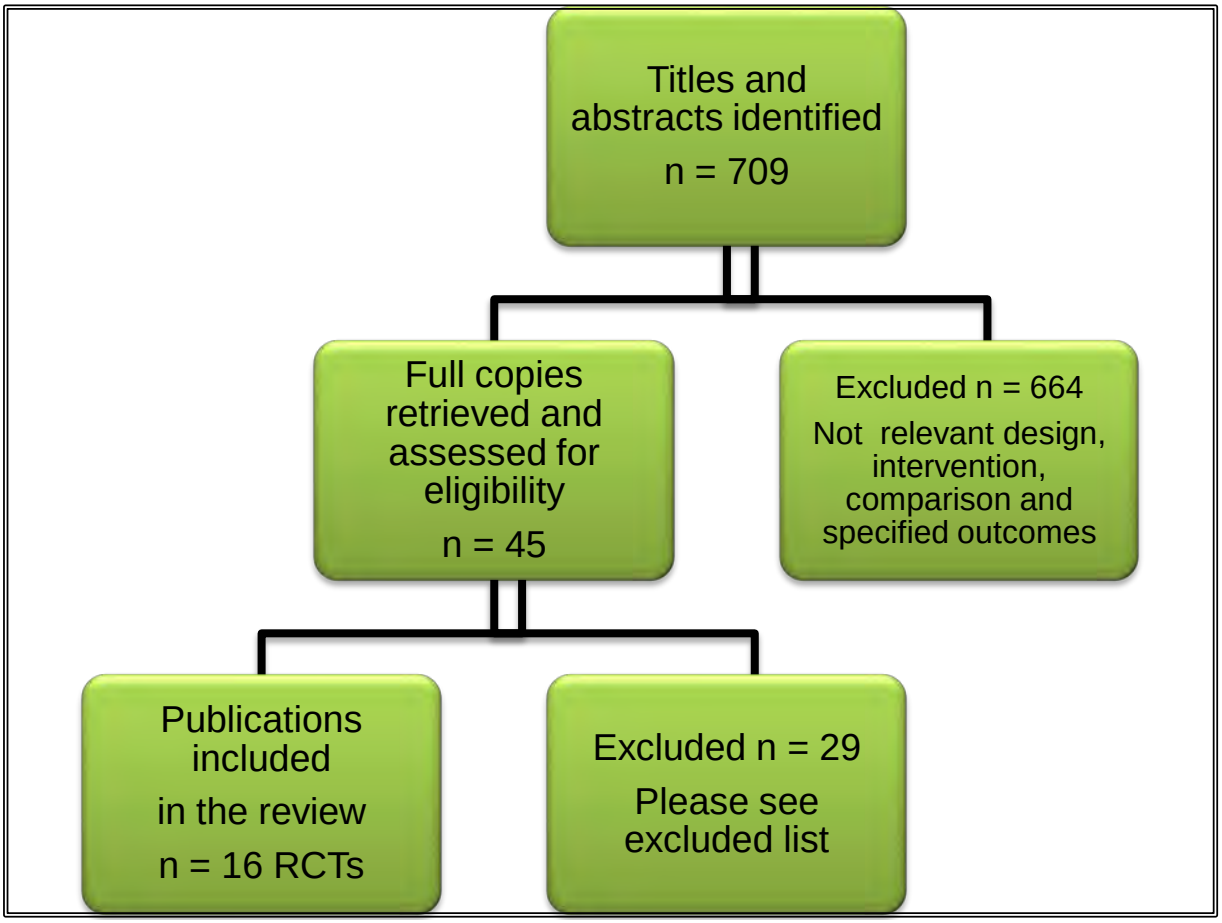
E.7 For acutely ill patients in high dependency and intensive care units are Proton Pump Inhibitors (PPI) or H2-receptor antagonists (H2-RA) more clinically effective compared to placebo (or each other) in the primary prophylaxis of Upper Gastrointestinal Bleeding (UGIB)? (chapter 6)



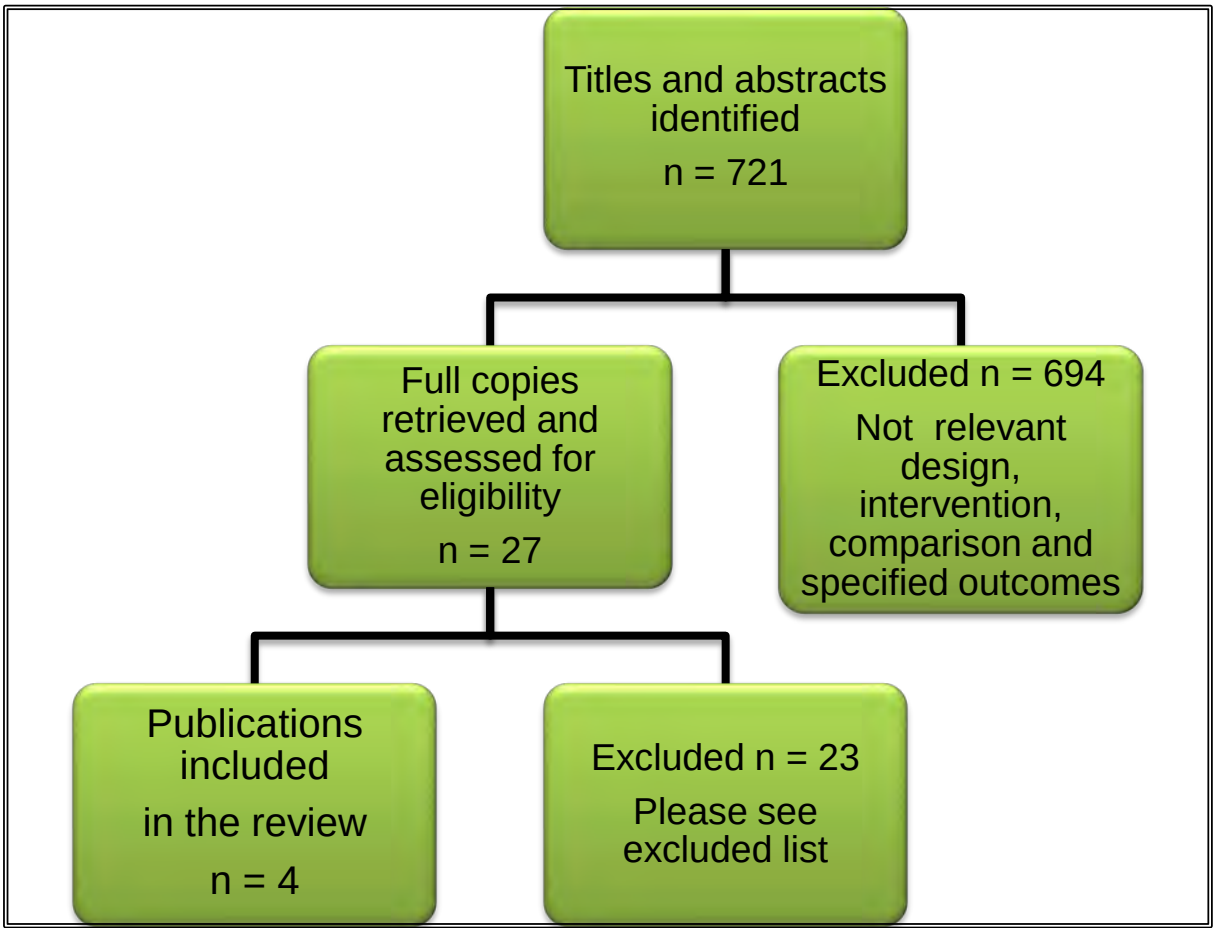
E.8 In patients with likely variceal bleeding at initial management are antibiotics better than placebo to improve outcome (mortality, rebleeding, length of hospital stay, rates of infection)?



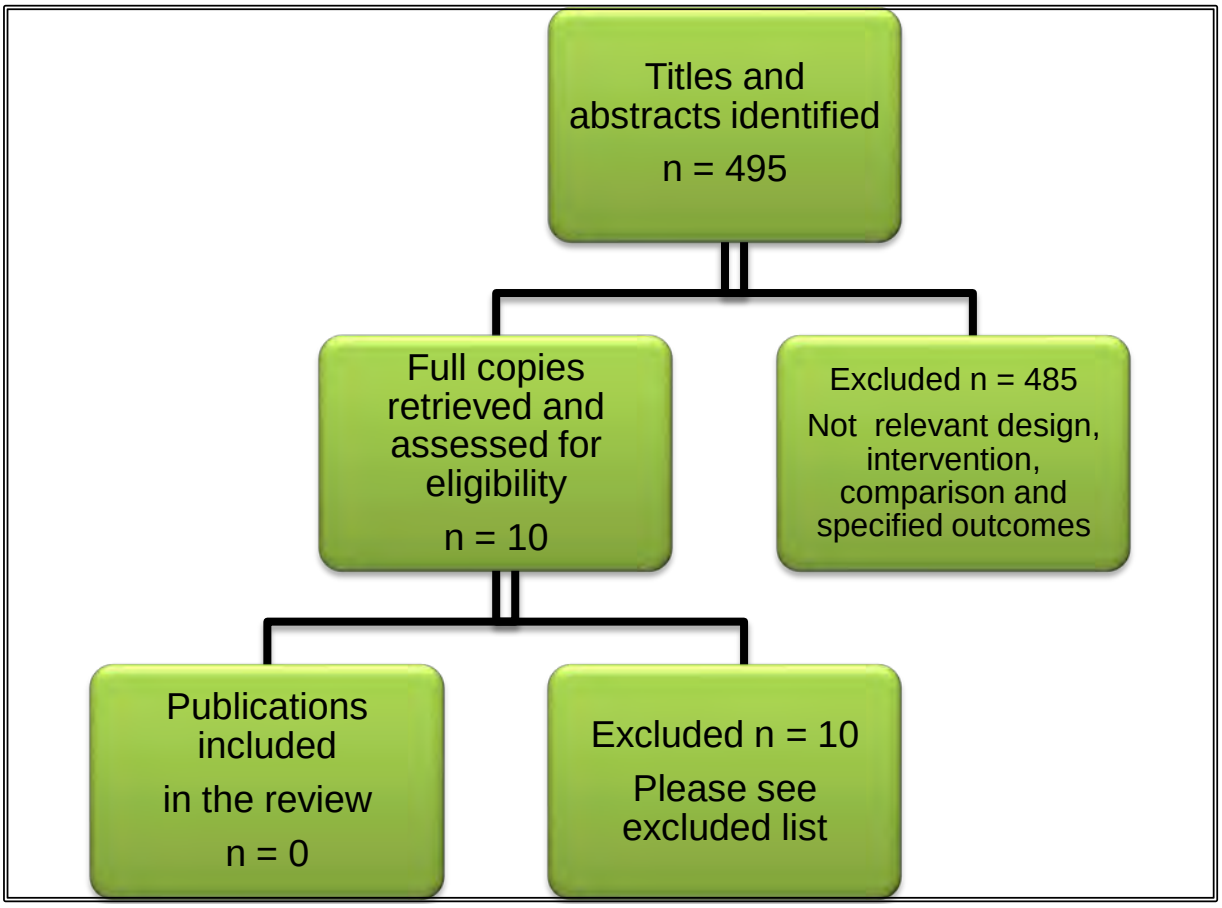
E.9 In patients with confirmed oesophageal varices is band ligation superior to injection sclerotherapy in terms of re-bleeding and death?



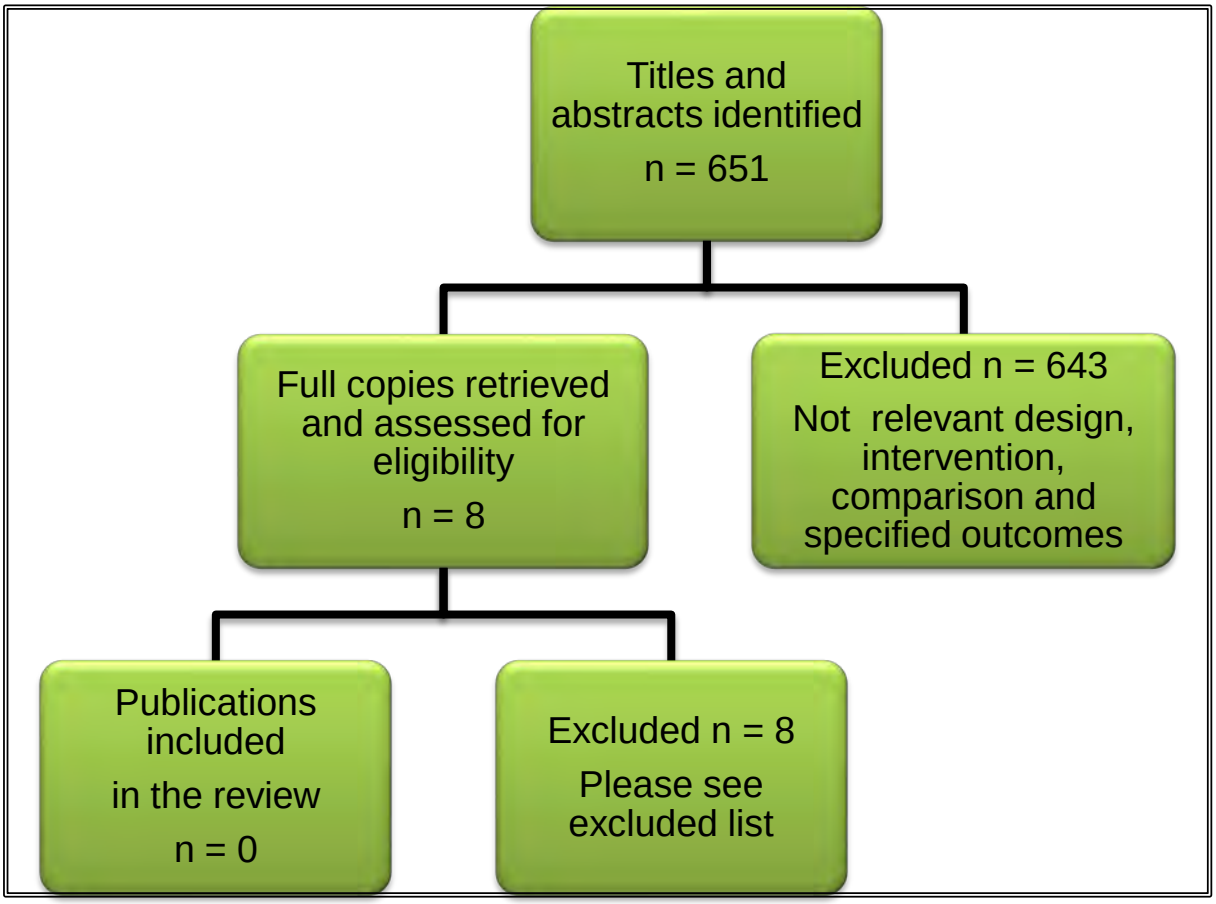
E.10 In patients with confirmed gastric varices which primary treatment (endoscopic injection of glue or thrombin and/or transjugular intrahepatic portosystemic shunts [TIPS]) is the most clinical and cost effective to improve outcome?



E.11 What is the evidence that TIPSs are better than repeat endoscopic therapy or balloon tamponade in patients where the variceal bleed remains uncontrolled?



E.12 What information is needed for patients with acute upper gastrointestinal bleeding and their carers (including information at presentation, prophylaxis and information for carers)?



Appendix F: Evidence tables – clinical studies

F.1 Initial management

F.1.1 Blood products – red blood cells

QUESTION In patients with upper GI bleeding with low level of haemoglobin, pre-endoscopy, what is the most clinical and cost effective threshold and target level at which red blood cell transfusions should be administered to improve outcome?

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Blair SD, Janvrin SB, McCollum CN et al. Effect of early blood transfusion on gastrointestinal haemorrhage. Br J Surg. 1986; 73(10):783-785. REF ID: 5202</td><td>Randomised control trial (country: UK)

Allocation concealment unclear, randomisation unclear, no blinding

ITT analysis</td><td>N=50 (24 in packed red cell group and 26 in no blood transfusion group)</td><td>Inclusion criteria: patients presenting with acute severe gastrointestinal haemorrhage with onset within the last 24 hours. Acute severe haemorrhage was defined as melaena or vomiting of more than a cupful of bright red blood.
Exclusion: patients with oesophageal varices.

Baseline characteristics:
<table>
<tr><td></td><td>Blood transfusion (n=25)</td><td>No blood transfusion (n=25)</td></tr>
<tr><td>Age</td><td>64(3.6)</td><td>60 (3.5)</td></tr>
<tr><td>Male:female ratio</td><td>2:1</td><td>2:1</td></tr>
<tr><td>Number with stigmata</td><td>4</td><td>4</td></tr>
</table></td><td>≥ 2 units or red blood cell transfusion</td><td>No transfusion (5 patients in this group did receive transfusions during the first 24 hours for anaemia worse than 8/dl – but were analysed in this group according to ITT principle)</td><td>24 hours – unclear for mortality</td><td>Mortality, coagulation profile, haematocrit, volume of blood given, rebleeding</td><td>Crawley and Jersey Research Fund</td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			of acute haemorrhage							
			Haemoglobin < 8 g/dl	6	5					
			Site of lesion on endoscopy:							
			Gastric	2	4					
			Duodenal	17	13					
			Carcinoma	1	2					
			Mallory-Weiss tear	2	3					
			Not visualized	2	4					

Effect size

Relevant outcomes:

	Transfusion (n=24)	No transfusion (n=26)	p
Hematocrit	37(1.6)	37(1.4)	n.s
Eventual blood transfused	4.6(0.3)	2.6(0.6)	<0.05
Mortality	2	0	n.s
Rebleeding	9	1	<0.01

Authors' conclusion

Reference	Study type	Number of patients	Patient characteristics	Interventio n	Comparison	Length of follow-up	Outcome measures	Source of funding
Early blood transfusion encourages rebleeding.								

Reference	Study type	Number of patients	Patient characteristics	Intervent ion	Comparison	Length of follow-up	Outcome measures	Source of funding
Hearnshaw SA, Logan RF, Palmer KR et al. Outcomes following early red blood cell transfusion in acute upper gastrointestina l bleeding. Alimentary pharmacology & therapeutics. 2010; 32(2):215-224. Ref ID: 5201	Prospective case review (audit of all NHS hospitals accepting acute admissions in the UK of which 82% took part)	N=4441 (of which n=1974 received early transfusion)	Inclusion criteria: Patients (16 years or over) presenting with acute UGIB – haematemesis, melaena and / or firm clinical or laboratory evidence of acute blood loss from the UGI tract. Exclusion: Patients presenting with iron deficiency anaemia without evidence of acute UGIB Characteristics of reviewed cases - % (n) *p<0.001:	Early red blood cell (RBC) transfusio n - defined as RBC transfusio n within 12 h of presentat ion with acute UGIB.	No early transfusion	24 hours	Rebleeding (further haematemesis , passage of fresh melaena, continuing or recurring hypotension and tachycardia +/- fall in haemoglobin after the first endoscopy) all cause mortality (death occurring within the hospital admission up to 30 days post index acute UGIB	NHS Blood and Transplan t and the British Society of Gastroen terology

	Early transfusio n (n=1974)	No earl transfusion (n=2467)
Age*	67.9(16.5 1)	63.4 (19.19)
female	39 (762)	39 (948)
Haemody namically stable*	46 (914)	68 (1679)
First Haemoglo	33 (649)	1.2 (41)

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			bin < 7.0 g/dl*							
			Pre endoscopy Rockall >3*	47 (930)	29 (2467)					
			Post endoscopy Rockall >5*	44 (863)	18 (451)					
			Endoscopic diagnosis:							
			Peptic ulcer	44 (862)	31 (750)					
			Varices*	16 (320)	7 (177)					
			MSRH*	49 (957)	21 (517)					
			MSRH – major stigmata of recent haemorrhage							

Effect size

Overall for all patients rebleeding occurred in 15% and mortality rate was 7.8%.

Mortality and rebleeding by initial haemoglobin level

	Early transfusion	No early transfusion
REBLEEDING		
Patients with an initial haemoglobin level of <8 gm/dl	23% (234/1015,95%CI 21-26%)	15% (17/111, 95%CI 8.6-22%)
Patients with an initial haemoglobin level of >8 gm/dl	24% (192/812, 95%CI 21-27%)	6.7% (147/2196, 95%CI 5.7-7.8%)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

MORTALITY		
Patients with an initial haemoglobin level of <8 gm/dl	13% (130/1025, 95%CI 11-15%)	13% (14/112, 95%CI 7.0-20%)
Patients with an initial haemoglobin level of >8 gm/dl	11% (91/819, 95%CI 9.4-13%)	4.3% (94/2208, 95%CI 3.5-5.2%)

Unadjusted and adjusted odds ratios for rebleeding and mortality after transfusion with 12 h:

	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI) by Rockall score	Adjusted odds ratio (95% CI) by Rockall and haemoglobin concentration
REBLEEDING			
Total	4.05 (3.36 - 4.87)	2.81 (2.32 - 3.42)	2.26 (1.76 - 2.90)
Excluding patients with varices	4.03 (3.29 - 4.93)	2.89 (2.34 - 3.57)	2.15 (1.63 - 2.83)
In-patients	2.28 (1.57 – 3.30)	1.70 (1.16 – 2.52)	1.35 (0.84 - 2.16)
MORTALITY			
Total	2.71 (2.14 – 3.42)	1.50 (1.17 – 1.92)	1.28 (0.94 – 1.74)
Excluding patients with varices	2.70 (2.08 – 3.50)	1.52 (1.15 – 2.01)	1.26 (0.89 – 1.79)
In-patients	1.70 (1.17 – 2.46)	1.21 (0.84 – 1.78)	1.33 (0.83 - 2.13)

Authors' conclusion

Early RBC transfusion in AUGIB was associated with a two-fold increased risk of re-bleeding with an increase in mortality which was not significant.

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Baradarian R, Ramdhaney S, Chapalamadugu R et al. Early intensive resuscitation of patients with upper gastrointestinal bleeding decreases mortality. Am J Gastroenterol. 2004; 99(4):619-622. Ref ID: 4820</td><td>Prospective case review

Single centre country: USA</td><td>N=72 (n=36 in the observational group and n=36 in the intensive resuscitation group)</td><td>Inclusion criteria: patients with UGIB complicated by hemodynamic instability related to the bleeding with (1) evidence of an UGIB (melena, hematemesis or massive hematochezia with positive nasogastric aspirate for blood and (2) hemodynamic compromise defined as either a pulse rate of greater than 100 or systolic blood pressue less than 100 mmHg.
Exclusion: None explicitly stated

Characteristics of reviewed cases – none significant:
<table>
<tr><th></th><th>Observation group (n=36)</th><th>Intensive rescuscitation (n=36)</th></tr>
<tr><td>Age</td><td>68(14)</td><td>71 (21)</td></tr>
<tr><td>female n</td><td>21</td><td>18</td></tr>
<tr><td>Co morbidities*</td><td>3.2 (2.4)</td><td>2.8 (2.1)</td></tr>
<tr><td>Prior peptic ulcer</td><td>6/36</td><td>4/36</td></tr>
<tr><td>Prior GI bleed</td><td>9/36</td><td>7/36</td></tr>
<tr><td>Coagulopathy</td><td>3/36</td><td>4/36</td></tr>
</table></td><td>No formal protocol was followed - Physicians involved in collecting the data provided guidance to the health care team managing the patients (Intensive resuscitation group) to allow more rapid correction of hemodynamic instability</td><td>The physicians in this group did not need to intervene. They were instructed to intervene only if they felt that care was inappropriate jeopardizing a patient's well-being. Their role was completely observational (observational group) and therefore did not directly encourage early resuscitation.</td><td>unclear</td><td>Time interval from admission to stabilization of hemodynamics
Days in hospital, days in ICU, units of blood given, rebleeding, surgical interventions, mortality and myocardial infarction</td><td>Maimonidea research and development foundation</td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

(INR>1.8)		
Rockall score	3.6(1.2)	4/36
Etiology of bleeding:		
Peptic ulcer	22	24
Esophageal ulcer	1	0
Varices	5	3
Mallory-Weiss tear	3	2
Malignancy	2	3
Other	3	4

* mean and sd: comorbidities listed as a total number that includes one point for each of the following: coronary artery disease, chronic obstructive pulmonary disease, diabetes, malignancy, coagulopathy, renal disease (creatinine > 2.0), blood dyscarsia.

Effect size

Intervals from admission to stablization (mean minutes and standard deviations) - significant group differences in shaded cells:

	Observation group N=36	Intensive resuscitation group N=36	p

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Hemodynamics	260 (88)	111 (33)	0.002
Hematocrit > 28	243 (109)	188 (39)	0.03
INR <1.8	277 (277 (74)	213 (89)	0.04
Endoscopic intervention	765 (232)	861 (312)	0.21

Clinical outcomes - significant group differences in shaded cells::

	Observation group N=36	Intensive resuscitation group N=36	p
Days in hospital	7.2 (13.8)	5.8 (8.3)	0.06
Days in ICU	2.4 (2.5)	3.9 (3.8)	0.04
Units of blood given	2.5 (2.7)	2.6 (2.9)	0.22
Rebleeding	7	8	0.33
Surgical intervention	6	4	0.09
Mortality	4	1	0.04
Myocardial infarction	5	2	0.04

Authors' conclusion

Early intensive resuscitation of patients with upper gastrointestinal bleeding significantly decreases mortality

F.1.2 Blood products – platelets and coagulation factors

QUESTION In patients with upper GI bleeding with low platelet count and / or abnormal coagulation factors, pre endoscopy, what is the most clinical and cost effective threshold and target level at which platelets and clotting factors should be administered to improve outcome?

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Bosch J, Thabut D, Albillos A et al. Recombinant factor VIIa for variceal bleeding in patients with advanced cirrhosis: A randomized, controlled trial. Hepatology. 2008; 47(5):1604-1614. REF ID:94	RCT (multicentre – international 31 hospitals in 12 countries in Europe and Asia) Randomisation (computer generated) through a central interactive voice-response system, adequate allocation concealment ITT analysis	N=256 (n=86 placebo, n=85 600 µg/kg rFVIIa, n=85 300 µg/kg)	Inclusion criteria: age 18-79 years; acute UGIB and advanced cirrhosis; Child-Pugh score > 8; treatment with vasoactive therapy at least 0.5 hours before endoscopy showing active esophageal or gastoesophageal variceal bleeding (oozing/ spurting), endoscpy performed within 6 hours (± 6 hours) of admittance to emergency room; and first trial producat dose within 1 hour of endoscopy with therapy (either ligation or sclerotherapy). Exclusion criteria: unfit for resuscitation; band ligation within 2 weeks or sclerotherapy within 1 week; clinically documented symptoms of unstable angina. Peripheral vascular disease, and/or known previous myocardial / pulmonary infarction or stroke; electrocardiogram (12-lead) verified signs of cardiac ischemia; history of pulmonary embolism; portal/deep vein thrombosis; previous diagnosis of advanced hepatocellular	600 µg/kg rFVIIa (200 plus 4 X 100 µg/kg) or 300 µg/kg rFVIIa (200, 100 plus 3 X placebo)	Placebo – the main comparison was between 600 µg/kg rFVIIa and placebo and if significant a further comparison was carried out with the lower dose.	42 days	Primary outcomes: 1. treatment failure (modified Baveno II-IV criteria) 2. rebleeding 3. death within 5 days of first trial product dosing Secondary endpoints: 5 day and 42 day mortality, failure to control 5 day bleeding; failure to control acute bleeding within 24 hours; failure	Novo Nordisk A/S (a medical writer was supported by this sponsor)

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td></td><td></td><td>carcinoma; pregnancy; previous dosing with trial drug in this trial; receipt of any investigational drug within 6 weeks; known throbogenic disorder , acquired FVIII deficiency, acquired hemophilia, or hereditary bleeding disorder; known or suspected allergy/hypersensitivity to rFVIIa; planned use of antifibrinolytic drugs; and planned hemofiltration or dialysis within 5 days of screening.

Baseline characteristics ('comparable between treatment groups')
<table>
<tr><td></td><td>Placebo N=86</td><td>600 µg/kg N=85</td><td>300 µg/kg N=85</td></tr>
<tr><td>Age</td><td>53.9 (10.2)</td><td>55.0 (11.3)</td><td>54.7 (11.7)</td></tr>
<tr><td>Male %</td><td>78</td><td>66</td><td>75</td></tr>
<tr><td>Child-Pugh score (median)</td><td>10.5</td><td>11.0</td><td>10.0</td></tr>
<tr><td>MELD score</td><td>18.5</td><td>17.4</td><td>18.0</td></tr>
</table></td><td></td><td></td><td></td><td>to prevent clinically significant rebleedings and all rebleedings at day 5; number of emergency procedures within 5 days; and transfusion requirements at 24 hours and day 5.

Secondary safety endpoints: frequency of adverse events (recorded up to day 42) and changes in coagulation-related parameters (the latter not reported here)</td><td></td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics				Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Bilirubin (µmol/L)	86 (127)	78 (111)	99 (122)					
			Prothrombin time (%)	41 (13)	42 (19)	43 (17)					
			International normalized ratio	2.01 (0.52)	2.04 (0.79)	2.08 (0.86)					
			Creatinine (µmol/L)	110 (86)	102 (76)	92 (56)					
			Hematocrit (%)	24.1 (7.4)	24.8 (5.7)	26.9 (6.4)					
			Hemoglobin (g/dl)	8.1 (2.5)	8.4 (2.0)	9.1 (2.3)					
			Platelet count (X 109/L)	112 (81)	107 (69)	92 (49)					

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Effect size

Analysis of primary and secondary endpoints N (%):

	Placebo N=86	600 µg/kg N=85	Odds ratio (95% CI)	P value	300 µg/kg N=85
Bleeding related endpoints					
Failure to control 24h bleeding	8(9)	8 (9)	1.05 (0.36-3.07)	1.0	8 (9)
Failure to prevent CS* rebleeding	8(9)	3 (4)	0.33 (0.08-1.42)	0.26	3 (4)
Mortality					
Deaths within 5 days	11(13)	10 (12)	0.69 (0.24-1.95)	0.22	4 (5)
Deaths within 42 days	25(29)	13 (15)	0.31 (0.13-0.74)	0.0035	26 (31)
Failure to control 5 day bleeding	16(19)	11 (13)	0.64 (0.27-1.52)	0.50	10 (12)
Failure to control all rebleeding	8(9)	5 (6)	0.54 (0.15-1.89)	0.62	5 (6)
Emergency procedures at day 5	16 (19)	19 (22)	Not reported		8 (9)
Red blood cell transfusions	N=82	N=83			N=82
Within 24 h – mean (sd)	2.3 (2.3)	1.7 (1.9)		0.11	1.5 (1.7)
	N=75	N=75			N=78
At day 5	3.3 (3.1)	2.8 (2.6)		0.30	2.3 (2.2)

* CS: clinically significant (defined as both new hematemesis/melena and transfusion of >2 U blood – whole or pRBCs in any 24-hour period).

A Kaplan-Meier plot of overall patient survival showed significant differences between Placebo and high dose rFVIIa (p=0.0291)

Cause of death at day 42 – N(%) no statistics given:

Cause of death	Placebo N=86	600 µg/kg N=85	300 µg/kg N=85
Bleeding related	10 (12%)	2 (2)	8 (9)
Liver failure, infection and other causes	15(17)	11 (13)	18 (21)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Adverse events (N, %, number of events) :

	Placebo N=89	600 µg/kg N=88	300 µg/kg N=88
Serious adverse events	39 (44%),56	30 (34%),46	41 (47%),63
Fatal adverse events	30 (34%),35	17 (19%),18	31 (35%),35

Authors' conclusion

Treatment with rFVIIa had no significant effect on the primary composite endpoint compared with placebo. Therefore decision on the use of this hemostatic agent in acute variceal bleeding should be carefully considered because results of this study do not support the routine use of rFVIIa in this setting.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Bosch J, Thabut D, Bendtsen F et al. Recombinant factor VIIa for upper gastrointestinal bleeding in patients with cirrhosis: a randomized, double-blind	RCT (multicentre – international 26 hospitals in Europe) Randomisation (computer generated) through a central interactive	N=245 (n=121 placebo, n=121 rFVIIa,)	Inclusion criteria: age 18-74 years; signs of active acute UGIB suspected to be of variceal origin (i.e. hematemesisi or melenawithin 24 horus of inclusion) requiring hospitalisation and volume replacement therapy; presence of cirrhosis, either confirmed histologically or with obvious clinical or endoscopic signs of cirrhosis and portal hypertension; scheduled to undergo endoscopy within 12 hours of hospital	100 µg/kg rFVIIa - 8 doses (the first dose was administered as a slow intravenous injection before first endoscopy and within 6 hours of	Placebo 8 doses	42 days	Primary outcomes: 1. treatment failure (modified Baveno II-IV criteria) 2. rebleeding 3. death within 5 days of first trial product	Novo Nordisk A/S (Copenhagen, Denmark)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
trial. Gastroenterology. 2004; 127(4):1123-1130. REF ID: 227	voice-response system, adequate allocation concealment ITT analysis		admission (or 12 hours of index bleed if already hospitalised); initiation of trial product administration before first endoscopy and within 6 hours of admission (or within 6 hours of index bleed if already hospitalised). Exclusion criteria: known hypercoagulopathy, acquired FVIII deficiency, or hereditary bleeding disorder; history of pulmonary embolism or deep vein thrombosis within 6 months; history of either portal vein thrombosis, stable/unstable angina pectoris, myocardial infarction, intermittent claudication, or transient ischemic attack/ischemic stroke; signs of cardiac ischemia; concomitant disease with a life expectancy of less than 6 months; tense ascites and obvious jaundice; grade IV encephalopathy; sclerotherapy or band ligation within 2 weeks; previous transjugular intrahepatic protosystemic shunt or orthotopic liver transplantation; known gastrointestinal/respiratory system cancer/hepatocellular carcinoma; planned use of any hemostatic drug other than rFVIIa in the management of bleeding episode;	admission, further doses were administered at 2, 4, 6, 12, 18, 24 and 30 hours after first dose).			dosing Secondary endpoints: 5 day and 42 day mortality, failure to control 5 day bleeding; failure to control acute bleeding within 24 hours; failure to prevent clinically significant rebleeding and all rebleedings at day 5; number of emergency procedures within 5 days (but data not reported); and transfusion requirements at 24 hours and day 5. Secondary	

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td></td><td></td><td>and known advanced cirrhosis reflected in a known Child-Pugh score ≥12 points at trial entry.

Baseline characteristics ('comparable between treatment groups')
<table>
<tr><td></td><td>Placebo N=121</td><td>rFVIIa N=121</td></tr>
<tr><td>Age</td><td>54.2 (10.6)</td><td>52.6 (11.9)</td></tr>
<tr><td>Male %</td><td>74</td><td>74</td></tr>
<tr><td>Index bleed of variceal origin %</td><td>68</td><td>65</td></tr>
<tr><td>Child-Pugh score (mean sd)</td><td>8.4 (1.9)</td><td>8.1 (2.0)</td></tr>
<tr><td>Child-Pugh grade A/B/C</td><td>23/58/38</td><td>23/66/29</td></tr>
<tr><td>Bilirubin</td><td>86 (127)</td><td>78 (111)</td></tr>
</table></td><td></td><td></td><td></td><td>safety endpoints: frequency of adverse events (recorded up to day 42) and changes in coagulation-related parameters (the latter not reported here)</td><td></td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			(µmol/L)							
			Systolic blood pressure (mm Hg)	124 (23)	118 (21)					
			Heart rate (beats/min)	95 (21)	96 (20)					
			Creatinine (mg/dL)	0.9 (0.4)	1.0 (0.4)					
			Hematocrit (%)	27.4 (7.2)	27.3 (7.0)					
			Hemoglobin (g/dl)	9.2 (2.5)	9.2 (2.4)					
			Platelet count (X 109/L)	103.3 (58.4)	110.8 (60.9					

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Effect size

Analysis of primary and secondary endpoints – shaded cells indicate significant results:

	Placebo N=121	rFVIIa N=121	p
Bleeding related endpoints			
Failure to control 24h bleeding:			
All patients	10/119	6/120	0.31
Variceal bleeders	8/80	2/78	0.10
Variceal bleeders Child-Pugh B-C*	7/63	0/62	0.01
Failure to prevent rebleeding (24h – day 5)			
All patients	10/116	9/116	1.00
Variceal bleeders	9/77	5/77	0.40
Variceal bleeders Child-Pugh B-C*	8/61	3/62	0.13
Mortality			
Within 5 days	4/119	7/118	0.38
Within 42 days	11/120	16/116	0.31
Red blood cell requirements			
Within 24 hours	0.7 (1.2)	0.9 (1.8)	0.51
Within 5 days	1.3 (1.9)	1.5 (3.7)	0.73

* exploratory end points (post hoc analysis)

A best- and worst-case scenario sensitivity analysis was carried out (nonassessable patients were scored as successes and failures respectively) showed only a minor influence with significant P values still being borderline statistically significant for the worst-case scenarios.

Adverse events (N, %, number of events) :

	Placebo	rFVIIa

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
		N=121	N=121					
All adverse events (number of patients)		288 (N=95)	249 (N=84)					
serious adverse events		67	55					

Authors' conclusion

Although no overall effect of rFVIIa was observed, exploratory analyses in Child-Pugh B and C cirrhotic patients indicated that administration of rFVIIa significantly decreased the proportion of patients who failed to control variceal bleeding and that dosing with rFVIIa appeared to be safe.

F.1.3 Terlipressin

QUESTION In patients presenting with likely variceal UGIB at initial management, is terlipressin compared to octreotide, somatostatin or placebo the most clinical / cost effective pharmaceutical strategy?

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Pedretti G, Elia G, Calzetti C et al. Octreotide versus terlypressin in acute variceal hemorrhage in liver cirrhosis. Emergency	Prospective randomised single blind trial. Country: Italy Allocation concealment	N=60 episodes (n=30 each)	Inclusion criteria Age over 18 years, no history of former myocardial infaction, no cardiac or renal failure and no pregnancy. Diagnosis of bleeding: by endoscopy. Source of bleeding: all confirmed or unconfirmed varices.	terlipressin 2 mg iv every 4 h for 24 h then 2 mg iv every 6 h from 24-48 h then 1 mg iv every 6 h	Octreotide 100 mcg once then 25 mcg/h for 24 h then 100 mcg sc tid on days two-seven.	60 days	Mortality at 60 days,failure of initial haemostasis at 24 h, rebleeding at 60 days, procedures required for	Italian Ministry University and scientific research project on liver cirrosis

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>control and prevention of early rebleeding. Clin Investig. 1994; 72(9):653-659. Ref ID: 220</td><td>unclear ‘number in closed envelope’, clear randomisation sequence generation, only patients blinded</td><td></td><td>Endoscopy performed in all patients before randomisation.
Diagnosis of cirrhosis by laparoscopy and / or liver biopsy.

Exclusion criteria
Patient with contraindications to endoscopy, intercurrent illness with death expected within 2 months or symptoms of esophageal dysfunction. Patients who were pregnant.

Baseline characteristics – no significant differences
<table>
<tr><td></td><td>Terlipressin N=30</td><td>Octreotide N=30</td></tr>
<tr><td>Age mean yr (SD)</td><td>64.7 (10.7)</td><td>66.7 (10.6)</td></tr>
<tr><td>Male /female</td><td>18/12</td><td>17/13</td></tr>
<tr><td>Child-Pugh score (A/B/C)</td><td>4/23/4</td><td>5/21/4</td></tr>
<tr><td colspan="3">Etiology of cirrhosis:</td></tr>
<tr><td>Alcoholic</td><td>11</td><td>9</td></tr>
</table></td><td>from day three - seven.</td><td></td><td></td><td>haemostasis and blood transfusions.</td><td></td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Posthepatitic							
			HCV	14	13					
			HBV	5	8					
			Data on admission							
			Hemoglobin (g/dl)	8.9 (0.8)	8.8 (0.8)					
			Hematocrit (%)	26.4 (2.2)	26.0 (4.1)					
			Systolic blood pressure (mmHg)	98.6 (6.7)	97.8 (7.3)					
			Diastolic blood pressure (mmHg)	66.3 (6.7)	67.4 (8.3)					
			Heart rate (beats/min)	99.6 (10.8)	102.4 (9.2)					
			Albumin (g/dl)	2.7 (0.4)	2.6 (0.3)					
			Prothrombin ratio (%)	60.5 (8.7)	61.4 (11.3)					

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Effect size

Bleeding control:

	Terlipressin (N=30)	Octreotide (N=30)	p
Primary control of bleeding	23/30 (76.6%)	16/30 (53.3%)	NS
Esophageal varices	17/21 (80.9%)	12/20 (60%)	NS
Gastric varices	6/9 (66.6%)	4/10 (40%)	NS

Control rate of rebleeding with octreotide and terlipressin in relation to Child-Pugh classification:

	Class	Control n	Bleeding %	P chi-square	Mortality n	P (A+B vs C) Fisher's exact test
Octreotide (n=30)	A	3/4	75		0	
	B	19/23	82.6	NS	0	0.001
	C	1/3	33.3		3/3	
Terlipressin (n=30)	A	3/5	60		0	
	B	14/21	66.6	NS	0	0.001
	C	0/4	0		4/4	

For mortality a survival analysis showed that the difference in progression rate between the two groups was not significant (95% confidence intervals: group A 8.21 – 9.62 weeks; group B 7.72 – 9.56 weeks)

Adverse effects were reported but none were leading to death or withdrawal of treatment.

Authors' conclusion:

The results suggest that octreotide is at least as effective as terypression as an adjuvant therapy, before treatment (sclerotherapy, TIPS) is carried out in bleeding cirrhotics.

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Walker S, Kreichgauer HP, Bode JC. Terlipressin (glypressin) versus somatostatin in the treatment of bleeding esophageal varices--final report of a placebo-controlled, double-blind study. Z Gastroenterol. 1996; 34(10):692-698. Ref ID: 193</td><td>RCT, Germany

Randomisation and allocation concealment unclear, double blind</td><td>106 episodes of bleeding from oesophageal or gastric varices in 72 patients</td><td>Inclusion: Patients with liver cirrhosis and endoscopically detected actively spurting or oozing bleeds from oesophageal or gastric varices, or recovery of fresh blood from the stomach with a white "nipple" or clot on oesophageal or gastric varices, and no other potential source of bleeding.

Exclusion: duodenal variceal bleeding; portal venous obstruction due to pancreatic carcinoma; recent cerebral apoplexy; multi-organ failure

<table><tr><td></td><td>Terl</td><td>Somat</td></tr><tr><td>Age</td><td>51.8 (13.0)</td><td>52.7 (13.5)</td></tr><tr><td>Male</td><td>28</td><td>31</td></tr><tr><td>Female</td><td>25</td><td>22</td></tr><tr><td>Alcoholic cirrhosis</td><td>40</td><td>38</td></tr><tr><td>Prior bleeds</td><td>1.4 (1.4)</td><td>1.4 (1.3)</td></tr><tr><td>Ascites</td><td>39</td><td>40</td></tr></table>
24 patients included twice; 7 patients 3 times; 2 patients 4 times; 1 patient 5 times. All had at least 1 sclerotherapy session prior to re-randomisation.</td><td>Intravenous terlipressin 2mg initially and 1mg every 4 hours for 24 hours and bolus/ continuous infusion of placebo (n=53 bleeding episodes)</td><td>Somatostatin 250microg bolus plus 250microg/ hour for 24 hours, and placebo injections (n=53 bleeding episodes)</td><td>30 days</td><td>Bleeding controlled (defined as bleeding stopped in the 24 hours of treatment, with no re-bleeding within 24 hours); failed if balloon tamponade necessary to stop bleeding, or re-bleed within 24 hours.

30-day survival shown graphically only</td><td>not stated</td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow -up	Outcome measures	Source of funding

Effect size

	Total n (%)	Terlipressin n (%)	Somatostatin n (%)	P value
Number of bleeds	106 (100)	53 (100)	53 (100)	
Initial stop of bleeding: using vasoactive drug using drug and balloon total	 91 (86) 13 (12) 104 (98)	 48 (91) 4 (8) 52 (98)	 43 (81) 9 (17) 52 (98)	 NS NS NS
Bleeding not stopped	2 (2)	1 (2)	1 (2)	NS
Rebleeding within 24 hours: stopped using drug stopped using drug + balloon	10 (9) 2 (2) 8 (8)	5 (9) 1 (2) 4 (8)	5 (9) 1 (2) 4 (8)	NS NS NS
Treatment failure (initial bleeding not stopped by drug and/or rebleeding during vasoactive treatment i.e. in 1st 24 hours)	24 (23)	9 (17)	15 (28)	NS
Rebleeding during hospital stay but after 24 hours	20 (19)	13 (25)	7 (13)	NS
Units of blood and plasma	5.5 (5.8)	5.5 (5.1)	5.5 (6.3)	NS
Hospital stay (days)	16.7 (11.6)	17.4 (11.9)	16.0 (11.3)	NS
Adverse effects needing withdraweal of therapy	none	none	none	
Mortality died of initial bleed or complication of balloon tamponade died despite initial control of bleeding and no rebleed recurrent variceal bleed other (hepatic coma, cerebral hypoxia, hepato-renal failure)	 	 1 4 3 3	 1 2 5 3	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
total			22 (21)	11 (21)	11 (21)	NS		

30-day survival shown graphically only; no significant difference between groups.

Authors' conclusion:

Many bleeds from oesophageal or fundic varices can be stopped initially (86%) and definitively controlled or at least 24 hours (77%) by vasoactive drugs alone. No significant differences were shown between terlipressin and somatostatin. In these patients, invasive emergency measures can be avoided, and sclerotherapy can then be carried out in the bleeding-free interval.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Feu F, Ruiz del AL, Banares R et al. Double-blind randomized controlled trial comparing terlipressin and somatostatin for acute variceal hemorrhage. Variceal	RCT, Spain Randomisation and allocation concealment adequate; double-blind	161	Inclusion: liver cirrhosis plus haematemesis or meleana in previous 24 hours, endoscopically proven to be from oesophagogastric varices (active oozing or spurting; clot or "white nipple" over varix, or fresh blood in stomach and no other source of bleeding); age 18-75 years; no previous randomisation in this study (i.e. patients, not episodes); no previous use of vasopressin and/or somatostatin to control the episode; no sclerotherapy in previous 5 days. Exclusion: severe cardiovascular disease (including acute MI, atrioventricular block, heart failure, chronic peripheral ischaemia, arterial hypertension); hypersensitivity to study drugs;	Terlipressin (plus placebo for somatostatin) i.v. 2mg every 4 hours for maximum 48 hours (n=80)	Somatostatin (plus placebo for terlipressin) i.v. infusion 250microg/ hour for maximum 48 hours after initial bolus 250microg; 3 additional boluses allowed (2 in	6 weeks	Success = 24 hour bleed-free period in 1st 48 hours (absence of haematemesis, signs of hypovloaemia, decrease in haematocri	Fondo de Investigaciones Sanitarias, Ferring AB

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Bleeding Study Group. Gastroenterology. 1996; 111(5):1291-1299. Ref ID: 196</td><td></td><td></td><td>chronic renal failure; ongoing treatment for asthma; body weight <40kg.

Stratified by severity of liver failure: low risk = 0 or 1 of: jaundice, ascites, encephalopathy, wasting; high risk = 2 or more of these.

<table><tr><td></td><td>Terlipressin</td><td>Somatostatin</td></tr><tr><td>Age (yr)</td><td>58 (12)</td><td>56 (12)</td></tr><tr><td>Male</td><td>58</td><td>61</td></tr><tr><td>Female</td><td>22</td><td>20</td></tr><tr><td>Alcoholic cirrhosis</td><td>43</td><td>44</td></tr><tr><td>Non-alcoholic</td><td>37</td><td>37</td></tr><tr><td>Prior bleed</td><td>28</td><td>24</td></tr><tr><td>Ascites</td><td>33</td><td>37</td></tr><tr><td>Low risk</td><td>52</td><td>52</td></tr><tr><td>High risk</td><td>28</td><td>29</td></tr></table></td><td></td><td>1st 6 hours after starting therapy and 1 during treatment if reactivation of haemorrhage without reaching failure criteria (n=81)</td><td></td><td>t >8 points, fresh blood in gastric aspirate).

Failure = haematemesis or fresh blood in 6 consecutive hourly nasogastric aspirates with hypovolaemia, need to transfuse 6 or more units in 6 hours, and continued bleeding after 1st 24 hours of therapy.

Rebleeding = haemorrha</td><td></td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
							ge after 24 hours control of bleeding. Death related to bleeding = any death within 6 weeks	

Effect size

	Terlipressin	Somatostatin	p value
Control of bleeding	64/80 (80%)	68/81 (84%)	0.54
Transfusion requirements	1.8 (1.5)	1.9 (1.7)	0.69
Method of stopping bleeding in those who failed randomised therapy:			
Balloon tamponade	6	4	
Sclerotherapy	7	4	
Conservative therapy	3	4	
Portacaval shunt	0	1	
Rebleeding in 6 weeks:			
In those initially successfully treated with randomised therapy	22/64 (34%)	21/68 (31%)	0.71
In those in whom initial treatment failed	2/16 (12.5%)	2/13 (15.4%)	not stated
Total	24/80 (30%)	23/81 (28.4%)	0.86
Death by 6 weeks	13/80 (16%)	13/81 (16%)	no difference
Loss to follow up	1	3	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Adverse events: requiring withdrawal of therapy leading to death				1 0	0 0			

Authors' conclusion:
Terlipressin and somatostatin have similar efficacy in controlling acute variceal haemorrhage.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Silvain C, Carpentier S, Sautereau D et al. Terlipressin plus transdermal nitroglycerin vs. octreotide in the control of acute bleeding from esophageal varices: a multicenter	RCT, France Table of random numbers used for randomisation; allocation concealment unclear; not blinded	87 episodes (84 patienst - 3 included twice, 1.5, 3 and 10 months after first inclusion	Inclusion: Patients with cirrhosis and acute variceal bleeding (diagnosed on endoscopy to arise from a varix in oesophagus or at oesophagogastric junction and no other source of gastrointestinal bleeding. Exclusion: known coronary artery disease, hepatocellular carcinoma, severe liver failure, another bleeding episode in previous 8 days. Terlipressin: Age (yr) mean (range) 58 (37-77) Octreotide: Age (yr) mean (range) 57 (37-76)	Terlipressin 2mg i.v. bolus plus 1mg bolus every 4 hours over 24 hours plus percutaneous nitroglycerin 10mg every 12 hours for up to 24 hours (n=41 episodes)	Octreotide 25 microg/ hour for 12 hours, then 100microg subcutaneously at hour 12 and hour 18 (n=46 episodes)	1 month	Control of bleeding at 12 hours Complications requiring cessation of treatment	Société Nationale Française de Gastroentérologie

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
randomized trial. Hepatology. 1993; 18(1):61-65. Ref ID: 243			Male	34	35					
			Female	7	11					
			Alcoholic cirrhosis	37 (90%)	42 (91%)					
			No. of prior episodes mean (range)	0 (0-13)	0 (0-3)					

Effect size

	Terlipressin (n=41 episodes)	Octreotide (n=46 episodes)	p value
Controlled bleeding at 12 hours	24 (59%)	36 (78%)	0.064
Transfusion requirements mean (range) Before randomisation During treatment	 0 (0-11) 3 (0-13)	 1 (0-9) 1 (0-5)	 NS 0.012
Initial treatment not successful	17	10	
Additional treatment in acute episode: Balloon tamponade Sclerotherapy The other drug (Octreotide/terlipressin) Conservative therapy Died before any could be tried	 9 (5 failed: 2 died, 2 sclerotherapy, 1 portacaval shunt) 2 1 2 3	 2 (2 also needed sclerotherapy) 5 1 2 0	
Side effects requiring withdrawal of treatment	2	0	
Side effects causing death	1	0	
Rebleeding:			NS

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
12-24 hours 24-48 hours 48 hours-1 month Total			0 5 (20%; 2 tamponade, 2 retreated with terlipressin [of whom 1 had tamponade also]) 1 (4%) 6/24 (25%)	7 (19%; 3 sclerotherapy; 2 tamponade) 3 (8%; 1 sclerotherapy; 1 terlipressin; 1 terlipressin + tamponade + sclerotherapy) 5 (14%) 15/36 (42%)				
Death 0-12 hours 0 to 48 hours 0 to 1 month			 3 (6%) 5 (12%) 11 (28%)	 0 (0%) 3 (6%) 10 (22%)		 NS NS NS		

Authors' conclusion:

Octreotide appears as effective as terlipressin plus nitroglycerin in emergency control of variceal bleeding in cirrhosis, with significantly smaller transfusion requirements and only minor side effects.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Soderlund C, Magnusson I, Torngren S et al. Terlipressin (triglycyl-lysine	RCT, Sweden Randomised in blocks of four stratified for	60	Inclusion: extensive upper gastrointestinal tract haemorrhage within last 24 hours before diagnostic endoscopy in patient with demonstrated or clinically suspected liver cirrhosis and, at endoscopy,	Terlipressin 2mg i.v. bolus at randomisation and every 4	Placebo (mannitol)	24 hours after control endoscopy	Failure = need for active intervention (e.g. tamponade,	Ferring AB supplied drugs

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>vasopressin) controls acute bleeding oesophageal varices. A double-blind, randomized, placebo-controlled trial. Scand J Gastroenterol. 1990; 25(6):622-630. Ref ID: 282</td><td>severity of liver disease but method not stated; allocation concealment not stated; double-blind</td><td></td><td>currently bleeding varices or varices of at least size 3 and fresh blood in upper gastric tract and no other lesion with bleeding stigmata.
Exclusion: pregnancy, body weight below 55kg.

<table><tr><td></td><td>Terlipressin</td><td>Placebo</td></tr><tr><td>Age (years)</td><td>57 (11)</td><td>60 (13)</td></tr><tr><td>Male</td><td>20</td><td>21</td></tr><tr><td>Female</td><td>11</td><td>8</td></tr><tr><td>Alcoholic cirrhosis</td><td>25</td><td>24</td></tr><tr><td>Prior bleed</td><td>19*</td><td>9*</td></tr></table>
*p=0.02</td><td>hours until "control" endoscopy with sclerotherapy performed after 24 or 36 hours (or until failure or withdrawal)</td><td></td><td></td><td>emergency sclerotherapy) to stop bleeding during treatment period.

Withdrawal = discontinuing the study before "control" endoscopy because of adverse reactions, new priorities, or any other reason apart from those included in "failure"

Success = no need for active intervention during treatment

Efficacy = no or just a slight blood mix in 2 consecutive</td><td></td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
							gastric rinses 4 hours apart in haemodynamically stable patient and no ongoing bleeding or fresh blood at "control" endoscopy Mortality	

Effect size

	Terlipressin (n=31)	Placebo (n=29)	p value
Control of haemorrhage: Success Failure	 28 (90%) 3 (10%; 3 emergency sclerotherapy)	 17 (59%) 12 (41%; 7 emergency sclerotherapy; 4 balloon tamponade [3 followed by sclerotherapy and 1 by surgery]; 1 no treatment)	0.0067
Efficacy Non-efficacy	26 (84%) 5 (16%)	16 (55%) 13 (45%)	0.024
Pulse rate	85 (3)	99 (4)	p<0.005
Blood transfusion before inclusion during treatment 24 hours after treatment	 16 (median 3 units) 20 (median 1.0, range 1-5 units) not stated	 13 (median 3 units) 25 (median 2.5, range 1-13 units) not stated	 NS for patients or units NS for patients; p<0.05 for u NS
Adverse reactions leading to withdrawal	1	0	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Adverse events leading to death	0	0	
Death before discharge	3 (10%)	11 (38%)	0.0141

Authors' conclusion:

Terlipressin is safe, well-tolerated, and significantly more effective than placeboin early control of variceal bleeding, leading to reduced requirements for blood transfusion, haematemesis, and lower mortality.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Freeman JG, Cobden I, Record CO. Placebo-controlled trial of terlipressin (glypressin) in the management of acute variceal bleeding. J Clin Gastroenterol. 1989; 11(1):58-60. Ref ID: 296	RCT, UK Randomisation and allocation concealment unclear, double blind	29 patients; 31 episodes	Inclusion: Actively bleeding from oesophageal varices, other sources of haemorrhage having been endoscopically excluded Exclusion: not stated Terlipressin: Age (yrs) 51; Alcoholic cirrhosis 11 Placebo: Age (yrs) 54; Alcoholic cirrhosis 13	Terlipressin 2mg i.v. every 4 hours until bleeding controlled (to 8 hours after episode of haematemesis or meleana; not more than 6 doses); then 4 further 1mg doses at 4 hour	Placebo (n=16 episodes)	5 days	Control (when hourly haemodynamic measurements and haemoglobin stable, no apparent continuing loss of blood, further transfusions	Ferring provided drugs

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				intervals (n=15 episodes)			unnecessary) Failure (after at least 2 doses of drug, continued haematemesis or fresh meleana necessitated passage of Sengstaken tube (followed by endoscopic sclerotherapy)	

Effect size

	Terlipressin (n=15 episodes)	Placebo (n=16 episodes)	p value
Initial control of bleeding	9/15 (60%)	6/16 (37%)	NS; p>0.10
Sengstaken tube/sclerotherapy	6/15 (40%)	10/16 (63%)	
Blood transfusion			

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Prior to therapy During therapy			2 units (range 1-12 units) 3 units (range 1-8 units)		3 units (range 1-12 units) 4 units (range 1-8 units)		NS NS	
Complications requiring cessation of therapy			0		0			
Complications causing death			0		0			
Rebleeding			1 (emergency sclerotherapy)		3 (emergency sclerotherapy)			
5-day control			8 (53%)		3 (19%)		p<0.025	
Death			3		4			

Authors' conclusion:

Terlipressin appears effective in patients with variceal bleeding; rebleeding was more common with placebo than terlipressin, so 5-day control was better with terlipressin.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Walker S, Stiehl A, Raedsch R et al. Terlipressin in bleeding esophageal varices: a placebo-controlled, double-blind study. Hepatology.	RCT, Germany Randomisation and allocation concealment unclear, double-blind. NB All patients had balloon tamponade	34 patients; 50 episodes (8 patients randomised twice, 1 patient 3 times, 2 patients 4 times; all discharged between randomisations)	Inclusion: patients with cirrhosis of the liver and endoscopically verified bleeding from oesophageal varices, grade 2+ and 3+ (Westaby) Exclusion: none Terlipressin / Placebo: Age (yr): 51 (11) / 49 (10) Male: 20 / 17 Female: 5 / 8	Terlipressin 2mg i.v. initially, then 1mg every 4 hours up to a total dose of 10mg in 32 hours (n=25 episodes)	Placebo (n=25 episodes)	10 days	Control (bleeding ceased within 36 hours; 24 hours without bleeding i.e. no fresh blood aspirated from stomach and haemodynamic parameters stable).	not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
1986; 6(1):112-115. Ref ID: 337	immediately after admission endoscopy unless patients declined or did not tolerate it (used in 20 episodes in terlipressin group and 19 in placebo group)		Alcoholic cirrhosis: 23 / 19 Prior bleed: 17 / 17 Prothrombin time: 49.9 (11.3)* / 60.6 (16.6)* * p<0.05 All other laboratory variables similar between groups				Failure (sclerotherapy performed)	

Effect size

	Terlipressin (n=25 episodes)	Placebo (n=25 episodes)	p value
Control within 36 hours	25/25	20/25	p<0.05
By medical therapy only	4/4	4/4	
Medical + balloon	16/16	9/14	
Medical + sclerotherapy	1/1	2/2	
Medical + balloon + sclerotherapy	4/4	5/5	
Sclerotherapy (at second endoscopy when bleeding not stopped within 8-12 hours by balloon tamponade and/or medical therapy; patients not in shock and accepted procedure)	5	7	
Units of blood required	5.4 (4.3)	7.5 (6.1)	NS
Units of plasma required	3.6 (3.2)	7.0 (6.1)	NS
Rebleeding:			
during medical treatment	1	3	NS
during hospital stay	5	5	NS

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Side effects requiring cessation of therapy				0			0	
Side effects causing death				0			0	
Death				3/25 (12%)			8/25 (32%)	NS

Authors' conclusion:

The addition of terlipressin to standard therapy (blood and plasma transfusion, fluid replacement, electrolyte correction, lactulose, plus all patients had balloon tamponade immediately after admission endoscopy unless patients declined or did not tolerate it) appeared to increase the control rate in acute variceal haemorrhage.

QUESTION In patients with confirmed variceal UGIB after endoscopic treatment, how long should pharmacological therapy (terlipressin or octreocide) be administered to improve outcome in terms of clinical and cost effectiveness?

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Bruha, 2009	Multicenter double blind RCT Country: Czech Republic Allocation concealment unclear, randomisation sequence generation unclear	N=25 (N=15 in 5 day group and N = 10 in 10 day group)	Inclusion criteria: Patients with histologically proven cirrhosis or clinical, laboratory and ultrasonographic data compatible with diagnosis of cirrhosis admitted to participating centres with hematemesis and / or melena. Patients also had to meet the following criteria: (1) clinical symptoms of acute bleeding into the digestive tract – i.e. hematemesis and / or melena in previous 24 hours; (2) diagnosis of	1 mg of terlipressin as intravenous injection in 4-hour intervals for day 1-5 and placebo in 6-hour intervals i.v. for day 6-10	1 mg of terlipressin as intravenous injection in 4-hour intervals for day 1-5 and in 6-hour intervals for day 6-10	6 weeks	Primary endpoint: occurrence of adverse events in both arms (events that endanger the health of the patient) Secondary endpoints: mortality rate within day 42	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
	Study was terminated early due to slow recruitment		liver cirrhosis with Child-Pugh classification B or C; (3) variceal bleeding confirmed by endoscopy performed within 12 hours after admission / i.e. active bleeding, stigmata of recent bleeding or fresh blood in stomach with no other possible source beside varices in stomach; (4) age between 18 and 70 years; (5) ability to cooperate and sign informed consent to participate in trial. Exclusion criteria: (1) previous participation in the study; (2) administration of vasoactive drugs other than terlipressin in the last 24 hours; (3) history of endoscopic treatment of varices in the last 5 days; (4) presence of contraindications to terlipressin treatment, i.e. history of symptomatic schemic heart disease, cerebrovascular stroke, stage II-III essential hypertension, arterial obliteration of lower extremities, bronchial asthma, epilepsy, pregnancy or lactation; (5) terminal stage of hepatic failure not indicated for resuscitation; and (6) functional portocaval shunt (including TIPS).				after inclusion, initial control of bleeding, rebleeding rate within day 42, consumption of blood derivatives, evaluation of renal impairment, risk of hyponatremia and coccurrence of hepatic encephalopathy	

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td></td><td></td><td>Baseline characteristics (* p<0.05):
<table>
<tr><td></td><td>5-day treatment (n=15)</td><td>10-day treatment (n=10)</td></tr>
<tr><td>Male*</td><td>7</td><td>10</td></tr>
<tr><td>Age (years)</td><td>49.4 (12)</td><td>56.3 (13.5</td></tr>
<tr><td>Etiology of cirrhosis: Alcoholic / other</td><td>14/1</td><td>10/0</td></tr>
<tr><td>Systolic blood pressure</td><td>127.5 (31.8)</td><td>139.1 (20.9)</td></tr>
<tr><td>Diastolic blood pressure</td><td>72.9 (21.3)</td><td>75 (15.9)</td></tr>
<tr><td>Heart rate</td><td>95.5 (20.8)</td><td>84.8 (21.3</td></tr>
<tr><td>Child – Pugh class B/C</td><td>9/6</td><td>8/2</td></tr>
</table></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="9">Effect size
<table>
<tr><td></td><td>5-day treatment (n=15)</td><td>10-day treatment (n=10)</td><td>p</td></tr>
<tr><td>Rebleeding within day 42</td><td>5</td><td>4</td><td>NS</td></tr>
<tr><td>Mortality</td><td>1</td><td>2</td><td>NS</td></tr>
</table></td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Transfusion needs: mean units (sd)	4.13 (5.8)	2.7 (2.6)	0.076
Fresh frozen plasma needs: mean (sd)	2.9 (3.9)	0.9 (1.76)	0.14
Adverse events leading to treatment withdrawal	1	0	NS

Authors' conclusion:

Prolonged treatment with terlipressin in patients with variceal bleeding has no effect on the rate of adverse events. However, a trend towards lower blood transfusion needs was observed in those with longer treatment.

F.2 Assessment of risk

QUESTION In patients with GI bleeding (with or without comorbidities) is there an accurate scoring system (Rockall, Blatchford [aka Glasgow], Addenbrooke) to identify which patients are high risk (of mortality, rebleeding, need for blood transfusion, surgical intervention) and require immediate intervention and those at low risk who can be safely discharged?

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Stanley AJ, Ashley D, Dalton HR et	Phase one: three UK centre (prospective	Phase one: N=676	Phase one: Consecutive patients presenting with upper GI haemorrhage over a 3 to 12 month	Phase one: Junior doctor or	Compared the GBS with admission	Phase one and two: consecutiv	Endoscopic or surgical procedure	None reported

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>al. Outpatient management of patients with low-risk upper-gastrointestinal haemorrhage: multicentre validation and prospective evaluation. Lancet. 2009; 373(9657):42-47. Ref ID: 826</td><td>data collection) and one UK centre (retrospective data collection)

Phase two: two UK centres (prospective data collection)</td><td>Missing data:
N=19 data missing for measurement of admission Rockall score
N=27 has omissions for GBS

Phase two:
N=572</td><td>period.

Exclusion criteria: Inpatients with the disorder; nasogastric lavage was not undertaken routinely

Upper gastro-intestinal haemorrhage defined as haematemesis, coffee-ground vomit or melaena.

Age median 62 (IQR 43 to 76)
Sex male 416 (62%) female 256 (38%)

Endoscopic findings
<table><tr><th></th><th>GBS=0 (n=66)</th><th>GBS>0 (n=419)</th></tr><tr><td>Normal/hiatus hernia (%)`</td><td>37 (56)</td><td>100 (24)</td></tr><tr><td>Oesophagitis</td><td>12 (18)</td><td>73 (17)</td></tr><tr><td>Gastritis</td><td>6 (9)</td><td>70 (17)</td></tr><tr><td>Duodentitis</td><td>9 (14)</td><td>33 (8)</td></tr><tr><td>Mallory-</td><td>3 (5)</td><td>17 (4)</td></tr></table></td><td>research nurse obtained data including patient characteristics. Recorded outcome data.

Phase two: All Glasgow A & E patients who were not admitted were offered outpatient endoscopy, as were those who were older than 50 yrs in Stockton (or younger patients at the discretion</td><td>(pre-endoscopy) and full (post-endoscopy) Rockall scores to predict intervention or death</td><td>e patients over a 3 to 12 month period</td><td>Blood transfusion
Hospital stay
In-hospital mortality</td><td></td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Weiss tear: 0 / 0 Barrett's oesophagus: 2 (3) / 11 (3) Dieulafoy's erosion: 0 / 2 (≤ 1) Duodenal ulcer: 0 / 67 (16) Gastric ulcer: 0 / 41 (10) Varices: O / 30 (7) Arteriovenous malformation: 0 / 10 (2) Upper-gastrointestinal cancer: 0 / 19 (5) Other: 1 (2) / 11 (3) Note: more than one finding per patient possible Phase two: Prospective consecutive patients for one year (Glasgow) or three months (Stockton). Low risk Glasgow-Blatchford bleeding score (GBS) (GBS=0) in two A & E depts.	of the clinician).				

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			used to identify patients with upper GI haemorrhage for who admission could be avoided. These individual were not admitted unless for other reasons.					
Low-risk criteria of GBS: Urea < 6.5 mmol/L Haemoglobin ≥ 130 g/L (men) or ≥ 120 g/L (women) Systolic blood pressure ≥ 110 mm Hg Pulse < 100 beats per min Absence of melaena, syncope, cardiac failure or liver disease								
Phase one Endoscopic or surgical procedure 137/676 (20%) Blood transfusion 175/676 (26%) Hospital stay median 4 days (IQR 1 to 7) In-hospital mortality 30/676 (4%) GBS=0 105/630 (16%) Admission Rockall 184/630 (28%) Median age of patients in the low risk group was significantly lower than that of other individuals with complete data (41 (IQR 28 to 55) vs 64 (48 to 78) yrs; p<0.0001). Of the105 low risk patients, 22 (21%) were older than 60 yrs and 14 (13%) were older than 70 yrs. Intervention or death GBS=0 No interventions or death AUC 0.92 (95%CI 0.90 to 0.94) Rockall score = 0 One death and 44 interventions (21 endoscopic or surgical, 23 transfusions) AUC 0.72 (95%CI 0.68 to 0.76)								

Reference	Study type	Number of patients	Patient characteristics	Interventio n	Comparison	Length of follow-up	Outcome measures	Source of funding
Of those undergoing endoscopy (n=485, n=467 with complete data for measurement of the admission and full Rockall scores and GBS) Intervention or death GBS AUC 0.90 (95%CI 0.88 to 0.93) Full Rockall AUC 0.81 (95%CI 0.77 to 0.84) Admission Rockall AUC 0.70 (95%CI 0.65 to 0.75) Phase two Low risk GBS=0 123/572 (22%), of which 84/123 (68%) not admitted Low risk patients not admitted were significantly younger than those who were (median age 30 (IQR 21 to 42) vs 37 (30 to 55) yrs; p=0.005) Of those offered outpatient endoscopy, only 23 (68%) attended. Endoscopic findings showed no malignant disease, varices, or ulcers and no need for further intervention in any patient. Of the low risk group, there were no cases readmitted with upper GI haemorrhage or had died after a minimum of six months follow-up. Of the 123 patients meeting the low risk criteria GBS=0, none (95%CI 0 to 3%) needed any intervention related to their disorder Authors conclusion Simple GBS low-risk criteria can identify a significant proportion of individuals presenting with upper GI haemorrhage who are suitable for outpatient management.								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Rockall TA, Logan RF,	Development and validation	N=4185 and N=1625	Cases were drawn from				Rebleeding, mortality (no	Not reported

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Devlin HB et al. Risk assessment after acute upper gastrointestinal haemorrhage. Gut. 1996; 38(3):316-321. Ref ID: 819	of a risk index	validation population (National Audit study)	patients presenting with an acute upper gastrointestinal haemorrhage from 74 'acute' hospitals (from 4 health regions in England – North West Thames, South West Thames, Trent and West Midlands). The validation sample was subsequently collected using identical methodology s part of the second phase of the National Audit.				rebleed), mortality (rebleed)	
To develop the risk index multiple regression analysis was used – applying a forward stepwise selection procedure. A variable was included at each step if the score statistics was less than 0.05 and was removed if the log likelihood ration test statistic was greater than 0.1. Confidence interval analysis was undertaken using CIA software. Two models were developed one initial predictive model as well as another model which includes in addition risk factors derived from endoscopic information and further haemorrhage. The final scoring system included risk factors: Age, Shock, Comorbidity (for the initial assessment index) plus Diagnosis and Major SRH (after endoscopy):								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

	Score			
Variable	0	1	2	3
Age	<60	60-79	≥80	
Shock	'No shock', systolic BP ≥100 pulse <100	'Tachycardia', systolic BP ≥100 pulse ≥100	'Hypotension', systolic BP <100	
Comorbidity	No major comorbidity		Cardiac failure, ischaemic heart disease, any major comorbidity	Renal failure, liver failu disseminated malignan
Diagnosis	Mallory-Weiss tear, no lesion identified and no SRH	All other diagnoses	Malignancy of upper GI tract	
Major SRH	None or dark spot only		Blood in upper GI tract, adherent clot, visible or spurting vessel	

Note. Gray shaded cells show the clinical score, values in the white cells are then added to the initial score to create the complete index

Overall rebleeding (N=736/4185 18%) and mortality (N=585/4142 14%)

Risk score	N; (%)	Rebleeding N; (%)	Death (no rebleed) N; (%)	Death (rebleed) N; (%)	Death (total) N (%)
0	144; (4.9)	7; (4.9)	0	0	0
1	281; (9.5)	9; (3.4)	0	0	0
2	337; (11.4)	18; (5.3)	1; (0.3)	0	1; (0.2)
3	444; (15.0)	50; (11.2)	8; (2.0)	5; (10.0)	13; (2.9)
4	528; (17.9)	76; (14.1)	16; (3.5)	12; (15.8)	28; (5.3)
5	453; (15.3)	83; (24.1)	30; (8.1)	19; (22.9)	49;(10.8)
6	312; (10.6)	102; (32.9)	20; (9.5)	34; (33.3)	54;(17.3)
7	267; (9.0)	113; (43.8)	23; (14.9)	49; (43.4)	72; (27.0)
8+	190; (6.4)	101; (41.8)	25; (28.1)	53; (52.5)	78; (41.1)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Validation: A comparison between the predictions of the full logistical regression model and the observed mortality in each category of the risk factor showed a 'high degree of association' (no statistic given). The risk score was validated in a second population of 1625 cases collected using an identical methodology as part of the second phase of the National Audit. All necessary variables were recorded in 1584 cases in 1190 cases, variables for endoscopic diagnosis and stigmata of recent haemorrhage were also recorded. The predicted outcomes based upon the observed outcome by risk category in the first audit were not significantly different from the observed outcome in the second audit in either the initial or complete models (confidence intervals for difference scores given in Table V and none of them are significantly different from 0). Authors conclusion This scoring system is a useful risk stratification tool since it can identify the one quarter of patients that are at negligible risk of dying.								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Vreeburg EM, Terwee CB, Snel P et al. Validation of the Rockall risk scoring system in upper gastrointestinal bleeding. Gut. 1999; 44(3):331-335. Ref ID: 822	Prospective Dutch Rockall validation study	N=951	All patients who were consecutively admitted to the endoscopy ward of two university and 10 regional hospitals in the same Amsterdam. Inclusion criteria: symptoms of haematemensis, melaena, haematochezia, or blood admixture on nasogastric aspiration who were suspected of having acute UGIB as well as patients who developed an acute UGIB while being hospitalised for other diseases.	Coexisting illnesses were classified according to the ICED scale			Rebleeding (defined as a new episode of bleeding during hospitalisation after the initial bleeding had stopped. Further haemorrhage necessitating surgery was also defined as rebleeding)	Not reported

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Plus Vreeburg EM, Snel P, de Bruijne JW et al. Acute upper gastrointestinal bleeding in the Amsterdam area: incidence, diagnosis, and clinical outcome. Am J Gastroenterol. 1997; 92(2):236-243. Ref ID: 827			*Detailed characteristics provided in Vreeburg et al. 1997: Median age 71 yrs (range 2-100) with 25% older than 80 yrs, Sex male 570 (60%) Medical characteristics: Shock 603 (63%) Dyspepsia 18% Epigastric pain 22% Heartburn 10% Previous ulcer disease 194 (20%) – in 90 of these previous complications of ulcer disease (bleeding or perforation) had occurred. 48 patients (5%) had had gastric surgery. Liver disease was present in 97 patients (10%), usually cirrhosis (n=92) 63 (6.6%) had a history of varices				mortality (defined as death within the hospitalisation period)	

Overall rebleeding (N=156/951 16%) and mortality (N=132/951 14%)

Risk score	N	Rebleeding %	Mortality %
0	11	9.1	0
1	36	3.8	0
2	71	8.5	1.4
3	145	13.8	7.6
4	175	11.4	9.7

Reference	Study type	Number of patients	Patient characteristics	Interventio n	Comparison	Length of follow-up	Outcome measures	Source of funding
5 178 16.3 10.7 6 142 22.5 17.6 7 107 20.6 24.3 8+ 86 26.7 46.5 Validity: Rebleeding – the goodness of fit test between predicted* and observed rates indicated a lack of fit (χ2 =61.6, df=6, p<0.0001) Mortality – correspondence between predicted and observed rates was better (χ2 =9.3, df=6, p=0.2) *Predicted probabilities based on observed percentages in original patient sample by Rockall Diagnostic accuracy: Rebleeding AUC 0.61 (SE 0.03) Mortality AUC 0.73 (SE 0.02) Authors conclusion The Rockall scoring system is a clinically useful system for stratifying patients with acute UGIB into high and low risk categories for mortality for the prediction of rebleeding however the performance of this scoring system was unsatisfactory.								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Blatchford O, Murray WR,	Development (study 1) and	N=1748 and N=197	All patients who were admitted	New risk score	Rockall score		Need for treatment	The first study was supported

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Blatchford M. A risk score to predict need for treatment for upper-gastrointestinal haemorrhage. Lancet. 2000; 356(9238):1318-1321. Ref ID: 818	prospective validation (study 2) of a risk scoring system for UGIB (aka Glasgow)	(validation group)	for acute upper gastrointestinal haemorrhage in all 19 hospitals in west Scotland. Validation sample: consecutive adult patients admitted with UGIB during a subsequent 3=months period in three hospitals in west Scotland. Exclusions: patients whose records were incomplete or whose final outcome could not be ascertained.				(defined as patients who had a blood transfusion, or any operative or endoscopic intervention to control their haemorrhage, or if they had undergone no intervention but had died, rebleed, or had a substantial fall in haemoglobin concentration after admission)	by the Scottish Office Clinical Resources and Audit Group and the second by the Chief Scientist's Office

Overall intervention rates:

Risk score	Score development group (n=1748)		Score validation group (n=197)	
	Intervention not needed	Intervention needed	Predicted need for intervention	Intervention needed
	N (%)	N (%)	N (%)	N (%)
0	276 (15.8)	5 (0.3)	0.6 (0.3)	1 (0.5)
1	185 (10.6)	11 (0.6)	1.8 (0.9)	3 (1.5)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
2	115 (6.6)	15 (0.9)		1.4 (0.7)	1 (0.5)			
3	101 (5.8)	10 (0.6)		1.2 (0.6)	3 (1.5)			
4	97 (5.5)	30 (1.7)		2.1 (1.1)	4 (2.0)			
5	72 (4.1)	44 (2.5)		4.2 (2.1)	4 (2.0)			
6	61 (3.5)	62 (3.5)		7.1(3.6)	11 (5.6)			
7	32 (1.8)	85 (4.9)		9.4 (4.8)	10 (5.1)			
8	14 (0.8)	58 (3.3)		10.5 (5.3)	10 (5.1)			
9	15 (0.9)	53 (3.0)		3.1 (1.6)	4 (2.0)			
10	3 (0.2)	77 (4.4)		5.8 (2.9)	5 (2.5)			
11	5 (0.3)	113 (6.5)		12.4 (6.3)	12 (6.1)			
12	1 (0.1)	74 (4.2)		8.9 (4.5)	9 (4.6)			
13	3 (0.2)	55 (3.1)		5.7 (2.9)	6 (3)			
≥14	0 (0)	76 (4.3)		6.0 (3.0)	6 (3)			
Total	980 (56.1)	768 (43.9)		80.2 (40.7)	89 (45.2)			

For the development of the risk index a regression model was built by stepwise selection of explanatory variables (clinical and laboratory data obtained at the time of admission). The coefficients obtained from the logistic regression were multiplied by a scaling factor to produce a scoring system that required the addition of integer values which were associated with specific risk factors identified at patients' initial assessments. In the validation study a ROC curve was plotted to compare the new index with the Rockall score.

Risk markers from the regression model were: Blood urea, Haemoglobin (for men and women separately scored), systolic blood pressure and other markers such as pulse ≥100, presentation with meleana, presentation with syncope, hepatic disease and cardiac failure:

Admission risk marker	Score component value
Blood urea (mmol/L)	
≥6.5 <8.0	2
≥8.0 <10.0	3
≥10.0 <25	4
≥25	6
Haemoglobin (g/L) for men	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
≥120 <130		1						
≥100<120		3						
<100		6						
Haemoglobin (g/L) for men								
≥100<120		1						
<100		6						
Systolic blood pressure (mm Hg)								
100-109		1						
90-99		2						
<90		3						
Other markers								
Pulse ≥100 (per min)		1						
Presentation with malaena		1						
Presentation with syncope		2						
Hapatic disease		2						
Cardiac failure		2						

The score was well calibrated for patients who needed clinical intervention (p=.84)
New score AUC:
0.92 95%CI(0.88-0.95)
Rockall admission AUC:
0.71 95%CI(0.64-0.78)
Rockall postendoscopy AUC:
0.75 95%CI(0.67-0.83)
The new score also showed high correlation with length of hospital stay and units of blood needed:
Spearman's Correlations:

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
	Length of stay	Units of blood						
New Score	0.57	0.74						
Rockall admission	0.45	0.32						
Rockall postendoscopy	0.38	0.41						
Authors conclusion The Blatchford score identified patients at low or high risk of needing treatment to manage their bleeding.								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Sanders DS, Carter MJ, Goodchap RJ et al. Prospective validation of the Rockall risk scoring system for upper GI hemorrhage in subgroups of patients with varices and peptic ulcers. Am J Gastroenterol. 2002; 97(3):630-635.	Prospective UK risk score validation study	N=325	Patients were drawn from all admissions due to either esophageal varices or peptic ulceration to the Royal Hallamshire Hospital in Sheffield. N=163 with esophageal varices, n=70 with gastric ulcers, n=92 with duodenal ulcers. Age (median) 55 (range 19-82)variceal group; 74 (range 19-97) peptic ulcer group Male / female =64/99 variceal group; 91/71 peptic ulcer group	Rockall score as well as Child-Pugh score			Rebleeding (defined as overt fresh bleeding after initial stabilization or a fall in Hb of more than 2 g within 24 h.) mortality	Not reported

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Ref ID: 821								

Overall mortality was 13.2% (n=43/325) and rebleeding occurred in 23.4% (n=76/325).

Mortality specifically from peptic ulcers was 13% (n=21)

Mortality for esophageal varices was 11% (n=22).

		Rockall Score								
		0	1	2	3	4	5	6	7	≥8
N (%)	Esophagal varices	0	1 (0.5)	0	26 (13.3)	26 (13.3)	47 (24)	44 (22.4)	33 (16.8)	19 (9.7)
	Peptic ulcers	0	6 (3.7)	7 (4.3)	15 (9.3)	25 (15.4)	30 (18.5)	23 (14.2)	27 (16.7)	29 (17.9)
Rebleed N (%)	Esophagal varices	0	0	0	0	1 (3.8)	8 (17)	14 (31.8)	6 (18.2)	9 (47.4)
	Peptic ulcers	0	0	1 (14.3)	1 (6.7)	2 (8)	8 (26.7)	7 (30.4)	12 (44.4)	15 (51.7)
Mortality N (%)	Esophagal varices	0	0	0	1 (3.8)	0	5 (10.6)	2 (4.5)	6 (18.2	8 (42.1)
	Peptic ulcers	0	0	0	0	2 (8)	4 (13.3)	3 (13)	4 (14.8)	8 (27.6)

The authors conclude that the Rockall risk scoring system is highly predictive of both mortality and risk of rebleeding in variceal hemorrhage. For peptic ulcers the initial Rockall score is predictive of mortality and the complete Rockall score correlates with rebleeding, but the complete score does not predict mortality with statistical significance.

Authors conclusion

Rockall scores can be used for the risk stratification of esophagal varices as well as peptic ulcers.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Cameron EA, Pratap JN,	Prospective risk score creation	N=1349 episodes of	All patients with acute upper-gastrointestinal haemorrhage				2-week, all-cause	Not reported

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Sims TJ et al. Three-year prospective validation of a pre-endoscopic risk stratification in patients with acute upper-gastrointestinal haemorrhage. Eur J Gastroenterol Hepatol. 2002; 14(5):497-501. Ref ID: 817	study (aka Addenbrooke)	haemorrhage	(primary and secondary) managed at Addenbrooke's Hospital, Cambridge between 1 June 1996 and 30 June 1999. Mean age 64.7 years (55.7% occurred in males). At endoscopy a cause of haemorrhage was identified in 73.8% of cases: 14.9% duodenal ulcer 13.8% gastric ulcer 12.9% gastritis 7.9% oesophagitis 7.4% varices 3.7% duodenitis 3.1% oesophageal ulcers 28.8% of patients required blood transfusion 12.2% received central venous monitoring 3% underwent emergency surgery				mortality (selected because the authors felt that this was most likely to represent mortality directly from GIB), re-bleeding, urgent treatment intervention	

Mortality in those with an identified cause was (73 / 996 - 7.3%) and overall 2-week mortality was 6.5% (88 / 1349)

Primary outcomes by risk stratification:

	Risk stratification			
Endpoint	High risk	Intermediate risk	Low risk	Overall

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Episodes		569	704	76	1349			
2-week, all cause mortality		11.8%	3.0%	0	6.5%			
Re-bleeding		44.1%	2.3%	0	19.8%			
Urgent treatment intervention		71.0%	40.6%	2.6%	51.3%			

Risk group	Variable
High	Recurrent bleeding (any of: resting tachycardia and supine hypotension with no obvious cause;
	further fresh blood haematemensis; ruddy melaena; falling haemoglobin concentration more than could be explained by haemodilution)
	Persistent tachycardia (pulse > 100 beats/min despite resuscitation)
	History of oesophageal varices
	Systolic blood pressure < 100 mmHg (supine)
	Coagulopathy (prothrombin time > 17 s)
	Thrombocytopenia (platelet count < 100 x 109/l)
	Postural hypotension > 20 mmHg on negative chronotropes (e.g. beta blockers)
Intermediate	Age > 60 years
	Haemoglobin < 11 g/dl (on admission)
	Co-morbidity (any clinically significant co-existing disease)
	Passage of melaena or presence on digital rectal examination
	Excessive alcohol (> 28 units/week or > 10 units in previous 24 h)
	NSAID (current or recent NSAID or aspirin)
	Previous gastrointestinal bleed or peptic ulceration
	Abnormal liver biochemistry (transaminases, alkaline phosphatise or bilirubin)
	Postural hypotension > 10 mmHg (sitting or standing compared with supine)
	Systolic blood pressure > 20 mmHg below patient's normal (if known)
Low	None of the aforementioned factors

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Best predictors for 2-week mortality using multiple logistic regression (forward stepwise selection): OR 95% CI Persistent tachycardia 1.84 1.09-3.10 Coagulopathy 1.85 1.06-3.24 Age > 60 3.17 1.72-5.86 Co-morbidity 1.83 1.15-2.93 Abnormal liver biochemistry 1.78 1.02-3.13 Systolic blood pressure (< 100 mmHg) 3.79 2.27-6.34 Stratification within the high-risk group predicted 2-week mortality with a sensitivity of 76.1% and specificity of 60.2%. In the low risk group there were no deaths.								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Phang TS, Vornik V, Stubbs R. Risk assessment in upper gastrointestinal haemorrhage: implications for resource utilisation. N Z Med J. 2000; 113(1115):331	Prospective New Zealand Rockall risk score validation study	N=565	All patients who were either admitted to Wellington Public Hospital with acute upper GI bleeding, or who had an acute upper GI bleed while in hospital for other reasons (identified prospectively) Median age 63 (range 10 months to 99 years). Male to female ration 342/223	Rockall initial score – data were recorded initially on a computerised database by a 'dedicated research assistant'. All patients were	Rockall compared to 'major' and 'minor' bleed at the time of presentation (criteria for 'major' bleed – any of: tachycardia (>100), systolic hypotension		mortality	Research grant from the New Zealand blood foundation

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
-333. Ref ID: 820			77% acute admissions, 17% inpatients, 6% transferred from another hospital 13% from long-stay care institutions	retrospectively assigned a score	(<100mmHg), postural hypotension (>15 mmHg fall in systolic pressure on standing)			

Overall mortality N=63 / 565 (11%)

Risk score	N	Mortality %
0	65	2
1	56	0
2	77	5
3	144	4
4	130	17
5	72	22
6	18	50
7	3	100

There was a significant difference in mortality in groups of patients with scores above or below 3:
342 (60.5%) had a score of 3 or less and a collective mortality of 3.2%.
223 (39.5%) had a score of 4 or more and a collective mortality of 22.4% - chi-square p<0.0001.

There was a trend of higher mortality in patients classified as having 'major' bleeding:
38 (13.5%) deaths occurred in 281 patients judged initially to have 'major' bleeding
whereas 23 (8.1%) deaths occurred in the 284 patients judged to have 'minor' bleeding– chi-square p=0.0522

Authors conclusion
The Rockall scoring system appears as valid in a New Zealand patient population as in the UK.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Kim BJ, Park MK, Kim S-J et al. Comparison of scoring systems for the prediction of outcomes in patients with nonvariceal upper gastrointestinal bleeding: A prospective study. Dig Dis Sci. 2009; 54(11):2523-2529.	Prospective South Korean risk score comparison study	N=239 (patient who had endoscopy) 77 excluded whose bleeding was caused by rupture of gastro-oesophageal varices (n=65) or by portal hypertensive gastropathy (n=12). 46 excluded because their endoscopy showed neither a source of bleeding nor traces of blood in the upper gastrointestinal tract 1 excluded due to the diagnosis of aorto-eneric fistula	Patients who had undergone upper gastrointestinal endoscopy due to UGIB by two experienced endoscopists this included patients who developed an UGIB while hospitalised for unrelated disease. Exclusions criteria: patients were excluded if less than 16 years old, if endoscopy was not performed within 24h from the earliest signs of UGIB, if bleeding was due to the rupture of gastro-oesophageal varices or due to portal hypertensive gastopathy and if endoscopy showed neither a non-variceal putative source of bleeding nor traces of blood in the upper gastrointestinal tract. Male N=191 (80%); mean age 59.1 SD(14.6); UGIB whilst in hospital for another reason 22 (9.2%) Type of bleeding: gastric ulcers 107 (44.8%); duodenal ulcer 47 (19.7%); malignancy 41 (17.2%); erosive gastritis (8.4%); refhix oesophagitis 21 (6.1%); Mallory-Weiss 6 (1.7%); other lesions 4 (1.2%); angiodysplasia 7 (2.9%); Esophagitis 7 (2.9%); Others 20 (8.4%) Forrest classification: Spurting		Forrest Classification, Rockall (RS), Baylor College scoring system (BS), Cedars-Sinai Medical Centre predictive index (CPI), Blatchford score		Mortality and Rebleeding (defined as objective evidence of UGIB with unstable vital signs, with a decreased hemogrlobin concentration of at least 2 g/dl per day, or need for more than two units of packed erythrocytes per day to maintain the stability of the hemoglobin concentration after initial endoscopic hemostasis and stabilisation of the vital signs in 24 h.)	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
		Final sample size N= 343	bleeding 18 (7.5%); oozing bleeding 67 (28.0%); Non-bleeding visible vessel 41 (17.2%); adherent blood clot 38 (16.0%); black base 11 (4.6%); lesion without stigmata of recent haemorrhage 64 (26.7%)					

Rebleeding rate was 14.6% (n= 35) and mortality was 8.4% (n= 20):

Comparison of scores by rebleeding and death according to scoring system:

	Rebleeding			Death		
	Present	Absent	p	Present	Absent	p
Rockall risk scoring system (n = 239	6.1 ± 1.9	5.0 ± 2.3	< 0.01	7.8 ± 1.4	5.0 ± 2.3	< 0.01
Cedars-Sinai Medical Centre Predictive Index (N = 239)	6.7 ± 2.5	5.4 ± 2.7	< 0.01	8.6 ± 2.4	5.3 ± 2.6	< 0.01
Blatchford scoring system (n = 239)	10.2 ± 4.0	9.4 ± 4.0	ns	11.8 ± 3.0	9.3 ± 4.0	< 0.01
Baylor college scoring system (n = 61)	10.4 ±4.5	8.2 ± 3.6	ns	13.1 ± 4.8	9.4 ± 4.1	0.02

Sensitivity, specificity, positive predictive value and negative predictive value for rebleeding and death in scoring systems:

Assigned score	Rebleeding	Death
Forrest classification		
Sensitivity	71.43 (54.95 – 83.67)	85.00 (63.96 – 94.76)
Specificity	50.49 (43.68 – 57.28)	50.23 (43.66 – 56.79)
Positive Predictive Value	19.84 (13.81 – 27.65)	13.49 (8.6 – 20.54)
Negative Predictive Value	91.15 (84.77 – 95.12)	97.35 (92.49 – 99.10)
Complete Rockall classification		
Sensitivity	77.14 (60.98 – 87.93)	100 (83.89 – 100)
Specificity	39.22 (32.78 – 46.06)	40.18 (33.91 – 46.79)
Positive Predictive Value	17.88 (12.59 – 24.76)	13.25 (9.67 – 17.89)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Negative Predictive Value			90.91 (83.08 – 95.32)		100 (95.82 – 100)			
Cedars Sinai classification								
Sensitivity			80.00 (64.11 – 89.96)		95.00 (76.39 – 99.11)			
Specificity			41.67 (35.12 – 48.53)		41.55 (35.22 – 48.17)			
Positive Predictive Value			19.05 (13.52 – 26.15)		12.93 (8.44 – 19.31)			
Negative Predictive Value			92.39 (85.12 – 96.26)		98.91 (94.09 – 99.81)			
Blatchford classification								
Sensitivity			94.29 (81.40 – 98.42)		100 (83.89 – 100)			
Specificity			0.98 (0.27 – 3.50)		1.83 (0.71 – 4.61)			
Positive Predictive Value			14.04 (10.17 – 19.06)		8.51 (5.58 – 12.79)			
Negative Predictive Value			50.00 (15.00 – 85.00)		100 (51.01 – 100)			
Baylor college classification								
Sensitivity			30.77 (12.68 – 57.63)		87.50 (52.91 – 97.76)			
Specificity			47.92 (34.47 – 61.67)		58.49 (45.09 – 76.74)			
Positive Predictive Value			13.79 (5.50 – 30.56)		24.14 (12.22 – 42.11)			
Negative Predictive Value			71.88 (54.63 – 84.44)		96.88 (84.26 – 99.45)			

Authors conclusion

The Forrest classification was superior to the others in predicting rebleeding and death and therefore the most useful scoring system for the prediction of rebleeding and death in patients with nonvariceal UGIB.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Chen IC, Hung	Retrospective	N=354	All patients 18 years or over	Rockall (RS	Blatchford		Mortality and	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
MS, Chiu TF et al. Risk scoring systems to predict need for clinical intervention for patients with nonvariceal upper gastrointestinal tract bleeding. Am J Emerg Med. 2007; 25(7):774-779.	case review Country: Taiwan		admitted to the emergency department with acute UGIB. Exclusions criteria: bleeding esophageal varices, Male N=237 (66.9%); mean age 61.6 SD(16.2); NSAIDs users 148 (42%); all treated with PPIs; 68 (19.2%) gastric ulcer; 64(18.1%) duodenal ulcer; 71 (20.0%) gastric ulcers with protruding vessel; 64 (18.1%) duodenal ulcer with protruding vessel; 87(24.6%) other causes	– initial and complete)			Rebleeding and being a 'high risk patient' (patients who needed a blood transfusion or any operative or endoscopic intervention to control their bleeding were defined as high risk and a Blatchford score of greater than 0, or a clinical Rockall score greater than 0 and a complete Rockall score of greater than 2 is then classified also classified as 'high risk' to predict the intervention	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
							'high risk' patients)	

Rebleeding rate was 6.5%% (n= 23 / 354) and mortality was 0.85% (n= 3 / 354).

The Blatchford score identified 326 (92.1%) of the 354 patients as those with high risk for clinical intervention (i.e. blood transfusion, endoscopic or surgical management for bleeding control). The clinical Rockall score identified 289 (81.6%) of the 354 patients as high-risk and the complete Rockall score identified 248 (70.1%) of the 354 patients as high risk. The yield of identifying high-risk patients with the Blatchford score was significantly greater than with the clinical RRockall score ($p < 0.0001$) or with the complete Rockall score ($p < 0.0001$).

Sensitivity, specificity, positive predictive value and negative predictive value for rebleeding and death in scoring systems:

Assigned score	High –risk patients	Rebleeding	Death
Blatchford score			
Sensitivity	99.6 (97.7 – 99.9)	100 (85.7 – 100)	100 (43.8 – 100)
Specificity	25.0 (17.8– 33.9)	8.5 (5.9 – 12.0)	8.0 (5.6 – 11.3)
Positive Predictive Value	75.2 (70.2 – 79.5)	7.1 (4.7 – 10.4)	0.9 (0.3 – 2.7)
Negative Predictive Value	96.4 (82.3 – 99.4)	100 (87.9 – 100)	100 (87.9 – 100)
Clinical Rockall score			
Sensitivity	90.2 (85.9 – 93.4)	69.6 (49.1 – 84.4)	100 (43.8 – 100)
Specificity	38.0 (29.4 – 47.4)	17.5 (13.8 – 22.0)	18.5 (14.8 – 22.9)
Positive Predictive Value	76.8 (71.6 – 81.3)	5.5 (3.4 – 8.8)	1.0 (0.4 – 3)
Negative Predictive Value	63.1 (50.9 – 73.8)	89.2 (79.4 – 94.7)	100 (94.4 – 100)
Complete Rockall score			
Sensitivity	91.1 (86.8 – 94.0)	87.0 (67.9 – 95.5)	33.3 (6.1 – 79.2)
Specificity	77.8 (69.1 – 84.6)	31.1 (26.4 – 36.3)	29.6 (25.1 – 34.6)
Positive Predictive Value	90.3 (86.0 – 93.4)	8.1 (5.3 – 12.1)	0.4 (0.1 – 2.2)
Negative Predictive Value	79.2 (70.6 – 85.9)	97.2 (92.0 – 99.0)	98.1 (93.4 – 99.5)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Authors conclusion The Blatchford score has higher sensitivity than the clinical and the complete Rockall score to identify 'high-risk' patients and since it does not need urgent endoscopy could be a useful tool in detecting which patients need clinical intervention.								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Sarwar S, Dilshad A, Khan AA et al. Predictive value of Rockall score for rebleeding and mortality in patients with variceal bleeding. Journal of the College of Physicians & Surgeons - Pakistan. 2007; 17(5):253-256.	Prospective Pakistani Rockall validation study in cirrhosis patients	N=402	All patients who were consecutively admitted to the Depatment of Gastoenterology and Hepatology at the Postgraduate Medical Institute from March 2005 to March 2006 with symptoms of hematemesis, melaena, haematochazia, or blood admixture on nasogastric aspiration, secondary to cirrhosis of liver. Medical characteristics: Age 52.57 (11.39) Male to female ratio 269/133 Tachycardia (pulse ≥ 100/min) 159 (39.4%) Systolic blood pressure < 100 mm / Hg 56 (13.9%) Ascites 234 (58.2%) Patients win porto-systemic	Rockall			Rebleeding (defined as a new episode of bleeding during hospitalisation after the initial bleeding had stopped and that manifested as recurrent haematemesis, haematochezia, fresh blood in the nasogastric aspirate or circulatory instability)	Not reported

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			encephalopathy 42 (10.4%) Cirrhosis due to Hepatitis C 380 (94.5%) Hep B cirrhosis 12 (3%) Alcoholic cirrhosis 6 (1.4%) Other cirrhosis 4 (0.9%)				mortality (defined as death within the hospitalisation period)	

Overall rebleeding (N=22/402 5.4%) and mortality (N=27/402 6.7%)

Risk score	N	Rebleeding N (%)	Mortality N (%)
0	6	0	0
1	123	1(0.8)	1(0.8)
2	101	2(1.9)	3(2.9)
3	88	6(6.8)	4(4.5)
4	46	3(6.5)	5(10)
5	20	6(30)	6(30)
6	9	3(33)	3(33)
7	8	1(12)	4(50)
8+	1	0	1(100)

Diagnostic accuracy:
Rebleeding
AUC 0.80
Mortality
AUC 0.83

Authors conclusion
The Rockall scoring system has good predictive and discriminative value for in-hospital rebleed and mortality in patients with variceal bleeding due to liver cirrhosis.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Tham TC, James C, Kelly M. Predicting outcome of acute non-variceal upper gastrointestinal haemorrhage without endoscopy using the clinical Rockall Score. Postgrad Med J. 2006; 82(973):757-759.	Retrospective Rockall validation study in non-variceal UGIB population Country: Northern Ireland	N=102	All patients who were consecutively admitted with acute non-variceal upper gastrointestinal haemorrhage to a University hospital in Belfast over a 2 year period. Medical characteristics: Age 59 (range 16-96) Diagnoses after endoscopy: Normal 30% Gastritis 21% Oesophagitis or Barrett's syndrome 15% Duodenitis 11% Duodenal ulceration 9% Gastric ulceration 6% Angiodysplasia 4% Gastric carcinoma 1%	Rockall score			Rebleeding (defined as a further haematemesis or melaena with signs of haemodynamic instability such as rise in heart rate, fall in blood pressure or fall in haemoglobin. Malaena without signs of haemodynamic instability was not considered as rebleeding.) mortality (not specified), surgery and number of patients requiring blood	Not reported

Reference	Study type	Number of patients	Patient characteristics	Interventio n	Comparison	Length of follow-up	Outcome measures	Source of funding
							transfusions	

Overall rebleeding (N=5/102 5%) and mortality (N=2/102 2%)

			Oucomes, n (% of those with the score)			
Clinical Rockall score	Patients n (% of total)	Taking aspirin or NSAIDs, n (% of those with scores)	Transfusion	Rebleeding	Surgery	Mortality
0	38(37)	3(8)	0	0	0	0
1	13(13)	4(30)	2(15)	0	0	0
2	16(16)	3(19)	4(25)	0	0	0
3	16(16)	12(75)	7(44)	0	0	0
4	14(14)	4(29)	7(50)	1(7)	1(7)	0
5	4(4)	2(50)	2(50)	3(75)	0	1(25)
6	0					
7	1(1)	1(100)	1(100)	1(100)	0	1(100)

Diagnostic accuracy:

Authors conclusion

The Rockall scoring system is the best for predicting mortality and n-hospital rebleeding in variceal bleeding. MELD and CTP scores can be used for survival prediction of bleeding patients but not for assessing chances of rebleeding.

Reference	Study type	Number of patients	Patient characteristics	Interventio n	Comparison	Length of follow-up	Outcome measures	Source of funding
Enns RA,	Retrospective	N=1869	All patients presenting with overt	Rockall			Rebleeding	Not

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Gagnon YM, Barkun AN et al. Validation of the Rockall scoring system for outcomes from non-variceal upper gastrointestinal bleeding in a Canadian setting. World Journal of Gastroenterology. 2006; 12(48):7779-7785.	Rockall validation study in non-variceal UGIB population Country: Canada (RUGBE initiative – endoscopic reporting software used to collect data from 6 community and 12 university affiliated health institutions)		UGI bleeding or a history of hematemesis/coffee ground vomiting, melena, hematochezia , or a combination of any of the above within 24 h preceding admission. All patients had to have a non-variceal source of bleeding confirmed by endoscopy. Medical characteristics: Age 66 (16.9) Male 62% Endoscopic findings: Peptic ulcer disease 55.5% Esophagitis 8.2% Mallory Weiss 4.4% Dieulafoy 2.5% Other 29.4%	score – case data was downloaded monthly between 09/1999 and 12/2001 – a sequential time series sampling of eligible subjects was carried out at regular intervals to avoid a possible selection bias.			(recurrent vomiting of fresh blood, melena or both with either shock or a decrease in haemoglobin concentration of at least 2 g/L following initial successful treatment), need for a surgical procedure and death Continued bleeding and rebleeding were combined to a single rebleeding category.	stated

Overall rebleeding (N=258/1869 14%), mortality (N=100/1869 5.4%) , surgical procedures (75/1869 4%) and length of hospital stay (5.7 ± 6.6 days)

Comparison of three scoring systems for predicting mortality and rebleeding in patients of variceal bleeding

Complete	Patients n (%)	Rebleeding n (%)	Surgical	Deaths n (%)	Length of hospital

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Rockall score			procedures n (%)		stay (d): Mean (SD)	Median (IQR)			
≤2	240(13)	21(8.8)	6(2.5)	0	3.6(3.5)	2.9(1.1-4.7)			
3	205(11)	18(8.8)	5(2.4)	3(1.5)	4.4(5.9)	3(2-5.25)			
4	359(19)	49(13.6)	11(3.1)	11(3.1)	5.7(5.7)	4(2.3-7)			
5	435(23)	63(14.5)	17(3.9)	20(4.6)	5.9(6.9)	4(2.3-7)			
6	290(16)	31(10.7)	12(4.1)	24(8.3)	6.7(7.9)	4.5(2.3-8)			
7	195(10)	39(20)	15(7.7)	18(9.2)	6.6(6.6)	4((2.3-9)			
≥8	145(8)	37(25.5)	9(14)	24(16.6)	7.4(7.9)	5(3-9)			
Total	1869	258 (14)	75 (4.0)	100 (5.4)	5.7(6.6)	4(2-7)			
Results for other risk score categories									
≤2	240(13)	21(8.8)	6(2.5)	0	3.6(3.5)	2.9(1.1-4.7)			
3-5	999(53)	130(13)	33(3.3)	34(3.4)	5.6(6.3)	4(2-7)			
≥6	630(34)	107(17)	36(5.7)	66(10.5)	7.2(7.7)	5(3-9)			

Calibration $\chi 2$ – goodness –of-fit statistic (non-significant p indicates good fit):

Overall events: $\chi 2$ (8) = 12.83, p=0.12

Surgical procedures and death: good correspondence between observed proportion and predicted probablilites (surgery: $\chi 2$ (8) = 5.3, p=0.73 and death: $\chi 2$ (8) = 3.78, p=0.88

Rebleeding $\chi 2$ not reported

Discriminative ability – AUC

Rebleeding: 0.59 (95%CI 0.55-0.62)

Surgical procedures: 0.60 (95%CI 0.54-0.67)

Death: 0.73 (95%CI 0.69-0.78)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Authors conclusion The Rockall scoring system provides an acceptable tool to predict death, but performs poorly for endpoints of rebleeding and surgical procedures.								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Masaoka T, Suzuki H, Hori S et al. Blatchford scoring system is a useful scoring system for detecting patients with upper gastrointestinal bleeding who do not need endoscopic intervention. J Gastroenterol Hepatol. 2007; 22(9):1404-1408.	Retrospective Blatchford validation study Country: Japan	N=93	All patients suspected to have UGI bleeding based on their presentation with hematemesis, tarry stool, or syncope with anemia who underwent emerbency endoscopy at the emergency department. Patients who were treated at other hospitals before transfer to the study's hospital were excluded. Emergency endoscopies were all performed within 3 hours of admission to the emergency department Medical characteristics: Age 61.4 (16.2) Male 72 70 required blood transfusions, operative or endoscopic interventions for the control of	Blatchford score extracted from patients' records			High and low risk groups (high defined as requiring blood transfusions, operative or endoscopic interventions)	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			haemorrhage Endoscopic findings: Gastric ulcer 47(50.5%) Duodenal ulcer 14 (15.1%) Esophageal or gastric varices 5 (5.4%) Acute gastric mucosal lesion 2 (2.2%) Gastric cancer 8 (8.6%) Esophageal cancer 1 (1.1%) Malloray Weiss syndrome 3 (3.2%) Erosive gastritis 3 (3.2%) Unknown and other 10 (10.8%)					

Sensitivity, specificity, negative likelihood ratio and negative predictive value with the cut-off value is set at 0-3

Cut-off score	Sensitivity	Specificity	Negative likelihood ratio	Negative predictive value
0	100.0	4.3	0.000	1.000
1	100.0	8.7	0.000	1.000
2	100.0	13.0	0.000	1.000
3	435(23)	21.7	0.066	0.833

Discriminative ability – AUC

Low and High risk group: 0.628 (confidence intervals not provided)

Authors conclusion

The Blatchford scoring system is accurate for identifying definitively low risk patients of GI haemorrhage, even prior to the performance of emergency UGI endoscopy at the emergency department.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Gralnek IM, Dulai GS. Incremental value of upper endoscopy for triage of patients with acute non-variceal upper-GI hemorrhage. Gastrointest Endosc. 2004; 60(1):9-14.	Retrospective case review study Country: US	N=175	Inclusion criteria: 18 years or over, admitted during the study period (calendar years 1997 or 1998) with the relevant International Classification of Disease codes and who underwent diagnostic upper endoscopy Exclusions: patients who developed bleeding while in the hospital, were transferred from another hospital, or bled from a lower-GI source. Medical characteristics: Age 62 (19) Male 95 (54%) NSAIDs users 81(46%) Endoscopic findings: Gastric ulcer 40(23%) Duodenal ulcer 23 (13%) Mallory Weiss tear 9% Esophagitis 13% Gastroduodenophathy 8% Gastroduodnal erosions 13%	Rockall (clinical and complete scores) Patients with a clinical score of 0 and a complete sore of 2 or below were defined as 'low risk' group	Blatchford Patients with a score of 0 were classified as a 'low risk' group		Rebleeding (if one of the following events occurred: repeat endoscopy before hospital discharge, surgery for control of UGIB, or re-admission to the hospital within 30 days of discharge because of UGIB) and mortality	First author is supported by an advanced career development award

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Angiomata 6% Unknown and other 15%					
Number of 'low risk' cases identified: Blatchford score of 0: 14 (8%) – no patient died or rebled Clinical Rockall score of 0: 21 (12%) - no patient died or rebled Complete Rockall score of 2 or below: - no patient died but 2 patients rebled Authors conclusion The complete Rockall score identified significantly more low-risk patients than either the clinical Rockall or the Blatchford score and this leads to a lower burden on healthcare resources.								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Bessa X, O'Callaghan E, Balleste B et al. Applicability of the Rockall score in patients undergoing endoscopic therapy for upper gastrointestinal bleeding.	Retrospective Rockall validation study patients undergoing endoscopic therapy for upper gastrointestinal bleeding Country: Spain	N=222	Patients with active bleeding: spurting or oozing, non-bleeding visible vessel or adherent clots treated endoscopically in the period between 1995 and 2001. All patients received endoscopic therapy with adrenaline plus polidocanol (peptic and non-peptic lesions). Medical characteristics: Male (72.5%)	Rockall score – from a specific database for patients with UGIB			Rebleeding (defined as a new epsisode of bleeding during hospitalisation, after the initial bleeding had stopped, manifested as a recurrence of haematemesis,	Grants from the Redes temáticas en Gastrenterologia y Hepatologia

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Digestive & Liver Disease. 2006; 38(1):12-17.			Endoscopic findings: Duodenal ulcer 47.3% Gastric ulcer 34.2% Mallory Weiss 9% Dieulafoy 5% Other 4.5% Rockall variables: Age: <60 30%; 60-79 48%; ≥ 80 22% Shock: No shock 50%; Tachycardia 30%; Hypotension 20% Comorbidity: No major comorbidity 45%; Cardiac failure, ischaemic heart disease, any major comorbidity 34%; Renal failure, liver failure, disseminated malignancy 21% Diagnoses: Mallory-Weiss tear, no lesion identified and no SRH/blood 9%; All other diagnoses 88%; Malignancy of upper GI tract 3% Major SRH: None or dark spot only 0; blood in upper GI tract , adherent clot, visible vessel 100%				hematochezia or fresh blood in the nasogastric aspirate.), mortality was defined as death within the hospitalisation period.	

Overall rebleeding (N=50/222 23%), mortality (N=20/222 9%).

Complete Rockall score distribution and scores for those patients who rebleed or died

Complete Rockall score	Patients n (%)	Rebleeding n (%)	Death (%)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
0	0	0	0					
1	0	0	0					
2	5	0	0					
3	15	3(20)	0					
4	33	9(27)	0					
5	34	4(11.7)	0					
6	32	7(21.9)	3(9.4)					
7	43	11 (25.6)	4 (9.3)					
8	29	6(20.7)	5(17.2)					
9	18	4(22.2)	3(16.7)					
10	13	6(46.2)	5(38.5)					
Total	222	50(23)	20(9)					

No differences were observed in the scores of patients with or without re-bleeding (mean=6.6±2.1 vs. 6.1±2.0). Low and high risk groups according to Rockall score division did not differ significantly in scores according to rebleeding.

The Rockall scores of patients who died was significantly higher than who did not (mean=8.2±1.4 vs. 6.0±2.0).

Authors conclusion

The Rockall score can be used in patients who undergo therapeutic endoscopy for upper GI bleeding to identify those with high risk for mortality.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Church NI, Dallal HJ, Masson J et al. Validity of the Rockall scoring system after endoscopic therapy for bleeding peptic ulcer: a prospective cohort study. Gastrointestinal Endoscopy. 2006; 63(4):606-612.	Retrospective Rockall validation study patients undergoing endoscopic therapy for peptic ulcer haemorrhage	N=247	All patients had peptic ulcers with active bleeding or non-bleeding visible vessles. In addition, all patients had at least one of the following criteria: age over 60 years, shock (defined as systolic blood pressure less than 100 mmHg and /or a pulse greater than 100 beats per minute) , significant co-morbid disease or haemoglobin less than 10 g/dl. Exclusions: not specified Retrospective data came from patients who participated in one randomised control trial, comparing heater probe and thermocoagulation alone or a combination of heater probe and thrombin injection. Recruited between 1996 and 2001 (there is an overlap with the sample reported by Church and Palmer, 2001) Baseline characteristics are not provided.	Rockall score – from a specific database of previous UGIB research trials by the same research group		30 day	Rebleeding (defined as fresh haematemesis or melaena associated with the development of shock or a a fall in haemoglobin concentration of 2 g/dl over 24 h), 30 day mortality and failed hemostasis.	Not stated

Reference	Study type	Number of patients	Patient characteristics	Interventio n	Comparison	Length of follow-up	Outcome measures	Source of funding

Overall rebleeding (N=35/211 17%), mortality (N=29/211 14%) .

Comparison of three scoring systems for predicting mortality and rebleeding in patients of variceal bleeding

Complete Rockall score	Patients n (%)	Failed hemostasis n (%)	Rebleeding n (%)	30 day mortality
0	0	0	0	0
1	0	0	0	0
2	0	0	0	0
3	20	0	0	0
4	48	2(4)	3(6)	0
5	54	0	8 (15)	0
6	37	2(5)	9(24)	4(11)
7	44	0	7(16)	6(14)
8	28	3(11)	5(18)	5(18)
9	14	0	4(29)	5(36)
10	2	1(50)	0	2(100)
Total	247	8(3)	36(15)	22(9)

Thirty day mortality – cause of death:

	N
Total	22
Exsanguinations	8
Myocardial infarction	1
Congestive cardiac failure	3
Respiratory failure	4
Pulmonary embolism	1

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Cerebrovascular accident			3					
Metastatic carcinoma diagnosed after recruitment to trial			2					
Median Rockall score			8					

Calibration χ2 – goodness –of-fit statistic (non-significant p indicates good fit):
Both for rebleeding and 30 mortality there was not a good fit between predicted and observed Rockall scores:
Rebleeding: Mantel-Haenszel test $\chi 2 = 25.8$, $p<0.0001$
30 day mortality: $\chi 2 = 15.1$, $p<0.0001$

Diagnostic accuracy:
Authors' own results:
AUC rebleeding: 63.4%
AUC mortality: 84.3%

Authors conclusion
The Rockall score can be used to predict poor outcome in patients who undergo therapeutic endoscopy for major peptic ulcer bleeding.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Stephens JR, Hare NC, Warshow U, et al. Management	Prospective Glasgow / Blatchford validation study with a	N=232 (first cohort) and N=304 (second cohort)	Primary upper GI haemorrhage was defined as bleeding from the upper gastrointestinal tract manifest clinically as haematemesis (including coffee ground vomiting)	Blatchford score	Also divided into different age groups and whether it's	4-6 weeks	Need for endoscopic therapy, blood transfusions, surgery, mean	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
of minor upper gastrointestinal haemorrhage in the community using the Glasgow Blatchford Score. European Journal of Gastroenterology & Hepatology 2009 Dec;21:1340-6. Ref ID: 6	second cohort to assess management in the community Country: UK		and / or melaena, occurring in a patient in the community. Exclusions: patients who have upper gastrointestinal haemorrhage while an in-patient in hospital for another cause First cohort were prospectively studied patients presenting with primary upper GI bleeding to the Royal Cornwall hospital during 2004. Data from the second cohort was prospectively collected from all patients presenting with primary upper GI bleeding from June 2006 for 12 months. Baseline characteristics not provided		appropriate to treat in the community or not.		length of stay and death	

Mortality in 2004 cohort: N=4/232 - 1.7%; mortality in 2006 cohort: N=13/304 – 4.3% .

Distribution of Glasgow Blatchord scores and outcomes in the first cohort (year 2004)

		Oucomes, n				
Glasgow	Patients n (%	Endoscopic	Blood	Surgery	Mean length of	Death

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Blatchford score	of total)	therapy	transfusions		stay (days)				
0	29	0	0	0	2.0	0			
1	24	1	0	0	2.6	0			
2	13	3	1	0	2.7	0			
3	19	3	0	0	2.4	0			
4	15	3	1	0	3.1	0			
5	19	3	1	0	3.1	0			
6	9	4	5	1	5.2	0			
7	15	4	5	1	4.4	0			
8	13	5	4	0	4.9	1			
9	13	8	9	1	4.6	1			
10	12	1	7	0	4.0	0			
11	12	5	13	0	5.5	0			
≥12	39	19	37	2	9.5	2			
Total	232	59	83	5	-	4			

Distribution of Glasgow Blatchord scores and outcomes in the second cohort (year 2006)

		Oucomes, n				
Glasgow Blatchford score	Patients n (% of total)	Endoscopic therapy	Blood transfusions	Surgery	Mean length of stay (days)	Death
0	46	0	0	0	3.0	0
1	47	0	0	0	4.0	0
2	30	1	0	0	3.5	0
3	22	2	0	0	5.5	1
4	21	1	1	0	7.0	0

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
5	11	2	3	0	6.2	2			
6	13	1	2	0	7.4	0			
7	17	2	8	0	8.5	0			
8	18	5	12	0	6.5	2			
9	11	2	8	2	13.9	1			
10	12	3	9	0	10.7	0			
11	16	3	14	1	7.3	1			
≥12	40	21	38	3	9.4	6			
Total	304	59	95	6	-	13			

Diagnostic accuracy:

Age group	AUC	95% CI
< 60 years	0.910	0.85 - 0.971
< 70 years	0.867	0.807 – 0.928
< 80 years	0.768	0.694 – 0.843

Authors conclusion

The authors concluded that the criteria of a GBS ≤ 2 for patients aged less than 70 years was useful to define patients at 'low risk' and allows 10.5% of patients with primary upper GI bleeding to be safely managed in the community.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Rotondano G, Cipolletta L, Grossi E, et al.	Prospective Multi-center Risk score /	N=2380	Patients with clinical evidence of overt upper gastrointestinal haemorrhage (UGIH) on admission	Artificial Neural Network	Rockall	30 days	30 day mortality	Not stated

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Artificial neural networks accurately predict mortality in patients with nonvariceal upper GI bleeding. Gastrointest Endosc 2011;73:218-26.
Ref ID: 30</td><td>artificial neural network comparison study

Country: Italy</td><td></td><td>(hematemesis or melena or dark, tarry materials on rectal examination documented and witnessed by nursing or medical staff); a history of hematemesis/coffee ground vomiting, melena, hematochezia or a combination of any of these within 24 hours preceding the admission; or clinical evidence of acute UGIH

Exclusions: Patients with a primary diagnosis other than acute UGIH, chronic anemia, variceal bleeding obscure bleeding, transfer from another institution or UGIH that occurred more than 3 days before presentation.

Demographic and clinical characteristics of study sample – presented as % (95%CI) or mean (sd) unless otherwise specified:
<table>
<tr><td></td><td>N=2380</td></tr>
<tr><td>Male</td><td>65 (62.8-67.7)</td></tr>
<tr><td>Age (y)</td><td>68 (16)</td></tr>
<tr><td>In-hospital</td><td>15 (12-16)</td></tr>
</table></td><td></td><td></td><td></td><td></td></tr>
</table>

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>bleeding</td><td></td></tr>
<tr><td>History of peptic ulcer</td><td>16 (14-17)</td></tr>
<tr><td>Previous gastric surgery</td><td>5.9 (4.2 – 7.3)</td></tr>
<tr><td>No. of comorbidities* % (median, range)</td><td>1 (1, 0-2)</td></tr>
<tr><td>Shock</td><td>19 (18.1-23.2)</td></tr>
<tr><td>Need for endoscopic therapy</td><td>41 (38.9-44.4)</td></tr>
<tr><td>Recurrent bleeding</td><td>5.16 (3.9-6.9)</td></tr>
<tr><td>Mortality</td><td>4.7 (3.5-5.7)</td></tr>
</table>
*comorbidities included were: cardiovascular, pulmonary, diabetes, chronic heart failure, neoplasia, cirrhosis
</td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="9">The artificial neural network (called the T

Predictive performance eof ANN and Rockall score (mean diagnostic yield of best predictive models), shaded cells represent significant differences – presented as % (95% CI):
<table>
<tr><td></td><td>ANN</td><td>Complete Rockall</td><td>p value</td></tr>
<tr><td>Accuracy</td><td>96.8 (93.0-97.5)</td><td>52.9 (50.8-55.0)</td><td><.001</td></tr>
<tr><td>Sensitivity</td><td>83.8 (76.7-90.8)</td><td>71.4 (62.8-80.0</td><td><.01</td></tr>
</table>
</td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Specificity		97.5 (96.8-98.2)	52.0 (49.8-54.2)	<.001					
PPV		63.3 (55.3-71.3)	7.0 (5.5-8.6)	<.001					
NPV		99.1 (98.7-99.5)	97.2 (96.3-98.2)						
LR +		33.8 (22.4-44.9)	1.49 (1.31-1.69)						
LR -		0.17 (0.11-0.26)	0.55 (0.40-0.74)						

Diagnostic accuracy:

Test	AUC	95% CI
ANN	0.95	0.92-0.98
Rockall	0.67	0.65-0.69

Authors conclusion

In patients with nonvariceal upper GI bleeding, ANNs are significantly superior to the complete Rockall score in predicting death.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Pang SH, Ching JY, Lau JY, et al. Comparing the Blatchford and pre-endoscopic Rockall score in predicting the need for endoscopic	Prospective risk score comparison study Country: China	N=1087	Inclusion: Patients admitted to with a principle diagnosis of UGIH and who arrived at the endoscopy room or the operating thertre for an EGD within 24 hrs. Exclusions: Patients with primary diagnoses other than UGIH.	Blatchford score	Admission Rockall score	4-6 weeks	Primary outcome: Need for endoscopic treatment	Pfizer

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
therapy in patients with upper GI hemorrhage. Gastrointest Endosc 2010 Jun;71:1134-40. Ref ID: 4810			UGIH was defined as hematemesis, coffee ground vomiting, melena or hematochezia. Baseline characteristics: Mean age (sd) 66.9 (17.6); Male (%) 61.7; more than half (65.6%) presented with melena					

Patients requiring endoscopic therapy: N=297 (27.3%)

Approximate Blatchford (cut-off 0) and Rockall (cut-off 0) results as extracted from the graphs provided:

Blatchford score:

		True need for endoscopy		Total
		No	Yes	
Predicted Need for therapy	No	297	740	1037
	Yes	0	50	50 (4.6%)
Total		297	790	1087

In other words of the 4.6% that were identified by the Blatchford score as low risk patients none later needed endoscopic therapy

Rockall score:

		True need for endoscopy		Total
		No	Yes	
Predicted Need for	No	188	605	793
	Yes	109	185	294 (27%)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
therapy								
Total	297	790		1087				

In other words of those 27% that were identified as low risk by the Rockall score 109/294 (37%) needed therapy

Diagnostic accuracy (AUC of admission Rockall not provided):

	AUC	95% CI
Blatchford (full range)	0.72	0.68 - 0.75

Authors conclusion

The Blatchford score is more useful for predicting low-risk patients who do not need therapeutic endoscopy and who may be suitable for outpatient management. The Rockall score is not helpful in predicting the presence of low-risk patients.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Srirajaskantha n R, Conn R, Bulwer C, et al. The Glasgow Blatchford scoring system enables accurate risk stratification of patients with upper gastrointestina	Retrospective risk score comparison study study (single centre) Country: UK	N=166	Inclusion: Patients presenting with UGIH to the accident and emergency department over a 12-month period. UGIH was defined as haematemesis, coffee-ground vomiting or melaena. Exclusions: Inpatients with UGIH UGIH was defined as hematemesis, coffee ground vomiting, melena or	Blatchford score	Pre endoscopy Rockall score	Records were examined for rebleeding in the within 6 months and death	Patients correctly identified as high risk Definition of 'high risk' was: those who required blood transfusion, operative or endoscopic interventions	No funding was received for this study

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
l haemorrhage. Int J Clin Pract 2010 Jun;64:868-74. Ref ID: 16			hematochezia. Baseline characteristics: Median age (range) 51 (16-92); Male (%) 67				to control haemorrhage, required admission to the high dependence or intensive care units, had episodes of rebleeding, were re-admitted with further UGI bleeding within 6 months, or who died.	

Patients identified as 'high risk' were 72/166 (43%)

Approximate Blatchford (cut-off 0) and Rockall (cut-off 0) results as extracted from the graphs provided:

Blatchford score:

		True 'low risk' No	Yes	Total
Predicted Need for therapy	No	72	52	124
	Yes	0	42	42 (25% of total)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Total	72	94	166

In other words of the 25% that were identified by the Blatchford score as low risk patients none later interventions

Rockall score:

		True 'low risk'		Total
		No	Yes	
Predicted Need for therapy	No	70	51	793
	Yes	2	43	45 (27%)
Total		72	94	166

In other words of those 27% that were identified as low risk by the Rockall score 2/45 (4.4%) were later identified as being in the 'high risk' category

Diagnostic accuracy (no confidence intervals reported:

	AUC
Blatchford	0.96
Rockall	0.81

Authors conclusion

The Glasgow/Blatchford score accurately identifies low risk patients who could be managed safely as outpatients.

F.3 Timing of endoscopy

QUESTION In patients with GI bleeding, does endoscopy carried out within 12 hrs of admission compared to 12-24 hours or longer improve outcome in respect of length of hospital stay, risk of rebleeding or mortality?

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Bjorkman DJ, Zaman A, Fennerty MB et al. Urgent vs. elective endoscopy for acute non-variceal upper-GI bleeding: an effectiveness study. Gastrointest Endosc. 2004; 60(1):1-8. REF ID 208	RCT, USA Allocation concealment: sequential, opaque envelopes Randomisation: not specified ITT analysis The study was terminated early due to a small difference in outcomes (interim analysis) such that 7000 patients would had to have been recruited to meet power calculation	N=93	All patients presenting to the emergency departments with acute non-variceal UGI bleeding initially were evaluated for hemodynamic stability. Patients could be referred from other outpatient settings, but inpatients were excluded. Patients were treated with intravascular volume replacement with crystalloid solutions Inclusion criteria: (1) Acute UGI bleeding as indicated by one of the following: hematemesis, melena, and/or hematochezia with blood or altered blood in the nasogatric aspirate. (2) Hemodynamic stabilisation (supine systolic bp >100 mm Hg without orthostasis and a supine heart rate < 100 beats per minute without orthostasis within 3 hrs after initial evaluation by a physician; during this time, the patients was vigorously	Within 6 h of initial evaluation	Within 48 h of initial evaluation	30 days	Hospitalisation, length of stay, ICU days, units of blood transfused, repeat endoscopy, mortality	American Society for Gastrointestinal Endoscopy, the American College of Gastroenterology, and the American Digestive Health Foundation

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td></td><td></td><td>resuscitated with fluids, if needed
(3) Absence of severe comorbidity (defined as a score of ≤ 5 on the Rockall)
Exclusion criteria: Hemodynamic instability (defined above) after 3 h of vigourous intravascular volume replacement
(2) < 18 yrs
(3) Severe comorbid illness, Rockall 6 or 7
(4) Child-Pugh class B or C cirrhosis
(5) Onset of bleeding while in the hospital

p>0.10 for all variables
<table>
<tr><td></td><td>Elective N=46</td><td>Urgent N=47</td></tr>
<tr><td>Male, n</td><td>33</td><td>29</td></tr>
<tr><td>Age mean yr (95%CI)</td><td>52 (47 to 57)</td><td>57 (52 to 62)</td></tr>
<tr><td>Rockall score mean (95%CI)</td><td>1.67 (1.25 to 2.09)</td><td>1.80 (1.37 to 3.23)</td></tr>
<tr><td>H6 (g/dL)</td><td>11.85 (10.25 to 13.45)</td><td>16.35 (11.26 to 21.54)</td></tr>
</table></td><td></td><td></td><td></td><td></td></tr>
</table>

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td></td><td></td><td>n. * p<0.05
<table><tr><td></td><td>Urgent N=47</td><td>Elective N=46</td></tr><tr><td>Duodenal ulcer</td><td>19</td><td>13</td></tr><tr><td>Gastric ulcer</td><td>14</td><td>15</td></tr><tr><td>GastritisErosive esophagitis</td><td>3
4</td><td>2
5</td></tr><tr><td>Esophageal ulcer</td><td>2</td><td>5</td></tr><tr><td>Mallory Weiss</td><td>9</td><td>4*</td></tr><tr><td>None</td><td>0</td><td>2</td></tr><tr><td>High risk lesions*</td><td></td><td></td></tr><tr><td>Active bleeding</td><td>11</td><td>6</td></tr><tr><td>Visible vessel</td><td>4</td><td>3</td></tr><tr><td>Adherent clot</td><td>4</td><td>5</td></tr></table></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="9">Effect
Health care resource utilisation or patient outcomes – all p > 0.05:
<table><tr><td></td><td>Urgent n=47</td><td>Elective n=46</td></tr><tr><td>Transfusion required</td><td>19</td><td>15</td></tr></table></td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics	Interventio n	Comparison	Length of follow-up	Outcome measures	Source of funding

Mean units transfused (95%CI)	2.14 (1.03 to 3.25)	1.54 (0.97 to 2.11)
Median units transfused	0	0
Surgery	1	1
Deaths	0	0
Hospital stay mean days (95%CI)	3.98 (2.84 to 5.11)	3.26 (2.32 to 4.21)
Median hospital stays days	3	3

Authors conclusion

Early endoscopy did not reduce hospitalization or resource utilization because the results of early endoscopy did not impact the decision by attending physicians regarding admission. For early (triage) endoscopy to impact resource utilization, the results of endoscopy must change subsequent patient care.

Reference	Study type	Number of patients	Patient characteristics	Interventio n	Comparison	Length of follow-up	Outcome measures	Source of funding
Lee JG, Turnipseed S, Romano PS et al. Endoscopy-based triage significantly reduces hospitalization rates and costs of treating upper GI bleeding: a randomized controlled trial (Structured	RCT, USA Allocation concealment: sequential, opaque envelopes Randomisation: unclear, ITT analysis Power calculations were carried out and and 49	N=110 (randomised) n= 54 control and n= 56 early group	Consecutive patients with upper GI bleeding who had been admitted and had hospital bed assignment by the emergency department physician to exclude patients with trivial bleeding. Formal inclusion criteria were not used to assign the location of the admission to maximize the generalizability of the data. Exclusion criteria: Comorbid illness requiring intensive care (e.g. myocardial ischemia), hemodynamic instability after resuscitation by infusion of 2L of	Early endoscopy - within 2 hours	Within 48 h of initial evaluation	Contacted on days 7, 14, 21 and 30 (only overall final numbers reported)	Transfusion requirements, Hospital stay, recurrent haemorrhage, repeat endoscopy, surgery, readmission, unplanned visits to any physician, death, total median costs	Supporte d in part by American Digestive Health Foundati on and the Hibbard E. Williams Research Award from

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
abstract). Gastrointest Endosc. 1999; 50(6):755-761. REF ID 45	patients needed to be enrolled in each group to detect a 25% difference in the risk of admission. The authors recruited a slightly higher number assuming that 10% would refuse to participate or lost to follow up.		fluid (heart rate greater than 115 beats/min, systolic blood pressure less than 90 mm Hg, or diastolic blood pressure less than 60 mm Hg), known or suspected variceal source, coagulopathy (use of any anticoagulant or thrombolytic agent within the preceding week, platelet count less than 50000. International normalized ratio less than 1.5, or any other coagulopathy, upper GI bleeding within the preceding 1 month, and age less than 18 years. A possible variceal source was suspected in any patient with a known history of varices , cirrhosis or portal hypertension who had jaundice, spider angioma, splenomaegaly, nodular liver, ascites, asterixis, or fetor, patients with thrombocytopenia, prolonged prothrombin time, hypoalbuminemia, hyperbilirubinemia, or any other laboratory tests suggestive of possible liver disease (e.g. CT showing a nodular liver). These conservative criteria were designed to minimize the possibility of enrolling a patient with a variceal bleeding rather then to diagnose					University of California

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td></td><td></td><td>acute variceal bleeding.

p>0.05 for all variables
<table>
<tr><td></td><td>Control N=54</td><td>Emergent N=56</td></tr>
<tr><td>Male, n</td><td>40</td><td>39</td></tr>
<tr><td>Age mean yr (SD)</td><td>51 (18)</td><td>47 (15)</td></tr>
<tr><td>Medical history N(%):</td><td></td><td></td></tr>
<tr><td>Prior upper GI bleeding</td><td>15(28)</td><td>20(36)</td></tr>
<tr><td>Prior ulcer</td><td>16(30)</td><td>20(36)</td></tr>
<tr><td>Prior endoscopy</td><td>15(28)</td><td>15(27)</td></tr>
<tr><td>Alcohol use</td><td>27(50)</td><td>30(54)</td></tr>
<tr><td>Aspirin use</td><td>10(19)</td><td>9(17)</td></tr>
<tr><td>NSAIDs</td><td>10(19)</td><td>12(21)</td></tr>
<tr><td>H_2-RA or PPI use</td><td>18(33)</td><td>13(23)</td></tr>
</table></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Vital signs on admission:							
			Heart rate	94(16)	96(16)					
			Systolic blood pressure	134(27)	135(23)					
			Diastolic blood pressure	81(18)	81(18)					
			Admission timing:							
			During day	15(28)	21(38)					
			During night or weekends	39(72)	35(63)					
			Location of planned admission:							
			ICU	8(15)	15(27)					
			Intermediate	19(35)	12(21)					
			Medical ward	27(50)	29(52)					

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Effect

Endoscopic findings (p>0.05 for all variables):

	Control n=48	Emergent n=56
Ulcers: N(%)	27(56)	38(68)
Gastric ulcer	6(13)	14(25)
Duodenal ulcer	16(33)	16(29)
Esophageal ulcer	5(10)	8(14)
Esophagitis	7(15)	7(13)
Mallory-Weiss tear	3(6)	3(5)
Miscellaneous	11(23)	8(14)
Stigmata of recent haemorrhage		
Spurting	1(2)	1(2)
Oozing	5(10)	7(13)

Early endoscopy performed in the emergency department downgraded the admission site in 38 of the 56 patients randomized and upgraded it in 8 patients. 26 of the 56 patients were discharged directly from the emergency department after endoscopy. Early endoscopy based triage significantly reduced the use of the medical ward (56% for control group vs. 18% for endoscopy group, p = 0.001), but not the intensive care unit or the intermediate care unit.

Reported outcomes (shaded cells indicate significant differences):

	Urgent n=54	Elective n=56	p
Transfusion required	1.1(1.7)	1.2(2.4)	0.44
Hospital stay: median days (interquartile range)	2(2-3)	1(0-3)	0.0001
Hospital stay: mean days*	1.5	1.3	0.004
Rebleeding	3(5.6)	2(3.6)	0.63

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Repeat endoscopy			4(7.4)	4(7.1)	0.98			
Surgery			1(1.9)	2(3.6)	0.99			
Readmission			8(14.8)	4(7.1)	0.21			
Unplanned visits to any physician			13(24.5)	5(8.9)	0.031			
Death			2(3.7)	0	0.54			
Total median costs: Dollars (interquartile range)			3662 (2473-7280)	2068 (928-3960)	0.00006			

*no standard deviations provided

Authors conclusion

Early endoscopy performed shortly after admission in the emergency department safely triaged 46% of patients with nonvariceal upper GI bleeding to outpatient care, which significantly reduced hospital stay and costs.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Lin HJ, Wang K, Perng CL et al. Early or delayed endoscopy for patients with peptic ulcer bleeding. A prospective randomized study. J Clin Gastroenterol. 1996; 22(4):267-271.	RCT, Taiwan Allocation concealment unclear: sealed envelopes Randomisation: unclear: arranged by a statistician who was not involved in the clinical study	N=325 (randomised) n=162 early and n=163 delayed Before randomisation patients were stratified according to whether they had clear, coffee-grounds	Inclusion criteria: patients with hematemesis and / or melena. In the emergency room a nasogastric tube was inserted in each patient and the color of the nasogastric aspirate was recorded (clear, coffee grounds or bloody) by a resident after initial irrigation with water. Restricted to patients with peptic ulcers. Exclusion criteria: Patients who were unwilling to consent, had a bleeding tendency (defined by a platelet count ≤ 50000/mm3, a	Early endoscopy - within 12 hours	12 hours or above	2 months	Number with rebleeding after endoscopic therapy, number with endoscopic therapy (injection, HP, MPEG), number with emergency operation, blood	Supported by NSC grant

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>REF ID: 483</td><td></td><td>or bloody nasogastric aspirate in the stomach at entry into the study.</td><td>prothrombin time <30%, or anticoagulant therapy), or were experiencing bleeding from the upper airway or lower gastrointestinal tract. Patients were also excluded if they had a bleeding source that could not be pinpointed, had continued bleeding due to malignancy, had bleeding from esophageal or gastric varices, had massive bleeding but refused to enter the trial, or were unable to cooperate during the endoscopic examination.

I think, due to nonsignificant differences in the clear aspirate group, only those for coffee-ground and bloody nasogastric aspirate are reported

Baseline characteristics for coffee-ground and bloody nasogastric aspirate groups combined. Differences between groups were not significant for all variables.
<table>
<tr><td></td><td>Early n=53</td><td>Delayed N=54</td></tr>
<tr><td>Male, n</td><td>49</td><td>47</td></tr>
<tr><td>Age mean yr (SD)</td><td>66(9.7)</td><td>66.8 (11.7)</td></tr>
</table>
</td><td></td><td></td><td></td><td>transfusion after entry, number of deaths due to bleeding, number of deaths due to underlying illness, days in hospital</td><td></td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Shock n (%)	25(47)	22(41)					
			Hemoglobin	10.1(2.5)	9.7(3.1)					
			Blood transfusion (ml)	434(481)	464(500)					
			Location of bleed							
			Esophagus	1	2					
			Stomach	33	25					
			Duodenum	19	27					
			SRH n coffee-ground / n bloody							
			Clear	5/0	6/0					
			Flat spots	4/3	9/2					
			Adherent clot	8/4	7/3					
			NBVVs	14/5	13/7					
			Oozing	5/1	3/3					
			Spurting	2/2	1/0					
Effect										

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Results of patients with coffee-grounds/bloody nasogastric spirate receiving early (EE) and delayed (DE) endoscopy:

	Early n=53	Delayed n=54	Early total (including clear aspirate group) n=162	Delayed total (including clear aspirate group) n=
Rebleeding	3/0	3/2	6	8
Endoscopic therapy	18/5	12/11	33	35
Injection	6/3	6/5		
HP	4/1	5/3		
MPEG	8/1	1/3		
Surgery	2/1	0/4	3	5
Blood transfusion (ml)	431(494)/450(465)	397(468)/666(548)*		
Deaths due to bleeding	1/0	0/1	1	1
Deaths due to underlying illness	1/0	0/0	1	0
Days in hospital	4.7(4.4)/4(3.5)	4.2(6)/14.5(10.8)*		

*$p < 0.001$ between patients with bloody aspirate.

Authors conclusion

Early endoscopy and endoscopic therapy are not needed in bleeding peptic ulcer patients with clear or coffee-grounds nasogastric aspirate. However, early endoscopy and endoscopic therapy benefit patients with bloody nasogastric aspirate.

F.4 Management of non variceal upper GI bleeding

F.4.1 Combination treatments

QUESTION In patients with non-variceal UGIB which combinations of endoscopic treatments (thermal / mechanical and adrenalin / thrombin injection) is the most effective to improve outcome?

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Lo C-C, Hsu P-I, Lo G-H, et al. Comparison of hemostatic efficacy for epinephrine injection alone and injection combined with hemoclip therapy in treating high-risk bleeding ulcers[1]. Gastrointest Endosc 2006;63:767-73.	RCT, cingle centre Country:Taiwan Allocation concealment adequate (person not associated with the study opened the sealed envelope) randomisation sequence generation adequate	N=52 combination treatment (hemoclip plus injection) and N = 53 single treatment	Inclusion criteria: Patients with a peptic ulcer with an actively bleeding visible vessel (spurting or oozing), a nonbleeding visible vessel or adherent clots. Exclusion:1) the presence of another possible bleeding site (e.g. esophageal varices, gastric cancer), 2) the coexistence of an acute significant illness (eg, sepsis, stroke, acute surgical abdomen), and 3) a systematic bleeding tendency (eg, platelet < 50,000/mm3, prolonged prothrombin time > 3 seconds, treatment with an antidoagulant) Baseline characteristics – no significant differences: Combination N=52 / Epinephrine N=53 Age 64(17) / 63(16) Male 40 (77) / 41(77)	Combination treatment: hemoclips – performed with stainless steel hemoclips with prongs that measured 6 mm in length and 12 mm in width. Clips were applied with a clip application device passed through the	Epinephrine injection only as described in the intervention column	8 weeks	Hemostasis – defined as endoscopically verified cessation of bleeding for at least 5 minutes after the first endoscopic treatment. Those patients who continued to bleed despite treatment underwent emergency surgery. mortality, Recurrent bleeding,	Research grant from the participating hospital

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			N(%)				emergency surgery, length of hospital stay	
			Hypovolemic shock 9(17) 6(11)	2.8 – mm – diameter accessory channel of a standard endoscope. Hemoclips were individually loaded and deployed as peviously described. Endoscopic epinephrine injection was performed with 1:10,000 solution immediately after hemoclip therapy. Injections were performed with 0.5 to 2 mL boluses to a				
			HB, g/dL (SD) 9.7(2.4) 10.4(2.7)					
			Comorbid disease 29(56) 27(51)					
			Ulcer size mm (SD) 12.6(10) 11.8(6.5)					
			Ulcer site					
			Stomach 30(58) 24(45)					
			Duodenum 22(42) 29(55)					
			Bleeding type					
			Spurting 8(15) 4(7.5)					
			Oozing 13(25) 17(32)					
			NBVV 20(38) 14(26)					
			Adherent clot 11(21) 19(36)					
			Endotherapy was carried out by 4 endoscopists each with at least 5 years of experience in the treatment of patients with bleeding ulcers.					

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				maximum of 20 mL. they were placed in all 4 quadrants that surrounded the bleeding point and then directly into the vessel. When a small blood clot was encountered, the hemostastic method was carried out directly without removal of the clot. If a large blood clot covered the ulcerative lesion, then the clot was removed				

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				with a 3-prong device after epinephrine injection, and hemoclip therapy was subsequently performed. If massive blooding obscured the visual field, epinephrine was injected initially to control bleeding, and then hemoclips were applied to clamp the vessel.				
Effect size Post treatment outcomes – significant differences in shaded cells N(%)								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

	Comination treatment N=52	Epinephrine injection N=53	Absolute difference (95% CI)	P value
Initial hemostasis	51(98)	49(92)	0.06 (-0.03 to 0.14)	0.18
Rebleeding	2 (3.8)	11 (21)	-0.17 (-0.29 to -0.04)	0.008
Emergency surgery	0	5(9)	-0.09 (-0.18 to -0.01	0.02
Length of hospital stay	7.2 (7.1)	10.5(11)	-3.3 (-8.4 to 1.81)	0.20
Mortality	1(2)	0	0.02 (-0.02 to 0.06)	0.32
Procedure related complications	0	0		

Authors' conclusion
Endoscopic combination therapy is superior to epinephrine injection alone in the treatment of high-risk bleeding ulcers.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Chung SS, Lau JY, Sung JJ, et al. Randomised comparison between adrenaline injection alone and adrenaline injection plus heat probe treatment for	RCT single centre country: China Adequate allocation concealment and randomisation sequence generation	N=134 single treatment N=136 combination treatment	Inclusion criteria: patients with actively bleeding ulcers Exclusion: patients with nonbleeding visible vessel, adherent blood clot, clean base ulcers or ulcers with contact bleeding only. Baseline characteristics: Injection N=134 | Injection plus	Combination treatment: captive coagulation with an Olympus heat probe unit. The French gauge heat probe was	Adrenaline injection: Same procedure as was used in the combination group	4 weeks	Initial hemostasis, clinical rebleeding, emergency surgery, median blood transfusions, median length of hospital stay, ulcer healing at 4	Croucher foundation

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>actively bleeding ulcers. BMJ 1997 May 3;314:1307-11.</td>
<td>Not double blinded

Power calculations were carried out</td>
<td></td>
<td>
<table>
<tr><td></td><td></td><td>heater probe N= 136</td></tr>
<tr><td>Age</td><td>58.8 (21-92)</td><td>58.2 (19-95)</td></tr>
<tr><td>Men</td><td>98</td><td>89</td></tr>
<tr><td colspan="3">Location of ulcer:</td></tr>
<tr><td>Duodenum</td><td>92</td><td>84</td></tr>
<tr><td>Gastric</td><td>39</td><td>48</td></tr>
<tr><td>Stoma</td><td>3</td><td>4</td></tr>
<tr><td>Haemoglobin <100 g/l on admission</td><td>77</td><td>77</td></tr>
<tr><td>No with shock</td><td>38</td><td>29</td></tr>
<tr><td colspan="3">Type of bleeding:</td></tr>
<tr><td>Spurting</td><td>27</td><td>31</td></tr>
<tr><td>Oozing</td><td>107</td><td>105</td></tr>
<tr><td>No with comorbid conditions</td><td>62</td><td>64</td></tr>
<tr><td>NSAIDs users</td><td>37</td><td>33</td></tr>
</table>
</td>
<td>used to tamponade the bleeding point firmlyfor theree pulses of 30 J at any one site. The endpoint of treatment with the heat probe was defined as flattening or caviation of the bleeding point

Adrenaline in 1:10,000 diluation was injected in 0.5-1 ml aliquots into and around the bleeding point until</td>
<td></td>
<td></td>
<td>wks, in hospital mortality, perforations</td>
<td></td>
</tr>
</table>

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				the bleeding was controlled.				

Effect size

Post treatment outcomes – significant differences in shaded cells (N and (%) unless otherwise stated):

	Injection plus heater probe N= 136	Injection N=134	p-value
Initial success	135(99)	131(97.8)	0.33
Clinical rebleeding	5(3.7)	12(9.0)	0.08
Emergency surgery	8(5.9)	14(10.4)	0.17
Median transfusions (range)	3 (0-29)	2(0-18)	0.93
Median length of stay (range)	4(1-59	4(0-34)	0.52
Ulcer healing at 4 weeks	71/96 (74)	72/91(79.1)	0.41
Mortality in hospital	8(5.9)	7(5.2)	0.81
Perforations	2(1.5)	0	0.50

Authors' conclusion

The addition of heat probe treatment after endoscopic adrenaline injection confers an advantage in ulcers with spurting haemorage (Note: separate results according to spurting or oozing vessels were reported in the article but were not extracted here)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Park CH, Joo YE, Kim HS, et al. A	RCT single centre country: Korea	N=45 injection group N=45 combination	Inclusion criteria: Patients with a confirmed gastric or duodenal ulcer with either an actively bleeding	Combination treatment:	11 to 25 mL of a 1:10,000 solution of	Until hospital discharge	Rebleeding, Initial hemostasis,	Not stated

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>prospective, randomized trial comparing mechanical methods of hemostasis plus epinephrine injection to epinephrine injection alone for bleeding peptic ulcer. Gastrointest Endosc 2004;60:173-9.</td><td>Single blind (but not clearly described)
Randomisation sequence generation adequate, allocation concealment adequate</td><td>group (mechanical plus injection)</td><td>vessel (spurting or oozing) or a nonbleeding visible vessel. Paitents with a nonbleeding visible vessel had to have one of the following signs of recent bleeding:’coffee ground’ material or blood in the stomach and/or duodenum, shock, or an initial Hb level of less than 10 g/dL.
Exclusion: Patients with a bleeding diathesis (platelet count <50,000/mm3, international normalized ratio >2), gastic malignancy and multiple bleeding sources.

Baseline characteristics no statistically significant differences - unless otherwise stated N(%):
<table>
<tr><th></th><th>Combination N=45</th><th>Injections N=45</th></tr>
<tr><td>Age mean (range)</td><td>61.1(58.9-63.3)</td><td>62.8(60.7-64.89)</td></tr>
<tr><td>Male</td><td>39</td><td>37</td></tr>
<tr><td>Location of ulcer</td><td></td><td></td></tr>
<tr><td>Stomach</td><td>38(84.4)</td><td>34(75.6)</td></tr>
<tr><td>Duodenum</td><td>7(15.6)</td><td>11(24.4)</td></tr>
<tr><td>Bleeding</td><td></td><td></td></tr>
</table></td><td>hemoclip placement or band ligation
The choice of mechanical method was determined by using the following criteria: endocopic band ligation was used for non-fibrotic ulcers: small (1.5 cm), shallow ulcers with an exposed vessel within 2 to 3 mm from the margin. For all other bleeding ulcers hemoclip application was used</td><td>epinephrine was injected around the bleeding site (2-4 mL/injection at 2-3 mm from the point of bleeding).</td><td></td><td>permanent hemostasis, therapeutic endoscopic sessions, surgery / embolisation, mortality, transfusion requirements, length of hospital stay</td><td></td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			types			with the hemostatic clip applied directly to the exposed vessel. Endoscopic band ligation was performed with a varioligator kit with a single shot device, without a flexible overtube. Epinephrine see comparison column				
			Spurting	9(20)	9(20)					
			Oozing	15(33.3)	13(28.9)					
			NBVV	21(46.7)	23(51.1)					
			Ulcer size:							
			≥2 cm	17(37.8)	12(26.7)					
			<2 cm	28(62.2)	33(73.3)					
			Shock	17(37.8)	16(35.6)					
			Comorbid disease	32(71.1)	24 (53.3)					
			NSAIDs	28(62.2)	20(44.4)					

Effect size

Post-treatment outcomes – shaded cells indicate significant group differences

	Combination N=45	Injection N=45	p-value
Rebleeding	2/44 (4.5)	9/44 (20.5)	0.024
Initial hemostasis	44(97.8)	44(97.8)	1.0
Permanent hemostasis	44(97.8)	41(91.1)	0.167
Number of endoscopic sessions – mean	1.04 (1.01-1.07)	1.22 1.15-1.30)	0.041

Reference	Study type	Number of patients	Patient characteristics	Interventio n	Comparison	Length of follow-up	Outcome measures	Source of funding

(95%CI)			
Surgery or embolisation	1(2.2)	2(4.4)	1.0
Bleeding related deaths	0	1(2.2)	1.0
Transfusion requirements mean (95% CI)	4.4 (3.9-4.9)	4.1(3.6-4.6	0.648
Total hospital stay mean days (95% CI)	12.5 (10.4-14.6)	11.0 (9.6-12.4)	0.541

Authors' conclusion

The combination of an endoscopic mechanical method of hemostasis plus epinephrine injection is more effective than epinephrine injection alone for the treatment of bleeding peptic ulcer.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Taghavi SA, Soleimani SM, Hosseini-Asl SM, et al. Adrenaline injection plus argon plasma coagulation versus adrenaline injection plus	RCT multi-centre Country: Iran Randomisation sequence generation adequate, allocation concealment unclear	N=89 adrenaline injection (AI) + Argon Plasma Coagulation (APC); N=83 AI + Hemoclip	Inclusion criteria: Patients with gastric or duodenal ulcers confirmed by endoscopy with an actively bleeding ulcer (spurting or oozing), a nonbleeding visible vessel or adherent clot. For those with a nonbleeding visible vessel, coffee-ground material or blood in the stomach and/or duodenum, hemodynamic instabilityor an initial haemoglobin level of less than 100	Adreneline (1:10,000 dilution) in 0.5 mL or 1 mL doses was injected through multiple punctures into and around the bleeding	Adrenaline injection as before Hemoclip therapy was performed with stainless steel hemoclips.	Four weeks	Primary outcome: rebleeding Secondary outcome: rate of initial hemostasis, definitive hemostasis, need for emergency	Grand from the research council of the Shiraz University of Medical Sciences, Shiraz

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>hemoclips for treating high-risk bleeding peptic ulcers: a prospective, randomized trial. Can J Gastroenterol 2009 Oct;23:699-704.</td><td></td><td></td><td>g/L, endoscopy was required to show recent bleeding.
Exclusion criteria: Patients with a platelet count of less than 50X109/L, an international normalized ratio of greater than 2, gastric malignancy, multiple bleeding sites or previous gastrectomy.

Baseline characteristics – n(%) or mean (SD) if continuous (shaded cells = significant differences):
<table><tr><td></td><td colspan="2">Adrenaline injection with</td></tr><tr><td></td><td>APC N=89</td><td>Hemoclip N=83</td></tr><tr><td>Age</td><td>48.6 (16.0)</td><td>51.3 (14.0)</td></tr><tr><td>Males</td><td>73</td><td>60</td></tr><tr><td>NSAID use</td><td>46 (51.7)</td><td>33 (39.8</td></tr><tr><td>Smoking</td><td>39 (36)</td><td>46 (55.4)</td></tr><tr><td>Shock</td><td>2 (2.2)</td><td>3 (3.6)</td></tr><tr><td>Comorbidity</td><td>83 (93.3)</td><td>75 (90.4)</td></tr><tr><td>Ulcer history</td><td>29 (32.6)</td><td>12 (14.5)</td></tr><tr><td>Previous ulcer</td><td>7 (7.9)</td><td>5(6)</td></tr></table></td><td>site, with at least 10 mL being injected.

Treatment with and argon plasma coagulation unit in spray mode was used with tow power/gas settings for gastric and duodenal ulcers (70 W and 40 W and 2 L/min to 1 L/min respectively). Suction was applied to remove smoke and prevent overinflation of the gastrointestinal tract.</td><td>Hemoclips were applied with a clip application device passed through the 2.8 mm diameter accessory channel of a standard endoscope. Hemoclips were individually loaded and deployed. For ulcers with clots, the base of the clot was manually irrigated with a 50 mL syringe (200 mL of water total).</td><td></td><td>surgery and bleeding related deaths, length of hospital stay</td><td>Iran.</td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

bleeding		
In-hospital bleeding	4 (4.5)	1 (1.2)
Bleeding type		
Spurting	9 (10.1)	7 (8.4)
Oozing	2 (2.2)	3 (3.6)
Visible vessel	69 (77.5)	61 (73.5)
Adherent clot	9 (10.1)	12 (14.5)

Effect size

Post-treatment outcomes

	Adrenaline injection with		
	APC N=89	Hemoclip N=83	p-value
Failing to reach initial hemostasis	3	1	0.337
Rebleeding	10	4	0.124
Need for surgery	2	0	0.266
Length of hospital stay	5.34 (1.56)	5.52 (1.19)	0.396
Mortality	2	1	0.526

Authors' conclusion

Hemoclips + AI has no superiority over APC + AI in treating patients with high-risk bleeding peptic ulcers.

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Lin HJ, Tseng GY, Perng CL, et al. Comparison of adrenaline injection and bipolar electrocoagulation for the arrest of peptic ulcer bleeding. Gut 1999 May;44:715-9.</td><td>RCT, Single centre Country: Taiwan

Randomisation sequence generation and allocation concealment unclear</td><td>N=-32 Adrenaline group; N=32 Gold probe group; N=32 Combined group</td><td>Inclusion criteria: patients aged 18 or over presenting with an actively bleeding ulcer (spurgtin or oozing), or a non-bleeding visible vessel (NBVV). Patients with an NBVV had to show one of the following signs of recent bleeding: coffee ground or blood in the stomach or duodenum; shock; or initial haemoglobin less than 10 g/l.
Exclusion criteria: Patients with a bleeding tendency (platelet count less than 50,000/mm3, prothrombin time less than 30%, or taking anticoagulants); bleeding gastric malignancy; pregnancy; or more than one bleeding source.

Baseline characteristics – p values not provided:
<table>
<tr><td></td><td>I</td><td>GP</td><td>IGP</td></tr>
<tr><td>N</td><td>32</td><td>32</td><td>32</td></tr>
<tr><td>Age</td><td>71.2</td><td>64.5</td><td>64.2</td></tr>
<tr><td>Male</td><td>29</td><td>30</td><td>28</td></tr>
<tr><td>Location</td><td></td><td></td><td></td></tr>
<tr><td>Stomach</td><td>18</td><td>20</td><td>19</td></tr>
<tr><td>Duodenum</td><td>13</td><td>12</td><td>12</td></tr>
</table></td><td>Combination: Injection was drenaline (1:10,000, 0.5-1.0 ml) at 2-3 mm around the bleeder until bleeding was controlled

Coagulation: A 7 Fr gold probe was used to compress the bleeder. Therafter, the bleeder was electrocoagulated with a setting 3 for 10 seconds before moving the probe until hemostasis was achieved.</td><td>Each of them individually</td><td>14 days</td><td>Initial rebleeding, number of treatment failures, requirement for blood transfusion and surgery, length of hospital stay, and mortality.</td><td>Stated but only grant numbers given rather than the funding body</td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics				Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Stoma	1	0	1					
			Shock	11	10	11					
			Comorbidities	23	21	21					
			Haemoglobin	9.6	9.9	10					
			Ulcer size (cm)	1.0	1.0	1.1					
			Endoscopic findings								
			Spurting	3	4	3					
			Oozing	8	5	8					
			NBVV	21	23	21					

Effect size

Post-treatment outcomes – for continuous outcomes it is mean (95% confidence interval) shaded cells include at least one significant group difference as described in the p-value column

	I N=32	GP N=32	IGP N=32	p-value
Volume of blood transfused after entry (ml)	1548 (846 – 2251)	1105 (574-1636)	491 (162-822)	p<0.001 I adrenaline and IGP, p<0.01 between GP and IGP
Achieving initial hemostasis	31	30	30	NS
Rebleeding	11	9	2	p=0.011 I adrenaline and IGP, p=0.04 between GP and IGP
Treatment failures	12	11	4	p=0.04 I adrenaline and IGP
Emergency surgery	5	2	1	NS
Length of hospital stay	8.3 (6.1-10.5)	8.6 (6.4-10.8)	6.2 (5.0-7.4)	NS

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Mortality		3	1	1		NS		

Authors' conclusion

For patients with peptic ulcer bleeding, combined adrenaline injection with gold probe electrocoagulation offers an advantage in preventing rebleeding compared to either injection or gold probe alone.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Gevers AM, De GE, Simoens M, et al. A randomized trial comparing injection therapy with hemoclip and with injection combined with hemoclip for bleeding ulcers. Gastrointest Endosc 2002 Apr;55:466-9.	RCT, single centre, Country: Belgium Randomisation sequence generation unclear; adequate allocation concealment	N=34 epinephrine injection (I), N=35 hemoclip (H), N=32 Combined ethanol injection and hemoclip (IH)	Inclusion criteria: Patients with gastric ulcers who had active bleeding from visible vessels (n=46) or nonbleeding visible vessel (N=55). Patients taking NSAIDs, aspirin, or anticoagulants were not excluded, but use of these medications was stopped at inclusion. Exclusion criteria: Not stated in method section All patients received acid suppressive therapy (H2-RA – ranitidine) Baseline characteristics – no standard deviations or standard errors provided:	Injection therapy with epinephrine (1:10,000 dilution) and polidocanol (1%). In total, 10 mL of the epinephrine solution and 5 mL of polidocanol were injected at 5 sites in and around the vessel. If hemostasis was not achieved, the epinephrine	Hemoclip alone. Hemostatic hemoclips (130◦ angle) were applied with a rotary application system to facilitate attachment of the hemoclip to the vessel. The hemoclip was applied directly to	4 weeks	A combined measure for initial failure to achieve hemostasis or early recurrent bleeding, overall treatment failure, Complications, bleeding related mortality, blood transfusion requirements (unclear at which stage)	Not stated

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td></td><td>I</td><td>H</td><td>IH</td></tr>
<tr><td>N</td><td>34</td><td>35</td><td>32</td></tr>
<tr><td>Age</td><td>66.4</td><td>64.6</td><td>68.0</td></tr>
<tr><td>Hemoglobin (g/dL)</td><td>8.98</td><td>9.11</td><td>8.58</td></tr>
<tr><td>Stomach</td><td>18</td><td>11</td><td>13</td></tr>
<tr><td>Duodenum</td><td>16</td><td>24</td><td>19</td></tr>
<tr><td>Active bleeding16</td><td>16</td><td>13</td><td>17</td></tr>
<tr><td>NBVV</td><td>18</td><td>22</td><td>15</td></tr>
</table>
</td><td>injection was repeated up to 20 mL</td><td>the vessel. If this resulted in only partial hemostasis, hemoclip placement was repeated until hemostasis was achieved.

Combination of the two.</td><td></td><td></td><td></td></tr>
<tr><td colspan="9">Effect size
Post-treatment outcomes
<table>
<tr><td></td><td>I (N=34)</td><td>H (N=35)</td><td>IH (N=32)</td><td>p-value*</td></tr>
<tr><td>Packed red cells</td><td>4.93</td><td>4.60</td><td>4.03</td><td>0.53</td></tr>
<tr><td>Initial failure or early recurrent bleeding</td><td>5 (1 initial failure 4 early rebleeding)</td><td>13 (5 initial failures, 1 complete failure and 7 early rebleeding)</td><td>8 (3 initial failures, 4 early rebleeding and 1 late rebleeding)</td><td>0.08</td></tr>
<tr><td>Overall failure</td><td>2</td><td>12</td><td>8</td><td>0.01</td></tr>
</table>
</td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Complications	1 perforation	0	1 septic arthritis	
Bleeding-related mortality	0	0	3	
All cause mortality	3 (bleeding worsened comorbid underlying diseases)		3	

* p-values provided for ANOVA and Fisher exact test but not followed up by group comparisons (i.e. unclear which differences were significant)

Authors' conclusion

Endoscopic treatment of bleeding peptic ulcers with the hemoclip was inferior overall to injection therapy.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Chung IK, Ham JS, Kim HS, et al. Comparison of the hemostatic efficacy of the endoscopic hemoclip method with hypertonic saline-epinephrine injection and a combination of the two for the management	RCT, single centre, Country: Korea Randomisation sequence generation adequate, allocation concealment adequate	N=41 Hemoclip (H); N=41 Injection (epinephrine); N=42 Combination (epinephrine plus hemoclip) 19 patients could not undergo follow-up endoscopic examination because of personal	Inclusion criteria: Patients with hematiemisis or melena who had endoscopic findings of modified Forrest class Ia, Ib, and IIa bleeding activity with a peptic ulcer. Exclusion criteria: Patients with known malignancy, procedural related GI bleed Baseline characteristics – no significant differences but only limited data supplied:	Injection: A mixture of 9 mL 3% NzCl and 1:1000 epinephrine was used. From 0.5 to 2.0 mL was injected through a plastic cannula (23 gauge 5-mm tip) at 4 to 10 sites around the visible vessel until a total of	Endoscopic hemoclip therapy was performed immediatel y for visible vessel with spurting. If hemostasis was incomplete, the same procedure was repeated unitl hemostasis	7 days	Initial hemostasis, recurrent bleeding, surgery, permanent hemostasis, mortality	Not stated

	I	H	IH
N	41	41	42
Age	55.9 (11.8	56.5 (12.6)	54.6 (16.3)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
of bleeding peptic ulcers. Gastrointest Endosc 1999 Jan;49:13-8.		objections or transfer to other hospital and were not included in the trial (this seemed to be prior to randomisation)	<table><tr><td></td><td>)</td><td></td><td></td></tr><tr><td>Hemoglobin (g/dL)</td><td>9.1 (2.8)</td><td>9.0 (2.6)</td><td>8.9 (2.0)</td></tr><tr><td>Male</td><td>33</td><td>34</td><td>36</td></tr></table>	10 mL was used. If there was active bleeding despicte injection of 10 mL solution, the procedure was repeated until complete hemostasis was achieved.	was achieved. If a large blood clot covered the ulcerative lesion, the clot was removed with a three-pronged device, and the same hemostatic method was performed. When a small blood clot or protubwerance on an ulcer crater were encountered, hemoclips were applied as mentioned above if a nonbleedin			

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
					g visible, define as a smooth protuberance of any colour aringe from the ulcer crater, could not be removed with saline rinsing. A third group had a combination of both injection and hemoclips			

Effect size

Post-treatment outcomes

	Hemoclip N=41	Injection N=41	Combination N=42	P value
Failure to achieve initial hemostasis	1	2	1	0.765
Recurrent bleeding	1	6	4	0.138
Surgery	2	6	1	0.076
Permanent hemostasis	39	35	40	0.081
Mortality	1	1	1	0.999

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Authors' conclusion The hemoclip method is an effective hemostatic procedure and is safer than hypertonic saline epinephrine injection. The combined method does not provide substantial advantage over use of the hemoclip method alone in the hemostatic management of bleeding peptic ulcers.								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Kubba AK, Murphy W, Palmer KR. Endoscopic injection for bleeding peptic ulcer: a comparison of adrenaline alone with adrenaline plus human thrombin. Gastroenterology 1996;111:623-8. Ref ID: 2358	RCT, multi-centre Scotland Unclear randomisation sequence generation, unclear allocation concealment, blinding not described ITT analysis	N=70 adrenaline (24 with active bleeding (AB) and 46 with nonbleeding visible vessel(NBVV)) and N=70 adrenaline + thrombin (27 AB and 43 with NBVV)	Inclusion criteria: Patients with a peptic ulcer that was either actively bleeding or had a nonbleeding visible vessel were included if they had one of the following risk factors: >60 years of age; initial hemoglobin concentration of <10 g/dl; or shock, defined as a pulse rate of more than 100 beats/min, a systolic blood pressure of <100 mm Hg, or both Exclusion criteria. Patients bleeding from another cause; patients with no major stigmata of recent hemorrhage within an ulcer bed (due to either significant liver disease or because they were treated with anticoagulant drugs, Baseline characteristics:	Epinephrine injections: multiple injections (each 1-2 mL) of 1:100,000 adrenaline into and around the bleeding vessel.	Epinephrine plus thrombin: Epinephrine as in the intervention column followed by at least a 2.8-mL (600IU) injection of human thrombin injected into the vessel.	30 days	Rebleeding, emergency surgery, surgical operation; units of blood transfused; duration of hospital stay;mortality	Not stated

	Adrenalin	Combi

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

	e N=70	N=70
Age, median (range)	AB 71.0 (42-90) NBVV 71.0 (26-91)	AB 68.0 (27-83) NBVV 69.5 (33-92)
Male	49	44
Mean admission hemoglobin (SD)	AB 8.4 (2.2) NBVV 8.5 (2.0)	AB 8.9 (2.1) NBVV 8.5 (1.9)
No. in shock	32	40
NSAID users	38	34
Ulcer site GU/DU/ES*	27/37/6	25/384
Comorbid disease*	45	38
Admitted for UGIB	60	59
Admitted for another medical condition	10	11
H. pylori	18	32

*Note GU=gastric ulcer; DU =

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			duodenal ulcer; ES = esophageal ulcer; Comorbid disease: either cardiovascular, respiratory, renal or neurological					

Effect size

Post-treatment outcomes – only the significant p values were provided.

	Adrenaline N=70	Combination N=70	p-value
No. rebleeding	14	3	<0.005
No. retreated	10	1	
Permanent hemostasis	63	67	
Emergency surgery	5	3	
Median unites transfused (range)	AB 2 (0-17) NBVV 3 (0-10)	AB 4 (0-9) NBVV 3 (0-6)	
Median duration of hospital stay (range)	AB 6 (2-37) NBVV 7 (3-65)	AB 6 (2-25) NBVV 6 (4-35)	
Death	7	0	<0.013

Authors' conclusion

Endoscopic injection using adrenaline plus human thrombin is superior to injection with dilute adrenaline alone and may represent the best treatment for bleeding peptic ulcers.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Balanzó J, Villanueva C, Sainz S, et al. Injection therapy of bleeding peptic ulcer. A prospective, randomized trial using epinephrine and thrombin. Endoscopy 1990;22:157-9.</td><td>RCT, single centre,
Country: Spain

Unclear randomisation sequence generation, unclear allocation concealment, blinding not described</td><td>N=32 epinephrine and N=32 epinephrine plus thrombin</td><td>Inclusion criteria: Patients with UGIB due to peptic ulcer in whom emergency endoscopy showed an active bleed or a nonbleeding visible vessel.
Exclusion criteria: Age under 15 or over 80 years; other exclusions were not directly specified.

Baseline characteristics – all differences reported as non-significant but no exact p-values provided (no other baseline characteristics provided):<table><tr><th></th><th>Adrenaline N=32</th><th>Combi N=32</th></tr><tr><td>Age mean</td><td>62.4</td><td>68.13</td></tr><tr><td>Bleeding site GU/DU/ST*</td><td>22/9/1</td><td>19/11/2</td></tr><tr><td>Active bleeding</td><td>13</td><td>11</td></tr><tr><td>Non-bleeding visible vessel</td><td>19</td><td>22</td></tr></table>*Note GU=gastric ulcer; DU=duodenal ulcer; ST=stomal ulcer</td><td>Epinephrine injection 1:10,000 epinephrine into and around the bleeding area or the visible vessel. Four to seven injections of 1 to 2 ml each were made.</td><td>Epinephrine plus thrombin In addition to the epinephrine injection as in the intervention column patients received 10 cc of thrombin (U.I/ml dilution) in a similar manner</td><td>5 days (but not clearly stated)</td><td>Permanent hemostasis, failure, persistent hemorrhage, recurrent hemorrhage, emergency surgery, mortality</td><td>Not stated</td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Effect size

Post treatment outcomes – all outcomes described as non-significant but no exact p-values were provided

	Adrenaline N=32	Combi N=32
Permanent hemostasis	26	27
Failure	6	5
Persistent hemorrhage	2	3
Recurrent hemorrhage	4	2
Emergency surgery	4	5
Transfusion mean – no standard deviation	3.94	3.14
Mortality	0	0

Authors' conclusion

The addition of thrombin to epinephrine does not improve the results of the injection method.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Pescatore P, Jormod P, Borovicka J, Pantoflickova D, Suter W, Meyenberger C, Blum AL, Dorta G. Epinephrine	RCT, Luxembourg. Undertaken at 3 separate hospitals. The effects of hospital site were considered for	N=135. (N=70 epinephrine; N=65 combination) During the study 4 patients (unclear which	Inclusion criteria: >18 years, with overt upper GI bleeding (malena or heametmesis) with a bleeding peptic ulcer identified as the source during initial endoscopy. Ulcers with endoscopic features indicative of a high risk of spontaneous recurrent bleeding (Forrest class Ia-IIb).	Injection of epinephrine diluted 1:10,000 in saline PLUS thawed deep fibrin glue, in vols of 1-2ml	Injection of epinephrine diluted 1:10,000 in saline, in vols of 1-2ml around the base of the ulcer and	30 days for mortality, but unclear for rebleeding and adverse events.	30 day mortality Recurrent bleeding. Suspicion was started by observed bleeding or a	Not stated

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>versus epinephrine plus fibrin glue injection in peptic ulcer bleeding: a prospective randomised trial. Gastrointestinal Endoscopy 2002; 55: 348-353</td><td>the recurrent bleeding outcome but not for the other outcomes.
Computer generated randomisation and sealed envelopes were correctly used.
Stratification according to Forrest class.
Intention to treat undertaken</td><td>study arm) were excluded because of endoscopically uncontrollable bleeding; these patients underwent immediate surgery. Two further patients were excluded because of a suspicion that the bleeding gastric ulcer was neoplastic.</td><td>Exclusion: torrential haemorrhage prior to endoscopy. Sources of bleeding other than a peptic ulcer.

Baseline characteristics:All NS<table><tr><th></th><th>COMBI (Adren and thrombin)</th><th>Adren only</th></tr><tr><td>n</td><td>65</td><td>70</td></tr><tr><td>Age</td><td>69.9</td><td>67.5</td></tr><tr><td>Male</td><td>40/65</td><td>50/70</td></tr><tr><td>Shock</td><td>20/65</td><td>19/70</td></tr><tr><td>Initial Hb (g/dL)</td><td>9.1</td><td>8.7</td></tr><tr><td>Number of transfusions (concentrates).</td><td>2</td><td>2</td></tr><tr><td>Comorbidity</td><td>52/65</td><td>52/70</td></tr><tr><td>Ia</td><td>8</td><td>7</td></tr><tr><td>Ib</td><td>22</td><td>25</td></tr><tr><td>IIa
IIb</td><td>24</td><td>27</td></tr><tr><td>Size ulcer</td><td>11</td><td>11</td></tr></table></td><td>around the base of the ulcer and beneath the bleeding source.
Fibrin glue was injected with a double lumen needle comprising one channel of 0.7,, for fibrinogen and one channel of 0.5mm for thrombin.

Before injection all patients had an endoscopy biopsy specimen test for H pylori, and were given</td><td>beneath the bleeding source</td><td></td><td>decrease in SBP of >20mmHg, or a decrease in Hb of >2 g/dL/24 hrs. This was then confirmed endoscopically, manifested by spurting or oozing, or the presence of fresh blood in the lumen together with a visible vessel or a fresh adherent clot.

Adverse events</td><td></td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			(mm)			omeprazole and antibiotics if positive. All patients managed in an ICU until the first follow up endoscopy.				
			% in stomach	23	24					
			+ve urease test	26	23					

Effect size

Post treatment outcomes – all outcomes described as non-significant but no exact p-values were provided

	COMBI (Adren and thrombin)	Adren only	p
Rebleeding	14/65	17/70	0.9
Mortality	3/65	3/70	
Adverse events			
Pneumonia	1/65	2/70	
Stroke	0/65	1/70	
Ulcer haemorrhage	0/65	1/70	
Perforation	1/65	0/70	
death	2/65	2/70	

Authors' conclusion: Adding fibrin glue to epinephrine for injection treatment of bleeding peptic ulcers does not improve outcome

F.4.2 PPI

QUESTION What is the most clinical /cost effective pharmaceutical treatment (Proton-pump inhibitor [intravenous or oral] compared to H_2 receptor antagonists or placebo) to improve outcome with regards to mortality, risk of rebleeding, quality of life and length of hospital stay in patients presenting with likely non-variceal UGIB pre- and post endoscopic investigation?

Pre-endoscopy

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Daneshmend TK, Hawkey CJ, Langman MJ et al. Omeprazole versus placebo for acute upper gastrointestinal bleeding: randomised double blind controlled trial. BMJ (Clinical research ed). 1992; 304(6820):143-147. Ref ID: 604	Large multicentre (two centres) UK double blind RCT Intention to treat analysis	N=1147 (PPI=578, Control treatment=569) – 98 protocol violations but this was addressed in IIT vs. Per protocol analysis	Inclusion criteria: All patients with overt upper gastrointestinal bleeding or a history Exclusion criteria: Age under 18, pregnancy, presence of severe physical illness making active treatment according to the protocol inappropriate, bleeding of such severity that immediate surgery was necessary or trivial bleeding such that active management was unnecessary, bleeding in patients admitted for something else, previous participation in study, inability to start treatment within 12h of admission, potential for drug interactions (patients taking phenytoin and warfarin) Baseline characteristics: N: Placebo 569, PPI i.v. 578	Omeprazole 80 mg i.v.on admission a second dose of 40 mgbetween four and 11 hours later and two further doses were given at eight hourly intervals over three days	Placebo was mannitol and was given in an identical fashion	40 days (for mortality), timing of assessment of rebleeding and surgery not clear	40 day mortality, rebleeding, surgery, stigmata of recent haemorrhage at index endoscopy, number of participants requiring blood transfusions. First three outcomes also reported by peptic ulcer site.	Astra Clinical Research grant

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Male</td><td>354</td><td>375</td></tr>
<tr><td>Mean Age (SD)</td><td>59(19)</td><td>60(19)</td></tr>
<tr><td>Mean systolic blood pressure (SD)</td><td>129(27)</td><td>127(25)</td></tr>
<tr><td>Mean pulse (SD)</td><td>90(16)</td><td>91(16)</td></tr>
<tr><td>Mean haemoglobin (SD)</td><td>11(3)</td><td>11(3)</td></tr>
<tr><td colspan="3">No (%) with:</td></tr>
<tr><td>Haematemesis</td><td>395(69)</td><td>402(70)</td></tr>
<tr><td>Maleana</td><td>324(57)</td><td>309(53)</td></tr>
<tr><td>Previous peptic uler</td><td>146(26)</td><td>152(26)</td></tr>
</table>
</td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="9">Effect size
For all of the following clinical outcomes differences between PPI and placebo of N (%) were not significantly different:
<table>
<tr><td></td><td>Placebo</td><td>PPI</td></tr>
<tr><td>Rebleeding</td><td>100(18)</td><td>85(15)</td></tr>
<tr><td>Transfusion</td><td>302(53)</td><td>298(52)</td></tr>
<tr><td>Transfusion of ≥3 units of blood</td><td>237(42)</td><td>226(39)</td></tr>
<tr><td>Operation</td><td>63(11)</td><td>62(11)</td></tr>
<tr><td>Median time to discharge</td><td>6</td><td>5</td></tr>
</table>
</td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Death	30(5.3)	40(6.9)

N (%) of patients with signs of bleeding on endoscopy (shaded cells significant group difference p<0.0001)†:

	Placebo	PPI
Any sign	236(45)	176(33)
Blood in stomach	131(25)	107(20)
Red clot on lesion	115(22)	85(16)
Active bleeding	73(14)	53(10)
Black spots on lesion	58(11)	39(7)
Visible vessel	16(3)	22(4)

The authors report that also that patients who received PPI had lower rates of blood in stomach, active bleeding, red clot on the lesion and black spots on the lesion compared to placebo (as can be seen in the table), but they do not state that these differences were statistically significant.

Authors' conclusion:

The authors interpret their finding as a failure to show beneficial effects of PPI on clinically important end points and state that the finding of PPI associated with a reduction in endoscopic signs of bleeding requires further investigation (since according to the authors it is not known whether a reduction in stigmata is of clinical benefit).

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Lau JY, Leung WK, Wu JC et al. Omeprazole before endoscopy in patients with	Single centre double blind placebo controlled RCT Country: China	N=638 (N=319 PPI and N=319 placebo – after exclusions in each group it lead to N=314 PPI and N=317	Inclusion criteria: All patients with overt upper gastrointestinal bleeding or a history Exclusion criteria: Age under 18, pregnancy, unable to provide written informed consent, or	Omeprazole 80 mg i.v.bolus injection followed by continuous infusion of	Placebo	30 days	Primary end point:need for endoscopic therapy at first endoscopic examination Secondary end	Funding received by authors are: AstraZeneca,

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>gastrointestinal bleeding. N Engl J Med. 2007; 356(16):1631-1640. Ref ID: 828</td><td></td><td>lacebo)</td><td>pregnant; those with a known allergy to PPIs and those who were using aspirin regularly for cardiovascular protection.

Baseline characteristics:
<table>
<tr><td></td><td>Placebo</td><td>PPI i.v.</td></tr>
<tr><td>N</td><td>317</td><td>314</td></tr>
<tr><td>Male</td><td>201</td><td>208</td></tr>
<tr><td>Mean Age (SD)</td><td>62.3(17.5)</td><td>61.7(17.9</td></tr>
<tr><td>Mean systolic blood pressure (SD)</td><td>117.3(21.9)</td><td>116.2(20.)</td></tr>
<tr><td>Systolic blood pressure <90mm Hg N (%)</td><td>28(8.8)</td><td>30(9.6)</td></tr>
<tr><td>Mean haemoglobin (SD)</td><td>11(3)</td><td>11(3)</td></tr>
<tr><td colspan="3">No (%):</td></tr>
<tr><td>Previous bleeding</td><td>66(20.8)</td><td>68(21.7)</td></tr>
<tr><td>Bleeding during</td><td>9(2.8)</td><td>12(3.8)</td></tr>
</table></td><td>8 mg per hour until endoscopic examination the next morning.</td><td></td><td></td><td>points: signs of bleeding, need for urgent endoscopy, duration of hospital stay, need for transfusion, need for emergency surgery,rates of recurrent bleeding and death from any cause within 30 days after randomization</td><td>Pfizer, Takeda and TAP Pharmaceutical Products and GlaxoSmithKline</td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			hospitalisation							
			Previous peptic uler	80(25.2)	80(25.5)					

Effect size

For all of the following clinical outcomes differences between PPI and placebo of N (%) were not significantly:

	Placebo	PPI
Rebleeding	8(2.5)	11(3.5)
Units of blood transfused mean (sd)	1.88(3.44)	1.54(2.41)
Transfusion of ≥3 units of blood	237(42)	226(39)
Emergency surgery	4(1.3)	3(1.0)
Median days in hospital (range)	3 (1-54)	3 (1-43)
Death	7(2.2)	8(2.5)

Significant differences shaded

	Placebo	PPI	p
Hospital stay <3 days	156(49.2)	190(60.5)	0.005
Endoscopic signs of bleeding in peptic ulcers:			
Active bleeding	28	12	0.01
Clean base	90	120	0.001
Endoscopic therapy	90 (28.4)	60 (19.1)	0.007
Endoscopic therapy for bleeding peptic ulcers	70/190	42/187	0.002
Number of pulses of heater probe – median (range)	6 (2-18)	5(2-16)	0.01

Authors' conclusion:

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
The authors conclude that infusion of high-dose omeprazole before endoscopy accelerated the resolution of sings of bleeding in ulcers and reduced the need for endoscopic therapy.								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hawkey GM, Cole AT, McIntyre AS et al. Drug treatments in upper gastrointestinal bleeding: value of endoscopic findings as surrogate end points. Gut. 2001; 49(3):372-379. Ref ID: 367	Two centre, UK. Double blind, placebo-controlled trial ITT on all randomised patients on all clinical outcomes Randomisation unclear Allocation concealment unclear	N=414 (randomised), n=228 (managed per protocol), n=55 placebo, n=58 Lansoprazole – there were two more groups randomised one received both drugs n=58 and the other received tranexamic acid n=57 – results not reported here) Endoscopic end points evaluate in those with a definite bleed	Inclusion criteria: All patients with possible upper gastrointestinal bleeding. Those who had not suffered a bleed based on clinical or endoscopic findings were excluded from the efficacy analysis. Exclusion criteria: Baseline characteristics of endoscopically evaluable patients: Placebo / PPI N: 55 / 58 Male %: 43.8 / 41.2 Mean Age (SD): 56.2 / 58.8 Endoscopic diagnosis Peptic ulcer: 20 / 22 Oesophag: 3 / 1	PPI Lansoprazole 60 mg (stat), followed by 30 mg four times daily, tranexamic acid 2 g, followed by 1 g four times daily. THE RESULTS OF PATIENTS RECEIVING LANSOPRAZOLE ONLY ARE REPORTED HERE Trial	Placebo	30 day mortality; 30 day surgery; rebleeding (timing unclear); number of participants requiring blood transfusion.	30 day mortality; 30 day surgery; rebleeding (timing unclear); number of participants requiring blood transfusion.	Shari Kashmir Institute of Medical Sciences

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
		Used logistic regression analysis. Included time to endoscopy as variable	eal Gastric Pyloric/duodenal	 8 9	 9 12	treatment continued for 4 days or until discharge/withdrawal Endoscopy was performed on the morning following admission or earlier.				
			Endoscopic findings Blood in stomach Fresh Definite active bleed	 15 12 8	 29 12 12					

Effect size

PPI compared with Placebo; No. with outcome

	PPI (N=102)*	Placebo (N=103)*
Endoscopic therapy	10	10
Blood transfusion (no of patients)	67	60
Rebleeding	10	10
Surgery	3	6
Death	2	5

* The larger N reflects the intention to treat analysis

Across the whole population of patients with upper GI bleeding average 0.41 (geometric mean, 95%CI 0.31 to 0.52) units were transfused

Authors' conclusion:

The authors interpret their finding as evidence that blood in the stomach reflects clinical features in patients with acute upper GI bleeding and is reduced by treatment with lansoprazole

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Wallner G, Ciechanski A, Wesolowski M et al. Treatment of acute upper gastrointestinal bleeding with intravenous omeprazole or ranitidine. European Journal of Clinical Research. 1996; 8:235-243. Ref ID: 3033</td><td>Single centre open RCT. Country: Poland

Sequence generation ok, allocation concealment unclear, no blinding.</td><td>102 participants (50 on PPI i.v. and 52 on H2RA i.v. group).</td><td>Inclusion criteria: All patients All patients age > 18 years admitted to the ICU with apparent signs of UGI bleeding.
Exclusion criteria: Existing hepatic insufficiency or neoplastic disorders.

Treatment was initiated immediately after hospital admission.

Baseline characteristics shaded cells indicate significant differences:
<table>
<tr><td></td><td>PPI i.v.</td><td>H2RA</td></tr>
<tr><td>N</td><td>50</td><td>52</td></tr>
<tr><td>Median Age (range)</td><td>54 (20-82)</td><td>56 (25-85</td></tr>
<tr><td>Age > 65</td><td>12</td><td>18</td></tr>
<tr><td>Male</td><td>36</td><td>38</td></tr>
<tr><td>Shock</td><td>5</td><td>4</td></tr>
<tr><td>Mean hemoglobin g/l</td><td>9.3 (1.98)</td><td>9.6 (2.17)</td></tr>
<tr><td colspan="3">Causes of UGIB:</td></tr>
<tr><td>Gastric erosion</td><td>11</td><td>10</td></tr>
</table></td><td>Omeprazole IV bolus delivery, dosing regime unclear: stated as "40 mg" or "80 mg" or "120 mg" (presumably representing total daily doses).

Unclear if participants within each treatment arm were allocated to each dosing group by a random method or not. Duration of treatment depending on</td><td>2. Ranitidine IV bolus delivery, dosing regime unclear: stated as "150 mg" or "200 mg" or "300-400 mg" (presumably representing total daily doses).</td><td>Timing of assessment unclear</td><td>Mortality; surgery; stigmata of recent haemorrhage at index endoscopy; number of participants requiring blood transfusion. Timing of outcome assessment not clear.

Rebleeding rates cannot be extracted because study is designed to assess time needed for bleeding cessation.</td><td>Not stated</td></tr>
</table>

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Gastric ulcer</td><td>15</td><td>8</td></tr>
<tr><td>Mallory Weiss</td><td>2</td><td>1</td></tr>
<tr><td>Duodenal ulcer</td><td>19</td><td>28</td></tr>
<tr><td>Anastomotic ulcer</td><td>1</td><td>4</td></tr>
<tr><td>Gastric and duodenal ulcer</td><td>1</td><td>1</td></tr>
<tr><td>Oesophageal ulcer</td><td>1</td><td>0</td></tr>
</table>

The authors also created a composite score ‘good’ or ‘bad’ condition of a patient based on blood pressure and heart rate. There was a baseline imbalance with a higher proportion of patients in the ‘bad’ condition in the PPI group.

These differences were highlighted by the authors, but statistical significance values were not reported.</td><td>continuation of bleeding.

Initial endoscopic haemostatic treatment not mentioned.</td><td></td><td></td><td></td><td></td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Effect size

Clinical outcomes (shaded cells show significant group differences – day 3:

	PPI i.v. N=50	H2RA N=52	p
Total number of patients requiring transfusions	30	36	n/s
Mean units for all patients	1.62	1.65	n/s
Mortality*	3	5	n/s

*Causes of mortality were (PPI: haemorrhagic shock, hepatic cirrhosis/coma, circulatory insufficiency; H2RA: haemorrhagic shock x 3, hepatic cirrhosis/coma, kidney and respiratory insufficiency).

Authors' conclusion:

The clinical outcomes for treatment of upper gastrointestinal bleeding therapy with omeprazole or ranitidine were similar.

Post endoscopy

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Lin HJ, Lo WC, Lee FY et al. A prospective randomized comparative trial showing that omeprazole	Single centre prospective RCT Country: Taiwan	N=100 (N=50 Cimetidine and N=50 Omeprazole)	Inclusion criteria: Patients presenting with a peptic ulcer with active bleeding or a nonbleeding visible vessel Exclusion criteria: Pregnant women, had bleeding tendency, uremia or bleeding gastric cancer	Omeprazole 40 mg i.v. bolus, then i.v. infusion 160 mg/day for 3 days, then 20 mg	Cimetidine 300 mg i.v. bolus, then i.v. infusion 1200 mg/day for 3 days, followed by 400 mg twice	2 months	At day 3 after entry: rebleeding. At day 14: mortality, re-bleeding (Rebleeding was suspected	Not stated

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>prevents rebleeding in patients with bleeding peptic ulcer after successful endoscopic therapy. Arch Intern Med. 1998; 158(1):54-58. Ref ID: 387</td><td></td><td></td><td>All received
initial endoscopic treatment

Baseline characteristics:<table><tr><td></td><td>PPI i.v.</td><td>H2 receptor</td></tr><tr><td>N</td><td>50</td><td>50</td></tr><tr><td>Male</td><td>46</td><td>43</td></tr><tr><td>Median Age (range)</td><td>65(17-84)</td><td>66.5(33-86)</td></tr><tr><td>Median volume of blood transfusion at entry, ml (range)</td><td>500 (0-2500)</td><td>0(0-5000)</td></tr><tr><td>No. with shock</td><td>14</td><td>9</td></tr><tr><td>Median haemoglobin g/L (range)</td><td>99 (58-150</td><td>105(37-152)</td></tr><tr><td colspan="3">Location of bleeding. No:</td></tr><tr><td>Esophagus</td><td>0</td><td>1</td></tr></table></td><td>oral/day for 2 months.</td><td>daily
for 2 months.</td><td></td><td>if unstable vital signs, continued tarry, bloody stools, or a drop in the haemoglobin level of more than 20g/L within 24h – confirmed by emergency endoscopy if either blood in stomach 24 h after therapy or a fresh blood clot or bleeding in the ulcer base was found)
surgery, blood transfusions</td><td></td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Stomach	21	27					
			Duodenum	28	19					
			Stoma	1	3					

Effect size

For all of the following clinical outcomes differences between PPI and H2-receptor antagonist of N:

	PPI	H2 receptor	p
Rebleeding day 3	0	8	0.003
Rebleeding day 14	2	12	0.004
Median volume of blood transfused after entry, mL (range)	0 (0-2500)	0 (0-5000)	0.05
No. of operations	0	0	n/a
Mortality	0	2	>0.05
Days in hospital	7 (3-1-27)	6(3-31)	>0.05

Authors' conclusion:

PPI is more effective in reducing rebreeding episodes in patients with bleeding peptic ulcers after successful endoscopic therapy. They go on to recommend that PPIs should be used routinely afer successful endoscopic therapy.

Strengths: power calculation was conducted. Weakness: More patients with active bleeding in control group (p = 0.09). Mean haemoglobin concentration was lower in the omeprazole group than in the control group (not significant)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Labenz J, Peitz U, Leusing C et al. Efficacy of primed	Single centre prospective RCT Country:	N=40 Stratified into 20 patients with bleeding	Inclusion criteria: patients with clinical (haematemesis or melaena) and endoscopic signs of a peptic ulcer bleeding	Omeprazole 80 mg i.v. bolus followed by	Ranitidine 50 mg i.v. bolus followed by 0.25 mg/kg/h	24 hours	Main endpoint: pH level Other	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
infusions with high dose ranitidine and omeprazole to maintain high intragastric pH in patients with peptic ulcer bleeding: a prospective randomised controlled study. Gut. 1997; 40(1):36-41. Ref ID: 452	Germany	duodenal ulcers and 20 with gastric ulcers	Exclusion criteria: age below 18 years , treatment with antisecretory drugs and antacids during the preceding week, renal failure, severe liver disease, previous intolerance to rantindine or omeprazole, pregnancy or lactation, pre-randomisation decision to perform surgery, status after stomach surgery except a simple closure of a perforation, clodding disorder and lack of informed consent Initial endoscopic treatment in 24 patients Baseline characteristics: Duodenal ulcer (ranitidine v omeprazole): median age 65.5 (36-89) v 64.5 (39-88), proportion of men 80% v 80% history of ulcer disease 60% v 60%, history of ulcer bleeding 20% v 30%, active bleeding ulcer or endoscopic signs of recent ulcer bleeding 1/9 v 2/8 Gastric ulcer (ranitidine v omeprazole): median age 65.5 (28-88) v 72 (40-78), proportion of men 30% v 60%	8 mg/h i.v. infusion for 24 hours.	i.v. infusion for 24 hours. Postintervention drug treatment not mentioned.		outcomes reported were rebleeding (blood or haematin in the stomach) mortality was also reported but not divided into PPI or H2	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			All study participants were either infected with H pylori (duodenal ulcer: n=13; gastric ulcer: n=4) or had taken ulcerogenic drugs (duodenal ulcer: n=2; gastric ulcer n=4), or both (duodenal ulcer: n=5; gastric ulcer: n=9).					

Effect size

	PPI i.v.	H2 receptor	p
Rebleeding	3	2	0.63

Authors' conclusion:

The study was mainly concerned with pH level and the authors concluded that pH level was more effectively controlled by PPI rather than H2-receptor antagonist. The authors did not refer to rebleeding rates or mortality in relation to pharmacological treatment.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Javid G, Zargar SA, Saif R et al. Comparison of p.o. or i.v. proton pump inhibitors on	Single centre prospective RCT Country: India Double blind	N=90 (N=45 patients in each group: 3 types of p.o. administered PPI and N=45	Inclusion criteria: All patients admitted with a history of peptic ulcer bleeding (i.e. hematemesis and / or melena) or who bled while in hospital	Omeprazole, pantoparzole or rabprazole 80 mg i.v.	Omeprazole, pantoprazole or rabprazole 80 mg p.o.. bolus, then followed by 40	3 days	Main outcome pH level. Relevant clinical outcomes: Blood	Not stated

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Interventio n</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>72-h intragastric pH in bleeding peptic ulcer. J Gastroenterol Hepatol. 2009; 24(7):1236-1243. Ref ID: 54</td><td>stated by authors, but only i.v. saline described not dummy oral med</td><td>three types of i.v. administerd PPI) for the purpose of this review all three PPIs are collapsed into 1 group)

There was a control group of 5 patients receiving only i.v. saline, but no baseline characteristics were provided for this group</td><td>Exclusion criteria: Under 18 years of age, pregnant or lactating women, taking anticoagulants; had more than one possible source of bleeding; had severe coagulopathy (prothrombin time 30% less than normal) or platelet count less than 50 000 mm3.2, had previous acid reducing surgeries (vagomoty, gastric resection); were moribund because of terminal cancer or severe comorbid illness; or had bleeding gastric cancer. Patients who did not obtain initial hemostasis with endoscopic therapy or rebled within 3 days were also excluded.

All received
initial endoscopic treatment

Baseline characteristics:<table><tr><td></td><td>PPI p.o.</td><td>PPI i.v.</td></tr><tr><td>N</td><td>45</td><td>45</td></tr><tr><td>H pylori infection</td><td>29</td><td>27</td></tr><tr><td>Mean Age (range)</td><td>35.4(18-60)</td><td>34.7 (18-60)</td></tr><tr><td>Mean Hb</td><td>9.3 (5-13)</td><td>9.3(5-13)</td></tr></table></td><td>bolus, then i.v. infusion
of 8 mg/day for 3 days,</td><td>mg (80 mg for pantoprazole) after every 12 hours for 3 days and i.v. saline</td><td></td><td>transfusions (units) , surgery, death and rebleeding (defined by fresh hematemesis, melena or both with either shock (systolic blood pressure of ≤100mmHg or pulse rate of ≥ 100 b.p.m., accompanied by cold sweats, pallor and oliguria); or a fall in haemoglobin of 2g.dL or more over a 24-h period after initial stabilization of vital signs)</td><td></td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			at presentation (range)							
			No. with shock	2	1					
			Median haemoglobin g/L (range)	99 (58-150	105(37-152)					
			Stigmata of bleeding. No:							
			Spurting	9	8					
			Oozing	10	10					
			Non-bleeding vessel	26	27					

Effect size

For all of the following clinical outcomes differences between PPI and H2-receptor antagonist were not significant N:

	PPI p.o.	PPI i.v.
Blood transfusion (units)	10	8
Hospital stay (days)	3.6	3.6
Surgery	2	3
Rebleeding	4	4
Mortality	0	0

Authors' conclusion:

There were no significant differences in according to mode of PPI administration.

Weaknesses: Blinding unclear, underpowered to detect differences between types of PPI

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Wei KL, Tung SY, Sheen CH et al. Effect of oral esomeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. J Gastroenterol Hepatol. 2007; 22(1):43-46. Ref ID: 95</td><td>Single centre double blind placebo controlled RCT
Country: Taiwan</td><td>N=70 (N=35 PPI and N=35)</td><td>Inclusion criteria: Patients who were older than 16 years and in whom endoscopic treatment of actively bleeding ulcers or ulcers with non-bleeding visible vessls had been successful.
Exclusion criteria: Patients where endoscopic treatment was unsuccessful or .

Baseline characteristics:
<table>
<tr><td></td><td>PPI p.o.</td><td>Pacebo</td></tr>
<tr><td>N</td><td>35</td><td>35</td></tr>
<tr><td>Male</td><td>24</td><td>21</td></tr>
<tr><td>Mean Age (SD)</td><td>57.3(12.6)</td><td>64.3(10.5</td></tr>
<tr><td>Initial blood transfusion (units)</td><td>2.8(1.4)</td><td>2.7(1.3)</td></tr>
<tr><td>Mean haemoglobin (SD)</td><td>9.9(2.2)</td><td>9.7(2.0)</td></tr>
<tr><td colspan="3">Types of stigmata (N):</td></tr>
<tr><td>Active bleeding</td><td>5</td><td>3</td></tr>
<tr><td>Non-bleeding</td><td>15</td><td>16</td></tr>
</table></td><td>Esomeprazole 40 mg p.o. twice per day for a period of 3 days. After 3 days al lpatients were given 30 mg lansomeprazole orally per day for 8 weeks</td><td>Placebo</td><td>8 weeks</td><td>Clinical endopoints:Re bleeding (defined by fresh hematemesis or melena with either shock or a decrease in the haemoglobin concentration of ≥2g/dL during a 24-h period after the initial stabilization of pulse, blood pressure and haemoglobin concentration) – confirmed by endoscopy. Surgical intervention was deemed warranted if the bleeding could not be controlled</td><td>Not stated</td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			vessel Adherent clot: 15 / 16 Ulcer site (N): Duodenum: 16 / 12 Stomach: 19 / 23				endoscopically or if there was a second recurrence of bleeding. Amount of blood transfusions and mortality	

Effect size

For all of the following clinical outcomes differences between PPI and placebo of N (%) were not significantly:

	Placebo	PPI	p
Rebleeding	3	2	0.999
Units of blood transfused mean (sd)	2.3(1.3)	2.1(1.4)	0.753
Emergency surgery	0	0	n/s
Median days in hospital (range)	3.82 (1.8)	3.58 (2.17)	0.792
Death	0	0	n/s

Authors' conclusion:

After successful endoscopic treatment of bleeding peptic ulcer, oral use of esomeprazole might offer no additional benefit on the risk of recurrent bleeding .

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Fasseas P, Leybishkis B, Rocca G. Omeprazole	Single centre single blind two treatment RCT Country: Italy	N=92 (N=45 PPI and N=47 Rantidine)	Inclusion criteria: All patients admitted to the emergency department with the diagnosis of acute non-variceal upper	Omeprazole 40 mg p.o. once daily for the	Ranitidine 50 mg i.v. four times daily for the duration	Unclear	Clinical outcome: Duration of hospital stay	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
versus ranitidine in the medical treatment of acute upper gastrointestinal bleeding: assessment by early repeat endoscopy. Int J Clin Pract. 2001; 55(10):661-664. Ref ID: 300			gastrointestinal bleeding (verified by endoscopy within 12 hours after admission) – not only peptic ulcers but also erosive gastritis. Exclusion criteria: Bleeding from oesophageal varices; actively bleeding lesions requiring surgical or endoscopic treatment ; malignancies of the upper gastrointestinal tract; bleeding from angiodysplasias; pregnancy or lactation; patients in whom the site of bleeding could not be localised; pyloric stenosis with gastric retention; refusal of the patient to undergo endoscopic procedures and age below 18 or above 90 years. Multiple biopsy specimens were obtained from all gastic lesions during the second endoscopic procedure in order to exclude malignancy. Patients were withdrawn from the study if the pathology report was positive for neoplasia. Baseline characteristics: | | PPI p.o. | H2 receptor	duration of the patients' hospitalisation	of the patients' hospitalisation		in ICMU (this included the the day of admission and transfer from the ward, patients were considered eligible to be transferred only when they were haemodynamically stable), recurrence of bleeding (a drop in haemoglobin ≥ 2 g/dl in any 24-hour period after the first 24 hours; recurrent haematemesis and or haematochezia; and a change in vital signs suggesting hypovolaemia	

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>N</td><td>45</td><td>47</td></tr>
<tr><td>Male</td><td>36</td><td>37</td></tr>
<tr><td>Mean Age (SD)</td><td>56.2(17.3)</td><td>59.8(16.0</td></tr>
<tr><td>NSAID use N (%)</td><td>29 (64.4)</td><td>27(57.4)</td></tr>
<tr><td>Prior history: peptic ulcer N (%)</td><td>21 (46.6)</td><td>20 (42.5)</td></tr>
<tr><td>Prior upper GI bleeding N (%)</td><td>13 (28.8)</td><td>11 (23.4)</td></tr>
<tr><td colspan="3">Smokers (n)</td></tr>
<tr><td>1-10</td><td>6</td><td>4</td></tr>
<tr><td>11-20</td><td>2</td><td>6</td></tr>
<tr><td>>20</td><td>3</td><td>3</td></tr>
<tr><td colspan="3">Alcohol consumption (n)</td></tr>
<tr><td>occasional</td><td>7</td><td>15</td></tr>
<tr><td>daily</td><td>20</td><td>26</td></tr>
</table>

There were more patients with alcohol and smoking exposure in the ranitidine group (no statistics given)
</td><td></td><td></td><td></td><td>in a previously haemodynamically stable patient – all verified by enoscopy confirming the presence of fresh blood in the stomach or duodenum)</td><td></td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Endoscopic data Site of bleeding(n)* Duodenal: 28 / 24 Erosive gastritis: 12 / 24 Gastric ulcers: 6 / 13 *In 5 patients more than 1 site of bleeding was identified					

Effect size

The following clinical outcomes differed significantly between PPI and H_2-RA:

	PPI	H2 receptor	p
Rebleeding (episodes)	0	8	<0.01
Mean days in ICMU (no sd given)	3.93	6.39	0.013

Authors' conclusion:

PPI is superior to H2 receptor antagonist in the pharmacological treatment of acute upper gastrointestinal bleeding due to peptic ulcer disease and/or erosive gastritis.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Khuroo MS, Yattoo GN, Javid G et al. A comparison of omeprazole	Single centre, India. Double blind, placebo-controlled trial	N=220 (PPI n =110, Control treatment n=110)	Inclusion criteria: All patients with upper gastrointestinal bleeding with staff witnessed hematemesis or melena. Patients with duodenal, gastric, or stomal ulcers and	PPI Omeprazole 40 mg oral given every 12 hrs for 5	Placebo	30 day mortality, duration of hospital stay no. of	30 day mortality (primary), duration of hospital stay	Shari Kashmir Institute of Medical

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>and placebo for bleeding peptic ulcer. N Engl J Med. 1997; 336(15):1054-1058. Ref ID: 455</td><td>No drop-outs reported
Randomisation – unclear
Allocation concealment – (sealed envelopes) unclear</td><td></td><td>stigmata of recent haemorrhage.

Exclusion criteria: Severe terminal illness, profuse haemorrhage with persistent shock during which the upper GI tract was filled with fresh blood, bleeding from a Mallory-Weiss tear, varices, erosions, tumours, or unknown source

Baseline characteristics:
<table>
<tr><td></td><td>Placebo</td><td>PPI p.o.</td></tr>
<tr><td>N</td><td>110</td><td>110</td></tr>
<tr><td>Male</td><td>66</td><td>68</td></tr>
<tr><td>Mean Age (SD)</td><td>56(8)</td><td>58(8)</td></tr>
<tr><td>Mean systolic blood pressure (SD)</td><td>115(5.0)</td><td>116(4.8)</td></tr>
<tr><td>Mean pulse (SD)</td><td>96(4.2)</td><td>98(5.5)</td></tr>
<tr><td>Mean haemoglobin (SD)</td><td>9.6(0.8)</td><td>9.8(0.6)</td></tr>
<tr><td colspan="3">No (%) with:</td></tr>
<tr><td>Haematemesis</td><td>21</td><td>25</td></tr>
</table></td><td>days.

Endoscopy was reported within 72 hrs when there was a clinical suspicion of further bleeding or need to define the initial findings further in patients with ulcers covered by adherent clots. Otherwise, decisions about patient care were made by the treating physicians</td><td></td><td>units transfused, surgery and rebleeding unclear</td><td>no. of patients receiving transfusion, mean no. of units transfused per patient, surgery (primary) and rebleeding (primary) unclear</td><td>Sciences</td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Maleana	61	64					
			Both	28	21					

Effect size

No with outcome/no. with stigmata (%). Shaded areas indicate significant group difference * p=0.02 ** p<0.001 *** p=0.01

	PPI (N=110)	Placebo (N=110)
Rebleeding	12	40
Spurting	8/11 (72.7)	14/15 (93.3)
Visible vessel	2/17 (11.8)	10/18 (55.6)*
Oozing	2/18 (11.1)	3/16 (18.8)
Clot	0/64	13/61 (21.3)**
Surgery	8	26
Spurting	6/11 (54.5)	11/15 (73.3)
Visible vessel	1/17 (5.9)	8/18 (44.4)*
Oozing	1/18 (5.6)	1/16 (6.3)
Clot	0/64	6/61 (9.8)*
Death	2	6
Spurting	1/11 (9.1)	3/15 (20.0)
Visible vessel	1/17 (5.9)	2/18 (11.1)
Oozing	0/18	0/16
Clot	0/64	1/61 (1.6)
No. of patients receiving transfusions	32	78**
Mean no. of units of blood transfused per patient (SD)	2.3 (1.0)	4.1 (2.1)**
Mean length of hospital stay (SD)	5.5 (2.1)	6.9 (2.1)***

Reference	Study type	Number of patients	Patient characteristics	Interventio n	Comparison	Length of follow-up	Outcome measures	Source of funding
No, of patients undergoing second endoscopy not reported by treatment Authors' conclusion: The authors interpret their finding as evidence that in patients with bleeding peptic ulcers and signs of rebleeding, omeprazole decreases the rate of further rebleeding and the need for surgery								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Lin H-J, Lo W-C, Cheng Y-C et al. Role of intravenous omeprazole in patients with high-risk peptic ulcer bleeding after successful endoscopic epinephrine injection: A prospective randomized comparative trial. Am J Gastroenterol. 2006; 101(3):500-505. Ref ID: 3224	Single centre, Single blind RCT Country: Taiwan ITT analysis Randomisation: Randomisation table Allocation concealment: Sealed envelopes	N=200	Inclusion criteria: Patients were accepted for endoscopic therapy with a peptic ulcer with active bleeding or a nonbleeding visible vessel (NBVV) observed within a 12 hr of admission. Exclusion criteria: Did not obtain hemostasis with endoscopic injection of epinephrine, had a bledding tendency, serum prothrombin < 30% of normal or were on anticoagulants Baseline characteristics (ITT):	PPI Omeprazole 40 mg q 12 hr N=66 40 mg continuous infusion every 12 hrs for 3 days followed by 20 mg orally once daily for 2 months Or 40 mg q6 hr N=67	H2 receptor antagonist Cimetidine 40 mg a 12 hr 400 mg infusion every 12 hrs for 3 days followed by 400 mg orally twice daily for 2 mths N=67	14 days	Primary: Rebleeding 14 days Secondary: Active bleeding, volume of blood transfused, nol.of surgeries performed, mortality rate	None reported

	OME 40q6 h N=67	OME 40q12 h N=66	CIM N-67
Age yrs mean	67	71	67
Male	58	57	61

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Location Stomach Duodenum Esophagus 26 35 6 29 33 4 32 32 3 Meal ulcer size mm 0.98 1.11 0.96	40 mg infusion every 6 hrs for 3 days followed by 20 mg orally once daily for two months Endoscopy undertaken 72 hr after enrollment				

Effect size

Omeprazole (PPI) and H2 receptor antagonist

Cimetidine H2 receptor antagonist N (%) *p=0.001 between OME gps, p < 0.001 OME 40q6hr and CIM ** p<0.01 OME 40q6h and CIM

	PPI (OME 40q6hr) N=67	PPI (OME 40q12h) N=66	H2 receptor (CIM) N=67
No of rebleeding	6	14	22**
Volume of blood transfused after therapy mL (95%CI)	710 (489-913)	1241 (487-1995)	1317 (947-1660)*
Mean hospital stay days (95%CI)	5.89 (4.69 to 7.09)	7.64 (6.42 to 8.85)	7.92 (6.52 to 9.33)
No. of surgeries	0	0	3
No. of deaths	0	1	3

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Authors' conclusion: Because of the small sample size there was no significant difference in ulcer bleeding rates								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Jensen DM, Pace SC, Soffer E et al. Continuous infusion of pantoprazole versus ranitidine for prevention of ulcer rebleeding: A U.S. multicenter randomized, double-blind study. Am J Gastroenterol. 2006; 101(9):1991-1999. Ref ID: 2965	Multi centre, double blind placebo controlled RCT Country: USA ITT analysis Randomisation central registry Allocation concealment: computer generated randomisation schedule The study was terminated early due to slow enrolment	N=153 N=149 (ITT)	Inclusion criteria: Patients with an ulcer ≥ 5 mm to < 20 mm diameter, with either active bleeding or an non bleeding visible vessel (NBVV). Emergency endoscopy and study drug started within 24 hrs of presentation to the emergency room. In addition, eligible patients were at high risk of rebleeding clinically by having two or more of the following risk factors: Transfusion of ≥ 2 units packed red blood cells at entry or haemoglobin ≤ (Hgb) 10 g/dL Hemodynamic instability Orthostatic increase in heart rate and/or decrease in systolic blood pressure Age ≥ 70 yrs Ulcer of the posterior wall of the duodenum	PPI IV Pantoprazole (PAN) 80 mg in a 5 min infusion followed by 8 mg/h continuous infusion Study drug initiated with 2 hrs after completition of endoscopic hemostasis and continued	H2 receptor IV Ranitidine (RAN) 50 mg in a 5 min infusion followed by 6.25 mg/h continuous infusion	30 days	Primary: Rebleeding No. of hospital days, mean transfusion, mortality	Wyeth Research. Author funded by NIH

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td></td><td></td><td>Exclusion criteria: Patients with more than one bleeding ulcer of an adherent clot that could not be removed or without active bleeding or NBVV evident under the clot. Inpatients with ulcer haemorrhage, malignant-appearing ulcer, unstable or very severe comorbid conditions, ulcer with flat spot, ulcer with clean base and no major stigmata of haemorrhage. Plus:

Severe coagulopathy
Need for anticoagulation after randomisation as treatment for comorbid condition

Baseline characteristics (ITT):
<table>
<tr><td></td><td>PAN</td><td>RAN</td></tr>
<tr><td>N</td><td>72</td><td>77</td></tr>
<tr><td>Male</td><td>71%</td><td>68%</td></tr>
<tr><td>Mean Age (SD)</td><td>59.6 (16.1)</td><td>55.6 (16.8</td></tr>
<tr><td>Ulcer size mm mean (SD)</td><td>11.1 (4.5)</td><td>12.0 (4.7)</td></tr>
<tr><td>Ulcer</td><td></td><td></td></tr>
</table></td><td>72 hrs after randomisation

After 72 hrs oral PPI once/day for 30 days</td><td></td><td></td><td></td><td></td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			type Duodenal Gastric Both	 37 34 1	 46 31 0					

Effect size

Pantoprazole (PPI) and Ranitidine (H2 receptor antagonist) N (%) no significant differences reported

	PPI N=72	H2 receptor
Rebleeding (No. of patients) Early ≤ 72 hrs 4-7 days 8-30 days Total	 3 2 0 5	 6 5 0 11
Mean hospital stay days (SEM)	6.24 (1.85)	7.55 (2.33)
Mean transfusions (SEM) Units of red blood cells	 2.32 (0.36)	 1.92 (0.3)
Mortality (N) 3 days 30 days	 1 3	 3 3

Authors' conclusion:

Because of the small sample size there was no significant difference in ulcer bleeding rates

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>Lau JY, Sung JJ, Lee KK et al. Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. N Engl J Med. 2000; 343(5):310-316. Ref ID: 395</td>
<td>Single centre, double blind placebo controlled RCT
Country: China

ITT analysis
Randomisation – computer generated
Allocation concealment – consecutively number sealed envelopes</td>
<td>N=240 (of 739 patients admitted with bleeding peptic ulcers) (n=120 omeprazole and n=120 placebo)

n=1 withdrawal from placebo group</td>
<td>Inclusion criteria: All patients 16 yrs or older with upper gastrointestinal bleeding (actively bleeding ulcers or ulcers with nonbleeding visible vessels) who received successful endoscopic treatment (all within 24 hrs)

Exclusion criteria: Endoscopy not required (ulcers with clean bases or flat pigments). Unsuccessful endoscopy and patient required surgery (n=5). N=22 exclusions due to other reasons

Baseline characteristics:
<table>
<tr><td></td><td>Placebo</td><td>PPI</td></tr>
<tr><td>N</td><td>120</td><td>120</td></tr>
<tr><td>Male</td><td>67</td><td>64</td></tr>
<tr><td>Mean Age (SD)</td><td>67 (15.9)</td><td>64 (17.2)</td></tr>
<tr><td>Mean haemoglobin (SD)</td><td>9.5 (2.6)</td><td>9.4 (2.7)</td></tr>
<tr><td colspan="3">No (%):</td></tr>
<tr><td>Previous ulcer bleeding</td><td>36</td><td>36</td></tr>
<tr><td>Bleeding</td><td>23</td><td>22</td></tr>
</table>
</td>
<td>PPI
Omeprazole 80 mg i.v.bolus injection followed by continuous infusion of 8 mg per hour for 72 hrs. Followed by 20 mg orally for eight weeks.</td>
<td>Placebo</td>
<td>30 days</td>
<td>Primary: 30 days Rebleeding
Seondary: 3 and 7 day rebleeding, surgery, median duration of hospitalisation, units of blood transfused, 30 day mortality</td>
<td>Research Grants Council of the Hong Kong Special Administration Region</td>
</tr>
</table>

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			during hospitalisation							
			Previous peptic uler	45	38					

Effect size

PPI and placebo N (%) Shaded areas indicate a significant difference

	Placebo	PPI	RR (95%CI); p value
Rebleeding			
By day 3	24	5	4.80 (1.89 to 12.2); p<0.001
By day 7	26	7	3.71 (1.68 to 8.23); p<0.001
By day 30 (total number)	27	8	3.38 (1.60 to 7.13); p<0.001
Recurrent bleeding within 30 days no. of patients/ total no.			
Actively bleeding ulcers	10/58	3/64	4.24 (1.10 to 16.3); p=0.04
Ulcers with nonbleeding visible vessels	17/62	5/56	3.85 (1.31 to 11.3); p=0.02
Surgery	9	3	3.00 (0.83 to 10.8); 0.14
Units of blood transfused mean (sd)	3.5 (3.8)	2.7 (2.5)	0.04
Before endoscopic treatment			
After endoscopic treatment	1.1 (1.5)	(1.3)	0.46
	2.4 (3.2)	1.7 (1.9)	0.03
Median days in hospital (range)			
Patients admitted for bleeding peptic ulcers	5 (3 to 64)	4 (3 to 65)	0.006
Patients who developed bleeding in hospital	9 (4 to 46)	13 (3 to 40)	0.33

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Death within 30 days		12		5		2.40 (0.87 to 6.60); 0.13		

Authors' conclusion:
The authors conclude that infusion of high-dose omeprazole before endoscopy accelerated the resolution of sings of bleeding in ulcers and reduced the need for endoscopic therapy.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Sung JJ, Barkun A, Kuipers EJ et al. Intravenous esomeprazole for prevention of recurrent peptic ulcer bleeding: a randomized trial. Ann Intern Med. 2009; 150(7):455-464. Ref ID: 69	Multi-centre double blind placebo controlled RCT Country: N=16 ITT analysis Randomisation – central computer generated Allocation concealment – code envelopes	N=764 ITT population n=375 Esomeprazole, N=389 placebo n=3 excluded from ITT Per protocol n=292 Esomeprazole, n=316 placebo	Inclusion criteria: Patients 18 yrs or older presenting at emergency departments, or already hospitalised, with overt signs of upper GI bleeding in the past 24 hrs with only 1 bleeding gastric or duodenal ulcer at least 5 mm in diameter Exclusion criteria: Patients with multiple ulcers or concomitant upper GI sources Baseline characteristics: Placebo / PPI N: 389 / 375 Male: 268 / 254 Mean Age (SD): 60.2 (17.6) / 62.1 (17.5	PPI Esomeprazole 80 mg i.v.bolus injection over 30 minutes followed by continuous infusion of 8 mg per hour for 71.5 hrs. Followed by 40 mg once daily orally for 27 days	Placebo followed by oral therapy as for intervention	30 days	Primary: 72 hrs Recurrent ulcer rebleeding Secondary: Rebleeding within 7 or 30 days, all-cause or bleeding-related mortality, surgery, blood transfusion, additional days hospitalised because of recurrent rebleeding	AstraZeneca

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Previous complications related to ulcer bleeding	41	44				within 30 days	

Effect size

PPI and placebo N (%) Shaded areas indicate a significant difference

	PPI	Placebo	Absolute risk reduction (95%CI); p value
Rebleeding Within 72 hrs 7 days 30 days	 22 27 29	 40 50 53	 4.4 (0.6 to 8.3); 0.026 5.7 (1.4 to 9.9); 0.010 5.9 (1.5 to 10.2); 0.009
30 day all cause mortality	3	8	1.3 (-0.4 to 2.9); 0.22
30 day bleeding-related mortality	2	3	0.2 (-0.9 TO 1.4); 1.00
30 day surgery	10	21	2.7 (-0.0 to 5.5); 0.059
30 day repeat endoscopy treatment	24	45	5.2 (1.1 to 9.2); p=0.012
30 day Mean units blood transfused (SD)	1.6 (2.5)	2.4 (4.5)	
Mean additional hospital days (SD)	0.8 (2.3)	1.3 (3.7)	

Authors' conclusion:

The authors conclude that high-dose esomeprazole given after successful endoscopic therapy to patients with high-risk peptic ulcer rebleeding at 72 hrs reduced recurrent rebleeding at 72 hrs and had sustained clinical benefit for up to 30 days

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
van Rensburg C, Barkun AN, Racz I et al. Clinical trial: Intravenous pantoprazole vs. ranitidine for the prevention of peptic ulcer rebleeding: A multicentre, multinational, randomized trial. Aliment Pharmacol Ther. 2009; 29(5):497-507. Ref ID: 4021	Multicentre (137 centres), multinational (15) double blind, parallel group RCT, Allocation concealment unclear	N=1256 (N = 625 Pantoprazole – 7 misdiagnosed patients; N = 631 Ranitidine – 5 misdiagnosed patients) for ITT analysis There were 85 protocol violations in PPI group and 101 in the H2 group	Inclusion criteria: Adults aged 18 or older who underwent successful endoscopic haemostasis for a bleeding gastric or duodenal peptic ulcer if active spurting, oozing, or a non-bleeding visible vessel was noted at endoscopy (Forrest Ia, Ib and IIa) Exclusion criteria: patients with oesophageal varices, portal hypertension, Child's C liver cirrhosis or concomitant disease that made inclusion inappropriate (e.g. terminal disease, malignancy of GI tract, GI bleeding from other sources). Medications with confounding effects on Rebleeding were not permitted H2RAs, PPIs somatostatins, misoprostol, sucralfate, prokinetics or antacids from the time of the patient's admission until the end of the treatment. Other exclusion criteria	Pantoprazole 80 mg bolus followed by 8 mg/h continuous infusion for 3 days	Ranitidine 50 mg bolus followed by 13mg/h continuous infusion for 3 days	3 days (mortality at 14 days)	Primary outcome measure (NOT REPORTED HERE): a routine second look endoscopy was performed at 72 h and an ordinal ranking was given – 0 = no Rebleeding; 1 = mior Rebleeding not requiring endoscopic haemostasis; 2 = major Rebleeding requiring additional	Various authors declared interest: Barkun is consultant for Nycomed and AstraZeneca, Beglinger has served as a speaker and advisor for Nycomed, Fedorak is consultant for Nycomed

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td></td><td></td><td>were the need for anticuagulants during the study period, use of concomitant medications with the potential for drug interactions, pregnancy, lactation, child-bearing potential not using adequate contraception or allergy to ranitidine or pantoprazole. Helicobacter pylori positive patients were also included in the study, but eradication was not permitted during the 72-h treatment period.
<table>
<tr><td></td><td>PPI</td><td>H2 receptor</td></tr>
<tr><td>N</td><td>618</td><td>626</td></tr>
<tr><td>Male %</td><td>68</td><td>70</td></tr>
<tr><td>Median Age (range)</td><td>63(18-95)</td><td>63(18-97)</td></tr>
<tr><td>≥ 60 years %</td><td>57.4</td><td>56.9</td></tr>
<tr><td>Haemodynamic instability %</td><td>12</td><td>12</td></tr>
<tr><td>Previous peptic ulcer bleed</td><td>16.3</td><td>18.7</td></tr>
</table></td><td></td><td></td><td></td><td>endoscopic haemostasis; 3 = Rebleeding requiring surgery; 4 = Rebleeding causing death.

Secondary outcome measure: the number of blood units transfused after randomization and mortality at 3 and 14 days (overall and attributable to rebleeding from routine endoscopy as assessed by blinded review comitee)

Post hoc analysis: Clinically suspected</td><td>Source of funding was was by Nycomed and initial data analysis were undertaken by Nycomed, writing support was also funded by Nycomed</td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Location of bleeding. %: Duodenum 56.1 58.3 Gastric 43.3 41.4				rebleeding (defined as any one of the following three signs: vomiting of fresh blood, insufficient increase in haemoglobin or increase in need for blood transfusion, or haemodynamic instability – decrease in haemoglobin to <10 g/dL or a drop ≥2 g/dL OR decrease in systolic blood pressure < 100 mm Hg or of a drop ≥ 20 mm Hg from baseline; mortality due to rebleeding day 3; surgery due to rebleeding	
Effect size								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

	PPI n = 618 N (%[95%CI])	H2 receptor n = 626 N (%[95%CI])	p
Clinically suspected rebleeding	18 (2.9[1.7, 4.6])	20 (3.2[2.0, 4.9])	0.90
Mortality due to rebleeding day 3	1 (0.2[0.0, 0.9])	2 (0.3[0.0, 1.1])	0.99
Mortality day-14*	9 (1.5[0.5, 2.4])	16 (2.6[1.3, 3.8])	n/s
Surgery due to rebleeding	12 (1.9[1.0, 3.4])	13**(2.1[1.1, 3.5])	0.97

* percentages and odds ratios given in text but no exact p-value is reported – these differ slightly from the mortality rates presented in an abstract by the same research group (Barkun, Gastroenterology 2004; 126 (4 Suppl 2)):A-78) used in the Health Technology Assessment, 2007

** includes 2 cases detected on routine follow up endoscopy in the absence of any clinical suspicion

Blood transfusions: 54% of patients in the PPI and 50% in the H2 group were transfused requiring a median of 2 units with 7.6% and 8.5% respectively requiring 5 units or more (p=0.18).

Authors' conclusion:

The authors conclude that high-dose esomeprazole given after successful endoscopic therapy to patients with high-risk peptic ulcer rebleeding at 72 hrs reduced recurrent rebleeding at 72 hrs and had sustained clinical benefit for up to 30 days

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hsu P-I, Lo G-H, Lo C-C et al. Intravenous pantoprazole versus ranitidine for prevention of rebleeding	Single centre pilot prospective randomised trial. Country: Taiwan	N=102 (N=52 PPI and H2 receptor N=50) All patients followed up no drop out	Inclusion criteria: All patients with hematemesis, melena , or both had emergency upper endoscopy and patients with active bleeding ulcers or ulcers with major signs of recent bleeding who had a successful initial hemostasis were eligible. Exclusion criteria: The presence of	Pantoprazole 40 mg i.v. initial dose and subsequently with 40 mg every twelve	Ranitidine i.v. initial dose 50 mg and subsequently every eight hours during the first three days followed	14d, 4 wk and 8 wk	Clinical endopoints:Rebleeding (defined by recurrent hemorrhage during an 8-wk observation	Grants from the Kaohsiung Veterans General Hospital

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>after endoscopic hemostasis of bleeding peptic ulcers. World Journal of Gastroenterology. 2004; 10(24):3666-3669. Ref ID: 2895</td><td>Allocation concealment unclear and blinding unclear</td><td></td><td>other possible bleeding sites (oesophageal varices or gastric cancer), coexistence of an acute significant illness, the presence of a systemic bleeding tendency.

Baseline characteristics:
<table>
<tr><td></td><td>PPI</td><td>H2 receptor</td></tr>
<tr><td>N</td><td>52</td><td>50</td></tr>
<tr><td>Male</td><td>41</td><td>37</td></tr>
<tr><td>Mean Age (SD)</td><td>63.2(18.2)</td><td>64.7(13.8</td></tr>
<tr><td>Hypovolemic shock - n</td><td>3</td><td>3</td></tr>
<tr><td>Mean haemoglobin g/dL(SD)</td><td>10.3(3.0)</td><td>10.0(2.8)</td></tr>
<tr><td colspan="3">Types of stigmata (N):</td></tr>
<tr><td>Active bleeding</td><td>22</td><td>19</td></tr>
<tr><td>Non-bleeding vessel</td><td>18</td><td>21</td></tr>
<tr><td>Adherent clot</td><td>12</td><td>10</td></tr>
<tr><td colspan="3">Ulcer site (N):</td></tr>
</table></td><td>hours during the first three days followed by 40 mg orally</td><td>by 150 mg of oral ranitidine every 12 h.</td><td></td><td>period – evidence of rebleeding included fresh hematemesis, aspration of fresh blood from NG tube, or continuous melena with a pulse rate great then 100 beats/min, a fall in systolic blood pressure exceeding 30mmHg, or a decrease in hemoglobin of at least 0.2g/L). Surgical intervention was deemed warranted if the bleeding could not be controlled endoscopically or if there was a second recurrence of</td><td></td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Duodenum 27 25 Stomach 25 25				bleeding. Amount of blood transfusions and mortality	

Effect size

Clinical outcomes shaded cells indicate significant differences:

	PPI	H2 receptor	p
Rebleeding	2	8	0.04
Units of blood transfused mean (sd)	4.9(5.8)	5.7(6.8)	0.42
Emergency surgery	0	1	0.31
Mean days in hospital (sd)	5.9 (3.2)	7.5 (5.0)	0.06
Death	1	1	1.00

Authors' conclusion:

Pantoprozole is superior to ranitidine as an adjunct treatment to endoscopic injection therapy in high-risk bleeding ulcers.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Khoshbaten M, Fattahi E, Naderi N et al. A comparison of oral omeprazole and intravenous	Two hospital single blind RCT. Country: Iran Good sequence generation and clear allocation	N=80 (N=40 PPI and H2 receptor N=40)	Inclusion criteria: All patients over 12 years of age with upper gastrointestinal bleeding (hematemesis and / or melena) were assessed. Patients with gastrointestinal bleeding due to duodenal ulcers and endoscopic risk factors for rebleeding (hematin	Omeprazole the content of one 20 mg capsule in 50 ml of normal saline p.o. (due to NG	Cimetidine i.v. continuous 200 mg every six hours for 3 days followed by oral cimetidine 400 mg every 12	14 days	Clinical endopoints:Re bleeding (observation of of red blood in the stomach, a drop of serum	

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>cimetidine in reducing complications of duodenal peptic ulcer. BMC gastroenterology. 2006; 6:2. Ref ID: 4173</td><td>concealment, no loss to follow up</td><td></td><td>covered flat spots, sentinel clot, visible vessels, arterial oozing bleeding, and arterial spurting bleeding
Exclusion criteria: Gastrointestinal bleeding not caused by duodenal ulcer, bleeding caused by drugs (e.g. anticoagulants) except NSAIDs or underlying diseases (e.g. thrombocyptopenia and coagulopathies), and absence of endoscopic risk factors of rebleeding.

Baseline characteristics:
<table>
<tr><td></td><td>PPI</td><td>H2 receptor</td></tr>
<tr><td>N</td><td>40</td><td>40</td></tr>
<tr><td>Mean Age</td><td>49.5</td><td>53.5</td></tr>
<tr><td>Mean BUN (mg/dl)</td><td>16.55</td><td>10.72</td></tr>
<tr><td>Mean Hb gr/dL (SD)</td><td>9.53</td><td>10.04</td></tr>
<tr><td colspan="3">Types of stigmata (N):</td></tr>
<tr><td>Arterial spurting bleeding</td><td>3</td><td>2</td></tr>
</table></td><td>tube) every 12 hrs for 3 days and then replaced by oral omeprazole 20 mg capsules every 12 horusto the 14th day after administration.</td><td>hours to the 14th day after admission.</td><td></td><td>haemoglobin > 2 gr/dl during 24 hrs, continuous melena for more than 7 days, or instability of vital signs – a pulse rate more than 110 per minute, positive tilt sign, or a drop of systolic blood pressure 90mmHg in supine position. Amount of blood transfusions (units) duration of hospital stay and mortality</td><td></td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Arterial oozing bleeding: 15 / 13 Visible vessel: 5 / 3 Sentinel clot: 12 / 15 Hematic covered flat spot: 5 / 7 Proportion of males to females was not given, but reported to be not significantly different between the two groups					

Effect size

Clinical outcomes shaded cells indicate significant differences:

	PPI	H2 receptor	p
Rebleeding	6	20	0.001
Mean units of blood transfused	1.68	3.58	0.003
Mean days in hospital	5.6	7.46	0.074
Death	1	3	0.24

Authors' conclusion:

Oral Omeprazole significantly excels intravenous cimetidine in reducing the need for blood transfusion and lowering rebleeding rates in patients with upper gastrointestinal bleeding.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Yilmaz S, Bayan K, Tuzun Y et al. A head to head comparison of oral vs intravenous omeprazole for patients with bleeding peptic ulcers with a clean base, flat spots and adherent clots. World Journal of Gastroenterology. 2006; 12(48):7837-7843. Ref ID: 4154	Single centre RCT. Country: Turkey Conducted between 2004-2006 Good sequence generation and clear allocation concealment, even though reported as double blind it is unclear how that was achieved with the two different modes of administration.	N=211 (N=112 PPI i.v. and N=99 in PPI p.o.) Unclear why there is a group difference of 13 patients	Inclusion criteria: All patients over 18 years of age with upper gastrointestinal bleeding (hematemesis and / or melena or the presence of blood in a patient's nasogastric tube lavage) were enrolled. After endoscopic examination all patients with benign gastroduodenal ulcers showing a clean ulcer base, flat spots or old adherent clots were included. Exclusion criteria: A history of chronic lever disease and portal hypertension, gastroduodemal malignancy, gastric surgery, known adverse drug reactions to the trial drugs, current use of antisecretory drugs, H2 receptor or PPIs, a history of endoscopic therapy for bleeding ulcer within the past fours weeks, pregnancy or lactation, had endoscopic findings of active bleeding (spurting, oozing vessels or nonbleeding visible vessel), patients found to have malignant ulcers after initial enrolment Baseline characteristics shaded cells show significant differences: [ ] PPI i.v. PPI p.o.	Omeprazole i.v. received a bolus injection of 80 mg, given at admission, followed immediately by a continuous infusion of 8 mg / h for 72 h, then 40 orally daily for 6 wks	Omeprazole p.o. 80 mg a day (2x20 mg twice daily) for 3 days followed by oral 40 mg daily for 6 wks.	Until discharged and people asked to inform about rebleeding by or other complications voluntarily by day 30 after discharge	Clinical endopoints:Re bleeding (new hematemesis, melaena, or hypotension - < 100 mmHg systolic blood presure) associated with a drop in haemoglobin and / or enoscopic evidence of fresh Amount of blood transfusions (units) duration of hospital stay and mortality	Not stated

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			N	112	99					
			Mean Age (SD)	52.7 (18.42)	52.8 (19.61)					
			Male	79	66					
			H pylori positive	63	56					
			Shock	6	5					
			Ulcer count:							
			Single	106	82					
			Multiple	6	17					
			Coexisting illness:							
			Cardiac	18	14					
			Pulmanory	16	15					
			Cerebral	7	6					
			Ulcer location:							
			Posteriors duodenal	61	52					
			Anterior duodenal	33	14					
			Gastric corporal	9	16					
			Gastric antral	9	17					
			Rockall ≤3	63	52					
			Rockall >8	21	19					

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Effect size

Clinical outcomes – none of the differences significant:

	PPI i.v. N=112	PPI p.o. N=99	p
Rebleeding early	5	4	0.879
Rebleeding N (by day 30 post discharge)	7	5	0.745
Surgery requirement N	3	2	0.773
Mean units of blood transfused	1.9 (1.1)	2.1 (1.7)	0.350
Mean days in hospital	4.6 (1.6)	4.5 (2.6)	0.710
Death inpatient	2	2	0.981
Death overall	3	2	0.980

Authors' conclusion:

Oral Omeprazole as effective as intravenous therapy in terms of rebleeding surgery transfusion requirements, hospitalization and mortality in patients with bleeding ulcers with low risk stigmata..

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Kaviani MJ, Hashemi MR, Kazemifar AR et al. Effect of oral omeprazole in reducing re-	Two-centre, double blind RCT Country: Iran Good sequence	N=160 (N=80 PPI p.o.and N=80 placebo) 11 were later excluded due to H2RA	Inclusion criteria: Patients older than 15 years in whom endoscopic treatment of actively bleeding ulcers or ulcers with non-bleeding visible vessels had been successful. Exclusion criteria: Low risk bleeders (white-based ulcers, ulcers with a	Omeprazole 20 mg every 6 hours oral, for 3–5 days	Identical placebo for 3–5 days.	3 wks	Rebleeding (defined as haematemesis, shock – systolic blood pressure of less than 90	Shiraz University of Medical Science provided financial

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>bleeding in bleeding peptic ulcers: a prospective, double-blind, randomized, clinical trial. Alimentary pharmacology & therapeutics. 2003; 17(2):211-216. Ref ID: 314</td><td>generation, allocation concealment</td><td>treatment (N=71 PPI p.o.and N=78 placebo)</td><td>simple clot after washing with 500 cm3 of tap water), cases in which the bleeding site was uncertain, cases with unknown or other sources of bleeding, patients currently taking antisecretory drugs and patients with highly probable gastric malignancies.

Baseline characteristics:
<table>
<tr><th></th><th>PPI p.o.</th><th>Placebo</th></tr>
<tr><td>N</td><td>71</td><td>78</td></tr>
<tr><td>Mean Age (SD)</td><td>52.79 (18.42)</td><td>51.51 (18.96)</td></tr>
<tr><td>Male</td><td>57</td><td>64</td></tr>
<tr><td>Haemoglobin level (g/dL)</td><td>10.2 (2.9)</td><td>10.5 (3)</td></tr>
<tr><td>Shock N</td><td>3</td><td>6</td></tr>
<tr><td>Patients with blood transfusions in first 6 h</td><td>17</td><td>18</td></tr>
<tr><td>Mean units</td><td>1.7 (0.7)</td><td>1.6 (0.7)</td></tr>
</table></td><td>Then, all received oral omeprazole 20 mg twice daily plus H. pylori eradication therapy (if positive for the infection).</td><td></td><td></td><td>mmHg in the supine position or pulse rate of more than 110 beats/min – orthostatic hypotension – decrease of more than 20 mmHg of systolic or 10 mmHg of diastolic blood pressure, 3 min after changing from the supine to the sitting position, respectively - orthostatic tachycardia – increase of ≥ 10 beats / min in the pulse rate, 3 min after changing from the supine to the sitting position – or a</td><td>support</td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			transfused in first 6 h						decrease of more than 1 g/dL in haemoglobin despite blood transfusion developed after the first endoscopic treatment) other end points: mortality, blood tansfusion – second endoscopy (lower than 9.5 g/dL age >60 younger patients 8 g/dL), surgery, hospital stay	
			Previous history of UGIB	13	9					
			Ulcer location:							
			Duodenal	55	57					
			Gastric	16	21					

Effect size

Clinical outcomes shaded cells indicate significant differences:

	PPI p.o.N=71	Placebo N=78	p
Rebleeding N (% 95%CI)	12 (17 12.7-39)	26 (33; 29.6-57.6)	0.022
Surgery requirement N	1	1	n/s
Mean units of blood transfused	1.13 (1.36)	1.68 (1.68)	0.029

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Mean days in hospital h (sd)		62.8 (28.6)		75 (39)		0.032		
Hospital stay > 5 days		1		8		0.034		
Death		0		1		n/s		

Authors' conclusion:

Oral high-dose omeprazole is effective e in reducing the hospital stay, need for blood transfusion and re-bleeding rate in patients with high-risk peptic ulcer bleeding after endoscopic treatment.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hasselgren G, Lind T, Lundell L et al. Continuous intravenous infusion of omeprazole in elderly patients with peptic ulcer bleeding. Results of a placebo-controlled multicenter study. Scand J Gastroenterol. 1997;	Multi-centre (20) double blind RCT. Country: Sweden Sequence generation ok, allocation concealment reported but not clearly described.	N=333 – randomised N=322 per protocol included in ITT analysis (N=159 PPI i.v. and N=163 in Placebo)	Inclusion criteria: All patients admitted with melena or hematemesis (starting less than 48 h before admission) were endoscoped within 12 h of admission, inclusion criteria were age ≥ 60 years, presence of peptic ulcer bleeding in the stomach of duodenum at endoscopy classified as spurting arterial bleeding, oozing bleeding, visible vessel or black base / clot. Exclusion criteria: Upper gastrointestinal malignancy; deficient hemostasis (defined as, prothrombin <40% or platelet count <100 x 109); severe renal, hepatic, or cardiac failure; clinically	Omeprazole 80 mg i.v. bolus, followed by continuous infusion 8 mg/h for 72 hours. Then, all received omeprazole 20 mg oral daily until day 21. Initial endoscopic treatment	Identical placebo (mannitol) regimen for 72 hours.	3 day and 3 wk assessment	"Overall outcome" (5-point scale ranking the outcome from worse to best as follows: death 5; surgery 4; endoscopic treatment 3; more than three units of blood transfused 2; 0–3 units of blood	Sponsored by Astra Hässle AB

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>32(4):328-333.
Ref ID: 453</td><td></td><td></td><td>significant abnormalities in the laboratory screen, or receipt of anticoagulation therapy within 5 days of admission.

Baseline characteristics shaded cells indicate significant differences:
<table>
<tr><td></td><td>PPI i.v.</td><td>Placebo</td></tr>
<tr><td>N</td><td>159</td><td>163</td></tr>
<tr><td>Mean Age (SD)</td><td>74.5 (8.2)</td><td>74.3 (7.4)</td></tr>
<tr><td>Male</td><td>90</td><td>97</td></tr>
<tr><td>Shock</td><td>18</td><td>19</td></tr>
<tr><td>Mean systolic blood pressure mmHg</td><td>132 (26.4)</td><td>138 (29.0</td></tr>
<tr><td>Mean hemoglobin g/l</td><td>99 (23.8)</td><td>105 (26.1</td></tr>
<tr><td>Hemoblobin ≤ 90 g/l</td><td>68</td><td>47</td></tr>
<tr><td>History of peptic ulcers</td><td>72</td><td>92</td></tr>
<tr><td colspan="3">Patients with:</td></tr>
<tr><td>Melena</td><td>132</td><td>126</td></tr>
</table></td><td>only for spurting bleeding</td><td></td><td></td><td>transfused 1). Mortality, surgery and endoscopic treatment in 3 and 21 days, treatment failure in 3 days, re-bleeding (from day 4 to 21), blood Transfusions.

Rebleeding not clearly defined</td><td></td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			hematemesis	88	98					
			Ulcer location:							
			Gastric	88	90					
			Duodenal	71	73					

Effect size

Clinical outcomes (shaded cells show significant group differences – day 3):

	PPI i.v. N=159	Placebo N=163	p
Surgery	4	16	0.003
Mortality	1	1	>0.20
Treatment failure	9	27	0.0009

Clinical outcomes – day 21*:

	PPI i.v. N=159	Placebo N=163	p
Rebleeding N	5	4	>0.20
Surgery requirement N	11	13	>0.20
Endoscopic treatment	7	17	0.016
Mortality	11	1	0.012

*Mortality in the group initially receiving placebo remained the same as at 3 day follow-up whereas in the PPI group it increased significantly. This was due to more serious fatal adverse events in the PPI group.

Inclusion into the trial was prematurely terminated by a steering group due to the higher mortality in the PPI group.

Authors' conclusion:

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Three days' infusion of omeprazole improved overall outcome and reduced need for intervention in peptic ulcer bleeding patients.								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Schaffalitzky de Muckadell OB, Havelund T, Harling H et al. Effect of omeprazole on the outcome of endoscopically treated bleeding peptic ulcers. Randomized double-blind placebo-controlled multicentre study. Scand J Gastroenterol. 1997; 32(4):320-327. Ref ID: 454 (Parallel study to Hasselgren,	Multi-centre (34) double blind RCT. Countries: Denmark, Netherland and France Sequence generation ok , allocation concealment reported but unclear.	N=274 randomised – ITT analysis N=265 (N=130 PPI i.v. and N=135 in Placebo) Per protocol analysis N=229 (N=111 PPI and N=118 Placebo)	Inclusion criteria: Patients over age 18 with signs of acute upper gastrointestinal bleeding (haematemesis, melena or visisble blood in nasogastric tube) and clinical signs of circulatory stress or blood loss (at least two of: systolic blood pressure below 100 mm Hg, heart rate over 100/min, or a blood haemoglobin concentration below 7.0 mmol/l for men and 6.5 mmol/l for women. Endoscopic criteria: peptic ulcer in the stomach or duodenum with spurting bleeding, oozing bleeding a visible vessel or adherent clot/black base. Exclusion criteria: Oesophageal varices, Mallory-Weiss lesion; deficient haemostasis; anticoagulant therapy; need for non-steroidal anti-inflammatory drugs during the study; malignancy; clinically significant abnormalities that might reduce life expectancy to less than 6 months; phenytoin	Omeprazole 80 mg i.v. bolus, then infusion of 8 mg/h for 72 hours. After 48 hours both groups received oral omeprazole 20 mg daily for 21 days. Initial endoscopic treatment to 192	Identical placebo (mannitol) regimen.	3 days, 3 wk and 5 wks assessments	"Overall outcome" (5-point scale ranking the outcome from worse to best as follows: death 5; surgery 4; endoscopic treatment 3; more than 3 units of blood transfused 2; 0–3 units of blood transfused 1). Mortality (in 3, 21 and 35 days with causes of death by	Not stated

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>1997 above)</td><td></td><td></td><td>treatment; childbearing potential not using adequate contraception, pregnancy or lactating, or omeprazole treatment less than 5 days before inclusion

Baseline characteristics shaded cells indicate significant differences:
<table>
<tr><td></td><td>PPI i.v.</td><td>Placebo</td></tr>
<tr><td>N</td><td>130</td><td>135</td></tr>
<tr><td>Mean Age (SD)</td><td>66.3 (14.6)</td><td>67.4 (16.0</td></tr>
<tr><td>Age ≥ 70</td><td>62</td><td>77</td></tr>
<tr><td>Age ≥ 80</td><td>24</td><td>38</td></tr>
<tr><td>Male</td><td>75</td><td>78</td></tr>
<tr><td>Shock or preshock</td><td>110</td><td>112</td></tr>
<tr><td>Mean systolic blood pressure mmHg</td><td>112 (27)</td><td>116 (26)</td></tr>
<tr><td>Hemoglobin below 6mmol/l</td><td>90</td><td>89</td></tr>
<tr><td>Systolic blood pressure below</td><td>21</td><td>11</td></tr>
</table></td><td>patients</td><td></td><td></td><td>treatment group); re-bleeding (from day 4 to 21); surgery (in 3 and 21 days); “bad outcomes” (in 3 days); most severe episode of bleeding; duration of bleeding; “adjusted” number of transfused units of blood. Adverse events
Rebleeding not clearly defined</td><td></td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			<80 mmHg							
			History of peptic ulcers	47	62					
			Smokers	69	51					
			Forrest classification IIb	69	58					
			Ulcer location:							
			Gastric	63	71					
			Duodenal	67	63					

Effect size

Clinical outcomes at various follow up points (shaded cells show significant group differences):

	PPI i.v. N=159	Placebo N=163	p
Mortality 3 days, 3wks and 5 wks	2, 8 and 10	0, 8 and 11	n/s
Surgery 3 days, 3wks	5.4% and 10.8%	11.1 %and 13.3%	0.003 and 0.04 respectively
Endoscopy 3 days, 3wks	4.6% and 5.3%	11.1 %and 13.3%	0.03 and 0.01 respectively
Rebleeding between days 4-21	7.1%	12.4%	0.06

Inclusion into the trial was prematurely terminated by a steering group due to the higher mortality in the PPI group (see Hasselgren, 1997 above).

Authors' conclusion:

There was a beneficial effect of i.v. omeprazole in severe ulcer bleeding with a reduction in the number of operations and endoscopic treatments.

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>Hung W-K, Li VKM, Chung C-K et al. Randomized trial comparing pantoprazole infusion, bolus and no treatment on gastric pH and recurrent bleeding in peptic ulcers. ANZ Journal of Surgery. 2007; 77(8):677-681. Ref ID: 2904</td>
<td>Randomised trial

Randomisation: computer-generated table
Allocation concealment: unclear
Blinding: none</td>
<td>N=168 randomised
N=153 analysed</td>
<td>All patients with upper GI bleeding who had upper endoscopy. Patients with successful haemostasis were included.

Exclusion: Patients with previous gastrectomy or vagotomy

<table>
<tr><th></th><th>Infusion (n=54)</th><th>Bolus (n=49)</th><th>No Treatment</th></tr>
<tr><td>Men, n</td><td>32</td><td>35</td><td>37</td></tr>
<tr><td>Mean age yrs</td><td>63.7</td><td>57.8</td><td>62.5</td></tr>
<tr><td>Mean haemoglobin on admission g/dL</td><td>9.4</td><td>10.1</td><td>9.8</td></tr>
</table>
</td>
<td>Infusion group
Pantoprazole 80 mg iv bolus followed by 8 mg/h got 3 days. For 8 wks, all patients were given oral famotidine 20 mg twice daily starting on day 4.

Bolus group
Pantoprazole 80 mg iv followed by 40 mg every 12 hrs for 3 days
No treatment
No acid suppressio</td>
<td>No treatment plus ‘all patient’ treatment</td>
<td>Rebleeding 30 days
Transfusion requirement, duration of hospital stay, mortality</td>
<td>Primary outcomes: Rebleeding 30 days
Secondary: Transfusion requirement, duration of hospital stay, mortality</td>
<td>None reported</td>
</tr>
</table>

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				n for 3 days				

Pantoprazole infusion vs bolus vs no treatment. Significant difference: * Infusion vs no treatment ** Bolus vs no treatment

	Infusion	Bolus	No treatment
Rebleed, n	2*	2**	8
Units of pack cells transfused	2.26	1.53 **	2.88
Operation, n	0*	1	4
Total hospital stay, days	6.37*	6.57	8.15
Mortality, n	0	0	1

Author's conclusion

Pantoprazole either as infusion or bolus decreased rebleeding after endoscopic treatment for bleeding peptic ulcer

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Bajaj JS, Dua KS, Hanson K et al. Prospective, randomized trial comparing effect of oral versus intravenous	Single centre randomised trial Randomisation: random number table Allocation concealment: unclear	N=25	Patients with nonvariceal upper GI bleeding. Patients underwent endoscopy within 24 hrs of admission. Exclusion criteria included bleeding from a Mallory-Weiss tear IV / PO / P	Oral pantoprazole 80 mg every 12 hrs. Followed by 40 mg oral bd pantoprazole for 30	IV pantoprazole 80 mg bolus and then 8 mg/hr infusion for 72 hrs.	Rebleeding with 30 days Duration of hospitalisation, no. of blood transfusions, 30 day	Primary outcomes: Rebleeding with 30 days Secondary outcomes: Duration of hospitalisation, no. of blood	None reported

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>pantoprazole on rebleeding after nonvariceal upper gastrointestinal bleeding: a pilot study. Dig Dis Sci. 2007; 52(9):2190-2194. Ref ID: 111</td><td>Blinding: oral vs iv</td><td></td><td>
<table>
<tr><td></td><td>n=13</td><td>n=12</td><td></td></tr>
<tr><td>Age yrs mean (SD)</td><td>66.2 (6.2)</td><td>59.5 (19.4)</td><td>0.36</td></tr>
<tr><td>Male No.</td><td>10</td><td>6</td><td>0.22</td></tr>
<tr><td>Systolic BPmean (SD)</td><td>125.1 (32.6)</td><td>106.8 (23.0)</td><td>0.12</td></tr>
<tr><td>Rockall score mean (SD)</td><td>5.3 (2.5)</td><td>2.2 (1.9)</td><td>0.28</td></tr>
</table>
</td><td>days</td><td></td><td>mortality</td><td>transfusions, 30 day mortality</td><td></td></tr>
</table>

Oral pantoprazole vs IV pantoprazole

	IV n=13	PO n=12	P
Rebleeding No.	2	0	0.46
Mortality No.	0	0	
Blood transfusions units mean (SD)	3.9 (3.7)	3.6 (2.4)	0.813
Duration of hospitalisation mean (SD)	6.8 (4.8)	5.2 (3.3)	0.34

Author's conclusion

We conclude in this pilot study, the effect of oral pantoprazole on 30-day rebleeding rate in patients with nonvariceal upper GI bleeding was similar to that of the IV

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
pantoprazole								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
3 SA, Javid G, Khan BA et al. Pantoprazole infusion as adjuvant therapy to endoscopic treatment in patients with peptic ulcer bleeding: prospective randomized controlled trial. Journal of Gastroenterology & Hepatology. 2006; 21(4):716-721. Ref ID: 183	Single centre double blind placebo controlled trial Randomisation: random number table Allocation concealment: opaque sealed numbered envelope Double blind	N=203	All patients admitted to hospital with a history of hematemsis and/or melena, or who bleed while in hospital undergo emergency endoscopy always within 12 hrs of bleeding Endoscopic therapy was given if the endoscopy showed a peptic ulcer in the stomach or duodenum with active bleeding or stigmata of recent haemorrhage Exclusion criteria: severe coagulopathy and previous acid reducing surgeries Shaded areas indicate a significant difference Placebo (N=101) / Pantoprazole (N=102) Age yrs mean: 52.4 (23 to 85) / 55.3 (24 to 82)	Pantoprazole 80 mg intravenous bolus followed by a continuous infusion 8 mg per hour for 72 hrs (N=102)	Placebo (N=101)	Rebleeding 3, 7 and 14 days Surgery, mortality, mean no. units blood transfused, mean hospital stay	Primary: Rebleeding 3, 7 and 14 days Secondary: Surgery, mortality, mean no. units blood transfused, mean hospital stay	None reported

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			(range)							
			Male No.	63	70					
			Location of ulcer Duodenum Stomach	85 16	84 18					

Pantoprazole vs placebo. Shaded areas indicate a significant difference

	Placebo N=101	Pantoprazole N=102	P value
No. with rebleeding at 2 weeks	20	8	0.01
At day 3	18	7	0.02
At day 7	19	8	0.02
Urgent surgery no.	8	3	0.12
Mortality no.	4	2	0.45
Mean units blood transfused (SD)			
Total	2 (3.3)	1 (2.5)	0.003
Before randomisation	0.4 (0.9)	0.4 (0.8)	0.9
After randomisation	1.6 (2.6)	0.7 (1.9)	0.0005
Mean hospital stay days (SD)	7.7 (7.3)	5.6 (5.3)	0.0003

Author's conclusion: In patients with bleeding peptic ulcers, the use of high dose pantoprazole infusion following successful endoscopic therapy is effective in reducing rebleeding, transfusion and hospital stay

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>Tsai J-J, Hsu Y-C, Perng C-L et al. Oral or intravenous proton pump inhibitor in patients with peptic ulcer bleeding after successful endoscopic epinephrine injection. Br J Clin Pharmacol. 2009; 67(3):326-332. Ref ID: 63</td>
<td>Single centre randomised trial

Randomisation: random number table
Allocation concealment: sealed envelopes
Blinding: oral vs iv</td>
<td>N=156</td>
<td>Peptic ulcer patients with high-risk stigmata. Inclusion criteria (i) underwent urgent endoscopy within 24 hr after presentation (ii) had peptic ulcers in the distal oesophagus, stomach or duodenum, (iii) had high-risk stigmata including active bleeding (Forrest IA, IB), non-bleeding visible vessel (NBVV, IIA), or adhere clots (Forrest IIB) and (iv) successful haemostasis was achieved with endoscopic injection of epinephrine
<table>
<tr><th></th><th>OME N=78</th><th>RAB N=78</th></tr>
<tr><td>Age yrs mean (95%CI)</td><td>69.4 (20.3 to 80.4)</td><td>67.9 (21.2 to 81.9)</td></tr>
<tr><td>Male %</td><td>70.5</td><td>74.4%</td></tr>
<tr><td>Location of ulcer %
Stomach
Duodenum
Oesphagus</td><td>
53.8
41
4</td><td>
50
47.4
2.6</td></tr>
<tr><td>Rockall score</td><td>5.4</td><td>5.3</td></tr>
</table>
</td>
<td>Omeprazole (OME) 40 mg continuous infusion every 12 hrs for 3 days. Followed by oral esomeprazole 40 mg once daily for two months (N=78)</td>
<td>Rabeprazole (RAB) 20 mg oral RAB twice daily for 3 days followed by once daily for two months (N=78)</td>
<td>14 days
Endoscopy repeated 72 hrs after enrolment. Discharged if no blood clot or haemorrhage observed.</td>
<td>Primary 14 day rebleeding. Secondary 14 days: volume blood transfusion, surgery, mortality, hospital stay</td>
<td>Tomorrow Medical Foundation Grant</td>
</tr>
</table>

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Omeprazole vs. Rabeprazole. There were no statistically significant differences between the groups

	OME (N=78)	RAB (N=78)
Recurrent bleeding n (%) (occurred within 3 days of enrolment)	12 (15.4%)	13 (16.7%)
Hospital stay days (95%CI) SD*	8.5 (7.4 to 9.6) 4.9	8.9 (7.3 to 9.7) 5.3
Volume of blood transfusion after therapy ml (95%CI)	1231 (487 to 1995)	1156 (489 to 1569)
Surgery no. (%)	1 (1.3%)	1 (1.3%)
Death no. (%)	1 (1.3%)	2 (2.6%)

*SD derived from confidence interval, mean and sample size (Katharina Dworzynski)

Author's conclusion

The results are interpreted as oral rabeprazole and IV regular-dose omeprazole are equally as effective in preventing rebleeding in patient with high-risk bleeding peptic ulcers after successful endoscopic injection with epinephrine

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Lin HJ, Lo WC, Perng CL et al. Can optimal acid suppression prevent rebleeding in peptic ulcer patients with a	Single centre randomised trial Randomisation: envelope arranged by a statistician (unclear)	N=52	Patients with hematemesis and/or tarry stool with a non-bleeding visible vessel (NBVV) at the ulcer base was observed during an emergency endoscopic examination within 12 hrs of arrival at the hospital. Patients were excluded if they had	CIM 300 mg intravenous bolus followed by infusion of CIM 300 mg for every 6 hrs during hospitalisati	OME 40 mg intravenous bolus followed by 40 mg intravenous infusion for 30 min daily for two days	unclear	Rebleeding Volume of blood transfused Days in hospital	NSC, R.O.C, VGH-Taipei

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>non-bleeding visible vessel: a preliminary report of a randomized comparative study. Hepatogastroenterology. 1997; 44(17):1495-1499. Ref ID: 444</td><td>Allocation concealment: envelope arranged by a statistician (unclear)
Blinding: unclear/not reported</td><td></td><td>bleeding gastric cancer; more than one bleeding source; had coagulopathy

Baseline characteristics were ‘comparable’

<table><tr><th></th><th>CIM N=13</th><th>HPT + CIM N=13</th><th>OME QD</th><th>OME Q!”H</th></tr><tr><td>Age yrs mean (SD)</td><td>63.6 (17.6)</td><td>64.9 (14.5)</td><td>61.7 (17)</td><td>61 (14.5)</td></tr><tr><td>Sex male (No.)</td><td>10</td><td>13</td><td>11</td><td>11</td></tr><tr><td>Location of ulcer
Stomach
Duodenum</td><td>3
7
3</td><td>4
9
0</td><td>5
8
0</td><td>6
7
0</td></tr></table></td><td>on

Heat probe thermocoagulation (HPT) plus CIM 300 mg intravenous bolus followed by infusion of CIM 300 mg for every 6 hrs during hospitalisation</td><td>OME 40 mg intravenous bolus followed by 40 mg intravenous infusion for 30 min every 12 hrs for two days</td><td></td><td></td><td></td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Stoma					

There were no statistically significant differences between the groups

	CIM N=13	HPT + CIM N=13	OMEQD N=13	OMEQ12H N=13
Rebleeding no. (%)	5 (38.4)	2 (15.4)	2 (15.4)	2 (15.4)
Vol. of blood transfusion mean ml (SD)	596 (813)	519 (688)	230 (345)	923 (1156)
Days in hospital mean (SD)	5.5 (2.5)	4.7 (1.8)	4.3 (0.9)	4.6 (2.4)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Villanueva C, Balanzo J, Torras X et al. Omeprazole versus ranitidine as adjunct therapy to endoscopic injection in	Open single centre RCT. Country: China Sequence generation ok , allocation concealment unclear (sealed envelopes)	N=96 randomised – ITT analysis N=86 (N=45 PPI i.v. and N=41 in H2RA i.v.)	Inclusion criteria: Patients over age 18 with signs of acute upper gastrointestinal bleeding (haematemesis or melena or both) who had peptic ulcer bleeding (continuous flow of blood pumping or oozing from the ulcer floor) confirmed by emergency endoscopy. Exclusion criteria: Patients not	Omeprazole 80 mg i.v. bolus followed by 40 mg i.v. every 8 hours for 4 days, then 20 mg/day	Ranitidine i.v. 50 mg every 6 hours for 12–24 hours, then 150 mg oral twice daily (duration not stated).	Followed up until discharge	Rebleeding (defined as active bleeding ulcer at a repeated endoscopy; vomiting of fresh blood or bloody aspirates after	Not stated

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>actively bleeding ulcers: a prospective and randomized study. Endoscopy. 1995; 27(4):308-312. Ref ID: 478</td><td></td><td></td><td>giving consent.

Baseline characteristics:<table><tr><td></td><td>PPI i.v.</td><td>H2RA i.v.</td></tr><tr><td>N</td><td>45</td><td>41</td></tr><tr><td>Mean Age (SD)</td><td>63 (15)</td><td>61 (17)</td></tr><tr><td>Male</td><td>38</td><td>29</td></tr><tr><td>Associated diseases N</td><td>32</td><td>33</td></tr><tr><td>Mean systolic blood pressure mmHg</td><td>106 (30)</td><td>110 (33)</td></tr><tr><td>Mean Hemoglobin g/dl</td><td>9.1 (3)</td><td>10.2 (2.9)</td></tr><tr><td>Onset of bleeding in hospitalised patients</td><td>10</td><td>4</td></tr><tr><td colspan="3">Ulcer location:</td></tr><tr><td>Gastric</td><td>12</td><td>19</td></tr><tr><td>Duodenal</td><td>30</td><td>20</td></tr></table></td><td>orally (duration not stated).

All received initial endoscopic treatment</td><td></td><td></td><td>clear lavages through nasogastric tube, or passage of fresh melena, plus hemodynamic instability or a drop in haemoglobin – repeat endoscopy only performed for confirmation of doubtful cases). mortality,surgery, blood transfusion requirements, length of hospital stay. Followed up until discharge or death</td><td></td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Stomal 3 1 Pyloric 0 1					

Effect size

Clinical outcomes (shaded cells show significant group differences):

	PPI i.v.	H2RA i.v.	p
Mortality	3	1	n/s
Surgery	9	9	n/s
Transfusions (mean units of red blood cells)	2.4 (2.2)	2.2 (2.1)	n/s
Hospital stay (days)	14 (13)	15 (14)	n/s
Rebleeding	11	9	n/s

Authors' conclusion:

Omeprazole is as effective as rantidine in improving clinical outcomes in patients with active arterial bleeding from peptic ulcer

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Lanas A, Artal A, Blas JM et al. Effect of parenteral omeprazole and ranitidine on gastric pH	Open single centre prospective RCT. Country: Spain Sequence	N=51 (N=28 PPI i.v. and N=23 in H2RA i.v.)	Inclusion criteria: Patients over age 18 with endoscopic predictors of rebleeding (bleeding, oozing, non-bleeding visible vessel or adherent red clot. Exclusion criteria: Pregnancy, severe physical illness such as	Omeprazole 80 mg i.v. bolus followed by 40 mg i.v. every 12 hours for 4	Ranitidine i.v. 50 mg every 4 hours (duration not stated).	No timing of assessment given (until discharge)	Rebleeding (defined as vomiting of fresh blood or bloody aspirates after clear lavages	Not stated

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>and the outcome of bleeding peptic ulcer. J Clin Gastroenterol. 1995; 21(2):103-106. Ref ID: 477</td><td>generation ok , allocation concealment unclear (sealed envelopes)</td><td></td><td>terminal disease or advanced malignancy, bleeding of such severity that immediate surgery was indicated, bleeding developing in patients who had been admitted to hospital for other reasons and inability or unwillingness to give informed consent

Baseline characteristics:
<table>
<tr><td></td><td>PPI i.v.</td><td>H2RA i.v.</td></tr>
<tr><td>N</td><td>28</td><td>23</td></tr>
<tr><td>Mean Age (SD)</td><td>63 (15)</td><td>61 (17)</td></tr>
<tr><td>Male %</td><td>67.8</td><td>86.9</td></tr>
<tr><td>Associated diseases N</td><td>15</td><td>13</td></tr>
<tr><td>Shock N</td><td>12</td><td>12</td></tr>
<tr><td colspan="3">Ulcer location:</td></tr>
<tr><td>Gastric</td><td>15</td><td>8</td></tr>
<tr><td>Duodenal</td><td>13</td><td>15</td></tr>
</table></td><td>days, then 20 mg/day orally (duration not stated).

No initial endoscopic treatment</td><td></td><td></td><td>through nasogastric tube, or passage of fresh melena, plus hemodynamic and clinical evidence of hypovolemia or a drop in haemoglobin requiring transfusion) mortality, surgery, blood transfusion requirements, length of hospital stay. Timing of outcome assessment not mentioned</td><td></td></tr>
<tr><td colspan="9">Effect size
Clinical outcomes (shaded cells show significant group differences):
<table>
<tr><td></td><td>PPI i.v.</td><td>H2RA i.v.</td><td>p</td></tr>
</table></td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Mortality	2	2	n/s
Surgery	1	5	0.05
Transfusions (mean units of red blood cells)	2.3 (2.6)	2.9 (2.6)	n/s
Hospital stay (days)	8.3 (8.8)	9.5 (5.4)	n/s
Rebleeding	6	9	n/s (0.1)

Authors' conclusion:
Omeprazole is more effective than rantidine in improving clinical outcomes (surgery) in patients with active arterial bleeding from peptic ulcer.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Coraggio F, Rotondano G, Marmo R et al. Somatostatin in the prevention of recurrent bleeding after endoscopic haemostasis of peptic ulcer haemorrhage: a preliminary report.	Multi centre RCT. Country: Italy Sequence generation ok , allocation concealment unclear (sealed envelopes)	N=73 (N=24 PPI i.v. and N=24 in H2RA i.v. and N= 25 somatostatin - not reported here)	Inclusion criteria: Patients were admitted if emergency endoscopy showed gastric or duodenal ulxer with major stigmatat of recent haemorrhage (arterial spurting or oozing, nonbleeding visible vessel or adherent clot) – age limits not given Exclusion criteria: Patients with either grey sloughs or flat spots at the ulcer base (no other exclusion criteria provided)	Omeprazole 40mg orally every 12 hours for 5 days. Post-intervention drug treatment not mentioned. All	Ranitidine: 50 mg i.v. every 6 hours for 5 days. Another group received: Somatostatin 250 µg i.v. bolus followed by continuous infusion 250 µg/h for 5	All patients were submitted to outpatient endoscopic controls with a mean follow up time of 3.1 months ± 1.1 months	Rebleeding (defined by haematemesis or melaena of bloody nasogastric aspirate – with either shock or a decrease in haemoglobin concentration by at least2 g/dl over 24 h period).	Not stated

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>European Journal of Gastroenterology & Hepatology. 1998; 10(8):673-676. Ref ID: 426</td><td></td><td></td><td>Baseline characteristics:
<table>
<tr><td></td><td>PPI i.v.</td><td>H2RA i.v.</td></tr>
<tr><td>N</td><td>24</td><td>24</td></tr>
<tr><td>Mean Age (SD)</td><td>59 (16)</td><td>57 (18)</td></tr>
<tr><td>Male</td><td>18</td><td>16</td></tr>
<tr><td>Patients with hypotension</td><td>6</td><td>5</td></tr>
<tr><td>Onset of bleeding in hospitalised patients %</td><td>16.6%</td><td>12.5%</td></tr>
<tr><td colspan="3">Ulcer location:</td></tr>
<tr><td>Gastric</td><td>6</td><td>7</td></tr>
<tr><td>Duodenal</td><td>18</td><td>17</td></tr>
</table></td><td>received endoscopic treatment</td><td>days.</td><td>All patients were submitted to a second examination 48 h after index endoscopy</td><td>mortality, surgery, blood transfusion requirements, length of hospital stay.

Unclear at which time the assessments were made</td><td></td></tr>
<tr><td colspan="9">Effect size
Clinical outcomes (none significant)
<table>
<tr><td></td><td>PPI i.v.</td><td>H2RA i.v.</td><td>p</td></tr>
<tr><td>Death occurring after injection</td><td>1</td><td>1</td><td>n/s</td></tr>
<tr><td>Death occurring after surgery</td><td>1</td><td>2</td><td>n/s</td></tr>
<tr><td>Surgery for persistent bleeding</td><td>2</td><td>1</td><td>n/s</td></tr>
</table></td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Surgery for rebleeding	3	4	n/s
Transfusions (mean units of red blood cells)	2.1 (0.4)	2.2 (0.6)	n/s
Hospital stay (days)	14 (3)	13 (4)	n/s
Rebleeding	5	5	n/s

Authors' conclusion:
Omeprazole is as effective as rantidine in improving clinical outcomes in patients with acute upper GI bleeding

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Brunner G, Chang J. Intravenous therapy with high doses of ranitidine and omeprazole in critically ill patients with bleeding peptic ulcerations of the upper intestinal tract: an open randomized controlled	Single centre open RCT. Country: Germany Sequence generation unclear , allocation concealment unclear	N=39 (N=19 PPI i.v. and N=20 in H2RA)	Inclusion criteria: Patients with Forrest Ib (oozing) bleeding. Exclusion criteria: No exclusion criteria given. Randomised after endoscopy Baseline characteristics:	Omeprazole 80 mg i.v. bolus, then 40 mg i.v. bolus 12-hourly for 5 days. On day 6, all commenced on oral omeprazole 40 mg once daily or ranitidine	Ranitidine 50 mg i.v. bolus, then 400 mg i.v. infusion/ 24 hours for up to 6 days.	Every patient had a control endoscopy on day 6 unless more than 2.5 liters of blood were necessary before tis day to maintain a hemoglobin value above 10 g/l.	Mortality, surgery, postrandomisation endoscopic treatment	Not stated

	PPI i.v.	H2RA i.v.
N	20	19
Mean Age (SD)	57.3	59.2
Male	8	13
Patients with shock	5	4

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>trial.
Digestion.
1990;
45(4):217-225.
Ref ID: 519</td><td></td><td></td><td>
<table>
<tr><td>Onset of bleeding in hospitalised patients N</td><td>10</td><td>9</td></tr>
<tr><td>Mean haemoglobin</td><td>10.5</td><td>10.7</td></tr>
<tr><td>Ulcer after liver transplantation</td><td>1</td><td>4</td></tr>
<tr><td colspan="3">Ulcer location:</td></tr>
<tr><td>Gastric</td><td>11</td><td>8</td></tr>
<tr><td>Duodenal</td><td>6</td><td>9</td></tr>
<tr><td>Anastomosis ulcer</td><td>2</td><td>3</td></tr>
</table>
</td><td>300 mg twice daily.

Initial endoscopic treatment not performed. Some patients had endoscopic treatment (sclerotherapy) when acid suppression treatment failed to control bleeding</td><td></td><td>Treatment was continued for 4 wks but unclear whether any follow up assessment took place</td><td></td><td></td></tr>
<tr><td colspan="9">Effect size
Clinical outcomes (no significance values given):
<table>
<tr><th></th><th>PPI i.v. N=19</th><th>H2RA i.v. N=20</th></tr>
<tr><td>Mortality</td><td>1</td><td>1</td></tr>
<tr><td>Surgery</td><td>1</td><td>4</td></tr>
<tr><td>Endoscopic treatment</td><td>2</td><td>1</td></tr>
</table>
</td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Authors' conclusion: The authors only draw conclusions with regard to pH level (which was significantly more reduced by PPIs).								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Javid G, Masoodi I, Zargar SA et al. Omeprazole as adjuvant therapy to endoscopic combination injection sclerotherapy for treating bleeding peptic ulcer. Am J Med. 2001; 111(4):280-284. Ref ID: 366	Single centre double blind RCT. Country: India Sequence generation unclear, good allocation concealment (sealed opaque envelopes)	N=166 (N=82 PPI p.o. and N=84 Placebo)	Inclusion criteria: Patients with duodenal, gastric, or stomal ulcers and stigmata of recent haemorrhage. Stigmata of recent haemorrhage were spurting vessles, active bleeding in an ulcer, a visible vessel, or a clot over the ulcer that could not be dislodged by with water delivered through the endoscope channel. Exclusion criteria: Patients with terminal cancer, or were moribund as a result of concomitant illnesses and could not provide legal consent, or had perfuse haemorrhage accompanied by persistent shock, during which the upper gastrointestinal tract was filled with fresh blood, limiting visibility with the endoscope and necessitating emergency surgery. Patients were also excluded if the continued to bleed within the first 4	Omeprazole 40 mg oral every 12 hours for 5 days. 2. Identical looking placebo for 5 days. Then all received oral omeprazole 20 mg daily for 3 weeks (with or without prior H. pylori eradication therapy).	Placebo.	Until discharge	Separately by SRH: Rebleeding (hematemesis, melena, or both, with either shock or a decrease in hemoblobin concentration of > 2 g.dL over a 24-hour period – confirmed by endoscopy), mortality, and surgery (timing of outcome assessment not reported). Length of hospital stay	Not stated

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td></td><td></td><td>hours of endoscopic treatment and needed emergency surgery to control their bleeding.

Randomised after endoscopy

Baseline characteristics:
<table>
<tr><td></td><td>PPI p.o.</td><td>Placebo</td></tr>
<tr><td>N</td><td>82</td><td>84</td></tr>
<tr><td>Mean Age (SD)</td><td>55 (9.8)</td><td>55.7 (8.3)</td></tr>
<tr><td>Male</td><td>52</td><td>51</td></tr>
<tr><td>Positive H pylori N</td><td>59</td><td>63</td></tr>
<tr><td>Mean haemoglobin</td><td>8.8 (1.3)</td><td>8.9 (1.5)</td></tr>
<tr><td>Comorbid illness (cardiac, pulmonary, renal)</td><td>5</td><td>4</td></tr>
<tr><td colspan="3">Ulcer location:</td></tr>
<tr><td>Gastric</td><td>7</td><td>8</td></tr>
<tr><td>Duodenal</td><td>74</td><td>75</td></tr>
<tr><td>Stomal</td><td>1</td><td>1</td></tr>
</table></td><td>All had initial endoscopic treatment</td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="9">Effect size</td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Clinical outcomes (no significance values given):

	PPI p.o.	Placebo	
Rebleeding	6	18	0.02
Mortality	1	2	0.98
Surgery	2	7	0.17
Days in hospital (sd)	4.6 (1.1)	6.0 (0.7)	<0.001

Authors' conclusion:
The authors only draw conclusions with regard to pH level (which was significantly more reduced by PPIs).

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Sheu BS, Chi CH, Huang CC et al. Impact of intravenous omeprazole on Helicobacter pylori eradication by triple therapy in patients with peptic ulcer bleeding. Alimentary pharmacology & therapeutics.	Single centre RCT. Country: Taiwan Sequence generation unclear, allocation concealment unclear	N=175 (N=86 PPI i.v. and N=89 in H2RA i.v.) ITT analysis and per protocol analysis	Inclusion criteria: Patients with confirmed peptic bleeding, confirmed during endoscopy and all had confirmed H. pylori infection. Exclusion criteria: Patients not giving consent. Baseline characteristics: PPI i.v. / H2RA i.v. N: 86 / 89 Mean Age (SD): 46.8(15.9) / 44.9 (15.6 Male: 56 / 60	Omeprazole 80 mg i.v. bolus, then 40 mg i.v. twice daily for 3 days. Spurting, oozing, NBVV and vessels below clots received	2. Ranitidine 50 mg infused i.v. every 8 hours for 3 days.	6 weeks	Re-bleeding at 3 days, 10 days and 6 weeks. Mortality and surgery. Re-bleeding also reported by severity of SRH	Partly supported by a grant from the National Health Research Institute

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
2002; 16(1):137-143. Ref ID: 349			Associated diseases N (chronic renal failure, liver cirrhosis, cardiovascular disease, pulmonary disease)	9	8	initial endoscopic treatment. All received triple eradication therapy from day 4 for 1 week. "Later", ranitidine 150 mg orally twice daily for additional 4 we				
			Previous ulcer bleeding	15	12					
			Ulcer location:							
			Gastric	39	40					
			Duodenal	47	49					

Effect size

Clinical outcomes (shaded cells show significant group differences):

	PPI i.v.	H2RA i.v.	p
Mortality	0	2	0.25
Surgery	1	4	0.18
Rebleeding total	5	15	0.02
Rebleeding by the first 3 days	3	11	0.03

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Rebleeding during triple therapy		2	2		0.97			

Authors' conclusion:
Omeprazole is more effective than ranitidine in improving rebleeding rates for patients with peptic ulcer bleeding and H. pylori infection.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Këlliçi, I, Kraja B, Mone I, et al. Role of intravenous omeprazole on non-variceal upper gastrointestinal bleeding after endoscopic treatment: a comparative study. Med Arh 2010;64:324-7. Ref ID: 237	Single centre RCT, Country: Albania Unclear allocation concealment, unclear randomisation sequence generation, blinding not described, ITT analysis	N=108 (N=54 Omeprazole and N=54 Ranitidine)	Inclusion criteria: Patients with non-variceal in whom haemostatic endoscopy had been successful. Exclusion criteria: Patients with gastroduodenal malignancy and those previously treated with antisecretory drugs. Baseline characteristics PPI / H2RA N: 54 / 54 Mean Age (SD): 55.4 (17.3) / 55.8 (16.9 Male: 35 / 37 Patients with shock: 7 / 6	80 mg intravenous omeprazole i.v. bolus followed by an 8 mg/h infusion for 72 hours	100 mg ranitidine i.v. bolus followed by 100 mg boluses every 6 hours for a period of 72 hours.	72 hours	Primary end point: rebleeding (defined as new hematemesis, melaena or hypotension , i.e. < 100 mm Hg systolic blood pressure, associated with a drop in haemoblobin and / or endoscopic evidence of fresh re-	Not stated

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Rockall score mean (SD)	5.2 (1.8)	5.1 (1.7)				bleeding. within 72 hours Secondary outcomes: volume of blood transfusion, hospital stay , need for surgery and mortality	
			Mean haemoglobin	8.24 (1.4)	8.29 (1.5)					
			Haematocrit (%)	27.7 (4.2)	27.5 (3.7)					
			Previous ulcer bleeding	11	12					
			Ulcer location:							
			Gastric	15	16					
			Duodenal	39	38					

Effect size

Post treatment outcomes – shaded cells highlight significant differences:

	PPI N=54	H2RA N=54	Relative risk (95% CI)	p
Mortality	1	2	1.9 (1.5-2.3)	NS
Surgery	2	5	0.5 (0.09-2.8)	NS
Rebleeding	6	14	3.4 (1.1 – 7.2)	< 0.05
Hospital stay	5.4 (2.6)	6.8 (3.3)	-	< 0.05
Volume of blood transfused (units)	1.1 (1.8)	2.3 (2.9)	-	< 0.05

Authors Conclusions

Intravenous omeprazole should be used in patients with non-variceal UGI bleeding after effective endoscopic treatment.

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>Mostaghni AA, Hashemi ST, Heydari ST. Comparison of oral and intravenous proton pump inhibitor on patients with high risk bleeding peptic ulcers: A prospective, randomized, controlled clinical trial. Iranian Red Crescent Medical Journal 2011;13. Ref ID: 5334</td>
<td>Single centre randomised trial, Country: Iran

Randomisation sequence generation not adequate (days of the months),
No allocation concealment: (based on even and odd days of the month)

No blinding</td>
<td>N=102 were randomised (in the abstract it states 106) 17 patients were excluded per protocol (unclear how many from which group). N=44 omeprazole p.o. N=41 pantoprazole i.v.</td>
<td>Inclusion criteria: Patients with successful endoscopic therapy for high risk ulcers (defined as active bleeding non-bleeding visible vessel or adherent clots.

Exclusion criteria Patients with low risk ulcers (clean base, ulcers with a simple washable clot), suspicious malignant ulcer, bleeding tendency, uremia, liver cirrhosis, Mallory Weiss tear or already on PPI as an outpatient.

Baseline characteristics – expressed as N (%) or mean (sd):
<table>
<tr><th></th><th>i.v. n=44</th><th>p.o. n=41</th></tr>
<tr><td>Age yrs mean (SD)</td><td>57.25 (16.5)</td><td>61.66 (17.2)</td></tr>
<tr><td>Male No.</td><td>33</td><td>30</td></tr>
<tr><td>Duodenal ulcer</td><td>17 (39)</td><td>20 (49)</td></tr>
<tr><td>Gastric ulcer</td><td>24 (54)</td><td>18 (44)</td></tr>
<tr><td>Both</td><td>3 (7)</td><td>3 (7)</td></tr>
<tr><td>Adherent clot</td><td>5 (11)</td><td>3 (7)</td></tr>
<tr><td>Visible vessel</td><td>25 (57)</td><td>26 (63)</td></tr>
<tr><td>Blood oozing</td><td>6 (14)</td><td>7 (17)</td></tr>
</table>
</td>
<td>i.v. pantoprazole 80 mg every 12 hrs for 72 hours. Followed by 20 mg oral omeprazole for 30 days</td>
<td>p.o. pantoprazole 80 mg bolus and then 8 mg/hr infusion for 72 hrs. Followed by 20 mg oral omeprazole for 30 days</td>
<td>Up to 5 weeks</td>
<td>Primary outcomes: Rebleeding
Secondary outcomes: Duration of hospitalisation, no. of patients needing blood transfusions, mortality, surgery, Re-endoscopy</td>
<td>Financed by the Shiraz University of Medical Sciences</td>
</tr>
</table>

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Active bleeding	6 (14)	7 (17)					

Effect size

Post treatment outcomes for oral omeprazole vs IV pantoprazole – shaded cells indicate significant differences

	PO n=44	IV n=41	P
Rebleeding No.	5 (11.4)	4 (9.8)	0.810
Mortality No.	1 (2)	1 (2)	NS
Surgery	0	0	NS
Blood transfusions units mean	1.82	1.95	0.641
Patients requiring transfusions	31 (71)	33 (81)	0.284
Duration of hospitalisation mean	3.1	3.6	0.130
Re-endoscopy	18 (41)	24 (59)	0.104

Author's conclusion

Oral omeprazole and iv pantoprazole had equal effect on prevention of rebleeding after endoscopic therapy in patients with high risk bleeding peptic ulcers.

F.4.3 Treatment options after first endoscopy or when first line treatment fails

QUESTION 1 In patients with UGIB after first endoscopic treatment, is a routine second-look endoscopy more clinically / cost effective than routine clinical follow-up?

QUESTION 2 In patients who rebleed after the first endoscopic therapy is repeat endoscopy more clinical / cost effective compared to surgery or embolisation / angiography to stop bleeding?

QUESTION 3 In patients where endoscopic therapy fails is angiography / embolisation more clinical / cost effective than surgery to stop bleeding?

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Villanueva C, Balanzo J, Torras X et al. Value of second-look endoscopy after injection therapy for bleeding peptic ulcer: a prospective and randomized trial. Gastrointest Endosc. 1994; 40(1):34-39. Ref ID: 4811	RCT, Spain Randomisation using table of random numbers and opaque, sealed envelopes; not blinded	104	Inclusion: Upper gastrointestinal haemorrhage (meleana and/or haematemesis confirmed by hospital staff); emergency endoscopy within 4 hours of admission showed peptic ulcer with active arterial bleeding (continuous flow of blood spurting or oozing from the ulcer) or a non-bleeding visible vessel (protruberant mound on ulcer base). Injection therapy during emergency endoscopy (adrenaline). Exclusion: Patients under 18 years old or unable/unwilling to give consent Baseline characteristics: N (%) of spurting + oozing per group- 2nd look: 17/52 (33%) No second look: 23/52 (46%)	Group A (n=52): second elective endoscopy 18-24 hours after emergency endoscopy; 2nd injection of adrenaline if visible vessel still identified (29 patients in whom vessel still visible; 59%)	Group B (n=52): no second look endoscopy	period of hospitalisation	Permanent haemostasis (initial haemostasis + no recurrence during hospitalisation); further haemorrhage (actively bleeding ulcer at repeat endoscopy OR vomiting fresh blood or bloody aspirates from nasogastric tube after clear lavages or fresh meleana plus signs of haemodynamic instability or fall in Hb requiring transfusion to	none stated

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
							maintain a level around 9g/dL); transfusion requirements; length of hospital stay; mortality	

	Group A (2nd look)	Group B (no 2nd look)
No. pts	52	52
Male	39	33
Female	13	19
Mean (SD) age (yr)	62.4 (16.4)	66.5 (13.5
NSAID use n (%)	21 (40%)	31 (60%)
Associated diseases	23 (44%)	31 (60%)
Mean (SD) Hb (g/dL)	10 (2.6)	9.5 (2.3)
Duodenal ulcer n (%)	34 (65%)	33 (63%)
Gastric ulcer n (%)	15 (29%)	12 (23%)
Stomal ulcer n (%)	1 (2%)	4 (8%)
Pyloric ulcer n (%)	2 (4%)	3 (6%)
Spurting n (%)	1 (2%)	3 (6%)
Oozing n (%)	16 (31%)	20 (38%)
Non-bleeding	35 (67%)	29 (56%)

Reference	Study type	No. pts	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			visible vessel n (%)						

Effect size

	Group A (n=52)	Group B (n=52)	p value	Difference (95%
Initial haemostasis	17/17 actively bleeding pts	21/23 (91%) actively bleeding pts; persistent bleeding in 2 cases; 1 treated with emergency surgery and 1 with 2nd emergency endoscopy (both these patients died)	0.636	
Further bleeding	11/52 (21%): 5/17 actively bleeding initially and 6/35 with non-bleeding visible vessel	13/50 initially controlled plus the 2 not controlled (15 in all 29%): 8/23 actively bleeding and 7/29 with non-bleeding visible vessel	0.36	-7.7% (-24.3 to +
Mean time to re-bleeding	67 hours (SD 41)	50 hours (SD 44)	0.364	
Emergency surgery	4 (8%)	8 (15%)	0.36	-7.7% (-19.9 to +
Mean (SD) units packed cells transfused	1.7 (1.9)	2.5 (2.5)	0.07	-0.8 (-1.6 to +0.0
Mean (SD) days hospital stay	9.3 (8.6)	11.8 (10.8)	0.19	-2.4 (-6.2 to +1.4
Mortality	1 (2%)	2 (4%)	1	

Authors' conclusion: The overall benefit, if any, of second-look endoscopy, with repeated injection of adrenaline if a visible vessel is still present, is unlikely to be very large.

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Messmann H, Schaller P, Andus T et al. Effect of programmed endoscopic follow-up examinations on the rebleeding rate of gastric or duodenal peptic ulcers treated by injection therapy: a prospective, randomized controlled trial. Endoscopy. 1998; 30(7):583-589. Ref ID: 4813	RCT, Germany Randomisation not stated, allocation concealment adequate, not blinded	107	Inclusion: Admitted with upper gastrointestinal bleeding; emergency endoscopy within 4 hours revealed peptic ulcer actively bleeding or signs of recent bleeding (treated with epinephrine and then fibrin glue). Exclusion: Failed initial endoscopic treatment, severe coagulopathy, malignant disease, under 18 years old, unable/unwilling to give consent. Clinically evident rebleeding: both groups treated with another emergency endoscopy and injection; second rebleeding, failure of second emergency endoscopy, or further haemorrhage with haemodynamic instability despite volume repletion all treated with surgery. Both groups had endoscopy after 1 week to take biopsies for Helicobacter pylori and histological examination of gastric ulcers to exclude malignancy; another endoscopy at 4 weeks to register healing Baseline characteristics: N (%) of spurting + oozing per group- 2nd look: 25/52 (48%) No second look: 21/53 (40%)	Group A (n=52) endoscopic monitoring with retreatment every 16-24 hours including injection therapy whenever an ulcer with Forrest criteria I (spurting arterial or oozing bleeding) or IIa (visible vessel) or IIb (adherent clot) was still present.	Group B (n=53) no scheduled second look endoscopy.	Duration of hospitalisation (at least 1 week)	Permanent haemostasis (cessation of bleeding and no recurrence during hospitalisation); recurrent bleeding: clinical (i.e. haematemesis or bloody aspirates after clear lavage from nasogastric tube, melaena plus haemodynamic instability or inadequate increase in Hb after transfusion) or endoscopic (fresh blood or clots in stomach or new clot on ulcer); surgery; transfusion	not stated

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td></td><td>Group A: 2nd endoscopy (n=52)</td><td>Group B: nc 2nd endoscopy (n=53)</td></tr>
<tr><td>Mean (SD) age (yr)</td><td>63.1 (6.2)</td><td>60.9 (5.9)</td></tr>
<tr><td>Male</td><td>29</td><td>34</td></tr>
<tr><td>Female</td><td>23</td><td>19</td></tr>
<tr><td>NSAID (%)</td><td>47</td><td>51</td></tr>
<tr><td>Additional diseases n (%)</td><td>27 (51.9%)</td><td>25 (47.1%)</td></tr>
<tr><td>Hb (g/dL) at baseline</td><td>10.3 (1.2)</td><td>9.8 (2.1)</td></tr>
<tr><td>Haematemesis (%)</td><td>10</td><td>7</td></tr>
<tr><td>Heart rate >100bpm or systolic BP <100mmHg (%)</td><td>60</td><td>54</td></tr>
<tr><td>Stomach ulcer (n)</td><td>22</td><td>24</td></tr>
<tr><td>Duodenal ulcer (n)</td><td>30</td><td>29</td></tr>
<tr><td>Ulcer size (cm)</td><td>1.3 (0.4)</td><td>1.1 (0.3)</td></tr>
<tr><td>Forrest classification (n)
Ia
Ib
IIa</td><td>
9
16
16</td><td>
7
14
17</td></tr>
</table>
</td><td></td><td></td><td></td><td>requirements; length of stay; mortality</td><td></td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			IIb	11	15					

Effect size

	Group A: 2nd endoscopy (n=52)	Group B: no 2nd endoscopy (n=53)	p value
Initial endoscopy:			
Epinephrine (mL)	5.4	5.2	NS
Fibrin glue (mL)	1.6	1.7	NS
Rebleeding n (%)			
Clinical	11 (21%)	9 (17%)	NS
Endoscopic (asymptomatic)	3 (6%) at 1 day after initial endoscopy	2 (4%) at 1 week after initial endoscopy	NS
Total	14 (27%)	11 (21%)	NS
Mean time to rebleeding from initial endoscopy (hours)	49 (6)	53 (7)	
Hospital stay (days)	14	12	NS
Blood units	3.5	3.1	NS
Emergency surgery n (%)	3 (5.7%)	2 (3.8%)	NS
Deaths	3 (1 as a direct result of bleeding; 2 other diseases); 5.9%	2 (other diseases); 3.9%	NS

Authors' conclusion:

Endoscopic monitoring of patients did not improve the rebleeding rate of endoscopically treated ulcer haemorrhage when the selection of patients for monitoring and prophylactic treatment was based on local ulcer stigmata alone.

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Chiu PW, Lam CY, Lee SW et al. Effect of scheduled second therapeutic endoscopy on peptic ulcer rebleeding: a prospective randomised trial. Gut. 2003; 52(10):1403-1407. Ref ID: 4815</td><td>RCT, Hong Kong

Randomisation method not stated; allocation concealment adequate, not blinded</td><td>194</td><td>Inclusion: Patients aged 15-90 years; bleeding peptic ulcers; primary endoscopy within 24 hours with successful haemostasis (cessation of bleeding plus achievement of cavitation over ulcer after injection of adrenaline plus heater probe); both groups received intravenous omeprazole 40mg every 12 hours for 3 days.
Exclusion: bleeding not controlled at primary endoscopy; no consent; bleeding from carcinoma of the stomach or other non-ulcer lesions; ASA grade 5.

Baseline characteristics:

N (%) of spurting + oozing per group-
2nd look: 43/100 (43%)
No second look: 46/94 (49%)

<table><tr><td></td><td>Control</td><td>2nd endoscopy</td><td>p valu</td></tr><tr><td>n</td><td>94</td><td>100</td><td></td></tr><tr><td>Mean (SD) age (yr)</td><td>67.5 (12.6)</td><td>68.7 (13.9)</td><td>0.53</td></tr><tr><td>Male</td><td>62</td><td>70</td><td>0.51</td></tr><tr><td>Female</td><td>32</td><td>30</td><td>0.51</td></tr><tr><td>Other illness (%)</td><td>69.1</td><td>65</td><td>0.54</td></tr><tr><td>Shock on admission n(%)</td><td>44 (46.8)</td><td>48 (48)</td><td>0.87</td></tr></table></td><td>Scheduled second endoscopy with appropriate therapy (injection of adrenaline plus heater probe if persistent spurting, oozing, visible vessel or adherent clot; used in 35% of patients) within 16-24 hours after initial endoscopy</td><td>Observed closely</td><td>30 days</td><td>Primary: recurrent bleeding (within 24 hours/1st week/1st 30 days) i.e. fresh haematemesis /blood in nasogastric tube; fresh melaena plus systolic BP <100mmHg or pulse >100bpm; drop in Hb >4g/dL wihtin 24 hours; transfusion >4 units wihtin 24 hours to maintain BP or Hb level. Secondary: number of operations performed (surgery when bleeding could not be stopped at</td><td>not stated</td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics				Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Prior peptic ulcer (n)	21	21	0.86				2nd scheduled endoscopy, clinical recurrent bleeding or failed emergency endoscopy after clinical recurrence), amount of transfusion, hospital stay, mortality	
			Mean (SD) Hb (g/dL)	9.4 (2.7)	8.9 (2.6)	0.33					
			Haemat-emesis (n)	13	13	0.87					
			Stomach ulcer (n)	40	44	0.84					
			Duodenum (n)	54	56	0.95					
			Ulcer size (cm)	0.9 (0.5)	1.0 (0.5)	0.088					
			Spurting (n)	14	10	0.55					
			Oozing (n)	32	33	0.55					
			Visible vessel (n)	27	37	0.55					
			Adherent clot (n)	21	20	0.55					
			H. pylori infection (n)	44	56	0.47					
			Use of aspirin (n)	6	12	0.18					

Effect size

	Control (n=94)	Intervention (n=100)	Relative risk (95% CI)	
Recurrent bleeding:				
Day 1	1	0	-	
Day 7	13 (13.8%)	4 (4%)	0.29 (0.09-0.92)	
Day 30	13 (13.8%)	5 (5.0%)	0.33 (0.11-0.96)	

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Successful endoscopic retreatment after recurrent bleeding				7/13	4/5		0.29 (0.03-3.37)	0.596
Surgery				6/13 (6.4% of total)	1/5 (1% of total)		0.15 (0.02-1.26)	0.050
Median (range) hospital stay (days)				4 (2-24)	4 (2-24)		-	0.109
Mean (SD) units transfused				2.1 (2.3)	1.9 (1.7)		-	0.44
Death within 30 days (%)				2 (2.1%)	2 (2%)		0.939 (0.13-6.80)	1.0
Morbidities (angina, MI, cardiac failure, wound infections, CVA)				6	3		0.45 (0.11-1.87)	0.32

Authors' conclusion:
Scheduled second endoscopy with appropriate therapy reduced the amount of recurrent bleeding from bleeding peptic ulcers.

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Rutgeerts P, Rauws E, Wara P et al. Randomised trial of single and repeated fibrin glue compared with	RCT, multi-centre European study Randomisation method not stated; allocation concealment	850	Inclusion: Patients aged 18 or older admitted with a bleeding gastroduodenal ulcer (spurting, oozing or non-bleeding visible vessel at endoscopy). Exclusion: simultaneous bleeding from two or more ulcers, malignant disorders of the upper gastrointestinal tract, coagulation disorders. Baseline characteristics:	Daily repeat endoscopies until ulcer base clean or covered with haematin; epinephrine injection; ranitidine. Single	Daily repeat endoscopies until ulcer base clean or covered with haematin, epinephrine injection; ranitidine. Standard	At least 5 days of daily endoscopies; 30 days for mortality, hospital outcome, safety	Primary endpoint: endoscopic rebleeding (spurting or non-spurting active bleeding, or visible vessel or ulcer with	not stated

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>injection of polidocanol in treatment of bleeding peptic ulcer. Lancet. 1997; 350(9079):692-696. Ref ID: 4812</td>
<td>adequate; non-blinded</td>
<td></td>
<td>
<table>
<tr><th></th><th>Polidocanol (n=281)</th><th>Fibrin glue single (n=285)</th><th>Fibrin glue repeated (n=284)</th></tr>
<tr><td>Male</td><td>191</td><td>189</td><td>200</td></tr>
<tr><td>Female</td><td>90</td><td>96</td><td>84</td></tr>
<tr><td>Median (range) age (yr)</td><td>67 (21-94)</td><td>66 (21-92)</td><td>66 (23-94)</td></tr>
<tr><td>Mean (SD) Hb (g/dL)</td><td>9.6 (2.3)</td><td>9.8 (2.4)</td><td>9.9 (2.4)</td></tr>
<tr><td>Mean (SD) pulse rate (bpm)</td><td>91 (17)</td><td>90 (17)</td><td>90 (18)</td></tr>
<tr><td>Stomach ulcer (%)</td><td>41.1</td><td>50.5</td><td>42.3</td></tr>
<tr><td>Duodenum (%)</td><td>49.5</td><td>43.5</td><td>53.2</td></tr>
<tr><td>Anastomotic (%)</td><td>6.4</td><td>6.0</td><td>4.6</td></tr>
<tr><td>Prior ulcer disease (%)</td><td>46.5</td><td>44.6</td><td>47.4</td></tr>
<tr><td>Prior bleeding (%)</td><td>21.9</td><td>22.9</td><td>23.0</td></tr>
<tr><td>Other ulcer complications (%)</td><td>5.0</td><td>2.6</td><td>4.4</td></tr>
<tr><td>Risk factor drugs</td><td>51.2</td><td>54.4</td><td>55.6</td></tr>
</table>
</td>
<td>application of fibrin glue or repeated application fibrin glue (daily prophylactic treatment until visible vessel disappeared; maximum 4 treatments)</td>
<td>therapy: polidocanol 1%</td>
<td></td>
<td>new fresh clot or fresh blood in lumen; treatment failure (assigned treatment not delivered or bleeding not stopped ro 2 episodes of recurrent bleeding); clinically relevant recurrent bleeding (fresh haematemesis, melaena, drop in Hb, tachycardia, fall in systolic blood pressure), two recurrences, rebleeding requiring surgery, death after</td>
<td></td>
</tr>
</table>

Reference	Study type	No. pts	Patient characteristics				Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			(mainly NSAIDs) (%)							rebleeding, adverse events.	
			Concomitant illness (%)	82.2	77.2	77.8					
			Systolic BP <90mmHg (%)	2.5	3.9	2.5					

Effect size

	Polidocanol (n=281)	Fibrin glue single (n=285)	Fibrin glue repeated (n=284)
No examination for recurrent bleeding done	21/281	14/285	10/284
N for intention to treat analysis	260	271	274
No initial haemostasis	6	5	4
Recurrent bleeding n (%)	58/254 who had initial haemostasis (22.8%)	51/266 who had initial haemostasis (19.2%)	41/270 who had initial haemostasis (15.2%), p=0.036 vs. pol group
Recurrent bleeding by original stratification of bleeding type n (%):			
Spurting	11/26 (42%)	11/25 (44%)	4/26 (15%), p=0.064 vs. polidocanol group in this stratum
Oozing	14/77 (18%)	10/82 (12%)	17/81 (21%)
Visible vessel	33/151 (22%)	30/159 (19%)	20/163 (12%), p=0.025 vs. polidocanol group in this stratum
Clinically relevant bleeding n (%)	46/254 (18.1%)	42/266 (15.8%)	27/270 (10.0%), p=0.011 vs. polidocanol group
Recurrent bleeding detected only by endoscopy n (%)	12/254 (4.7%)	9/266 (3.4%)	14/270 (5.2%)
Therapy failure n (%)	34/261 (13.0%)	34/274 (12.4%)	21/274 (7.7%), p=0.046 vs. polidocanol group
Further treatment: surgery	13/254 (5.1%)	13/266 (4.9%)	9/270 (3.3%)

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Mean amount of blood products after randomisation (units)			3.3 (3.9)	3.2 (4.2)	3.7 (5.8)			
30-day mortality n (%)			13 (4.7%)	15 (5.3%)	12 (4.3%)			

Authors' conclusion:
Repeated endoscopic injection of fibrin glue is more effective than a sclerosant (polidocanol) in the treatment of acute ulcer bleeding.

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Saeed ZA, Cole RA, Ramirez FC et al. Endoscopic retreatment after successful initial hemostasis prevents ulcer rebleeding: a prospective randomized trial. Endoscopy. 1996;	RCT, USA Randomisation method not stated; allocation concealment adequate, not blinded	40	Inclusion: major peptic ulcer haemorrhage (haematemesis or melaena or both, plus1 or more of syncope, hypotension [systolic BP<100mmHg], orthostatic changes in pulse [>20bpm] and BP [>20mmHg]). Endoscopy within 24 hours and therapy if active bleeding, visible vessel or fresh adherent clot. High risk patients: pre-endoscopy Baylor Bleeding Score >5 or pre-endoscopy score 5 or less but post-endoscopy score over 10; low risk pre-endoscopy score 5 or less. Exclusion: Low risk patients; high-risk patients but endoscopy not indicated; initial endoscopic haemostasis unsuccessful; moribund. Baseline characteristics: all men.	Re-treatment: 2nd endoscopy and treatment (heat probe alone or preceded by epinephrine injection) at 24 hours where necessary (in 16/19 patients; 3 patients had lesions with no raised	No re-treatment: no 2nd endoscopy (n=21)	Until hospital discharge	Treatment success (no recurrent re-bleeding); treatment failure (recurrent bleeding, i.e. haematemesis or blood per nasogastric tube or melaena after stools had returned to normal colour, plus decrease of at least 5%	not stated

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
28(3):288-294. Ref ID: 4814			Median (range) age (years)	62 (23-75)	70 (51-94)	areas and were not re-treated) (n=19)			in haematocrit, hypotension, continued transfusion requirements to maintain haematocrit 30% or above)	
			Median (range) pre-endoscopy score	7 (2-12)	7 (3-14)					
			Median (range) endoscopy score	5 (1-9)	5 (1-7)					
			Median (range) post-endoscopy score	12 (7-18)	12 (9-19)					
			Median transfusion units	3	2					
			Haematemesis n (%)	11 (58)	11 (53)					
			Melaena n (%)	19 (100)	20 (95)					
			Haematochezia n (%)	6 (31)	7 (32)					
			Duodenal ulcer n (%)	11 (58)	9 (43)					
			Gastric ulcer n (%)	6 (32)	12 (57)					
			Oesophageal ulcer n (%)	2 (10)	0					
			Active bleeding n (%)	13 (68)	14 (67)					
			Pigmented protuberance n (%)	3 (16)	6 (28)					
			Fresh adherent	3 (16)	1 (5)					

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			clot n (%) | | Taking aspirin/ NSAID n (%) | 7 (39) | 9 (42)					

Effect size

	Re-treatment	No re-treatment	p value
Re-bleeding n (%)	0	5 (24%	p<0.05
Transfusions for rebleeding (units)	0	0.9 (0.4)	p=0.02
Emergency surgery	0	0	
Deaths n (%)	1 (5%); multi-organ failure and sepsis 123 days later; no re-bleeding	2 (11%); 1 end-stage renal disease; 1 multi-organ failure	

Authors' conclusion:
Re-treatment at 24 hours after an initial successful endoscopic haemostasis was effective in preventing re-bleeding.

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Lau JY, Sung JJ,	RCT, Hong	92	Inclusion: Adults with bleeding peptic ulcers;	Endoscopic	Surgery	30 days	Duration of	not

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Lam YH et al. Endoscopic retreatment compared with surgery in patients with recurrent bleeding after initial endoscopic control of bleeding ulcers. N Engl J Med. 1999; 340(10):751-756. Ref ID: 4826</td><td>Kong

Randomisation method not stated; allocation concealment adequate, not blinded</td><td></td><td>endoscopy within 12 hours, treated with epinephrine and heater probe, successful if active bleeding stopped and flattening or cavitation of bleeding vessels; recurrent bleeding (haematemesis, hypotension [systolic BP 90mmHg or less or pulse 110 bpm or more], melaena, or requirement for >4 units of blood in 72 hour period after endoscopy.
Exclusion: patients dying of cancer.

Baseline characteristics:

<table><tr><td></td><td>Endoscopy</td><td>Surgery</td></tr><tr><td>Mean (SD) age (yr)</td><td>65 (17)</td><td>65 (15)</td></tr><tr><td>Male</td><td>37</td><td>33</td></tr><tr><td>Female</td><td>11</td><td>11</td></tr><tr><td>Other illness (n)</td><td>33</td><td>24</td></tr><tr><td>Bleeding during hospitalisation (n)</td><td>10</td><td>6</td></tr><tr><td>Hb (g/dL)</td><td>8.4 (2.6)</td><td>8.4 (2.9)</td></tr><tr><td>Median (range) units transfused before randomisation</td><td>4.5 (1-15)</td><td>5 (2-8)</td></tr><tr><td>Ulcer size (cm)</td><td>1.2 (0.7)</td><td>1.4 (0.9)</td></tr><tr><td>Duodenal ulcer</td><td>24</td><td>24</td></tr></table></td><td>retreatment (epinephrine and heater probe) n=48</td><td>(choice of operation left to surgeon: 22 partial gastrectomy, 12 vagotomy and pyloroplasty, 8 ulcer plication or simple ulcer excision, 2 with anastomotic ulcers had simple plication with completion of teh vagotomy and revision of the partial gastrectomy, respectively) n=44</td><td></td><td>hospitalisation; need for ICU; need for transfusion; treatment-related complications; 30-day mortality.</td><td>stated</td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			(n)							
			Gastric ulcer (n)	17	17					
			Anastomosis (n)	7	3					
			Positive rapid urease test (n)	20	22					
			NSAID use (n)	21	10 (NS)					
			Coagulopathy (n)	5	7					

Effect size

	Endoscopy (n=48)	Surgery (n=44)	p value
Median (range) hospitalisation (days)	10 (2-111)	11 (4-42)	0.59
Length of stay in ICU (days; not stated if mean or median) Number of patients	59 5	59 10	0.16
Median (range) units of blood transfused	8 (1-21)	7 (3-150)	0.27
Number of complications Number of patients with complications	22 7 (2 perforations due to heater probe)	28 16	0.03; odds ratio 3.45, 1.2-9.1
Haemostasis not achieved	4	-	-
Salvage surgery	13 (haemostasis not achieved at endoscopy or recurrent bleeding or ulcer perforation)	-	-
Post-operative bleeding recurrence	-	3	-
30 day mortality (number of patients) Abdominal sepsis Bronchopneumonia Acute MI	5 2 2	8 2 1 2	0.37

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Multi-organ dysfunction Hepatic failure Ventricular arrhythmia			1			1 1 1		

Authors' conclusion:

In patients with peptic ulcers and recurrent bleeding after initial endoscopic control of bleeding, endoscopic re-treatment reduces the need for surgery without increasing the risk of death and is associated with fewer complications than surgery.

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Ripoll C, Banares R, Beceiro I et al. Comparison of transcatheter arterial embolization and surgery for treatment of bleeding peptic ulcer after endoscopic treatment failure. J Vasc	Retrospective case review Country: Spain	70 (N=31 embolisation; N=39 surgery)	Inclusion: Patients who were referred for alternative treatment strategies because of bleeding recurrence or uncontrolled bleeding and inability to perform endoscopic therapy because of difficult access or insufficient visibility of the bleeding point. Exclusion: Incomplete patient records. Baseline characteristics: Patients with hypovolemic shock: embolisation 21/31 (67.7%)	Embolisation: embolotherapy was performed after diagnostic angiography even if no active bleeding was demonstrated. The gastroduodenal artery or left gastric artery was selectively catheterized with standard	Surgery: surgical intervention was performed according to standard procedures, most frequently truncal vagotomy with pyloroplasty and	period of hospitalisation	Recurrent bleeding (severe hypotension of presh hematemesis or melena requiring at least 2 U of packed red blood cells after the initial episode had resolved) transfusion requirements,	none stated

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Interv Radiol. 2004; 15(5):447-450.
REF ID: 4806</td><td></td><td></td><td>surgery 33/39 (84.6%)
Shaded cells indicate significant differences:
Numbers in parantheses are % unless otherwise stated
<table>
<tr><th></th><th>Embolisation</th><th>Surgery</th></tr>
<tr><td>No. pts</td><td>31</td><td>39</td></tr>
<tr><td>Age</td><td>75.2 (10.9)</td><td>63.3 (14.5)</td></tr>
<tr><td>Male</td><td>19</td><td>28</td></tr>
<tr><td>Underlying condition*</td><td>28 (90.3)</td><td>31 (79.5)</td></tr>
<tr><td>Cardiac disease</td><td>21 (67.7)</td><td>8 (20.5)</td></tr>
<tr><td>Liver disease</td><td>4 (12.9)</td><td>6 (15.4)</td></tr>
<tr><td>Cardiovascular risk factors</td><td>17 (54.8)</td><td>22 (56.4)</td></tr>
<tr><td>NSAID use</td><td>12 (38.7)</td><td>14 (35.9)</td></tr>
<tr><td>Anticoagulation treatment</td><td>8 (25.8)</td><td>2 (5.1)</td></tr>
<tr><td>Mean pre-treatment transfusions (SD)</td><td>5.8 (2.6)</td><td>6.1 (4.6)</td></tr>
<tr><td>Active hemorrhage</td><td>20 (64)</td><td>22 (56.4)</td></tr>
</table></td><td>performed angiographic catheters of microcatheters. Gelatine sponge particles and / or vascular coils (0.035-inch steel coils or platinum microcoils) were then released close to the bleeding site until cessation of agiographic extravasion and / or occlusion of the targeted vessel</td><td>oversewing truncal vagotomy with distal gastrectomy.</td><td></td><td>mean days of hospitalisation, surgery and death.</td><td></td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			at endoscopy Endoscopic treatment: 23 (64.2); 21 (53.8) *Cardiac disease, pulmonary illness, liver disease, neurological disease, renal – presence of an underlying condition was identified if the patient had any of these illnesses or cardiovascular risk factors.					

Effect size

Posttreatment outcomes:

	Embolisation (n=31)	Surgery (n=39)
Mean transfusion requirements (SD) (packed red cell units)	4.2 (4.6)	4.1 (4.2)
Mean days of hospitalisation (SD)	30.1 (24.6)	25.8 (20.8)
Recurrence of bleeding (%)	9 (29)	9 (23.1)
Surgery (%)	5 (16.1)	12 (30.8)
Death (%)*	8 (25.8)	8 (20.5)

*In the embolisation group four deaths were related to a bleeding episode and four related to underlying conditions. In the surgery group one death was related to a bleeding episode and eight to underlying conditions (note: these are the numbers reported in the articles but do not add up to the 8 reported in the table).

Authors' conclusion:

The lack of differences between the two treatments alternatives, despite the more advanced age and greater prevalence of heart disease, provides support for the need for future prospective randomised studies aimed to evaluate the role of embolotherapy in the management of refractory peptic ulcer bleeding.

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>Eriksson LG, Ljungdahl M, Sundbom M et al. Transcatheter arterial embolization versus surgery in the treatment of upper gastrointestinal bleeding after therapeutic endoscopy failure. J Vasc Interv Radiol. 2008; 19(10):1413-1418. REF ID: 4807</td>
<td>Retrospective case review

Country: Sweden</td>
<td>91 (N=40 embolization; N=51 surgery</td>
<td>Inclusion: patients with repeated bleeding or who continued to bleed after initial emergency endoscopic treatment
Exclusion: None stated.

Baseline characteristics:
Shaded cells indicate significant differences:
Numbers in parantheses are % unless otherwise stated (p values not stated)
<table>
<tr><th></th><th>Embolisation</th><th>Surgery</th></tr>
<tr><td>No. pts</td><td>40</td><td>51</td></tr>
<tr><td>Age</td><td>76 (10)</td><td>71 (12)</td></tr>
<tr><td>Male</td><td>18 (45)</td><td>32 (62)</td></tr>
<tr><td colspan="3">Comorbidities:</td></tr>
<tr><td>Ischemic heart disease</td><td>23(58)</td><td>24 (47)</td></tr>
<tr><td>Chronic obstructive pulmonary disease (COPD)</td><td>4 (10)</td><td>6 (12)</td></tr>
<tr><td>Hypertension</td><td>14 (35)</td><td>14 (27)</td></tr>
<tr><td>Cerebrovascular disease</td><td>0</td><td>7(14)</td></tr>
</table>
</td>
<td>Embolisation (n=40): a transfemoral approach was used in all cases by placing a 5-F introducer into the common femoral artery. The celiac trunk and superior mesenteric artery were selectively examined by using a 4-F catheter. The gstroduodenal or left gastric artery was then selectively catheterized by using a 3-F microcatheter system. In the beginning of the study, a few patients underwent embolization with catheter larger than 3 F</td>
<td>Surgery (n=51): emergency surgery with a Billroth II resection was performed in 29, duodenotomy or gastrotomy with simple over-sewing of the bleeding ulcer and / or artery was performed in 14 patients, repeat resection after previous Billroth II resection was performed in five patients, repeat resection after</td>
<td>period of hospitalisation</td>
<td>Total amount of transfusions required, length of hospital stay, post procedure complications and mortality rates</td>
<td>none stated</td>
</tr>
</table>

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			diabetes	9 (22)	6 (12)	to permit the use of 0.035-inch coils. Iodinated contrast medium was injected by hand at 5-10 mL per injection.	previous Billroth I resection was performed in one patient, and other surgical procedures were performed in two patients (explorative laparatomey, small intestine resection).			
			Endoscopic treatment	23 (64.2)	21 (53.8)					

Effect size

Posttreatment outcomes:

	Embolisation (n=40)	Surgery (n=51)
Failed to achieve primary hemostasis	10 (25)	9 (18)
median pre-treatment transfusions – red blood cells (range)	17 (3-15)	19 (0-90)
Median days in hospital	10 (3-43)	13 (2-67)
Second surgical procedure (from flow chart)	5 (12.5)	3 (5.9)
30 day mortality	1 (3)	7 (14) (described as p=0.07)

Adverse events

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

	Embolisation	Surgery
Postoperative abscess	0	3 (6)
Cardiopulmonary insufficiency	3 (8)	2 (4)
Leakage from anastomosis	1 (3)	3 (6)
Renal failure	1 (3)	2 (4)
Atrial fibrillation	3 (8)	2 (4)
No complications	32 (80)	32 (63)

Causes of death: embolization – multiorgan system failure; surgery – multiorgan failure (4 patients), myocardial infarction (1 patient), respiratory failure in one patient and septicaemia with shock in one patient

A Kaplan-Meier estimate showed that initial differences in mortality rates between the two groups were equalised after 1 year.

Authors' conclusion:

The results of this study suggest that embolization may be preferred over surgery in the treatment of upper gastrointestinal bleeding after failure of therapeutic endoscopy..

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Defreyne L, De S, I, Decruyenaere J et al. Therapeutic decision-making in endoscopically unmanageable	Retrospective case review Country: Belgium Patients undergoing	97 (N=46 embolization; N=51 surgery	Inclusion: All patients who underwent endoscopy for UGIH, followed within 24 h by a laparotomy or an arteriography, were candidates for inclusion. Patients were retrospectively traced in the 1993–2003 logbooks of the operation theatre and the computer database of interventional radiology.	Embolisation: Embolic agents used were coils (5 pts), gelfoam pledgets (6 pts), N-butyl 2-yanoacrylate (5 pts), and polyvinyl alcohol	Surgery: Surgical salvage consisted of undersewing a gastric or duodenal ulcer (36	period of hospitalisation	Primary rebleeding rates at 3 days (''very early rebleeding'') and 30 days were calculated, as well as,	none stated

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
nonvariceal upper gastrointestinal hemorrhage. Cardiovasc Intervent Radiol. 2008; 31(5):897-905. Ref ID: 4808	surgical exploration without hemostatic action or arteriography without embolization were included on an ''intention-to-treat'' basis.		Exclusion: patients with no documentation of an overtly bloody lumen at upper GI endoscopy within 24 h prior to the rescue intervention. Portal hypertensive and transpapillar bleedings as well as bleedings from malignancy were excluded as well. If patients had already received surgery or angiography for the same episode of UGIH at another hospital, they were excluded, too. Baseline characteristics: Critical care score systems, such as APACHE II, were applied to stratify patients in low- and high-risk groups: Not available: 10 (21.7%) TAE 15 (29.4%) Surgery Apache ≤15: 11 (23.9%) TAE 12 (23.5%) Surgery Apache ≥15: 25 (54.3%) TAE 24 (47.1%) Surgery Shaded cells indicate significant differences: Numbers in parantheses are % unless otherwise stated (p values not stated)	particles (2 pts). In 10 other patients, embolization required a combination of these occlusive agents.	pts), ligature of the gastroduodenal artery (4 pts), ulcer excision (2 pts), undersewing of a Dieulafoy lesion (1 pts), hemostasis of a mucosal bleeding (1 pts), removal of a bleeding polyp (1 pts), and Billroth II gastrectomy (1 pts).		clinical success, defined as the absence of UGIH after all therapy. Mortality was checked at the end of the hospitalization. Causality between death and acute UGIH was determined in consensus.	

	Embolisation	Surgery

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			No. pts	46	51					
			Age groups:							
			≤16	2	0					
			17-60	16	18					
			61-80	20	29					
			≥80	8	4					
			Male	18 (45)	32 (62)					
			Comorbidities:							
			No	8	15					
			1	30	28					
			>1	8	8					
			Intensive care							
			Yes	19	12					
			No	27	39					
			Forrest classification							
			Forrest I a / b	2/4	12/9					
			Forrest II a/b/c	0/2/1	9/3/2					
			Forrest III	3	2					

Effect size

Posttreatment outcomes N (%) – shaded cells significantly different group differences:

	Embolisation (n=46)	Surgery (n=51)
Failed to achieve primary hemostasis	6 (13)	6 (11.7)
3 day rebleeding*	20 (43.5)	4 (7.8)

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

30 day rebleeding	20 (43.5)	13 (25.4)
Median days in hospital	10 (3-43)	13 (2-67)
In hospital mortality	18 (39.1)	14 (27.5)

* significance taken from Forrest plot – not stated in the text.

Causes of death: embolization – therapy failure 6/18 the rest underlying disease or multiorgan system failure; surgery – therapy failure 6/14 the rest multiorgan failure or underlying illness

Authors' conclusion:

There were no significant differences in mortality between embolization and surgery.

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Wong TC, Wong KT, Chiu PW, et al. A comparison of angiographic embolization with surgery after failed endoscopic hemostasis to bleeding peptic ulcers. Gastrointest Endosc 2011 May;73:900-8. Ref ID: 119	Retrospective case review Country: China	N = 88 (N=32 embolisation N=56 surgery)	Inclusion: Patients with peptic ulcer bleeding in whom endoscopic hemostasis failed. Exclusion: not explicitly stated. Salvage intervention (either surgery or transarterial embolization) was deemed to be warranted if active bleeding could not be controlled by endoscopic means or if a patient had a second rebleeding episode. Baseline characteristics: None were significantly different : Numbers in parantheses are % unless	Embolisation – all angiographic procedures were performed with transfemoral catheterization by using a 5F sheath and catheter. A mesenteric angiogram would be performed with selective cannulation of the celiac axis	Surgery – choice of surgery was left to the discretion of the operating surgeon. Operative records were reviewed from patients' case notes	Length of case notes	Mortality (30 days) – and causes of mortality, rebleeding additional follow up treatments	All authors disclosed no financial relationships relevant to this publication

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td></td><td></td><td>otherwise stated
<table>
<tr><th></th><th>Embolisation</th><th>Surgery</th></tr>
<tr><td>No. pts</td><td>32</td><td>56</td></tr>
<tr><td>Age mean (sd)</td><td>73.1 (12.3)</td><td>71.1 (14.0)</td></tr>
<tr><td>Male</td><td>21 (65.6)</td><td>40 (71.4</td></tr>
<tr><td>>1 Comorbidities</td><td>28 (87.5)</td><td>49 (87.5)</td></tr>
<tr><td>In hospital bleeding</td><td>10 (31.3)</td><td>14 (25)</td></tr>
<tr><td>Fresh blood in stomach</td><td>25 (78.1)</td><td>41 (73.2)</td></tr>
<tr><td>GU:DU</td><td>7:25</td><td>20:36</td></tr>
<tr><td>SBP < 90 mm Hg at presentation</td><td>12 (37.5)</td><td>23 (41.1)</td></tr>
<tr><td>Hb < 10 g/dL at presentation</td><td>27 (84.4)</td><td>46 (82.1)</td></tr>
<tr><td>NSAID user</td><td>8 (25)</td><td>10 (17.9)</td></tr>
<tr><td>Ulcer size >2 cm</td><td>17 (53.1)</td><td>28 (50)</td></tr>
</table>
GU – gastric ulcer, DU – duodenal ulcer</td><td>and superior mesenteric artery to identify the site of contrast extravasation and to delineate vascular anatomy. If contrast extravasation was apparent, then a 3F microcatheter would be inserted coaxially for superselective cannulation of the bleeding artery. Vortex fibered platinum coil would be deposited to the bleeding artery in a distal to proximal manner until extravasation ceased together with complete occlusion of the</td><td></td><td></td><td></td><td></td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				bleeding vessel. In the absence of active extravasation, deposistion of coils would then be guided by hemoclips placed during endoscopy.				

Effect size:

Clinical outcomes – N (%)

	Embolisation (n=32)	Surgery (n=56)	p-value
Failed to achieve primary hemostasis	3 (11.5)	0	
30 day rebleeding	11	7	
Mortality (30 days)	8 (25)	17 (30.4)	0.77
Mean length of hospital stay total	24.5 (24.7)	26.1 (22.5)	0.32
Post procedure hospital stay	17.3 (18.2)	21.6 (21.0)	0.09
Blood transfusions (mean units)	15.6 (14.0)	14.2 (9.9)	0.60
No. of patients with complications	13 (40.6)	38 (67.9)	0.01

Authors' conclusions:

In patients with ulcer bleeding after failed endoscopic hemostasis, TAE reduces the need for surgery without increasing the overall mortality and is associated with fewer complications.

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Venclauskas L, Bratlie SO, Zachrisson K, et al. Is transcatheter arterial embolization a safer alternative than surgery when endoscopic therapy fails in bleeding duodenal ulcer? Scand J Gastroenterol 2010;45:299-304. Ref ID: 1124	Retrospective case review Country: Sweden	N = 74 (N=24embolisatin N=50 surgery)	Inclusion: patients who were treated with embolization or surgery for massive or recurrent bleeding from duodenal ulcer. Exclusion: incomplete patient records All patients with the exception of one man who had previously undergone a gastric bypass procedure underwent urgent therapeutic endoscopy. In cases of active bleeding or if signs of recent bleeding were presented endoscopic treatment was performed. The doctor performing endoscopy was free to choose any haemostatic method. All patients had acid-suppressive treatment after endoscopy and endoscopic re-treatment was not routinely done at either of the centres. Baseline characteristics: Unless otherwise stated expressed as N (%) or means (sd). Shaded cells indicate significant group differences.	Embolisation – diagnostic angiography preceded embolization and was performed using a 5-F Simons-type catheter inserted through a 6-F sheath placed in either the right or left common femoral artery. Selective e cathereterization of the gastoduodenal artery (GDA) was achieved and angiograms were made to demonstrate the anatomy of the GDA and its branches. Continued bleeding was defined as extravasation of contrast	Surgery – emergency duodenotomy and over-sewing of the ulcer/bleeding vessel with (n=8) or without (n=10) ligation of the GDA, as well as Billroth I (n=14) or Billroth II (n=18) resections were performed in the surgery group. The surgeon decided on an individual basis which type of operation was to be done.	Length of case notes	Mortality (overall as well as divided by APACHE II scores low/high), rebleeding, length of hospital stay, morbidity and surgical morbidity.	Authors declared no conflict of interest.

	Embolisation	Surgery

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			No. pts	24	50	medium into the lumen of the intestine or the appearance of a pseudoaneurysm-like lesion. Embolization was as superselective as possible. The material used for embolisation was glue (n=2), polyvinyl-alcohol substance (n=6) or coils (n=12).				
			Age mean (sd)	69.6 (16.1)	61.9(14.1)					
			Male	11	12					
			Haemoglobin on admissing (g/l)	76.0 (20)	81.8 (22.4)					
			Shock on admission	17/23*(73.9)	31 (62.0)					
			Concomitant disease	18 (75)	20 (40)					
			No of gastroscopies: 0 1 2 3 4	 1 6 6 9 2	 0 26 18 5 1					
			Active / recent bleeding at the first gastroscopy	10/13	36/14					
			Endoscopic treatment	15/23* (62.5)	39 (78.0)					
			APACHE II score	17.0 (5.1)	12.8 (5.7					

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			*total number of evaluated patients in cases with missing data.					

Effect size:

Clinical outcomes – N (%) or means (sd). Shaded cells highlight significant group differences

	Embolisation (n=24)	Surgery (n=50)	p-value
Overall hospital stay (days)	20.1 (15.0)	17.6 (13.9)	0.501
Hospital stay before procedure (days)	6.2 (4.1)	2.0 (2.25)	0.001
Hospital stay after procedure (days)	13.8 (14.9)	15.7 (13.5)	0.581
Rebleeding	3/20* (15.0)	4 (8)	0.659
Morbidity	13 (54.2)	27 (66.7)	0.989
Surgical morbidity	5 (20.8)	21 (42.0)	0.131
Mortality	5 (20.8)	11 (22.0)	0.909
Mortality for patients with APACHE II score < 16.5	1/10* (10.0)	4/36*	0.635
Mortality for patients with APACHE II score ≥ 16.5	3/13* (23.1)	7/14* (50.0)	0.236

*Total number of evaluated patients in case of missing data.

Authors' conclusions:

TAE of the gastroduodenal artery appears to be a safe alternative when endoscopic therapy for bleeding duodenal ulcers fails, at least in high-risk patients.

F.5 Control of bleeding and prevention of rebleeding

QUESTION In patients presenting with UGIB who are already on NSAIDs, Clopidogrel, Aspirin or dipyridamol (single or combination) what is the evidence that discontinuation compared to continuation of the medication leads to better outcome?

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Sung JJY, Tsoi KKF, Ma TKW et al. Causes of mortality in patients with peptic ulcer bleeding: A prospective cohort study of 10,428 cases. Am J Gastroenterol. 2010; 105(1):84-89.	Single centre RCT Country: China (Hong Kong) Single centre, parallel, placebo-controlled noninferiority trial, double blind, adequate allocation concealment ITT analysis	N = 156 (N=78 aspirin and N=78 placebo)	Inclusion criteria: Patients with peptic ulcer showing active bleeding, visible blood vessels, or adherent colts that were successfully treated by endoscopic therapy and continued to require low-dose aspirin (≤325 mg/d) for prophylaxis or treatment of cardiovascular diseases. The indications for low-dose aspirin included prophylaxis of established cardiovascular or cerebrovascular diseases that required regular antiplatelet therapy. Exclusions: Patients who received aspirin for primary prophylaxis and patients who had unsuccessful endoscopic hemostasis of bleeding ulcers; those with gastric outlet obstruction, ulcer perforation, known sensitivity to proton-pump inhibitors, or previous partial gastrectomy or vagotomy; those receiving concomitant anticoagulant, corticosteroid, and non-steroidal anti-inflammatory drugs; and those that were pregnant. Patients who received clopidogrel in conjunction with aspirin were not excluded, but clopidogrel therapy	Aspirin 80 mg once a day All patients received PPIs and had endoscopic therapy	placebo	8 weeks	Primary endpoint: Recurrent peptic ulcer bleeding within 30 days of endoscopic treatment (confirmed by endoscopic evidence). Secondary endpoints: all-cause mortality; death attributed to cardiovascular, cerebrovascular, or gastrointestinal complications; requirement of blood transfusion; duration of hospital stay (measured from day of recruitment);	Independent educational grant from the instituate of digestive disease, Chinese University of Hong Kong (independence of Pharma industry explicitly stated)

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td></td><td></td><td>was discontinued after randomization until the ulcer healed completely.

Baseline characteristics – no significant differences reported:
<table>
<tr><td></td><td>Aspirin (N=78)</td><td>Placebo (N=78)</td></tr>
<tr><td>Men (%)</td><td>48 (62)</td><td>49 (63)</td></tr>
<tr><td>Mean age (SD)</td><td>74 (9)</td><td>74 (8)</td></tr>
<tr><td colspan="3">ASA grade</td></tr>
<tr><td>1/2/3</td><td>0/43/34</td><td>0/50/26</td></tr>
<tr><td>4/5</td><td>1/0</td><td>2/0</td></tr>
<tr><td colspan="3">Indication for aspirin, n (%)</td></tr>
<tr><td>Cardiovascular disease</td><td>40 (52)</td><td>47 (60)</td></tr>
<tr><td>Cerebrovascular diseases</td><td>30 (38)</td><td>23 (30)</td></tr>
<tr><td>Both</td><td>8 (10)</td><td>8 (10)</td></tr>
<tr><td>Mean baseline hemoglobin level (SD), g/dl</td><td>9.1 (2.4)</td><td>8.4 (2.2)</td></tr>
<tr><td>Bled during</td><td>12 (15.3)</td><td>11(14.1)</td></tr>
</table></td><td></td><td></td><td></td><td>requirement of surgery; and recurrence of acute ischemic events (the acute coronary syndrome and cerebrovascular accident).</td><td></td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			hospital stay, n (%)							
			Endoscopic stigmata n (%)							
			Active bleeding	24 (31)	27 (35)					
			Visible vessel	35 (45)	32 (41)					
			Adherent clot	19 (24)	19 (24)					

Effect size

Post treatment outcomes – primary and secondary endpoints (shaded cells highlight significant group differences):

	Aspirin (n=78)	Placebo (n=78)	Difference (95% CI)*	Hazard Ratio (95% CI)
Suspected recurrent bleeding in 30 days	13 (16.8)	9 (12.0)	-	
Confirmed recurrent bleeding in 30 days	8 (10.3)	4 (5.4)	4.9 (-3.6 to 13.4)†	1.9 (0.6 – 6.0)
Median units of blood transfused (range)	2(0 – 10)	3(0-9)	0 (-1 – 0.0) ‡	
Surgery n (%)	0	1 (1.3)	1.3 (-6.5 – 12.1) †	
Median hospital stay (range)	5 (3-25)	4.5 (1 -45)	1 (0.0 – 1.0)‡	
Death, n (%) 30 days	1 (1.3)	7 (9)	7.7 (0.9 – 14.5) †	0.2 (0.05 – 0.90)
Death, n (%) 56 days	1 (1.3)	10 (12.9)	11.6 (3.7 – 19.5) †	0.2 (0.06 – 0.60)
Cause of death:				
Cardiovascular complications	1	5		0.2 (0.05 – 0.70)
Gastrointestinal complications	0	3		
Pneumonia	0	2		
Adverse events:				

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Acute ischemic events			2	4				
Other adverse events			14 (1 vasovagal attack, 1 type 2 respiratory failure, 1 seizure, 1 gout, 2 fever, 2 dizziness, 1 cough, 1 chest infection, 1 ankle edema, 1 anemia and 2 nausea and vomiting)	3 (1 hallucination, 2 chest infection)				

* When the difference is between 2 percentages, it is expressed as percentage points.

† 95% CIs are Kaplan-Meier estimates

‡ Difference in medians (95% CI of the difference)

Authors' conclusion

Among patients with peptic ulcer bleeding who received low-dose aspirin, continuous aspirin therapy may increase the risk for recurrent bleeding. However, antiplatelet agents potentially reduce overall mortality. Early resumption of low-dose aspirin therapy with PPIs in patients with bleeding ulcers and cardiovascular disease should be considered.

F.6 Primary prophylaxis

QUESTION For acutely ill patients in high dependency and intensive care units are Proton Pump Inhibitors (PPIs) compared to H2-receptor antagonists and / or placebo more clinically effective in the primary prophylaxis of Upper Gastrointestinal Bleeding (UGIB)?

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Apte NM et al. Gastric colonization and pneumonia in intubated critically ill patients receiving stress ulcer prophylaxis: A randomized, controlled trial. Critical Care Medicine. 1992; 20: 590-593. Ref ID: 142</td><td>RCT, India

Randomisation and allocation concealment unclear</td><td>34; ranitidine 16; no prophylaxis 18</td><td>Inclusion criteria: Patients admitted to intensive care units with tetanus and tracheotomy
Exclusion: Patients with pneumonia before tracheostomy or ranitidine prior to randomisation

Baseline characteristics:
<table>
<tr><th></th><th>Ranitidine</th><th>Control</th></tr>
<tr><td>n</td><td>16</td><td>18</td></tr>
<tr><td>Male</td><td>12</td><td>11</td></tr>
<tr><td>Female</td><td>4</td><td>7</td></tr>
<tr><td>Median age (yr) (range)</td><td>27 (10-55)</td><td>26 (11-68</td></tr>
<tr><td>Median maximum tetanus severity score (17)*</td><td>11 (4-16)</td><td>10 (6-16)</td></tr>
<tr><td>Days intubation</td><td>7.5 (3-28)</td><td>12.5 (3-6</td></tr>
<tr><td>Patients requiring mechanical ventilation</td><td>5</td><td>4</td></tr>
</table>
* ≥4 mild, 5-10 moderate and 10-20 severe tetanus</td><td>Ranitidine (H_2-RA) 50 mg i.v. every 6 hrs</td><td>No ranitidine or antacids</td><td>Until 48 hours after tracheal extubation.</td><td>Mortality, upper GI bleeding (bright red or altered blood per nasogastric tube or occult blood on benzidine test;aeronbic bacterial culture of tracheal secretions and gastric aspirates; pneumonia; pH level (not reported here)</td><td>Seth GS Medical College and KEM Hospital Research Society (Torrent Pharmaceuticals provided ranitidine)</td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Effect size

Post treatment outcomes:

	Ranitidine (n=16)	Control (n=18)	p value
Gross gastric bleeding Occult bleeding	5 13	6 10	NS
Blood transfusion	0	0	NA
Median gastric pH	4.7 (3.6-6.1)	2.1 (1.2-4.9)	p<0.05
Gastric colonisation Time of gastric colonisation (median; range)	15 2 days (1-5)	18 4 days (1-9)	not stated p<0.05
Pneumonia Time of pneumonia (median; range)	13 3 days (1-5)	9 5 days (3-14)	p<0.05 p<0.01

Authors' conclusion

Increasing the gastric pH increased the risk of pneumonia in intubated critically ill patients and pneumonia occurs earlier than in control patients; there was no difference in gastrointestinal haemorrhage.

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Ben-Menachem T, Fogel R, Patel RV et al. Prophylaxis for stress-related gastric	RCT, USA Randomisation adequate (permuted block design),	Placebo = 100, Cimetidine = 100	Inclusion criteria: All patients admitted to the medical ICU – even though admitted to the ICU 15% in the control group and 10% in the cimetidine group had no risk factors for stress-related hemorrhage (NS).	Cimetidine (H_2-RA) the dose was titrated to maintain	Patients did not receive antacids, sucralfate, omeparzole or H_2-RA treatment	Until hospital discharge	Primary endpoint: substantial hemorrhage from stress gastritis (investigators	Partly supported by a Henry Ford Hospital Research

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>hemorrhage in the medical intensive care unit. A randomized, controlled, single-blind study. Ann Intern Med. 1994; 121(8):568-575. Ref ID: 5255</td><td>allocation concealment unclear (sealed envelopes)

Power analysis was carried out

At the second research committee meeting termination of the study was recommended because of low conditional power</td><td></td><td>Exclusion: expected stay of 24 hrs or less; evidence of gastrointestinal bleeding at the time of admission to ICU; treatment with antacids, H_2-RAs, sucralfate or omeprazole during the 24 hrs before entering the ICU; use of NSAIDs, systemic anticoagulants or thombolytic agents during the 7 previous days; surgery requiring general anaesthesia during the previous 2 weeks; closed head injury or clinical evidence for increased intracranial pressuer; grade 4 hepatic encephalopathy; esophageal or gastric surgery in the previous year; history of gastrointestinal bleeding during the previous year; pregnancy; several ICU admissions during study period.

Baseline characteristics – no significant differences:
<table><tr><td></td><td>Cimetidine</td><td>Placebo</td></tr><tr><td>n</td><td>100</td><td>100</td></tr><tr><td>Male</td><td>51%</td><td>51%</td></tr><tr><td>Admission for AE</td><td>66%</td><td>61%</td></tr><tr><td>Age (yr)</td><td>59.0 (18.1)</td><td>59.6 (18.</td></tr><tr><td>Mean risk factor score</td><td>2.5 (1.8)</td><td>2.0 (1.5)</td></tr></table></td><td>gastric pH equal to or greater than 4.0. if two consecutive gastric pH values were less than 4.0, the dose was increased by the following amounts based on creatinine clearance: 300 mg/d, 200mg/d, and 100 mg/d. the maximum allowabl</td><td>(placebo treatment not specified)</td><td></td><td>blinded)

Adverse drug effects

Secondary endpoints: Nosocomial pneumonia; totoal transfusion requirements, recurring hemorrhage, duration of hospitalisation, death in the ICU, duration of ventilation</td><td>and Enducation fund</td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			APACHE II score	18.0 (8.0)	16.5 (6.9	e cimetidine doses for the patients grouped by renal function were 2400 mg/d, 1600 mg/d, and 800 mg/d. gastric pH was checked every 2 hrs.				
			APACHE score >20	33%	32%					
			Ventilation	76%	65%					

Effect size

Post treatment outcomes:

	Placebo (N=100)	Cimetidine (N=100)	p value
Clinically important bleeding	13	16	NS
Nosocomial pneumonia	6	13	0.09
Death: During ICU stay During hospital stay	 11 19	 19 28	 NS NS

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
ICU stay – median (range)			3 (2 to 8)		4 (2 to 9)		NS	
Hospital stay – median (range)			10 (6 to 18.5)		12 (5 to 18)		NS	
Transfusion requirements (packed red blood cells)			1.2 (1.4)		1.6 (1.3)		NS	
Ventilator (days)			7.9 (9.6)		8.1 (11)		NS	

Authors' conclusion
The observed effect of cimetidine on the incidence and severity of hemorrhage from stress-related gastritis were not significant when compared with not treatment.

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Burgess P, Larson GM, Davidson P et al. Effect of ranitidine on intragastric pH and stress-related upper gastrointestinal bleeding in patients with severe head injury. Dig Dis Sci. 1995; 40(3):645-650. Ref ID: 5254	RCT, single centre USA Randomisation sequence generation adequate (computer generated),allocation concealment unclear, double blind	Placebo = 18, Ranitidine = 16	Inclusion criteria: Adults with severe head injury and a Glasgow coma scale score ≤ 10 admitted to ICU. Exclusion: Patients with concomitant peptic ulcer disease, other gastrointestinal injury, receiving antiulcer therapy, or having any oral intake. All patients were comatose on admission and required ventilatory support. There were no significant differences in the number or type of risk factors and	Within 24 hrs of injury 6.25 mg/hr continuous intravenous ranitidine infusion (prepared by diluting 150 ;mg	Continuous saline transfusion	24 hrs	Primary endpoint: pH level Secondary endpoints: gastrointestinal bleeding, mortality	Grant from Glaxo Inc Research Institute

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td></td><td></td><td>all patients had at least two risk factors (e.g., mechanical ventilation, multiple trauma, organ system failure, coagulopathy, surgery).

Baseline characteristics – no significant differences:
<table>
<tr><th></th><th>Ranitidine</th><th>Placebo</th></tr>
<tr><td>n</td><td>18</td><td>16</td></tr>
<tr><td>Male</td><td>11</td><td>14</td></tr>
<tr><td>Mean age (SEM)</td><td>38.4 (4.5)</td><td>34.5 (3.7)</td></tr>
<tr><td>Mean Glasgow coma scale score (range)</td><td>8 (4-10)</td><td>6.7 (3-10)</td></tr>
<tr><td>Injury severity score (range)*</td><td>32 (25-41)</td><td>30 (25-57)</td></tr>
</table>
*This score was not described in the text or table caption.</td><td>of parenteral rantitine to a volume of 240 ml with 0.9% sodium chloride and delivered at a rate of 10 ml/hr (150 mg/d)</td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="9">Effect size
Relevant post treatment outcomes (numbers in bold represent significant group differences):
<table>
<tr><th></th><th>Placebo (N=100)</th><th>Cimetidine (N=100)</th><th>p value</th></tr>
<tr><td>Death</td><td>0</td><td>1</td><td>NS</td></tr>
<tr><td>Evidence of bleeding</td><td>0</td><td>5</td><td><0.05</td></tr>
</table></td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Authors' conclusion 6.25 mg continuous ranitidine infusion provided consistent intragastric pH control and effective prophylaxis against stress-related upper gastrointestinal bleeding.								

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Chan KH, Lai ECS, Tuen H, Ngan JHK, Mok F, Fan YW, Fung CF, Yu WC. Prospective double-blind placebo-controlled randomised trial on the use of ranitidine in preventing postoperative gastroduodenal complications in high risk neurosurgical patients. Journal of Neurosugery 1995; 82: 413-417.	RCT, Hong Kong. Randomised in a "standard double-blind manner". No mention of allocation concealment or method of randomisation.	101	Inclusion: patients suffering from nontraumatic neurosurgical lesions with 2 or more risk factors for UGIB. Exclusion: presence of UGIB before neurosurgery, PMH of chronic gastro-duodenal diseases or chronic ulcers, identified at endoscopy, concomitant major illnesses such as heart, lung, and kidney, haematological and liver problems. Baseline characteristics: No statistical testing performed, but groups appear well-matched.	Raniditine 50mg administered intravenously every 6 hours, starting on call to the operating theatre and continued into the post-operative period. The dose was changed to twice daily doses of oral ranitidine when the patients	Placebo 50mg, identical in appearance and volume to the raniditine, administered intravenously every 6 hours, starting on call to the operating theatre and continued into the post-operative period. The dose was changed to twice daily	6 months	Post operative UGIB, as shown on endoscopy or abdominal surgery performed if there were signs of bleeding- ie: coffee ground/frank blood in NG aspirate, malena, decreased Hb conc, hypovoleamic shock or abdominal pain. Need for	University of Hong Kong Research Grant and Lee Wing Tat Research Grant.

	Ranitidine	Placebo
Males	26/49	28/52
Age (range)	61 (17-84)	61 (32-89
Median number risk factors (ran.)	2 (2-5)	2 (2-5)
Median preop GCS (range)	6 (3-8)	6 (3-8)
Pathology		
Vascular	36/49	33/52
Tumor	14/49	15/52

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Infection hydrocephalus	2/49 7/49	1/52 3/52	were deemed ready for enteric feeding. Concomitant meds also given – dexamethasone 4mg /6 hrs, and a single dose of ceftriaxone	doses of oral ranitidine when the patients were deemed ready for enteric feeding. Concomitant meds also given – dexamethasone 4mg /6 hrs, and a single dose of ceftriaxone		blood transfusion Adverse events	
			Lesion location Supratentorial Basal ganglia and suprasellar Posterior fossa	 19/49 13/49 17/49	 24/52 14/52 14/52					
			Operation Shunt/ventriculostomy Craniotomy Post fossa exploration	 37/49 20/49 8/49	 37/52 26/52 7/52					
			All underwent emergency neurosurgery, after which all were managed according to a standard regimen that included artificial ventilation with muscle paralysis using pancuronium and sedation with midazolam.							

Effect size

	Ranitidine	Placebo	p value
UGIB – bleeding UGI lesions Non bleeding UGI lesions No UGI lesions	9/49 30/49 10/49	21/52 24/52 7/52	<0.05
Need for blood transfusion (decided on whether bled or not)	9/49	21/52	<0.05

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Adverse events Chest infections			18/49	11/52	>0.05			
Authors' conclusion: Ranitidine is useful in preventing postoperative GD complications in high-risk neurosurgical patients.								

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Conrad SA, Gabrielli A, Margolis B et al. Randomized, double-blind comparison of immediate-release omeprazole oral suspension versus intravenous cimetidine for the prevention of upper gastrointestinal bleeding in critically ill patients. Crit Care Med.	RCT, USA Double blind; intention-to-treat; randomisation and allocation concealment not stated	359	Inclusion criteria: 16 years or older; in ITU with anticipated stay 72 hours or more; required mechanical ventilation for 48 hours or more; had an Acute Physiology and Chronic Health Evaluation (APACHE II) score 11 or more at baseline; intact stomach with nasogastric or orogastric tube and at least 1 other risk factor for upper GI bleeding (closed head injury, multiple trauma, major surgery, extensive burns, acute renal failure, acid-base disorder, coagulopathy, marked jaundice, coma, hypotension, shock, sepsis). Exclusion: no CPR; delay >48 hours from initial eligibility; history of gastric surgery; allergy to study drug; active gI bleeding; significant risk of swallowing blood (e.g. facial trauma)enteral feeding required for 1st 2 days of trial; admission for GI surgery; known GI lesions that might bleed (e.g. varices); inability to take suspension by nasogastric	immediate-release omeprazole (PPI) 40mg at 0 and 6-8 hours, then daily	intravenous cimetidine (H2 receptor antagonist) 300mg loading dose then 50mg/hr (or 25mg/hr if creatinine clearance <30mL/min)	Median 108.9 hours for omeprazole and 109.8 hours for cimetidine	1ry: clinically significant GI bleeding (bright red blood not clearing after tube adjustment and 5-10 mins lavage; 8 hrs persistent Gastroccult-positive coffee-grounds material with aspirates not clearing with lavage on days 1-2; or	Santarus, San Diego, CA

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>2005;
33(4):760-765.
Ref ID: 5214</td><td></td><td></td><td>tube; end stage liver disease.

Baseline characteristics:
<table>
<tr><td></td><td>Omeprazole</td><td>Cimetidine</td></tr>
<tr><td>n</td><td>178</td><td>181</td></tr>
<tr><td>Age 65 yr or over</td><td>64 (36%)</td><td>64 (35%)</td></tr>
<tr><td>Male</td><td>105 (59%)</td><td>105 (58%)</td></tr>
<tr><td>Female</td><td>73 (41%)</td><td>76 (42%)</td></tr>
<tr><td>At least 3 risk factors</td><td>123 (69%)</td><td>117 (65%)</td></tr>
<tr><td>APACHE II score</td><td>24.7 (7.5)*</td><td>22.7 (7.1)*</td></tr>
<tr><td>Baseline gastric pH 4.0 or less</td><td>45 (25%)</td><td>47 (26%)</td></tr>
</table>
*p=0.01 (higher APACHE II score = worse prognosis)</td><td></td><td></td><td></td><td>persistent Gastroccult-positive coffee-grounds material over 2-4 hrs on days 3-14 in 3 consecutive aspirates not cleared with lavage.
2ry: gastric pH, % pts with pH>4; % pts with inadequate gastric pH control; nosocomial pneumonia</td><td></td></tr>
<tr><td colspan="9">Effect size
<table>
<tr><td></td><td>Omeprazole</td><td>Cimetidine</td><td>p value</td></tr>
<tr><td>Clinically significant bleeding</td><td>7/178 (3.9%)</td><td>10/181 (5.5%)</td><td>NS</td></tr>
<tr><td>Transfusion</td><td>5 pts</td><td>5 pts</td><td>-</td></tr>
<tr><td>Any overt bleeding</td><td>34 (19.1%)</td><td>58 (32.0%)</td><td>p=0.005</td></tr>
<tr><td>Nosocomial pneumonia</td><td>20 (11.2%)</td><td>17 (9.4%)</td><td>NS</td></tr>
<tr><td>Death</td><td>27 (15.2%)</td><td>21 (11.6%)</td><td>NS</td></tr>
</table>
Authors’ conclusion</td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Immediate-release omeprazole suspension is effective in preventing upper gastrointestinal bleeding and more effective than cimetidine in maintaining gastric pH of >4 in critically ill patients.								

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Friedman CJ et al. Prophylaxis of upper gastrointestinal hemorrhage in patients requiring mechanical ventilation. Critical Care Medicine 1982; 10: 316-319. Ref ID: 5259	RCT, USA Randomisation and allocation concealment unclear	36; Placebo = 14, Cimetidine = 11 (and another group of 11 patients receiving antacid called Mylanta II not reported here)	Inclusion criteria: Patients receiving mechanical ventilation <12 hours Exclusion: Patients with upper GI bleeding, creatinine >3mg/dL, antacids and/or cimetidine immediately before ventilation, pregnant Baseline characteristics: n: 11 Cimetidine, 14 Placebo Duration of ventilation (unclear if mean or median; no range or SD given): 6.2 days Cimetidine, 9.2 days Placebo Baseline age, gender, number of risk factors etc not stated; stated to be comparable.	Cimetidine (H_2-RA) 300 mg i.v. every 6 hrs.	Placebo	Until gastrointestinal bleeding, weaned off ventilator or died	Mortality, upper GI bleeding (overt = fresh or old blood in nasogastric aspirate even after lavage, or melaena; occult = drop in haematocrit of 5 or more points plus positive stool tests for occult blood for 3 consecutive days without obvious non-upper GI bleeding)	Drugs provided by Smith Kline & French Laboratories, Philadelphia, PA
Effect size Post treatment outcomes:								

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

	Placebo (N=14)	Cimetidine (N=11)	p value
Complications of therapy: diarrhoea	5	5	NS
Gastrointestinal bleeding	5/14	1/11	NS

Authors' conclusion

Prophylactic therapy (cimetidine or antacids) is associated with a lower frequency of gastrointestinal haemorrhage than when no medication is given (based on comparison with patients who could not tolerate antacids and they were withdrawn, not randomised comparison).

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Groll A, Simon JB, Wigle RD et al. Cimetidine prophylaxis for gastrointestinal bleeding in an intensive care unit. Gut. 1986; 27(2):135-140. Ref ID: 759	RCT, Canada Double-blind	221	Inclusion criteria: Admitted to general medical-surgical ITU with at least one of the following risk factors: major operative procedure, respiratory failure, sepsis, shock, trauma, soma, renal failure, liver failure. Exclusion: bleeding on admission to ITU; pregnancy; renal failure requiring dialysis; drug overdose; acute myocardial infarction; use of antacids; stay on ITU <24 hours; no consent; death within 24 hours NB These patients may not be sick enough to include: most patients only had 1 risk factor for bleeding, and most of these were major operative procedure, not the ones listed in the protocol Baseline characteristics:	Intravenous cimetidine (H2RA) 300mg every 6 hours	Placebo	Followed until bleeding or discharge: 70% of patients in study 1-3 days; maximum 23 days	Bleeding (frank haematemesis or gastric aspirate >50mL fresh blood; melaena or fresh blood per rectum with upper GI source confirmed by endoscopy if gastric aspirate clear; fall in Hb	Smith Kline and French Canada Ltd

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td></td><td></td><td>Cimetindine: 45 patients had 1 risk factor
33 had 2 risk factors
36 had 3 or more risk factors
PPI: 40 patients had 1 risk factor
35 had 2 risk factors
32 had 3 or more risk factors

<table><tr><td></td><td>Cimetidine</td><td>Placebo</td></tr><tr><td>n</td><td>114</td><td>107</td></tr><tr><td>M:F</td><td>68:39</td><td>75:39</td></tr><tr><td>Mean age (yr)</td><td>57</td><td>58</td></tr><tr><td>Age range (yr)</td><td>15-88</td><td>16-90</td></tr></table></td><td></td><td></td><td></td><td>>2g/dL in 24 hours with 4+ occult blood in stools or coffee ground gastric drainage at least 100mL.</td><td></td></tr>
<tr><td colspan="9">Effect size
<table><tr><td></td><td>Cimetidine</td><td>Placebo</td><td>p value</td></tr><tr><td>Bleed</td><td>11 (10%)</td><td>6 (5%)</td><td>NS</td></tr><tr><td>Mean volume packed cells transfused (range)</td><td>600mL (0-900mL)</td><td>550mL (0-1200mL)</td><td>not given</td></tr><tr><td>Death</td><td>13 (12%)</td><td>13 (11%)</td><td>NS</td></tr></table>
Authors' conclusion
Cimetidine should not be prescribed prophylactically to all patients entering a general medical-surgical ITU due to the lack of statistical benefit over placebo.</td></tr>
</table>

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Halloran LG et al. Prevention of acute gastrointestinal complications after severe head injury: A controlled trial of cimetidine prophylaxis. Ref ID: 5260</td><td>RCT, USA

Randomisation and allocation concealment adequate</td><td>Placebo = 24, Cimetidine = 26</td><td>Inclusion criteria: Patients admitted to intensive care units with severe closed head injury within last 12 hours; unable to obey simple commands
Exclusion: Patients with apnoea, fixed dilated pupils, no motor response to painful stimuli, peptic ulcer disease, pregnant, concomitant injury of upper gastrointestinal tract or severe hepatic or renal disease.

Baseline characteristics – no significant differences – no standard deviations given:
<table>
<tr><td></td><td>Cimetidine</td><td>Placebo</td></tr>
<tr><td>n</td><td>26</td><td>24</td></tr>
<tr><td>Male</td><td>23</td><td>18</td></tr>
<tr><td>Female</td><td>3</td><td>6</td></tr>
<tr><td>Mean age (yr) (range)</td><td>29.6 (15-54)</td><td>30.6 (8-6</td></tr>
</table></td><td>Cimetidine (H_2-RA) 300 mg i.v. every 4 hrs; changed to oral when tube feeding or diet started.</td><td>Placebo</td><td>3 weeks where possible</td><td>Upper GI bleeding (bright red blood or persistent guaic 4+ positive nasogastric aspirate continuous for 3 8-hour periods excluding 1st day of injury and no oropharyngeal source of bleeding); classified as marked (transfusion of 2 or more units required within 24 hours to stabilise haematocrit) or mild/moderate or absent; hourly gastric acid output and volume; endoscopy (in 25/50 patients)</td><td>Not stated</td></tr>
<tr><td colspan="9">Effect size</td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Post treatment outcomes:

	Placebo (N=24)	Cimetidine (N=26)	p value
Gastrointestinal bleeding Severe Mild/moderate	18 (75%) 8 10	5 (19%) 2 3	p=0.001
Units of blood required	41	11	not stated
Study medication stopped because of bleeding	7	3	not stated
Mean duration of study drug	10 days	20 days	not stated
Gastric pH ≥3.5 at 3 days	18%	65%	not stated
Gastric pH ≥3.5 at 6 days	12%	57%	not stated
Endoscopy (n) No lesion Gastritis Ulcers	11 4 (36%) 6 (55%) 1 (18%)	14 6 (43%) 5 (36%) 3 (21%)	not stated
Good neurological recovery	9 (37.5%)	10 (38.5%)	not stated
Moderate to severe neurological disability	5 (20.8%)	8 (30.8%)	not stated
Dead or vegetative	10 (41.7%)	8 (30.8%)	not stated

Authors' conclusion

Cimetidine prophylaxis significantly reduced risk of gastrointestinal bleeding after severe head injury without adverse effects.

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hanisch EW et al. A randomized, double-blind trial for stress ulcer prophylaxis shows no evidence of increased pneumonia. Am J Surg 1998; 176: 453-457. Ref ID: 5263	RCT, Germany Randomisation and allocation concealment adequate	Placebo = 293, Ranitidine = 255 (and pirenzipine 279, not considered here)	Inclusion criteria: Patients admitted to intensive care units Exclusion: Patients with upper GI bleeding, active peptic ulcer disease and medication, < 18 years old, transplant, pre-existing pneumonia, gastric resection Baseline characteristics:	Ranitidine (H_2-RA) 3 x 50 mg	Placebo	Unclear	1ry: pneumonia if mechanical ventilation ≥48 hours 2ry: clinically relevant stress bleeding (bright red bleeding per nasogastric tube or melaena plus haemodynamic changes and need for transfusion and endoscopic identification of bleeding site)	Not stated

	Ranitidine	Placebo
n	57	57
Mean age (yr) (range)	55 (22-88)	58 (22-88
APACHE II score	19 (2-30)	18 (1-28)

Effect size

Post treatment outcomes:

	Ranitidine (N=57)	Placebo (N=57)	p value
ICU stay (days)	9.7 (2-95)	12.6 (2-58)	p=0.02
Days mechanical ventilation	8.2 (2-93)	10.2 (2-55)	p=0.01
Pneumonia	10	12	NS
Stress bleeding	3	2	Number too small to assess
Death	7	12	Not stated

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Authors' conclusion H2 receptor antagonists with the dosage used do not increase the pneumonia risk of long-term ventilated patients in critical condition.								

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Kantorova I, Svoboda P, Scheer P et al. Stress ulcer prophylaxis in critically ill patients: A randomized controlled trial. Hepatogastroenterology. 2004; 51(57):757-Gastroenterology. Ref ID: 1490	RCT, Czech Republic Randomisation and allocation concealment adequate; double-blind; intention-to-treat	287	Inclusion criteria: 18 years or older; polytrauma or major intra-abdominal or intrathoracic surgery; admitted to ITU; projected to require mechanical ventilation for at least 48 hours or had coagulopathy and nasogastric tube. Exclusion: expected stay in ITU <48 hours; history of oesophagogastric surgery; bleeding on admission or during previous year; pneumonia; PPI, H2RA, antacids or sucralfate in previous 72 hours; peptic ulcer disease in last year; anticoagulants, high-dose oral steroids or thrombolytic in previous week; renal insufficiency requiring haemodialysis; thrombocytopenia <30,000/mL; life expectancy <3 months; no consent. Baseline characteristics:	IV omeprazole (PPI) 40mg daily OR IV famotidine (H2RA) 40 mg twice daily OR sucralfate 1g 6-hourly	Placebo	To hospital discharge (duration not stated)	Clinically important haemorrhage: overt bleeding plus at least 1 of: drop of systolic BP 20mmHg or more or increase of pulse 20 bpm or more within 24 hours of upper GI bleeding; or decrease in Hb 2g/dL or more, both in the absence of any other reason. Pneumonia on chest X-ray	Grant of IGA MZ CR ND 5932-3/2000

	Omeprazole	Famotidine	Sucralfate	Placebo
n	72	71	69	75
Male	48 (67%)	44 (62%)	50 (72%)	50 (67%)
Age (yr)	44 (15)	47 (17)	51 (18)	46 (19)

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			APACHE II: 17.5 (8.6) / 19.1 (9.3) / 18.8 (8.1) / 18.1 (9.3)				plus at least 1 of: purulent tracheal aspirate (>25 leucocytes per low power field); peripheral leucocytosis (>11 x 109/L or >10%bands); central body temp >38.5°C; isolation of respiratory pathogens; positive blood or pleural fluid culture. Death	

Effect size

	Omeprazole	Famotidine	Sucralfate	Placebo	p value
Clinically important bleeding	1 (1%)	2 (3%)	3 (4%)	1 (1%)	NS
Nosocomial pneumonia	8 (11%)	7 (10%)	6 (9%)	5 (7%)	NS
Death on ITU	9 (12.5%)	10 (14.2%)	9 (13.0%)	8 (10.7%)	NS
Death before hospital discharge	14 (19.4%)	11 (15.5%)	13 (18.8%)	13 (17.3%)	NS
Length of ICU stay	7.7 (7.3)	10.1 (9.8)	7.9 (9.3)	8.6 (11.3)	NS
Days on ventilator	6.6 (9.5)	7.3 (8.4)	6.9 (7.9)	6.1 (10.4)	NS

There were no serious drug-related adverse events.

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Authors' conclusion None of the interventions affected the already very low rate of bleeding in high-risk surgical intensive care unit patients; routine use of these treatments does not seem justified.								

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Karlstadt RG, Iberti TJ, Silverstein J, Lindenberg L, Rright-Asare P, Rockhold F, Young MD. Comparison of Cimetidine and Placebo for the prophylaxis of upper gastrointestinal bleeding due to stress-related gastric mucosal damage in the intensive care	RCT, USA. Double blind placebo controlled, but for ethical reasons they randomised less patients to the placebo group – reduced by half compared to the cimetidine group. Details of randomisation and allocation concealment not given. Not stated if the	87	Inclusion criteria: ICU patients had to have at least one of the following risk factors: major abdominal or thoracic surgery; major multiple trauma; hypotension (decrease in 30 systolic and 20 diastolic); hypovoleamic shock; sepsis; acute respiratory failure. Exclusion: Active UGIB; Hx of UGI ulcers; severe chronic hepatic failure; renal failure; Rx with other drugs with a similar effect; pregnancy/lactation; age<16 yrs. All patients had NG tube in situ. Baseline characteristics: Cimetidine (n=54) / Placebo (n=33) Age mean (sd): 56.5 / 61.9 (18	Initial 300mg dose of cimetidine infused over 15-20 minutes, followed by continuous infusion at the rate of 50mg/hour.	Initial matching dose of placebo in 0.9% saline infused over 15-20 minutes, followed by continuous infusion at the rate of 50mg/hour.	83 (53) hours for cimetidine group and 53 (41) hours for placebo group. This difference was because more placebo pts bled and left the study early.	Signs of UGIB monitored every 6 hours. Clinically significant bleeding defined by one of these criteria: Heametmesis or >10ml of frank bllod in NG tube aspirate; malena or hematochezia; coffee grounds positive for Hb and a 1g decrease in Hb over 24 hours;	Not stated

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
unit. Journal of Intensive Care medicine. 1990; 5: 26-32	researcher collecting outcome data was blinded.			(22.8)					gastrooccult coffee grounds in aspirate taht did not clear with lavage. Mortality	
			Male	57%	48%					
			1 risk factor	81%	76%					
			2 risk factors	15%	24%					
			3 risk factors	4%	0%					
			Types of risk factors							
			Surgery	48%	48%					
			Acute resp. failure	44%	45%					
			Sepsis	13%	12%					
			Trauma	17%	12%					
			hypotension	6%	6%					

Effect size

Post treatment outcomes:

	Cimetidine	Placebo	p value
Bleeding	1/54	7/33	0.002
Mortality	5/54	2/33	
Pneumonia	1/54	0/33	
Adverse effects	2/54	1/33	

Authors' conclusion

Cimetidine, administered as a continuous intravenous 50-mg/hour infusion, is safe and significantly more effective than placebo for preventing upper GI bleeding in critically ill patients.

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Levy MJ, Seelig CB, Robinson NJ et al. Comparison of omeprazole and ranitidine for stress ulcer prophylaxis. Dig Dis Sci. 1997; 42(6):1255-1259. Ref ID: 390	RCT, USA Randomisation adequate, allocation concealment not reported	67	Inclusion criteria: Admitted to ITU; affected by at least 1 of 9 risk factors (burns, coagulopathy, acute hepatic failure, major neurological insult, acute renal failure, respiratory failure, sepsis, shock, trauma). NB Only 1 risk factor required for inclusion but mean 2.3 per patient overall. Exclusion: <18 years; pregnant; admitted for GI haemorrhage; contraindication to use of enteral medicines; admitted to ITU >24 hours prior to identification for enrolment. Baseline characteristics:	Omeprazole (PPI) 40mg daily orally or by nasogastric tube	Ranitidine (H2RA) 50mg bolus then 150mg daily IV (continuous) or 50mg IV 8-hourly	Until discharge from critical care unit (mean 8.7 [6.9] days for omeprazole and 7.8 [12.0] for ranitidine) or condition improved so prophylaxis no longer indicated; overall duration not stated	Clinically important bleeding (haematemesis, aspiration of coffee ground material, melaena plus haemodynamic instability; or decrease in Hb >2g/dL plus need for transfusion or haemodynamic instability). Pneumonia (clinical diagnosis). Death	not stated

	Omeprazole	Ranitidine
n	32	35
Male	17 (53%)	20 (57%)
White	24 (75%)	28 (80%)
Age (yr)	57.3 (23.5)	56.9 (17.5)
APACHE II score	17.5 (7.7)	20.2 (9.4)
Risk factors/pt	1.9 (1.0)*	2.7 (1.8)*
Ventilation	16	26

* p<0.05

Effect size

	Omeprazole	Ranitidine	p value
Clinically important bleeding	2 (6%)	11 (31%)	p<0.05
Nosocomial pneumonia	1 (3%)	5 (14%)	NS

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Death	11 (34%)	12 (34%)	NS
ICU stay	8.7 (6.9)	7.8 (12.0)	NS
Ventilator (days)	8.8 (5.7)	6.8 (7.8)	NS

Authors' conclusion

Omeprazole is safe, effective and clinically feasible for stress ulcer prophylaxis.

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Macdougall BRD et al. H2-receptor antagonists and antacids in the prevention of gastrointestinal haemorrhage in fulminant hepatic failure. Lancet 1977; March 19: 617-619. Ref ID: 5265	RCT, UK Randomisation and allocation concealment not stated	Control = 24, Cimetidine = 26	Inclusion criteria: Patients admitted to liver failure unit with grade IV coma for intensive care Exclusion: Patients with upper GI bleeding Baseline characteristics not stated	H_2-RA (metiamide 150mg or cimetidine 150mg i.v. at a rate of 100mg/hour, repeated as necessary to maintain intragastric pH above 5	No H_2-RA	Until recovery of conscious level to grade II (drowsy but responding to simple commands)	"Failure" (aspiration of fresh blood via nasogastric tube)	Smith Kline & French supplied drugs

	Cimetidine	Control
n	26	24

Effect size

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Post treatment outcomes:

	Control (N=24)	Cimetidine/metiamide (N=26)	p value
Bleeding from gastric erosion from oesophageal erosion both	13 (54%) 5 4 4	1 (4%) 1	p<0.001
Blood transfusion requirement (mean)	2.6 litres	0.5 litres	stated to be a significant difference but p value not given
Hospital discharge	14%	6 (23%)	NS

Authors' conclusion

H_2-RA reduced bleeding and transfusion requirements in patients with fulminant hepatic failure.

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Martin LF et al. Continuous intravenous cimetidine decreases stress-related upper gastrointestinal hemorrhage without promotiong	RCT, USA Randomisation and allocation concealment not stated	131: Placebo = 66, Cimetidine = 65	Inclusion criteria: Critically ill patients ≥16 years admitted to intensive care units for at least 36 hours with at least one stress condition (risk factor for bleeding: major surgery; multiple trauma; hypotension; hypovolaemic shock; sepsis; acute respiratory failure; jaundice; burns affecting ≥30% of body surface area); nasogastric tube in place Exclusion: Patients who were pregnant or lactating; >24 hours elapsed since	Cimetidine (H_2-RA) 300mg (50mL) loading dose over 20 minutes then 50mg/hr;	Placebo	30 days	1ry: clinically important upper GI bleeding: haematemesis or bright red bleeding per nasogastric tube that did not clear after lavage, or	SmithKline Beecham Pharmaceuticals

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>pneumonia. Critical Care Medicine 1993; 21: 19-30. Ref ID: 131</td><td></td><td></td><td>eligible for study; intubated >24 hours; oesophageal, gastric or duodenal surgery; gastrectomy or history of upper gastrointestinal lesions that were likely to bleed; H_2-RA within 12 hours of admission to study or treatment within 24 hours with omeprazole, anticoagulants, aspirin, NSAIDs or investigational drug wihtin 30 days; if 2 gastric aspirates at leasat 30 mins apart in screening phase had bright red blood, coffee ground material or strongly positive test for occult blood.

Baseline characteristics:
<table><tr><td></td><td>Cimetidine</td><td>Placebo</td></tr><tr><td>n</td><td>65</td><td>66</td></tr><tr><td>Male</td><td>41 (63%)</td><td>48 (73%)</td></tr><tr><td>Female</td><td>24 (37%)</td><td>18 (27%)</td></tr><tr><td>Mean (SD) age (yr)</td><td>59 (19)</td><td>60 (17)</td></tr><tr><td>White</td><td>50 (77%)</td><td>52 (79%)</td></tr><tr><td>Black</td><td>11 (17%)</td><td>18 (20%)</td></tr><tr><td>Other</td><td>4 (6%)</td><td>1 (2%)</td></tr><tr><td>No. of risk factors: 1
2
3 or more</td><td>
50 (77%)
11 (17%)
4 (6%)</td><td>
49 (74%)
14 (21%)
3 (5%)</td></tr><tr><td>Mean (SD)</td><td>16.9 (7.8)*</td><td>15.1 (5.8</td></tr></table></td><td>dose reduced by 50% if severe renal failure or increased to 100mg/hr (or 50mg/hr in renal failure) if pH of gastric aspirate <4.0 on 2 occasions 1 hour apart; maximum 7 days treatment</td><td></td><td></td><td>persistent Gastroccult-positive coffee ground material (8 consecutive hours) not clearing with lavage and/or 5% decrease in the hematocrit; time to occurrence of bleeding; nosocomial pneumonia; mortality</td><td></td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

APACHE II score		
Mean (SD) baseline pH	5.0 (1.9)	5.1 (1.7)
Pre-treatment pneumonia	9 (14%)	5 (8%)

*p=0.05

Effect size

Post treatment outcomes:

	Placebo (N=66)	Cimetidine (N=65)	p value
Mean intragastric pH on study drug	3.9	5.7	p=0.0001
pH >4.0 (percent of the time)	41%	82%	p=0.0001
Dosage adjustment due to low pH	52 (79%)	32 (49%)	not stated
Upper gastrointestinal haemorrhage	22 (33%)	9 (14%)	p=0.009
Pneumonia (of those without pneumonia at baseline) while on study medication	4/61 (7%)	0/56 (0%)	NS
Pneumonia after study drug stopped	2	2	
Adverse events possibly related to study drug	27%	25%	NS
Death within 30 days	7/66 (11%)	8/65 (12%)	NS

Authors' conclusion

Cimetidine reduced upper gastrointestinal haemorrhage in patients at risk of stress-related gastric mucosal damage, with no increased risk of pneumonia during 1 week

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
of treatment.								

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Metz CA et al. Impact of multiple risk factors and ranitidine prophylaxis on the development of stress-related upper gastrointestinal bleeding: a prospective, multicenter, double-blind, randomized trial. Critical Care Medicine 1993; 21: 1844-1849. Ref ID: 113	RCT, USA Randomisation and allocation concealment adequate	167: Placebo = 81, Ranitidine = 86	Inclusion criteria: Patients admitted to intensive care units with an expected stay of at least 72 hours, with severe head injury (Glasgow coma sore ≤10) in last 24 hours; at least 18 years old; nasogastric tube in place Exclusion: Patients with upper GI bleeding; severe burns (>20% of body surface area); renal insufficiency; peptic ulcer disease in last 6 months; platelet count <50,000 thrombocytes/microlitre; antacids within 4 hours; H_2-RA within 24 hours Baseline characteristics:	Ranitidine (H_2-RA) 6.25mg/hr for a maximum of 5 days	Placebo	Max 5 days of treatment; further follow up unclear	Upper GI bleeding (Gastroccult-positive nasogastric aspirate; bright red bleeding per nasogastric tube; haematemesis; Haemoccult-positive stool; melaena; haematochezia) plus yes to anu of 4 questions: coffee grounds present for 8 hours prior to positive occult blood in gastric drainage? minimum 50mL bright red blood in nasogastric tube?	Glaxo Pharmaceuticals

	Ranitidine	Placebo
n	86	81
Male	67	56
Female	19	25
Age (yr)	35.4 (1.91)	32.5 (1.8
GCS <6	41%	41%
Mechanical ventilation	80 (93%)*	65 (80%)

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			at study entry Pneumonia at baseline 2 2 *p=0.021				haematemesis in last 8 hours? endoscopic or surgical confirmation of upper GI source of bleeding? Nosocomial pneumonia	

Effect size

Post treatment outcomes:

	Placebo (N=81)	Ranitidine (N=86)	p value
Stress-related upper gastrointestinal bleeding	15 (19%)	3 (3%)	p=0.002
Nosocomial pneumonia (in those not having pneumonia at baseline)	15/79 (19%)	12/84 (14%)	NS

Authors' conclusion

Ranitidine reduced stress-related upper gastrointestinal bleeding.

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Misra UK, Kalita J, Pandey S, Mandal SK, Srivastava M. A randomised placebo controlled trial	RCT, India. Randomised using computer generated random numbers. No	141	Inclusion: Patients with CT-proven ICH within 7 days of ictus were included. None on ventilator and all on general ward. Exclusion: AV malformation, aneurismal bleed, bleeding and	50mg ranitidine intravenously eight-hourly	As intervention but placebo (saline or starch) given instead.	1 month	UGIB, decided by gross blood, coffee ground aspirate	None given.

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>of ranitidine versus sucralfate in patients with spontaneous intracerebral haemorrhage for prevention of gastric haemorrhage. Journal of the Neurological Sciences 2005; 239: 5-10</td><td>mention of allocation concealment. Blinding unclear. Not clear if the person providing treatment or the patient was blinded. The evaluation of outcomes was blinded, however, by using an assessor unaware of the treatment allocations.</td><td></td><td>coagulation disorders, hepatic and renal failure, history of peptic ulcer, those on anti-platelet and anticoagulation therapy.

There were 3 groups: ranitidine (n=45), placebo (n=47) and sucralfate (n=49). The sucralfate results are not given in this summary.

Baseline characteristics: Broadly similar; stats done on comparisons of the 3 groups, and all NS. However the Ranitidine group did seem to have higher levels of delayed admission, and the study's multivariate analysis showed that this tended to increase incidence of UGIB. This discrepancy will therefore have led to an overestimation of any harmful ranitidine effect, and is therefore not a threat to the validity of overall findings.
<table>
<tr><td></td><td>Ranitidine</td><td>Placebo</td></tr>
<tr><td>Age >60</td><td>14/45</td><td>18/47</td></tr>
<tr><td>male</td><td>29/45</td><td>34/47</td></tr>
<tr><td>Time to admission
Up to 48 hrs
>48 hrs – 5 days
>5 days</td><td>
25/45
8/45
12/45</td><td>
28/47
11/47
8/47</td></tr>
<tr><td>GCS <6</td><td>7/45</td><td>7/47</td></tr>
<tr><td>CNS scale <3</td><td>28/45</td><td>36/47</td></tr>
</table></td><td></td><td></td><td></td><td>from nasogastric tube, heametmesis or malena.

1 month mortality</td><td></td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			hyperventilation	9/45	12/47					
			Pupillary asym	1/45	2/47					
			Decerebration	6/45	6/47					
			Supratentorial location	40/45	39/47					
			Medium or large size	24/45	27/47					
			Midline shift	20/45	19/47					
			Intraventricular extension	24/45	22/47					
			Septicaemia	12/45	17/47					
			pneumonia	2/45	5/47					

Effect size

	Ranitidine	Placebo	p value
UGIB	5/45	11/47	sig
Mortality at one month	5/45	13/47	sig

Authors' conclusion: Ranitidine does not seem to significantly prevent UGIB or reduce 1-month mortality.

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Nagasue N, Yukaya H, Ogawa Y, Sasaki Y, Hirose S. Prophylaxis of upper gastrointestinal bleeding with cimetidine in patients undergoing partial hepatectomy. Annales Chirurgiae et Gynaecologiae 1984; 73: 6-10</td><td>RCT, Japan.

No evidence of allocation concealment and the randomisation method not given. In any event, not fully randomised, as after 18 patients had been randomly recruited to each group, the interim findings of better outcome for the cimetidine group prompted the final 16 patients to be non-randomly allocated to the cimetidine group. The group characteristics were similar (NS) but there appeared to be a trend for those in the cemetidine group to have had more large scale excisions.</td><td>52</td><td>Inclusion: Patients who had undergone partial hepatectomies of varying magnitude for surgical diseases of the liver. The majority had hepatocellular carcinoma. They were not reported as being on ventilation post operatively.
2/18 in the cimetidine group and 3/34 in the control group had a history of bleeding pre-operatively, but these were not excluded, despite this being a prophylactic study. It is not made clear whether these patients overlapped with those bleeding post-operatively.
Baseline characteristics:<table><tr><th></th><th>Cimetidine</th><th>Control</th></tr><tr><td>M/F</td><td>27/34</td><td>18/1</td></tr><tr><td>Age</td><td>58 (11)</td><td>51 (12)</td></tr><tr><td>Hepatocellular carcinoma</td><td>25/34</td><td>15/1</td></tr><tr><td>Cholangioma</td><td>1/34</td><td>0/18</td></tr><tr><td>Secondary liver cancer</td><td>4/34</td><td>2/18</td></tr><tr><td>Others</td><td>4/34</td><td>1/18</td></tr><tr><td>Liver cirrhosis</td><td>23/34</td><td>11/1</td></tr><tr><td>Peptic ulcer or UGIB history</td><td>3/34</td><td>2/18</td></tr></table></td><td>200mg cimetidine administered intravenously every 6 hours, for at least 1/52 post liver resection. If a patient had pre-operative bleeding, or post operative complications such as intra-abdominal abscess, liver failure or ARDS, then the dose given was 800-1200mg /day for 1 month. When upper GI bleeding was found postoperatively (unclear), IV cimetidine was given as 800-1600mg for control subjects and up to 1600 for cimetidine patients.</td><td>No information given.</td><td>Unclear but at least 19 days.</td><td>Upper GI bleeding postoperatively, detected by analysis of heamatocrit decrease.

Mortality

Blood transfusion

Adverse effects</td><td>Fujisawa Pharmaceutical Co., Osaka, provided cimetidine during the investigation.</td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Preop complications							
			Diabetes mellitus	3/34	2/18					
			Gallstone	2/34	0/18					
			Jaundice	1/34	0/18					
			Resp insufficiency	1/34	0/18					

Effect size

	Cimetidine	Control	p value
Upper GI bleeding postoperatively	2/34	5/18	P<0.05
Severe	0/34	2/18	
Moderate	0/34	1/18	
Mild	2/34	2/18	
Mortality	2/34 (hepatic coma secondary to liver failure)	1/18 (UGIB and resultant renal failure)	
Blood transfusion	0/34	3/18	
Adverse effects			NS
Intra-abdominal infection	3/34	2/18	
Liver failure	3/34	0/18	
Post-op hepatitis	3/34	0/18	
Biliary fistula	1/34	0/18	
ARDS	1/34	0/18	

Authors' conclusion: Cimetidine therapy is an effective modality to prevent upper GI bleeding post liver resection but there is a trend that it may induce postoperative liver failure and hepatitis. Further studies are needed to further assess safety.

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Reusser P et al. Prospective endoscopic study of stress erosions and ulcers in critically ill neurosurgical patients: current incidence and effect of acid-reducing prophylaxis. Crit Care Med 1990; 18: 270-274. Ref ID: 5257</td><td>RCT, Switzerland

Randomisation and allocation concealment not stated</td><td>40; Placebo = 21, Ranitidine = 19</td><td>Inclusion criteria: Patients admitted to intensive care units critically ill with 2 risk factors (severe acute intracranial lesion caused by trauma or spontaneous haemorrhage requiring neurosurgery and respiratory failure due to impaired neurological condition requiring intubation and mechanical ventilation >48 hours)
Exclusion: Patients with upper GI bleeding, history of upper GI surgery or peptic ulcer disease, anti-ulcer treatment, <15 years old

Baseline characteristics:
<table>
<tr><th></th><th>Ranitidine</th><th>Placebo</th></tr>
<tr><td>n</td><td>19</td><td>21</td></tr>
<tr><td>Male</td><td>13</td><td>17</td></tr>
<tr><td>Female</td><td>6</td><td>4</td></tr>
<tr><td>Median age (yr) (range)</td><td>40 (19-63)</td><td>33 (15-76</td></tr>
<tr><td>Median GCS on admission (range)</td><td>5 (3-9)</td><td>5 (3-10)</td></tr>
<tr><td>No. of risk factors per patient</td><td>3.3</td><td>3.4</td></tr>
</table></td><td>Ranitidine (H_2-RA) 50 mg i.v. every 8 hrs (increased to every 6 hours if 2 gastric pH <4) up to 7 days.</td><td>No prophylactic treatment for stress ulcers</td><td>Up to 7 days of treatment plus 7 more days; to end of hospital stay for mortality</td><td>Occult blood in gastric aspirate; overt blood (bright red bleeding per nasogastric tube, melaena, decrease in Hb >2g/dL within 24 hours plus positive stool guaiac test or gastric drainage >100mL coffee grounds); endoscopic evidence of erythema/ oedema, erosions (none, 1-5, >5) ulcer, bleeding (petechiae/ submucosal haematoma, fresh blood or coffee grounds, frank bleeding) gastric pH level</td><td>Not stated</td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Effect size

Post treatment outcomes:

	Placebo (N=21)	Ranitidine (N=19)	p value
pH ≥4 (percentage of readings)	32%	78%	p<0.001
Endoscopic findings:			NS
Erythema/oedema	15	13	
Erosions:			
none	8	6	
1-5	4	4	
>5	9	9	
Ulcer	1	1	
Bleeding:			
none	15	15	
petechiae/ submucosal haematoma,	5	3	
fresh blood or coffee grounds,	1	1	
frank bleeding	0	0	
Overt bleeding	0	0	NA
Occult bleeding (3 consecutive positive tests) but this did not correlate with transfusion requirements or presence of multiple erosions	5	11	p<0.05
Total deaths	6 (29%)	5 (26%)	
Median time to death (range)	25.5 days (20-72)	15 days (6-24)	

Authors' conclusion

Drug prophylaxis had no detectable benefit.

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Ruiz-Santana S et al. Stress-induced gastroduodenal lesions and total parenteral nutrition in critically ill patients: frequency, complication, and the value of prophylactic treatment. A prospective, randomized study. Crit Care Med 1991; 19: 887-891. Ref ID: 5262</td><td>RCT, Spain

Randomisation and allocation concealment not stated</td><td>73; TPN only = 30, TPN plus ranitidine = 19; (also TPN plus sucralfate group = 24)</td><td>Inclusion criteria: Patients admitted to intensive care units with an expected duration of 6 days of mechanical ventilation; metabolic stress; haemodynamically stable; normal hepatic and renal function; on total parenteral nutrition (starting on 3rd day of ICU admission)
Exclusion: Patients with upper GI bleeding, history of gastroduodenal ulcer in last 12 months, operation on upper GI tract; hepatic or renal failure; catabolic index score ≤0; antacids, H_2-RA or sucralfate in previous 48 hours; spinal cord injury

Baseline characteristics:
<table>
<tr><th></th><th>TPN only</th><th>TPN plus ranitidine</th></tr>
<tr><td>n</td><td>30</td><td>19</td></tr>
<tr><td>Male</td><td>19</td><td>14</td></tr>
<tr><td>Female</td><td>11</td><td>5</td></tr>
<tr><td>Mean (SD) age (yr) (range)</td><td>39 (14) (19-63)</td><td>39 (17) (18-77)</td></tr>
<tr><td>Stress index</td><td>9 (7)</td><td>7 (6)</td></tr>
<tr><td>APACHE II score</td><td>16 (5)</td><td>16 (6)</td></tr>
</table></td><td>Ranitidine (H_2-RA) 50 mg i.v. every 6 hrs until tolerated enteral feeding</td><td>No prophylactic treatment for stress ulcers</td><td>Up to 7 days of treatment plus 7 more days; to ICU discharge or death</td><td>Endoscopy: 1) normal mucosa or only erythema; 2) non-haemorrhagic erosions/ petechiae; 3) ulcers without bleeding; 4) ulcers with bleeding. Acute upper GI bleeding (haematemesis, blood in aspirate, melaena, coffee grounds); death</td><td>Not stated</td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Effect size

Post treatment outcomes:

	TPN only (N=30)	TPN + Ranitidine (N=19)	p value
Endoscopic findings: 1) normal mucosa or only erythema; 2) non-haemorrhagic erosions/ petechiae; 3) ulcers without bleeding; 4) ulcers with bleeding	 20 3 3 1	 8 3 2 2	NS
Haemodynaically unstable	1	0	NS
Deaths due to bleeding	0	0	NS
Total deaths	7	7	
Days on mechanical ventilation [mean (sd)]	16 (7)	19 (9)	

Authors' conclusion

Drug prophylaxis had no detectable benefit.

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Somberg L, Morris J, Jr., Fantus R et al. Intermittent intravenous pantoprazole and	RCT, USA Randomisation method not stated, allocation concealment	202	Inclusion criteria: Men or non-pregnant women 18 yrs or more with at least 1 risk factor (post-operative major surgery, major trauma, shock, sepsis, acute respiratory failure, burns 30% of body or more, coagulopathy); baseline gastric aspirate clear with no more than moderate positivity on Gastroccult testing.	Pantoprazole (PPI) IV (A: 40mg daily; B: 40mg twice	F: Cimetidine IV 300mg bolus then 50mg/hr for at least 48 hours	30 days	1ry: Percentage of time gastric pH 4.0 or more. 2ry: upper GI bleeding (clinically significant bleeding defined as: haematemesis or bright red blood in aspirate	not stated

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>continuous cimetidine infusion: effect on gastric pH control in critically ill patients at risk of developing stress-related mucosal disease. J Trauma. 2008; 64(5):1202-1210. Ref ID: 5215</td><td>adequate</td><td></td><td>NB Most patients only had 1 risk factor so probably not ill enough to meet protocol criteria.
Exclusion: hypersensitivity to PPI; pregnant; any condition that would compromise patient safety; intubated >24 hours before drug administered; ITU admission following oesophageal, gastric or duodenal surgery or acute illicit drug overdose; history of gastrectomy or upper GI lesion with risk of haemorrhage; hypersecretory condition; peptic ulcer disease in last year; H2RA < 12 hours before study drug or sucralfate <24 hours before or GI promotility agents< 24 hours before or PPIs < 72 hours before; use of antacids, PPIs, H2RAs or sucralfate during study; inability to tolerate nasogastric or orogastric tube; previous participation in study; aspiration or pneumonia.

Baseline characteristics:
<table>
<tr><td></td><td>A</td><td>B</td><td>C</td><td>D</td><td>E</td><td>F</td></tr>
<tr><td>n</td><td>32</td><td>38</td><td>23</td><td>39</td><td>35</td><td>35</td></tr>
<tr><td>Age (yr)</td><td>42.3</td><td>38.7</td><td>33.5</td><td>42.3</td><td>41.3</td><td>44.5</td></tr>
<tr><td>Male (%)</td><td>69</td><td>63</td><td>65</td><td>74</td><td>80</td><td>77</td></tr>
<tr><td>White (%)</td><td>84.4</td><td>76.3</td><td>69.6</td><td>74.4</td><td>82.9</td><td>71.4</td></tr>
<tr><td>Black (%)</td><td>6.3</td><td>15.8</td><td>21.7</td><td>18.0</td><td>17.1</td><td>17.1</td></tr>
<tr><td>Hispanic</td><td>6.3</td><td>5.3</td><td>8.7</td><td>5.1</td><td>0</td><td>11.</td></tr>
</table></td><td>daily; C: 80mg daily; D: 80mg twice daily; or E: 80mg 8-hourly for at least 48 hours up to 7 days (mean treatment duration 2.8 days)</td><td>up to 7 days (mean treatment duration 2.8 days)</td><td></td><td>that did not clear with lavage; coffee ground material for 8 consecutive hours that did not clear with lavage or was associated with a 5% decrease in haematocrit; decrease in haematocrit requiring transfusion in the absence of obvious source; melaena or frankly bloody stools from upper GI source); pneumonia (x-ray findings, fever, raised white cell count, >15% immature neutrophils (bands) or leucopenia; at least 3 of: cough; purulent sputum; rales or consolidation; dyspnoea, tachypnoea or respiratory rate 20 breaths per min or more; hypoxaemia or respiratory failure requiring ventilation; tachycardia; pleuritic chest pain; new or</td><td></td></tr>
</table>

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>(%)</td><td></td><td></td><td></td><td></td><td></td><td>4</td></tr>
<tr><td>APACHE II score</td><td>15.2</td><td>16.1</td><td>14.6</td><td>14.3</td><td>15.6</td><td>15.3</td></tr>
<tr><td>1 risk factor (%)</td><td>78.1</td><td>81.6</td><td>82.6</td><td>82.1</td><td>82.9</td><td>80.0</td></tr>
<tr><td>2 risk factors (%)</td><td>18.8</td><td>13.2</td><td>13.0</td><td>15.4</td><td>17.1</td><td>14.3</td></tr>
<tr><td>3 or more risk factors (%)</td><td>3.1</td><td>5.3</td><td>4.4</td><td>2.6</td><td>0</td><td>0</td></tr>
</table>
</td><td></td><td></td><td></td><td>worsened confusion); adverse events; death.</td><td></td></tr>
<tr><td colspan="9">Effect size
<table>
<tr><td></td><td colspan="6">Pantoprazole</td><td>Cimetidine</td></tr>
<tr><td></td><td>A</td><td>B</td><td>C</td><td>D</td><td>E</td><td>Pantoprazole total</td><td>F</td></tr>
<tr><td>Pneumonia</td><td>3/32 (9%)</td><td>8/38 (21%)</td><td>1/23 (4%)</td><td>2/39 (5%)</td><td>2/35 (6%)</td><td>16/167 (9.6%)</td><td>3/35 (9%)</td></tr>
<tr><td>Possible treatment-related adverse events</td><td></td><td></td><td></td><td></td><td></td><td>7/167 (4%)</td><td>0</td></tr>
<tr><td>Serious adverse events</td><td></td><td></td><td></td><td></td><td></td><td>73/167 (44%)</td><td>18/35 (51%)</td></tr>
<tr><td>Death (none related to study drug)</td><td></td><td></td><td></td><td></td><td></td><td>18/167 (11%)</td><td>3/35 (9%)</td></tr>
</table>
On day 1 and 2, no difference between groups on primary endpoint of mean percentage time pH 4.0 or more. No patients had bleeding.</td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Authors' conclusion Intermittent pantoprazole can maintain gastric pH at 4.0 or more.								

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
van den Berg B, van BM. Prevention of stress-induced upper gastrointestinal bleeding by cimetidine in patients on assisted ventilation. Digestion. 1985; 31(1):1-8. Ref ID: 5266	RCT, Netherlands Double blind, randomisation sequence generation and allocation concealment unclear (not described)	Placebo = 14, Cimetidine = 14 Study started with 34 patients but 6 were excluded after the study – 1 patient died on the 2nd day of the study from sepsis, 1 patient had a bleeding duodenal ulcer proven at endoscopy at the	Inclusion criteria: All patients were on assisted ventilation on either a medical or a surgical intensive care unit and had to be admitted within the 24 hrs before randomisation. Exclusion: not clearly specified Baseline characteristics – no significant differences: List of risk factors: requiring ventilation, fall in systolic blood pressure below 100 mg Hg lasting over 2 h, sepsis, jaundice, renal insufficiency, peritonitis. | | Cimetidine | Placebo | | n | 14 | 14 | | Male | 9 | 9 | | Age (yr) (no sd reported) | 43.9 | 48.4 |	Continuous i.v. infusion of 20 mg / kg weight per 24 h	Continuous i.v. infusion of saline In cases of manifest bleeding the code was broken and patients received open cimetidine.	At least 3 days (minimum day of treatment)	Primary endpoint gastric pH level, blood loss Also reported mortality and bleeding	Not stated

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td></td><td>beginning of the study, 1 patient developed anuria and 1 patient proved to have had previous gastric surgery (unclear which group these were from)</td><td>
<table>
<tr><td>Mean risk factor score (no sd reported)</td><td>2.6</td><td>1.9</td></tr>
<tr><td>Surgical ICU</td><td>7</td><td>8</td></tr>
<tr><td>Medical ICU</td><td>7</td><td>6</td></tr>
<tr><td>Number of patients with 3 or more risk factors</td><td>9</td><td>4</td></tr>
</table>
</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="9">Effect size
Post treatment outcomes:
<table>
<tr><td></td><td>Placebo (N=14)</td><td>Cimetidine (N=14)</td></tr>
<tr><td>Bleeding</td><td>1</td><td>5</td></tr>
<tr><td>mortality</td><td>1</td><td>4</td></tr>
</table>
Authors’ conclusion
These results do not suggest that cimetidine was effective in preventing stress-induced upper GI bleeding</td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Zinner MJ, Zuidema GD, Smith P et al.	RCT, two centre USA	Placebo = 100, Cimetidine =	Inclusion criteria: Patients admitted for at least 48 hrs to surgical intensive care units	Cimetidine (H_2-RA) 300	No treatment	Until hospital discharge	Mortality, upper GI bleeding (persistent guaic	Not stated

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>The prevention of upper gastrointestinal tract bleeding in patients in an intensive care unit. Surg Gynecol Obstet. 1981; 153(2):214-220. Ref ID: 5264</td>
<td>Randomisation adequate (table of random numbers), allocation concealment unclear (not stated)</td>
<td>100 (an additional 100 were included in an antacid group – not reported here)

40 were additionally entered but were removed from the protocol (31 due to protocol error – or because of the request of the physician). No reason provided for the remaining 9 patients.</td>
<td>Exclusion: Patients with upper GI bleeding, those with recent active peptic ulcer disease or those who had undergone an operation on the esophagus or the stomach.

Baseline characteristics – no significant differences – no standard deviations given:
<table>
<tr><td></td><td>Cimetidine</td><td>Placebo</td></tr>
<tr><td>n</td><td>100</td><td>100</td></tr>
<tr><td>Male</td><td>63%</td><td>63%</td></tr>
<tr><td>Age (yr)</td><td>56.7</td><td>55.5</td></tr>
<tr><td>Cardiac / general surgery N</td><td>84</td><td>83</td></tr>
<tr><td>Neurosurgery N</td><td>13</td><td>9</td></tr>
<tr><td>Medical N</td><td>3</td><td>8</td></tr>
<tr><td colspan="3">Illness severity distribution*</td></tr>
<tr><td>0-2 - N</td><td>64</td><td>64</td></tr>
<tr><td>3-6 - N</td><td>34</td><td>30</td></tr>
<tr><td>≥ 7 - N</td><td>2</td><td>4</td></tr>
<tr><td>Mean illness severity score</td><td>2.1</td><td>2.3</td></tr>
</table>
*Consisted of 9 categories: Pulmonary,</td>
<td>mg i.v. every 6 hrs during the entire stay in the ICU.</td>
<td></td>
<td></td>
<td>4+ positive nasogastric aspirate continuous for longer than 16 hrs, even after nasogastric lavage; bright red bleeding per nasogastric tube or by emesis or guaiac positive stools and a documented decrease in the hematocrit valve), length of hospital stay, minor adverse events (not reported here), pH level (not reported here)</td>
<td></td>
</tr>
</table>

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			patients requiring ventilatory assistance for longer than 24 hrs postoperatively or with documented respiratory insufficiency or pneumonia; shock, patients with hypotension of less than 90 ml systolic from any cause or the required use of cardiovascular pressors; sepsis, patients with documented systemic infections and positive blood cultures; cardiac, patients with congestive heart failure , myocardial infarction or those having significant arrhythmias requiring drugs for control; renal, acute renal failure defined as a creatinine level greater than 3.0 mg percent or blood area nitrogen level greater than 50 mg, central nervous system, patients with obtunded mental status from a defined neurologic cause or coma; steroid use, those requiring hydrocortisone acetate, or its equivalent, of more than 250 mg per 24 hrs; coagulopathy, patients with a platelet count of less than 50,000 cubic ml or a prothrombin time of less than 30 percent of that of the control group and hepatic, patients with a bilirubin value greater than 5.0 mg percent or with documented hepatitis (1 point for each category)					
Effect size Post treatment outcomes:								

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

	Placebo (N=100)	Cimetidine (N=100)	p value – no exact p values given
Overall incidence of UGI bleeding	20	14	NS
Bleeds for which the patient required transfusions*	8	7	NS
Death	17	9	NS
Hospital stay – median	3	3	NS
Transfusion requirements (packed red blood cells)			
Ventilator (days)			

*Authors had excluded 2 patients from the cimetidine and 1 patient from the placebo group requiring transfusion for upper GI bleeding (reason being that they had additional bleeding sites – not sure whether they had been included in the overall group or not)

Authors' conclusion

The incidence of upper gastrointestinal bleeding in patients in intensive care units can be decreased by prophylactic treatment (particular the antacid treatment that was not reported above).

F.7 Management of variceal upper GI bleeding

F.7.1 Antibiotics

QUESTION In patients with likely variceal bleeding at initial management are antibiotics better than placebo to improve outcome (mortality, rebleeding, length of hospital stay, rates of infection)?

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Lin YT, Lo GH, Lai KH, et al. Prophylactic antibiotics in cirrhotics with upper gastrointestinal hemorrhage: A prospective, controlled trial. Chinese Medical Journal (Taipei) 2002;65:365-71.</td><td>RCT, Single centre, Country: Taiwan

Randomisation sequence generation adequate, allocation concealment unclear</td><td>N=47 antibiotic group; N=50 control group

Exclusion criteria applied before enrolment</td><td>Inclusion criteria: Cirrhotic patients admitted because of UGI bleeding.
Exclusion criteria: Life expectancy of less than 7 days; fever or other signs of infection on entry; bacterial culture either from blood or body fluids positive on entry; having received antibiotics within 2 weeks prior to admission

Both groups received resuscitation, including blood transfusions, fluids, electrolytes and lactulose if necessary.

Baseline characteristics – no significant differences:
<table>
<tr><th></th><th>Antibiotic N=47</th><th>Control N=50</th></tr>
<tr><td>Age</td><td>55.3(11.9)</td><td>53.6 (13.0)</td></tr>
<tr><td>Male</td><td>38</td><td>40</td></tr>
<tr><td>Aetiology of cirrhosis alc/HepB/ HepC/other</td><td>12/24/9/2</td><td>20/18/11/ 1</td></tr>
<tr><td>Hemoglobin (gm/dL)</td><td>8.6 (2.5)</td><td>9.3 (2.7)</td></tr>
</table></td><td>Intravenous infusion of cefazolin at 1 gram per 8 hours before endoscopy. After 3 days of prophylactic parenteral antibiotics, antibiotics were shifted to oral cephalexin (generic name: Keflex) of 500 mg per 6 hours for 4 days.</td><td>Control group received no antibiotics except when infection was noted.</td><td>7 days</td><td>Number of endoscopies, number of patients with infections, proved infections, possible infections, length of hospital stay, mortality (with causes of death: i.e. infection or liver failure)</td><td>Not stated</td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Hepatocellular carcinoma	10	11					
			Albumin (gm/dL)	2.8 (0.5)	3.0 (0.5)					
			Bilirubin (mg/dL)	2.5 (3.1)	2.3 (2.0)					
			Child-Pugh class A/B/C	12/24/11	15/26/9					
			Child-Pugh score	8.1 (1.9)	7.7 (2.1)					
			Bleeding source:							
			Portal hypertension related	33	29					
			Oesophageal	23	18					
			Gastric	9	4					
			Gastropathy	1	7					
			Ulcers	14	21					
Effect size Post treatment outcomes										

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

	Antibiotic N=47	Control N=50	p-value
Endoscopies	1.1 (0.2)	1.2 (0.4)	NS
Patients with infections	3	13	0.013
Proved infections	0	6*	0.027
Possible infections	3	7	NS
Hospital stay	10.2 (2.4)	11.4 (7.8)	NS
Mortality	2	3	NS
Cause of death:			
Infection	0	2	NS
Liver failure	2	1	NS

*Four patients had fever and positive blood culture (unspecified); one patient had fever, dysuria and positive urine culture; anther patient had fever wound formation and positive wound culture (none of the 6 patients had more than one source of infection)

Authors' conclusion

The antibiotic prophylactic treatment proved safe and effective in reducing the infection rate in patients with cirrhosis with upper gastrointestinal bleeding.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Jun CH, Park CH, Lee WS, et al. Antibiotic prophylaxis using third generation cephalosporins can reduce the risk of	RCT, Single centre, Country: Korea Randomisation sequence generation adequate, allocation	Per protocol: N=62 in prophylactic group; N=58 in the 'on-demand' group (usual care) Numbers	Inclusion criteria: Diagnosis of cirrhosis on the basis of previous liver biopsy or clinical, biochemical, and radiological findings of hepatic failure and portal hypertension; bleeding from oesophageal varices or gastric varices; and no signs of infection at admission. Exclusion criteria: Patients with a	Intravenous cefotaxime 2 gram q 8 hr for 7 days	Antibiotics only when infection was suspected or established (antibiotics were changed according to the antibiotic	Mean follow-up ~22 months ± 14	Primary outcome: rebleeding Secondary endpoints: treatment failure, infection rates,	Not stated

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>early rebleeding in the first acute gastroesophageal variceal hemorrhage: a prospective randomized study. J Korean Med Sci 2006 Oct;21:883-90.</td><td>concealment unclear, not blinded

Per protocol analysis</td><td>randomised: N=76 prophylactic group (N=8 infection on entry; N=6 refusal to continue); N=76 control group (N=7 infection on entry; N=11 refusal to continue)</td><td>past history of oesophageal variceal bleeding or surgical or endoscopic treatment of gastro-oesophageal varices; patients who received antibiotics within the last 2 weeks; patients with a terminal illness of any major organ system or hepatic malignancy; patients with any other causes of upper gastrointestinal bleeding.

All patients presented with the first episode of bleeding

Baseline characteristics – usually expressed as means (sd) or N; none of the group differences reached significance:
<table>
<tr><td></td><td>Antibiotic N=62</td><td>On demand N=58</td></tr>
<tr><td>Age</td><td>54.7 (10.1)</td><td>54.2 (11.9</td></tr>
<tr><td>Male</td><td>54</td><td>56</td></tr>
<tr><td>Viral/ alcohol/mixed/others</td><td>18/38/5/1</td><td>16/33/9/0</td></tr>
<tr><td>Hepatocellular</td><td>16</td><td>10</td></tr>
</table></td><td></td><td>sensitivity profile of cultured micro organisms.</td><td></td><td>transfusion requirements, total hospital stay, mortality (plus causes of mortality)</td><td></td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			carcinoma							
			Child-Pugh score	8.7 (1.9)	8.3 (2.1)					
			Albumin (g/dL)	2.5 (0.5)	2.6 (0.5)					
			Bilirubin (mg/dL)	2.2 (2.4)	2.5 (2.3					
			Prothrombin time (INR)	1.5 (0.4)	1.5 (0.4)					
			Encephalopathy	6	4					
			Ascites	34	33					
			Hemoglobin (g/dL	8.9 (1.9)	8.3 (2.1)					
			Esophageal / gastric varices	51/11	50/8					
			Follow-up period months	22.1 (14.5)	22.3 (14.6)					

Effect size

Infection sources and bacteriology in patients – post treatment:

	Antibiotics N=62	On-demand N=58	p-value

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

No. of patients infected	2	9	0.026
Bacteraemia	2	2	1.000
Pneumonia	0	1	0.483
Spontaneous bacterial peritonitis	0	4	0.052
Urinary tract infections	0	1	0.483
Undetermined	0	1	0.483

Post-treatment outcomes – shaded cells highlight significant differences

	Antibiotics N=62	On-demand N=58	p-value
Rebleeding	21	36	0.004
Time of rebleeding:			
Early*	3	12	0.012
1-7 days	0	3	0.071
1 to 2 weeks	0	2	0.143
2 to 6 weeks	3	7	0.195
Late (>6 weeks)	18	24	0.220
Treatment failure	7	8	0.890
Transfusion requirements	1.6 (1.4)	2.2 (1.5)	0.002
Total hospital stay	13.6 (9.7)	14.8 (10.0)	0.489
Mortality	20	24	0.300
30 day mortality	3	3	1.000
Causes of death:			
Hepatic failure	9	12	0.374
Multiple organ failure	6	6	0.903
Bleeding	3	3	1.000

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
sepsis		2	3	0.672				

*Early rebleeding is defined as all rebleeding up to 6 weeks (i.e. the sum of the three subcategories)

Authors' conclusion

Antibiotic prophylaxis with third generation cephalosporins can prevent bacterial infection and early rebleeding in patients with the first acute oesophageal variceal bleeding.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hou MC, Lin HC, Liu TT, et al. Antibiotic prophylaxis after endoscopic therapy prevents rebleeding in acute variceal hemorrhage: a randomized trial. Hepatology 2004 Mar;39:746-53.	RCT, Single centre, country: Taiwan Adequate randomisation sequence generation, unclear allocation concealment (consecutively numbered envelopes), not blinded Per protocol analysis	Numbers analysed: N=59 prophylactic group N=61 on-demand group Exclusions after randomisation: prophylactic group N=9 (loss to follow-up) 'on-demand' group N=19 (occult infections) and N=7 (loss to follow-up)	Inclusion criteria: patients with endoscopy proven gastro-oesophageal variceal bleeding Exclusion criteria: patients with a terminal illness of any major organ system, like heart failure, uraemia, COPD, or non-hepatic malignancy; patients with a history of surgical or endoscopic treatment of gastro-oesophageal varices. Baseline characteristics: Prophylaxis (N=59) / On-demand (N=61) Age: 60.02 (13.92) / 59.39 (14.85) Male: 43 / 48 Viral/alco: 29/6/10/1 / 34/10/10/	I.v. ofloxacin 200 mg q12h for 2 days and followed by oral ofloxacin 200 mg q12h for 5 days	The 'on demand' group received antibiotic therapy only when infection was suspected or established. Antibiotics were changed according to the antibiotic sensitivity test of cultured micro-organisms.	Endoscopic treatment was performed weekly for the first 3 weeks when possible, then treatment was performed every 3 weeks until the varices were eradicated. Follow-up endoscopy was	Early rebleeding (rebleeding within 7 days of enrolment after initial control of bleeding); treatment failure (failure to control active bleeding after two attempts of endoscopic treatment, rebleeding more than twice, or bleeding death;	Taipei-Veterans General Hospital and National Science Council

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>hol/mixed /other</td><td>4</td><td>7</td></tr>
<tr><td>Hepatocellular carcinoma</td><td>16</td><td>14</td></tr>
<tr><td>Child Pugh class A/B/C</td><td>10/35/14</td><td>19/29/13</td></tr>
<tr><td>Child Pugh score</td><td>8.54 (1.90)</td><td>7.90 (2.04)</td></tr>
<tr><td>Albumin</td><td>2.86 (0.42)</td><td>3.99 (0.43)</td></tr>
<tr><td>Bilirubin</td><td>2.90 (3.48)</td><td>2.19 (1.50)</td></tr>
<tr><td>Prothrombin time</td><td>3.50 (3.04)</td><td>2.70 (2.60)</td></tr>
<tr><td>Encephalopathy</td><td>8</td><td>5</td></tr>
<tr><td>Creatinine</td><td>1.05 (0.38)</td><td>1.19 (0.47)</td></tr>
<tr><td>Active spurting or oozing</td><td>17</td><td>14</td></tr>
<tr><td>Follow up period median (range)</td><td>255 (22-843)</td><td>270 (6-851)</td></tr>
</table>
None of the group differences
</td><td></td><td></td><td>subsequently performed every 3 months and, if unremarkable twice, was moved to every 6 months.</td><td>spontaneous bacterial peritonitis; mortality</td><td></td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			reached significance. However, there was a trend towards lower mean Child-Pugh scores and higher creatinine levels in the 'on demand' group (p=0.07 and p=0.08 respectively)					

Effect size

Post-treatment outcomes – significant results highlighted in shaded cells

	Prophylaxis (N=59)	On-demand (N=61)	p-value
Number of infection patients (events)	2	16 (18)	0.004
Bacteremia	0	7 (9)	0.0229
Spontaneous bacterial peritonitis	1	2	0.977
Pneumonia	0	2	0.492
Urinary tract infection	1	5	0.229
Number of rebleeding patients (episodes)	12 (14)	27 (39)	0.0094
Time of rebleeding			
24 to 48 hours	4	12	0.770
3 to 7 days	0	9	0.065
7 to 14 days	1	2	0.584
15 to 42 days	7	2	0.0029
> 6 weeks	0	2	0.894
Mortality*	19	13	0.597
In-hospital mortality	2	3	0.799
30 day mortality	2	1	0.858
Units of blood transfused	1.40 (0.89)	2.81 (2.29)	0.030
Treatment failure	2	6	0.295

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
*Cause of death: hepatic failure, bleeding, sepsis, multiple organ failure Kaplan-Meier survival analysis was carried out for rebleeding in the first 7 days with a HR of 5.078 (21/61 vs. 4/59; 95% CI: 1.854-13.908; p=0.0029) Kaplan-Meier survival analysis was carried out for mortality (in hospital mortality and 30 day mortality) – only described as not significant p=0.523) Authors' conclusion Antibiotic prophylaxis can prevent infection and rebleeding as well as decrease the amount of blood transfused for patients with acute GEVB following endoscopic treatment								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Rolando N, Gimson A, Philpott-Howard J, et al. Infectious sequelae after endoscopic sclerotherapy of oesophageal varices: role of antibiotic prophylaxis. J Hepatol 1993 Jul;18:290-4.	RCT, single centre Country: UK Adequate sequence generation, allocation concealment unclear, not blinded, Per protocol analysis	Per protocol: N= 50 control group; N=47 antibiotic group 3 patients were excluded due to protocol violation, but not specified which group they stemmed from	Inclusion criteria: Patients with bleeding oesophageal varices Exclusion criteria: Not explicitly stated Baseline characteristics – described as being non significant but no p-values provided:	intravenous imipenem + cilastin, 500 mg before and after the sclerotherapy	intravenous dextrose-saline solution	7 days	Bacterial infections, mortality	Merck, Sharpe & Dohme Ltd. (supplied the antibiotic medication)

	Antibiotic N=47	Control N=50
Age median (range)	54 (20-76)	46 (18-84)
Male	24	30
Bilirubin mmol/l mean, median	95, 72 (7-485)	117, 71 (13-633)

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			(range)							
			INR mean, median (range)	1.4, 1.3 (1.0-2.9)	1.5, 1.4 (1.0-3.9)					
			Albumin g/l mean, median (range)	28,28 (21-41)	28, 28 (9-58)					
			Coma grade 0/1/2/3/4	34/1/1/4/7	31/10/2/2/5					
			Ascites grade 0/1/2/3	17/9/6/15	15/10/10/15					
			Intubation	9	8					
			Previous bleeds	17	22					

Effect size

Post-treatment outcomes – shaded cells highlight significant differences

	Antibiotic N=47	Control N=50	p-value
Mortality	10	14	≥ 0.1, ns
Bacterial infections – number of episodes	18	25	≥0.1, ns
Spontaneous bacterial peritonitis	1	6	≥ 0.1, ns
Pneumonia	2	4	≥0.1, ns
Urinary tract infection	3	6	≥ 0.1, ns

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Clinical bacteraemia		4	4	ns				
Authors' conclusion A short prophylactic antibiotic regime does not reduce the risk of early bacteraemia or the frequency of infection after sclerotherapy.								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Pauwels A, Mostefa-Kara N, Debenes B, et al. Systemic antibiotic prophylaxis after gastrointestinal hemorrhage in cirrhotic patients with a high risk of infection. Hepatology 1996;24(4):802-6.	RCT single centre Country: France Unclear randomisation sequence generation, unclear allocation concealment, not blinded Per protocol analysis	Per protocol analysis: Control group N=34 antibiotics group N=30 Numbers randomised: antibiotic group N=41 (3 patients with signs of infection; 2 died within 24 hrs; 2 underwent surgery) Control group N=40 (6 patients had signs of infection; 2	Inclusion criteria: patients with cirrhosis admitted to hospital because of gastrointestinal haemorrhage. Exclusion criteria: patients treated with antibiotics during the week before admission; patients with a history of allergy to penicillins or quinolones; and patients with signs of infection on admission. The authors also excluded patients with proven infection on admission, patients who died within the first 12 hours after admission or patients who underwent surgery within the first 24 hrs after admission were excluded from analysis of results. Patients were first divided into Child-Pugh classes A/B (as one	intravenous + oral ciprofloxacin 400mg per day, amoxicillin-clavulanic acid 3g per day, until three days after cessation of haemorrhage	No antibiotic prophylaxis	10 days after bleeding stopped (4 weeks)	Bacterial infections, 4 week mortality, length of ICU stay	Not stated

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td></td><td>died within 24 hrs; 2 underwent surgery)</td><td>group) and C. Child-Pugh class C patients were randomised on admission to the trial. If patients in the Child-Pugh grade A/B group re-bled they were then randomised at a later stage. Those who did not re-bleed were not randomised and received placebo treatment.

Baseline characteristics – baseline indifference highlighted in shaded row:
<table>
<tr><td></td><td>Control group N=34</td><td>Antibiotic group N=30</td></tr>
<tr><td>Age</td><td>53 (3)</td><td>51 (2)</td></tr>
<tr><td>Male</td><td>24</td><td>14</td></tr>
<tr><td>Aetiology A/O</td><td>21/13</td><td>27/3</td></tr>
<tr><td>History of bleeding</td><td>15</td><td>17</td></tr>
<tr><td>Child Pugh A/B/C</td><td>0/10/24</td><td>2/3/25</td></tr>
<tr><td>Bilirubin (µmol/L)</td><td>89(18)</td><td>90(18)</td></tr>
<tr><td>Albumin (g/L)</td><td>25.6 (0.6)</td><td>24.7 (0.5)</td></tr>
<tr><td>Prothrom</td><td>41 (2)</td><td>42 (2)</td></tr>
</table></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			bin (%)							
			Encephalopathy Degree 3-4	5	4					
			Creatinine (µmol/L)	97 (7)	86 (6)					
			Shock	17	15					
			Rebleeding*	19	20					
			Diuretics	2	8					
			*not entered as an outcome since half of the randomised patients stemmed from a group experiencing rebleeding							

Effect size

Post treatment outcomes

	Control group N=34	Antibiotic group N=30	p-value*
Mortality at 4 weeks**	10/38	6/34	
Haemorrhage	1	2	
Septic shock	3	1	
Liver failure	4	1	
Patients with infections	18	4	<0.001
Proven infections	13	2	
Bacteraemia	13	2	
Spontaneous bacterial peritonitis	7	1	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Respiratory			3 (2 purulent bronchitis; 1 pneumonia)	0				
Urinary			2	0				
Meningitis			1	0				
Possible infections†			2	2				
Patients with sepsis syndrome or septic shock			12	2		<0.01		
Length of ICU stay			7.4 (1.1)	6.5 (0.9)				
Surgery			3/38	3/34				

*only significant p-values reported

** This included patients that had died within the first 12 hrs who were excluded by the authors (no other outcome data available for these patients)

† * Patients with fever and/or leukocytosis with a shift to the left but without any other evidence of infection were considered as having 'possible infections'.

Authors' conclusion

Patients with a Child-Pugh C and/or a rebleeding are a subgroup of cirrhotic patients with a high risk of infection after gastrointestinal haemorrhage and in these patients, a prophylactic treatment with systemic antibiotics is very effective in preventing bacterial infections.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Blaise M, Pateron D, Trinchet JC, et al. Systemic antibiotic therapy prevents bacterial infection in	RCT, single centre, country: France Unclear randomisation sequence generation,	Randomised: N=58 antibiotic group; N=59 control (on demand) group Per protocol analysis: N=12	Inclusion criteria: Patients with cirrhosis hospitalised in intensive care units for upper gastrointestinal haemorrhage. Exclusion criteria: Patients already on antibiotics during the 2 wks before hospitalisation; patients with infections on admission;	intravenous + oral ofloxacin, 400 mg/day, 10 days; amoxicillin + clavulanic acid (bolus,	Received antibiotic therapy adapted to the clinical and bacteriological data only if infection occurred	14 days	Occurrence of infection, mortality	Not stated

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>cirrhotic patients with gastrointestinal hemorrhage. Hepatology 1994 Jul;20:34-8.</td><td>unclear allocation concealment, not blinded

Per protocol analysis</td><td>antibiotic group (N=7 signs of infection; N=5 no variceal bleeding) N=14
control group (N=8 signs of infection; N=6 no variceal bleeding)</td><td>patients with allergy to quinolone or beta-lactamines; patients with valvular posthesis; patients who had no oesophageal varices; and patients whose initial bacteriological samplings turned out positive.

All patients had a central venous catheter.

Baseline characteristics – no significant group differences (but p-values not reported). Expressed as mean (sd) or N:
<table>
<tr><th></th><th>Antibiotic N=46</th><th>Control N=45</th></tr>
<tr><td>Age</td><td>52 (11)</td><td>54 (9)</td></tr>
<tr><td>Male</td><td>33</td><td>36</td></tr>
<tr><td>Aetiology A/O</td><td>41/5</td><td>39/6</td></tr>
<tr><td>Child-Pugh class A/B/C</td><td>0/11/35</td><td>0/9/36</td></tr>
<tr><td>Ascites</td><td>22</td><td>17</td></tr>
<tr><td>Bilirubin (mmol/L)</td><td>38 (4.6)</td><td>42 (5.3)</td></tr>
<tr><td>Albumin (gm/L)</td><td>22 (3.2)</td><td>24 (3.7)</td></tr>
</table></td><td>1g) before each endoscopy procedure</td><td></td><td></td><td></td><td></td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Prothrombin level (%)	31 (11)	36 (7)					
			Shock	27	32					

Effect size

Post treatment outcomes

	Control group N=34	Antibiotic group N=30	p-value*
Mortality at 4 weeks**	10/38	6/34	
Haemorrhage	1	2	
Septic shock	3	1	
Liver failure	4	1	
Patients with infections	18	4	<0.001
Proven infections	13	2	
Bacteraemia	13	2	
Spontaneous bacterial peritonitis	7	1	
Respiratory	3 (2 purulent bronchitis; 1 pneumonia)	0	
Urinary	2	0	
Meningitis	1	0	
Possible infections†	2	2	
Patients with sepsis syndrome or septic shock	12	2	<0.01
Length of ICU stay	7.4 (1.1)	6.5 (0.9)	
Surgery	3/38	3/34	

*only significant p-values reported

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
** This included patients that had died within the first 12 hrs who were excluded by the authors (no other outcome data available for these patients) † * Patients with fever and/or leukocytosis with a shift to the left but without any other evidence of infection were considered as having 'possible infections'. Authors' conclusion Patients with a Child-Pugh C and/or a rebleeding are a subgroup of cirrhotic patients with a high risk of infection after gastrointestinal haemorrhage and in these patients, a prophylactic treatment with systemic antibiotics is very effective in preventing bacterial infections.								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Selby WS, Norton ID, Pokorny CS, et al. Bacteremia and bacterascites after endoscopic sclerotherapy for bleeding esophageal varices and prevention by intravenous cefotaxime: a randomized trial. Gastrointest Endosc 1994;40:680-	RCT, single centre, Country: Australia Unclear randomisation sequence generation, unclear allocation concealment (sealed envelopes) not blinded Per protocol analysis	Numbers randomised: N=19 antibiotic group N=20 control group (1 patient from the control group was excluded from their analysis due to signs of infection)	Inclusion criteria: patients with bleeding oesophageal varices (who had emergency sclerotherapy) Exclusion criteria: patients who had received antibiotics within 72 hrs or if antibiotics were required for other indications; patients with known allergies to antibiotics Patients could be enrolled on more than one occasion provided the exclusion criteria did not apply Baseline characteristics: Antibiotics N=19 / Control N=20 Age: 58.9 (14.2) / 49.5 (10.7)	intravenous cefotaxime, 1 g immediately before sclerotherapy	No antibiotic prophylaxis	24 hrs	Presence of infection, mortality	Not stated

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>4.</td><td></td><td></td><td>
<table>
<tr><td>Male</td><td>15</td><td>13</td></tr>
<tr><td>Cause of cirrhosis Alc/HepC/ HepB/other</td><td>11/3/2/3</td><td>12/4/1/3</td></tr>
<tr><td>Child-Pugh class A/B/C</td><td>4/8/7</td><td>4/10/6</td></tr>
<tr><td>Ascites</td><td>5</td><td>7</td></tr>
<tr><td>Intubation</td><td>7</td><td>9</td></tr>
<tr><td>Balloon tamponade</td><td>2</td><td>3</td></tr>
</table>
</td><td></td><td></td><td></td><td></td></tr>
</table>

Effect size

Post-treatment outcomes – shaded cells highlight significant differences

	Antibiotics N=19	Control N=20	p-value
Bacteraemia	1	6	0.04
Mortality (24 hrs)	2	5	0.16

Authors' conclusion

The frequency of bacteraemia after endoscopic sclerotherapy for bleeding oesophageal varices can be reduced by prophylactic administration of intravenous cefotaxime. However, this may not be clinically relevant, given the absence of ascites and infection in this study. These findings do not support the routine use of antibiotics before sclerotherapy.

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Soriano G, Guarner C, Tomas A, et al. Norfloxacin prevents bacterial infection in cirrhotics with gastrointestinal hemorrhage. Gastroenterology 1992;103:1267-72.</td><td>RCT, single centre,
Country: Spain

Unclear randomisation sequence generation, unclear allocation concealment, not blinded

Per protocol analysis</td><td>Per protocol analysis: N=60 antibiotic group, N=59 control group

Number randomised: N=64 antibiotic (3 patients died / surgery unclear which applied; 1 discharged himself)
N=64 control group (5 patients died / surgery unclear which applied)</td><td>Inclusion criteria: patients with cirrhosis and gastrointestinal haemorrhage
Exclusion criteria: patients with signs of infection at admission; patients treated with antibiotics during the 2 weeks before admission; and patients transferred from other hospitals

Baseline characteristics – all described as non-significant but no statistics provided:
<table><tr><th></th><th>Antibiotic N=60</th><th>Control N=59</th></tr><tr><td>Age</td><td>13.5 (9.2)</td><td>14.4 (10.9)</td></tr><tr><td>Male</td><td>31</td><td>30</td></tr><tr><td>Aetiology (alc/oth)</td><td>33/27</td><td>34/25</td></tr><tr><td>Child-Pugh class A/B/C</td><td>19/30/11</td><td>21/25/13</td></tr><tr><td>Ascites</td><td>15</td><td>14</td></tr><tr><td>Encephalopathy</td><td>11</td><td>10</td></tr><tr><td>Bilirubin (µmol/L)</td><td>41.9 (48.5)</td><td>35.3 (26.7)</td></tr></table></td><td>oral norfloxacin 400 mg twice/day during seven days</td><td>No antibiotic prophylaxis</td><td>Unclear, but day 26 of hospitalisation (for late infection diagnosis) was reported</td><td>Presence of infections, mortality (causes of), encephalopathy, rebleeding, transfusion requirements, need for surgery, length of hospitalisation</td><td>Not stated</td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Albumin (g/L)	30.4 (4.2)	31.2 (6.4)					
			Prothrombin time (%)	57.2 (15.7)	57.5 (14.5)					
			Creatinine (µmol/L)	104.9 (58.2)	100.8 (60.0)					

Effect size

Post-treatment outcomes – no exact p-values given (only significant p-values reported

	Antibiotic N=60	Control N=59
Mortality	4	7
Length of hospitalisation (days)	13.5 (9.2)	14.4 (10.9)
Encephalopathy	13	11
Rebleeding	10	9

Details of infections – expressed as number of patients (number of instances)

	Antibiotic N=60	Control N=59	
Infections	6 (6)	22 (26)	0.001
Bacteraemia	0 (0)	6 (6)	<0.05
spontaneous bacterial peritonitis or culture negative neutrocytic ascites	2 (2)	4 (4)	
Urinary	0	11 (11)	0.001
Respiratory	4(4)	4 (4)	
Perianal abscess	0	1 (1)	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Possible infections*			6 (6)	6 (6)				

* Patients with fever and/or leukocytosis with a shift to the left but without any other evidence of infection were considered as having 'possible infections'.

Authors' conclusion

Selective intestinal decontamination with norfloxacin is useful in preventing bacterial infections in patients with cirrhosis with gastrointestinal haemorrhage.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hsieh WJ, Lin HC, Hwang SJ, et al. The effect of ciprofloxacin in the prevention of bacterial infection in patients with cirrhosis after upper gastrointestinal bleeding. Am J Gastroenterol 1998 Jun;93:962-6.	RCT, single centre, Country: Taiwan Unclear randomisation sequence generation, unclear allocation concealment, not blinded (placebo not described) ITT analysis	N=60 Ciprofloxacin; N=60 Placebo	Inclusion criteria: patients with cirrhosis and upper gastrointestinal bleeding Exclusion criteria: patients who showed signs of infections (fever chills and leukocytosis), patients who had received oral or parenteral antibiotics in the prior 2 wks before enrolment in the study Baseline characteristics – expressed as mean (sd) or N:	oral ciprofloxacin, 1 g/day, 7 days	placebo	30 days	Primary endpoint: rate and type of infections Secondary outcomes: mortality, rebleeding, length of hospital stay, surgery, transfusion requirements	Grant from the participating hospital (Veterans General Hospital Taipei) and grant from the National Science Council of Taiwan

	Ciprofloxacin N=60	Placebo N=60
Age	58 (14)	62 (13)
Male	47	42
Aetiology Alc/HepB	6/53/1	9/48/3

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			or HepC/others							
			Esophageal or gastric ulcers	42	41					
			Peptic ulcers	13	13					
			Others types of hemorrhage	1	3					
			Child-Pugh grade A/B/C	5/33/22	6/31/23					
			Ascites	28	30					
			Previous SBP*	10	12					
			Hepatocellular carcinoma	29	19					
			Encephalopathy	17	17					
			Stage 1-2/3-4	12/5	12/5					
			*spontaneous bacterial peritonitis							

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Effect size

Post-treatment outcomes: infections – shaded cells indicate significant differences:

	Ciprofloxacin N=60	Placebo N=60	p-value
Patients with bacterial infections	6	27	<0.001
Bacteraemia	0	14	<0.001
Spontaneous bacterial peritonitis	2	8	<0.05
Urinary tract infections	3	11	<0.05
Pneumonia	2	3	NS

Post- treatment outcomes: clinical – none of the differences described as significant but p-values were not provided

	Ciprofloxacin N=60	Placebo N=60
Hypovolemic shock	19	13
Early rebleeding (during first 7 days)	4	7
Transfusion requirements (units of RBCs)	9.1 (7.4)	10.0 (15.0)
Urinary catheter insertion	21	20
Surgery	5	2
Length of hospital stay	19 (12)	26 (18)
30 day mortality	13	18

Authors' conclusion

Prophylactic intestinal decontamination by oral ciprofloxacin reduced the incidence of bacterial infections in cirrhotic patients with upper gastrointestinal haemorrhage without major side effects..

F.7.2 Band ligation vs. sclerotherapy

QUESTION In patients with confirmed oesophageal varices is band ligation superior to injection sclerotherapy in terms of rebleeding and death?

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Baroncini D, Milandri GL, Borioni D et al. A prospective randomized trial of sclerotherapy versus ligation in the elective treatment of bleeding esophageal varices. Endoscopy. 1997; 29(4):235-240.	RCT, Italy Randomisation, allocation method and blinding not stated	111	Inclusion: recent (up to 1 week previously) bleeding from oesophageal varices Exclusion: under 18 years old; already treated with surgery or endoscopically for varices; gastric varices; hepatocellular carcinoma; other severe diseases likely to reduce survival; active bleeding at index endoscopy; patients who did not undergo at least 3 endoscopic examinations per year. Recurrence treated with same randomised technique. After eradication, endoscopy every 3 months. Patients having orthoptic liver transplant censored at time of transplant. Baseline characteristics:	Ligation (n=57): 1st 10 patients, treatments at 7-day intervals, rest every 14 days. Largest number of elastic bands possible positioned in distal oesophagus. Treatment continued until all varices eradicated (the presence only of vessels too small to treat).	Sclerotherapy (n=54) with 1% polidocanol (peri- and intra-variceal) on distal 5-6cm of oesophagus; 1st 3 sessions at weekly intervals; rest every 2 weeks; 1st session peri-variceal only; 2nd peri- and intra-variceal; 3rd onwards; intra-variceal only. Treatment continued until all varices eradicated (absence of any varices in treated	At least 45 days; mean follow up 496 (40) days for ligation and 534 (42) fr sclerotherapy (NS)	Percentage eradication of varices; number of treatment sessions required for eradication; frequencies of rebleeding (haematemesis or melaena + reduction in haemoglobin of at least 2g/dL) and recurrence of varices (endoscopic finding of varices in patients in whom eradication had been previously obtained); complications (resulting event requiring	not stated

	Ligation	Sclero	p value
Age (yr)	63.0 (9.1)	61.4 (9.8)	NS
M:F	38:19	37:17	NS
Aetiology of cirrhosis: Alcoholic Viral hepatitis	 7 49	 8 44	NS

Reference	Study type	No. pts	Patient characteristics				Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			1ry biliary Sarcoid	1 0	1 1			segment).		treatment, supplementary therapy or extension of hospital stay); mortality. Treatment failure (failure to eradicated varices, rebleeding, recurrence during follow up or death).	
			Child-Pugh: Class A Class B Class C	 17 24 16	 18 22 14	NS					
			Hb (g/dL)	10.4 (0.2)	9.5 (0.2)	0.01					
			Platelet count (k/mm3)	74.0 (5.4)	98.3 (9.1)	0.02					
			Variceal size (f3/f2)	42/15	36/18	NS					

Results:

	Ligation (n=57)	Sclerotherapy (n=54)	p va
Patients with variceal eradication n (%)	53 (93.0%)	50 (92.5%)	NS
Sessions to eradication	3.5 (0.1)	4.0 (0.1)	0.00
Mean time to eradication (days)	33.8 (2.1)	27.3 (1.4)	0.01
Patients with rebleeding: Rebleeding due to oesophageal varices Before eradication After eradication	9 (16%) 2 4 (treatment-induced ulcer) 5	10 (19%) 3 3 (treatment-induced ulcer) 7	NS

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Source of rebleeding:								-
Oesophageal ulcer			5	3				
Oesophageal varices			2	3				
Gastric varices			0	2				
Portal hypertensive gastropathy			2	1				
Indeterminate			0	1				
Patients with recurrent varices n (%)			17 (30%)	7 (13%)				0.03
Complications:			6 (11%)	20 (37%)				0.001
Stricture			0	17 (31%; treated successfully with endoscopic dilatation)				
Sepsis			0	1				
Oesophageal ulcer			1	1				
Pleural effusion			0	1				
Treatment-induced bleeding			2 (accidental detachment of band)	0				
Oesophageal perforation			1	0				
Submucosal haematoma			2	0				
Complications resulting in death			0	1				
Patients in whom eradication not achieved			4 (1 died of rebleeding; 2 died of hepatic failure; 1 declined further treatment)	4 (1 died of rebleeding; 3 died of hepatic failure)				
Mortality:			12 (21%)	12 (22%)				NS
Hepatic failure			9	6				
Oesophageal bleeding			1	3				
Sepsis			0	1				
Other			2	2				
Author's conclusions: Ligation is an effective technique in the elective treatment of oesophageal varices. Compared with sclerotherapy, it has advantages in the short-term but a higher rate of recurrences in the longer term. All patients should have frequent endoscopic examinations throughout the first year to allow detection and								

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
treatment of recurrences.								

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Bhuiyan MMR, Rahman MM, Kibria MG, Hasan M. Comparative study of endoscopic band ligation and sclerotherapy for treatment of oesophageal varices in cirrotic patients.	RCT. Country: Bangladesh. Randomisation method not stated, and no evidence of allocation concealment. No blinding. Loss to follow up reported, but no imputation of values.	150 (75 in ligation group and 75 in sclerotherapy group)	Inclusion: Cirrhotic patients with active or recent bleeding from oesophageal varices. Exclusion: Contraindicationd to endoscopy; previous endoscopic or operative treatment for esophageal varices; presence of gastric varices; concurrent illness or death expected in 6/12; Malignancy. Baseline characteristics: Mean (sd) given. No statistical significance indicated. Stated the two groups "did not differ". Ligation (n=75) / Sclero (n=75 Age: 35 (13) / 33(15) Sex (M/F): 45/30 / 50/25	Band ligation performed with the rubber band ligating device. All varices ligated at least once during treatment and larger varices ligated at two separate points. A maximum of 6 bands applied during individual sessions. Banding begun at the oesophagealgast	5% ethanolamine oleate solution used as sclerosant, and varices injected both intra and paravariceally with a 25 guage disposable needle. Up to 2ml of sclerosant injected at each varix, with a maximum of	337 days for sclerotharapy and 376 days for band ligation group.	Mortality Rebleeding Treatment failure Number of sessions required to eradication Adverse events	None stated

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Bangladesh Medical Research Council Bulletin 2007; 33: 31-39.	In ligation group, 2 withdrawn and 2 lost to follow up. Also reported that 2 unable to comply with repeated endoscope exams, but point at which these were withdrawn not clear. In sclerotherapy group, 3 withdrawn and 2 lost to follow up. Also reported that 5 unable to comply with repeated endoscope exams, but point at which these were withdrawn not clear.		Cirrhosis due to hepatitis BV	48	50	ric junction, and continued to 7cm above. Treatment repeated at 7 days and then at 21 day intervals until varices obliterated or complications led to withdrawal.Treatment temporarily withheld if oesophageal ulceration or strictures observed.	20ml per session. Treatment begun at the oesophagealgastric junction, and continued to 7cm above. Treatment repeated at 7 days and then at 21 day intervals until varices obliterated or complications led to withdrawal. Treatment temporarily withheld if oesophageal ulceration or strictures observed.			
			Cirrhosis due to HCV	13	15					
			Alcoholic	4	4					
			Unknown etiology	4	6					
			Child Pugh A/B/C	23/33/17	25/38/12					
			Mean Child score	9.2 (2.4)	8.9 (3.1)					
			Patients with active bleeding	39	36					
			Blood transfusion for index episode (units)	3.5 (2.6)	3.7 (2.1)					
			Serum albumin (g/dl)	25.6 (5.2)	28.9 (6.0)					
			Total bilirubin (mmol/lit)	35 (60)	24 (75)					
			Prothrombin time	14 (6)	13.5 (3)					
			Number with active haemorrhage at endoscopy	39	36					

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Mean time since previous haemorrhage (weeks/ range)	6 (1-12)	7 (1-10)					
			Grade of varices at index treatment 4/3/2	33/35/7	28/40/7					
			Portal hypertensive gastropathy							

Results:

	Ligation (n=75; see notes in "study type" section)	Sclerotherapy (n=75; see notes in "study type" section)	p va
Mortality Survival: KM graph given but no other data	3/75	4/75	Not
Rebleeding	8/75	20/75	
Treatment failure (no initial hemostasis of those with active bleeding at baseline at 12 hours)	Unclear data. Ambiguity about the total to which the %s of failure (5%) refer to – 75 or the 39 who had active bleeding. The latter seems more relevant as this yields a whole number (cannot have a half person).	Unclear data. Ambiguity about the total to which the %s of failure (7%) refer to – 75 or the 36 who had active bleeding. The former seems more relevant as this yields a whole number. Unfortunately this is inconsistent with the ligation group!	
Number of sessions required to eradication	2.3 (3.1)	5.2 (2.1)	0.00
Adverse events (not stated if they led to death or withdrawal from treatment)			

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Bleeding from oesophageal ulcers requiring hospitalisation and transfusion			1/75	6/75				
Severe odynophagia and dysphagia requiring hospitalisation			0/75	1/75				
Stricture			8/75 0/75	10/75 10/75				

Author's conclusions: We suggest that band ligation has less local complications and causes earlier eradication of varices than sclerotherapy. Therefore, band ligation may be teh first choice of therapy for oesophageal varices.

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
De la Pena, Rivero M, Sanchez E, Fabrega E, Crespo J, Pons-Romero F. Variceal	RCT. Country; Spain. Valid randomisation	88 (46 sclero, 42 ligation). ITT results presented. Loss to follow up was 7 in	Inclusion: esophageal* variceal hemorrhage diagnosed by endoscopy; aged 18-75 years; hepatic cirrhosis. Exclusion: >5 days since index event; hepatocarcinoma; previous endoscopic or surgical treatments; portal vein thrombosis; Hx of bleeding from large fundal varices. Baseline characteristics:	After variceal and gastric endoscopic exploration, a guidewire was left in the stomach, and the endoscope was removed. A dilator was passed over the	Sclerotherapy was performed with an Olympus 1T-130 endoscope and a 25 guage disposable injection needle.Ethanolamine (5%) was injected	Ligation 16 months (range 1-46); sclera 18	Mortality Rebleeding	Not stated

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>ligation compared with endoscopic sclerotherapy for variceal hemorrhage: prospective randomised trial. Gastrointestinal Endoscopy 1999; 49: 417-423.</td>
<td>method but no allocation concealment evident. No evidence of blinding.</td>
<td>sclerotherapy group and 3 in the ligation group.</td>
<td>
<table>
<tr><th></th><th>Ligation (n=42)</th><th>Sclero (n=46)</th><th>p value</th></tr>
<tr><td>M/F</td><td>34/8</td><td>30/16</td><td>NS</td></tr>
<tr><td>Age (range)</td><td>59 (28-74)</td><td>59 (32-75)</td><td>NS</td></tr>
<tr><td>Alcoholic aetiology</td><td>29</td><td>29</td><td>NS</td></tr>
<tr><td>Viral aetiology</td><td>9</td><td>12</td><td>NS</td></tr>
<tr><td>Other aetiology</td><td>4</td><td>5</td><td>NS</td></tr>
<tr><td>Child Pugh (A/B/C)</td><td>10/22/10</td><td>11/22/13</td><td>NS</td></tr>
<tr><td>Shock</td><td>39/3</td><td>41/5</td><td>NS</td></tr>
<tr><td>Elective</td><td>18/24</td><td>22/24</td><td>NS</td></tr>
<tr><td>Variceal size (II/III/IV)</td><td>6/25/11</td><td>10/31/5</td><td>NS</td></tr>
<tr><td>Blood transfusion (units)</td><td>3.3 (2.7)</td><td>4.33 (3.8)</td><td>NS</td></tr>
<tr><td>Follow up months (range)</td><td>16(1-46)</td><td>18(1-48)</td><td>NS</td></tr>
</table>
*the word esophageal is only used once,
</td>
<td>guidewire with an overtube mounted on the dilator. The dilator and guidewire were removed, and the endoscope, with the ligating device attached, was introduced via the overtube as many times as needed for bands placement. Beginning at the cardia, each varix was ligated as many times as necessary to make it no longer visible. The maximum number of bands placed per session was 9.
After reduction to grade I by banding it would occasionally be hard to place more bands, so in such a case the sclerotherapy regime would be instituted for those varices.</td>
<td>(1mL per puncture) intravariceally, beginning at the cardia and moving proximally at 1cm interval, with a maximum of 5ml injected per varix. This was followed by perivariceal injections (o.5 mL per injection) of Polidocanol (1.5%) with injection volume being limited to no more than 3 ml per varix.
Sessions performed at 1,2 and 3 weeks, and every 3 weeks thereafter, until variceal eradication was achieved. After eradication, endoscopy was performed at 3,6 and 12 months and then yearly with further treatment if necessary.</td>
<td>months (1-48)</td>
<td>Adverse effects

Blood transfusion</td>
<td></td>
</tr>
</table>

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			obliquely, throughout the article ["The aim of this study was to compare the efficacy of VL and ES after esophageal variceal bleeding..."], but does suggest that only oesophageal varices were included. The descriptions of the techniques partially support this.	Sessions performed at 1,2 and 3 weeks, and every 3 weeks thereafter, until variceal eradication was achieved. After eradication, endoscopy was performed at 3,6 and 12 months and then yearly with further treatment if necessary.				

Results:

	Ligation (n=42)	Sclerotherapy (n=46)	p va
Mortality	8/42	10/46	NS
Rebleeding	13/42	23/46	0.03
Adverse effects leading to death	0/42	1/46	Not
Adverse effects (not stated if leading to withdrawal) - total	6/42	19/46	0.00
Dysphagia	1/42	8/46	Not
Peptic oesophagitis	0/42	2/46	Not
Esophageal ulcer bleeding	3/42	2/46	Not
Large submucosal hematoma	0/42	2/46	Not
Perforation	0/42	2/46	Not
Chest pain	0/42	1/46	Not

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Dysphagia			0/42	1/46				Not given
Bacteremia			1/42	1/46				Not given
Accidental banding in the arytenoids			1/42	0/46				Not given
Stricture (stenosis)			0/42	2/46				
Blood transfusion (units)			3.5 (1.77)	3.15 (1.77)				NS

Author's conclusions: variceal ligation was superior to sclerotherapy in terms of the rate of recurrent bleeding and the occurrence of complications but worse with respect to recurrence of varices.

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Gimson AE, Ramage JK, Panos MZ et al. Randomised trial of variceal banding ligation versus injection sclerotherapy for bleeding oesophageal varices. Lancet. 1993; 342(8868):391-394. Ref ID: 5200</td><td>RCT, UK

randomisation method not stated; allocation concealment adequate</td><td>103</td><td>Inclusion: Patients admitted within 10 days of upper gastrointestinal haemorrhage from oesophageal varices. Active bleeding not controlled by randomised therapy was controlled using vasoconstrictor therapy, balloon tamponade or both. Endoscopy every week until obliteration, then at 1, 3, 6 and 12 months or if rebleeding occurred. All patients received sucralfate.

Exclusion: age under 18 years, previous endoscopic treatment of oesophageal varices, expected survival less than 6 months.

Baseline characteristics:
<table><tr><td></td><td>Ligation</td><td>Sclero</td></tr><tr><td>Mean age (yr)</td><td>53.9 (13.8)</td><td>48.8 (14.4)</td></tr><tr><td>M:F</td><td>32:22</td><td>25:24</td></tr><tr><td>Aetiology:
Alcoholic
1ry biliary
Cryptogenic
Chronic active
Other</td><td>
25
7
8
6
7</td><td>
24
7
4
3
11</td></tr><tr><td>Child-Pugh:
Class A</td><td>
14 (26%)</td><td>
15 (31%)</td></tr></table></td><td>Ligation (n=54); single elastic rings at or near gastro-oesophageal junction and continued up oesophagus for 4-5cm (not below g-o junction</td><td>Sclerotherapy (n=49) with ethanolamine intra-variceally within lower 4cm of oesophagus.</td><td>337 (range 2-1230) days for ligation group vs. 322 (2-1200) days for scleroth erapy</td><td>Control of active variceal bleeding (haemostasis 12 hours after 1st endoscopy + stable vital signs and packed cell volume and no haematemesis), time to obliteration of varices, frequency of variceal rebleeding (upper g-I haemorrhage requiring endoscopy and fall in Hb >20g/L), complications, mortality. Patients withdrawn from trial if did not attend follow up for more than 30 days; too frail to continue regular</td><td>not stated</td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Class B	25 (46%)	22 (45%)				endoscopy, or referred for liver transplant.	
			Class C	15 (28%)	12 (24%)					
			No (%) with							
			Gastric varices	17 (31%)	21 (43%)					
			Portal hypertensive gastropathy	23 (43%)	20 (41%)					
			Active haemorrhage at endoscopy	21 (39%)	23 (47%)					

Results:

	Ligation	Sclerotherapy	p value
Haemostasis of active varcieal haemorrhage at 12 hours (%)	91%	92%	
Additional therapy required (n)	3 (1 vasoconstrictor therapy, 1 balloon tamponade, 1 injection sclerotherapy)	3 (1 balloon tamponade, 2 further injection sclerotherapy)	
Mean time to obliteration (when achieved) days	39 (4)	72 (7)	0.004
Number of sessions to obliteration	3.4 (2.2)	4.9 (3.5)	0.006
Variceal obliteration not achieved (n)	22	22	
Number of patients surviving >30 days with visible varices	7/38 (18%)	11/37 (29%)	
Rebleeding n (%) due to:	16 (30%)	26 (53%)	<0.05
Oesophageal varices	13	25	
Gastric	4	1	
Treatment-induced oesophageal ulcer	1 (4%)	3 (10%)	
Indeterminate	5	4	

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Complications:							NS	
Oesophageal ulcer				36	28			
Stricture				0	0			
Withdrawal from trial:				5	14		0.023	
Liver transplant				1	7		0.047	
Loss to follow up				2	5			
Too frail for endoscopies				2	2			
Survival				28 (52%)	18 (37%)		NS	

Author's conclusions: Variceal band ligation is a safe and effective technique which obliterates varices more quickly and with a lower rebleeding rate than injection sclerotherapy.

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Gralnek IM, Jensen DM, Kovacs TOG et al. The economic impact of esophageal variceal hemorrhage: cost-	RCT (for cost-effectiveness analysis). Country: USA. Allocation concealment	35 ligation, 31 sclerotherapy.	Inclusion: active or recent severe UGI hemorrhage, documented from esophageal varices, requiring hospitalisation and blood transfusion Exclusion: pregnancy, advanced liver disease in which the patient was not expected to survive hospitalisation, known hepatoma, serious intercurrent illness, the acquired immune deficiency syndrome, prothrombin time greater than 6 seconds prolonged from	The varix was initially ligated using a single-shot endoscopic ligating device (Bard Interventional Products). For severe	The varix was injected intravariceally with TES solution (3% tetradecyl sulphate mixed in equal volumes with absolute	12 months	Variceal rebleeding, variceal obliteration, treatment failure, rates of surgical or radiographic protosystemic shunt	NIH

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>effectiveness implications of endoscopic therapy. Hepatology. 1999; 29:44-50:44-50. Ref ID: 358</td><td>adequate but randomisation sequence generation not described

ITT analysis,
Loss to follow up (13% sclerotherapy, 14% ligation)</td><td></td><td>control, platelet count less than 50 000, two different nonbleeding lesions on endoscopy from which it was not possible to determine the exact bleeding site, or lack of written, informed consent.

Baseline characteristics: significant difference highlighted in bold

Unless otherwise specified values represent means (SEM):
<table>
<tr><td></td><td>Sclero (n=31)</td><td>Ligation (n=35)</td></tr>
<tr><td>M/F</td><td>26/5</td><td>26/9</td></tr>
<tr><td>Age yrs – mean</td><td>50(2)</td><td>54 (2)</td></tr>
<tr><td>Etiology
Hep B or C
Alcoholic cirrhosis
Cryptogenic
Other</td><td>
11
21
4
0</td><td>
9
22
3
1</td></tr>
<tr><td>Child’s Pugh A/B/C</td><td>11/7/13</td><td>10/916</td></tr>
<tr><td>Serum total albumin (g/dL)</td><td>3.0 (0.1)</td><td>3.8 (1.1)</td></tr>
<tr><td>Platelet count (K/mm3)</td><td>122</td><td>123</td></tr>
</table></td><td>active bleeding that was not controlled by attempting to ligate the site of bleeding changes in patient position, banding distal to the bleeding site and substitution endoscopes with large suction channels were used. All remaining esophageal varices were then ligated in sdistal-to-proximal manner same as in sclerotherap</td><td>ethanol and normal saline) up to 2 mL per injection using a 5-mm, 25-gauge sclerotherapy needle. All remaining esophageal varices were then similarly injected intravariceally beginning at the gastoesophageal junction, 2.5 cm and 5 cm above the gastroesophageal junction.</td><td></td><td>(TIPS), and death, days in hospital (ICU days, non-ICU days), transfusion requirements, major complications (esophageal perforation, esophageal stricture)</td><td></td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

	(11)	(23)	y
Prothrombin time (s)	14.8 (0.7)	14.9 (0.4)	
Shock, n	2	4	
Varix size:			
Giant	1	11	
Large	22	21	
Medium	6	2	
Small	2	1	

Results:

Post-treatment outcomes – significant differences in bold (mean and SD):

	Sclerotherapy (n=31)	Ligation (n=35)	p value
Mortality	9	14	NS
Bleeding	13	15	NS
Failures n	0	6	0.016
Surgical shunt	3	0	0.10
TIPS	1	2	NS
Number of sessions required to achieve obliteration of varices.	3.4(1.5)	3.3 (2.4)	NS
Hospital days:			
ICU	7.0 (10.0)	7.5 (13.6)	NS
Non-ICU	16.8 (21.7)	17.3 (20.7)	NS
Transfusion units:			
Packed red cells	2.1 (3.3)	2.2 (3.5)	NS

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Fresh frozen plasma			1.6 (3.9)	1.6 (4.1)		NS		
Platelets			0.9 (3.9)	1.0 (4.1)		NS		
Major complications: Esophageal perforation Esophageal stricture			 0 6	 1 1		 NS 0.03		

Author's conclusions: Since rebleeding rates and mortality was not significantly different between treatment groups sclerotherapy was more cost effective than band ligation.

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Harras F, Sheta ES, Shehata M, El Saadany S, Selim M, Mansour L. Endoscopic band ligation plus argon plasma coagulation versus scleroligation for eradication of esophageal varices	RCT. Country: Egypt Block randomisation and no allocation concealment No drop	200 (50 in band ligation group, 50 in sclerotherapy group, 50 on combined band ligation and sclerotherapy group, and 50 in band ligation and argon plasma coagulation	Inclusion criteria: Portal hypertension (secondary to post hepatitis cirrhosis or mixed cirrhosis with schistosomal hepatic periportal fibrosis) presenting with oesophageal bleeding not influencing conscious level. Exclusion criteria: Other lesions with bleeding potential; previous sclerotherapy or band ligation treatment; fundal varices, severe systemic disease, hepatocellular carcinoma. Baseline characteristics: Sclerother / Ligation	Variceal band ligation. Banding started at the gastroesophageal junction, and then continued proximally for several centimetres.	Endoscopic injection sclerotherapy performed by intravariceal injection of 5% ethanolamine oleate via an endoscopic injector. 3ml of sclerosant	24 months.	Mortality Rebleeding Adverse effects	Not stated

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td></td>
<td>outs or number without treatment completion or follow-up data given.

No description of whether ITT or not</td>
<td>group).

Only the 100 in the sclerotherapy only and ligation only groups will be reported here.</td>
<td>
<table>
<tr><td></td><td>apy (n=50)</td><td>(n=50)</td></tr>
<tr><td>Hepatomegaly</td><td>13 (26%)</td><td>9 (18%)</td></tr>
<tr><td>Shrunken liver</td><td>37 (74%)</td><td>41 (82%)</td></tr>
<tr><td>Splenomegaly</td><td>32 (64%)</td><td>34 (68%)</td></tr>
<tr><td>Anti- hep C viris positive</td><td>48 (96%)</td><td>50 (100%)</td></tr>
<tr><td>Age</td><td>51.8 (13.3)</td><td>48.96 (10.3)</td></tr>
<tr><td>Total bilirubin</td><td>1.7 (0.97)</td><td>1.5 (0.95)</td></tr>
<tr><td>Child Pugh grade A</td><td>32%</td><td>28%</td></tr>
<tr><td>Child Pugh grade B</td><td>58%</td><td>64%</td></tr>
<tr><td>Child Pugh grade C</td><td>10%</td><td>8%</td></tr>
<tr><td>Grade I esophageal varices</td><td>0</td><td>0</td></tr>
<tr><td>Grade II esophageal varices</td><td>2 (4%)</td><td>0</td></tr>
<tr><td>Grade III esophageal varices</td><td>48 (96%)</td><td>50 (100%)</td></tr>
<tr><td>Mild congestive gastropathy</td><td>13 (26%)</td><td>18 (36%)</td></tr>
<tr><td>Severe congestive gastropathy</td><td>4 (8%)</td><td>3 (6%)</td></tr>
</table>

All patients showed clinical symptoms and signs of massive upper GI bleeding. Any patients presenting with hemodynamic instability (systolic bp < 90 mmHg, HR > 110 bpm) were first resuscitated</td>
<td>Repeated treatments given at 4 week intervals until varices eradicated. Follow up examinations carried out every 3 months, or whenever bleeding recurred.</td>
<td>injected at each puncture. A maxiumum of 5% ethanolamine oleate given during each session. Treatment sessions every 1-2 weeks for 3 sessions, then every month until variceal eradication.</td>
<td></td>
<td></td>
<td></td>
</tr>
</table>

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			before being given emergency endoscopic diagnosis and treatment.					

Results:

Post-treatment outcomes (no p-values provided in article):

	Sclerotherapy (n=50)	Ligation (n=50)
Mortality within 24 months	9/50	6/50
Rebleeding within 24 months (but unclear, and no adjustment for those dying)	2/50	4/50
Adverse effects		
Transient fever	22/50	4/50
Transient dysphagia	27/50	6/50
Ulceration	2/50	1/50
Stricture	0	0
Perforation	0	0
Other cause of death (hepatocellular failure)	7/50	5/50

A Kaplan-Meier analysis was carried out, a figure was given, but no statistics or explanation described the results.

The cost of the different treatments was provided in Egyptian pounds with sclerotherapy being the cheapest option

Author's conclusions: Band ligation has a rapid effect, but associated with greater cost and greater recurrence of varices

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Hou MC, Lin HC, Lee FY et al. Recurrence of esophageal varices following endoscopic treatment and its impact on rebleeding: Comparison of sclerotherapy and ligation. J Hepatol. 2000; 32(2):-208.</td><td>RCT, Taiwan

Computer-generated randomisation ; allocation and blinding unclear</td><td>200</td><td>Inclusion: cirrhotic patients with active or recent oesophageal variceal haemorrhage; continued to receive maintenance ligation or sclerotherapy (weekly for 1st 3 weeks, then every 3 weeks until eradication) and achieved eradication. Follow up endoscopy twice 3-monthly then 6-monthly if no recurrences; if rebleeding suspected, emergency endoscopy and same method used again.

Exclusion: hepatoma or other malignancies; terminal illness; fundal varices; prior surgical or endoscopic treatment for oesophageal varices.

Baseline characteristics:

<table>
<tr><td></td><td>Ligation</td><td>Sclero</td></tr>
<tr><td>Age (yr)</td><td>60.4 (12.1)</td><td>60.0 (11.9)</td></tr>
<tr><td>M:F</td><td>56:15</td><td>57:13</td></tr>
<tr><td>Aetiology of cirrhosis:
Alcoholic
Viral
Combined
Other</td><td>
11
41
12
7</td><td>
13
44
5
8</td></tr>
<tr><td>Child-Pugh:
Class A
Class B
Class C</td><td>
20
26
25</td><td>
17
34
19</td></tr>
</table>
</td><td>Ligation (n=101)</td><td>Sclerotherapy (n=99) with 1.5% sodium tetradecyl sulfate</td><td>Mean 5.1 (1.2) years, range 2.2 to 6.7 years</td><td>Variceal eradication (non-visualisation of varices, or varices that could not be ligated or injected).

Variceal recurrence (development of new varices which could be injected or ligated).

Rebleeding (new onset haematemesis, coffee-ground vomit, haematochezia or melaena + increased pulse rate over 110 bpm and BP below 90mmHg)</td><td>Veterans General Hospital Taipei; National Science Council Taiwan.</td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Platelet count (k/mm3)	81.2 (56.6)	87.1 (50.2)					
			Variceal size (f3/f2)	57/14	51/19					

Results:

	Ligation	Sclerotherapy	p value
Rebleeding before eradication (n)	18	27	
Number of sessions to eradication	3.7 (1.6)	5.1 (2.1)	<0.001
Time to eradication (days)	85.6 (52.9)	78.2 (32.2)	
Occurrence of hepatoma (after 6 months) (n)	9	12	
Rebleeding after eradication (n) Death due to rebleeding	6 1	10 3	NS
Source of rebleeding: Oesophageal varices Oesophageal ulcer Gastric varices Portal hypertensive gastropathy Gastric vascular ectasia Undetermined	 6 3 1 3 1 2	 7 2 7 0 1 2	NS
Patients with recurrent varices n Recurrence at 2 years Recurrence at 6 years	46	40	NS 0.04 in favour of sclerotherapy NS

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Sessions required to eradicate recurrences				1.4 (1.0)	1.6 (0.9)	NS		
Transfusion for bleeding from recurrent varices (units)				2.7 (3.0)	2.6 (2.4)	NS		
Transfusion for bleeding from portal-hypertension-related sources (units)				1.8 (2.4)	3.8 (5.5)	NS		
Complications before eradication:				4/71	14/70	<0.05		
Oesophageal stricture				1	9			
Intramural haematoma				0	1			
Aspiration pneumonia				0	1			
Spontaneous bacterial peritonitis				1	2			
Sepsis				0	1			
Deep neck infection				1	0			
Rectal variceal bleeding				1	0			
Complications after eradication								
Oesophageal stricture				0	1			

Author's conclusions: Ligation required fewer sessions to eradicate varices and resulted in fewer complications than sclerotherapy; recurrences occurred earlier than with sclerotherapy but recurrence did not lead to a higher risk of rebleeding or require more sessions for treatment.

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>Laine L, El Newihi HM, Migikovsky B, Sloane R, Garcia F. Endoscopic ligation compared with sclerotherapy for the treatment of bleeding esophageal varices. Annals of Internal Medicine 1993; 119: 1-7</td>
<td>RCT.
Country: USA

Computer generated randomisation sequence, but no evidence of allocation concealment.

Drop out number given (N=13 – but not described from which group)</td>
<td>77 (39 in sclerotherapy group and 38 in the ligation group)</td>
<td>Inclusion criteria: Chronic liver disease with no sclerotherapy in the past 6 months; had experienced one of: hemetmesis, bloody nasogastric aspirate, melena or hematochezia; systolic bp <90mmHg, HR> 110 bpm or orthostatic change in bp of >20 mmHg, or HR of >20 bpm, or decrease in hematrocrit of 0.06 within 12 hours; endoscopy carried out within 24 hours of admission showing active variceal bleeding or grade 2-4 oesophageal varices
Exclusion criteria: Other lesions in GI tract, severe portal hypertensive gastropathy; unable to sign informed consent; malignancy; homelessness.

Baseline characteristics (mean (sd)) – significicant difference in bold:
<table>
<tr><th></th><th>Sclerotherapy (n=39)</th><th>Ligation (n=</th></tr>
<tr><td>Age</td><td>48 (12.5)</td><td>44 (6.2)</td></tr>
<tr><td>Men : women</td><td>27:12</td><td>31:7</td></tr>
<tr><td>Cause of cirrhosis

Alcohol
Viral
Cryptogenic</td><td>

30 (77%)
2 (5%)
5 (13%)
1 (3%)</td><td>

31 (82%)
6 (16%)
0
1 (3%)</td></tr>
</table>
</td>
<td>Ligation done with endoscopic ligating device, via endoscope.

Each treatment session was</td>
<td>Intravariceal injection of 3% sodium tetradecyl sulphate mixed in equal volumes with 50% dextrose in water. Injections of size 0.5 to 2.5mL were given based on the size of the varix. Given via same type of endoscope tube as intervention group.

Each treatment session was begun in the region of the gastroesoph</td>
<td>307 days for sclerotherapy group and 295 for ligation group (both approximately 10 months)</td>
<td>Mortality

Rebleeding

Treatment failure

Total blood transfusion

Total hospital days

Adverse effects</td>
<td>Not stated</td>
</tr>
</table>

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
	ITT analysis apparently carried out but not defined in text		Primary biliary cirrhosis autoimmune	1 (3%)	0	begun in the region of the gastroesophageal junction, and was worked proximally. Treatment repeated weekly until variceal obliteration achieved. Treatment would be withheld if there was extensive stricture or ulceration, but endoscopies would always be done. All patients also received oral	ageal junction, and was worked proximally. Treatment repeated weekly until variceal obliteration achieved. Treatment would be withheld if there was extensive stricture or ulceration, but endoscopies would always be done. All patients also received oral sucralfate, 1g 4xpd during			
			Child-Pugh score Child-Pugh class A Child-Pugh class B Child-Pugh class C	7.7 (1.87) 9 (23%) 25 (64%) 5 (13%)	8.8 (1.85) 4 (11%) 21 (55%) 13 (34%)					
			Heamatocrit	0.24 (0.06)	0.23 (0.06)					
			Blood transfusion (units)	1.8 (1.87)	1.8 (1.85)					
			Active bleeding	9 (23%)	9 (24%)					
			Variceal size grade 2 Variceal size grade 3 Variceal size grade 4 (p=0.07)	6 (15%) 21 (54%) 12 (31%)	5 (13%) 13 (34%) 20 (53%)					
			Prothrombin	46 (12.3)	56 (12.4)					

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			time There was a trend for the ligation group to have more severe disease (according to Child-Pugh, prothrombin time and grade of varices).	sucralfate, 1g 4xpd during treatment until eradication occurred. After eradication all had 3 monthly endoscopic exams to assess for rebleeding.	treatment until eradication occurred. After eradication all had 3 monthly endoscopic exams to assess for rebleeding.			

Results:

Post-treatment outcomes – numbers in bold indicate significant differences

	Sclerotherapy (n=39)	Ligation (n=38)
In hospital mortality	2/39	3/38
Overall Mortality KM graph given but no other data provided	6/39	4/38
Mortality due to rebleeding	3/39	3/38
Rebleeding	17/39	10/38
Treatment failure	1/39	1/38
Total blood transfusion (mean (sd))	1.9 (5.6)	1.5 (2.7)
Total hospital days (mean (sd))	10.2 (12.4)	8.2 (6.2)

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Adverse effects								
Complicated esophageal ulcer				6 (15%)	1 (3%)			
Esophageal stricture				13 (33%)	0			
Pneumonia				1 (3%)	2 (5%)			
Bacterial peritonitis				7 (18%)	6 (16%)			
Brain abscess				1 (3%)	0			
Total complications				22 (56%)	9 (24%)			

Author's conclusions: Endoscopic ligation causes statistically fewer local complications than sclerotherapy and achieves variceal eradication more rapidly. Ligation is a viable alternative to sclerotherapy and may have some advantages as a treatment for bleeding oesophageal varices.

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Lo GH, Lai KH,	RCT.	27 in	Inclusion: unresectable hepatocellular	Standard	Standard	2	Mortality	Not

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Chang CF, Shen MT, Jeng JS, Huang RL, Hwu JH. Endoscopic injectionsclerotherapy vs endoscopic variceal ligation in arresting acute variceal bleeding for patients with advanced hepatocellular carcinoma. Journal of hepatology 1994; 21: 1048-1052.</td><td>Country: Taiwan.

Valid randomisation method but no allocation concealment evident.
No evidence of blinding.</td><td>sclero group and 30 in lig group.</td><td>carcinoma complicated by acute esophageal variceal bleeding.
Exclusion: Deep comatose state on admission; death within 24 hours of admission.

Baseline characteristics:
<table><tr><th></th><th>Ligation (n=30)</th><th>Sclero (n=27)</th><th>p valu</th></tr><tr><td>Age</td><td>57 (15)</td><td>55 (11)</td><td>NS</td></tr><tr><td>M/F</td><td>28/2</td><td>24/3</td><td>NS</td></tr><tr><td>HBsAg</td><td>22</td><td>17</td><td>NS</td></tr><tr><td>Alcoholism</td><td>4</td><td>5</td><td>NS</td></tr><tr><td>Ascites</td><td>23</td><td>19</td><td>NS</td></tr><tr><td>Pugh (B/C)</td><td>7/23</td><td>6/21</td><td>NS</td></tr><tr><td>Portal vein thrombosis</td><td>20</td><td>16</td><td>NS</td></tr><tr><td>AFP>400 ng/ml</td><td>22</td><td>20</td><td>NS</td></tr><tr><td>History of TAE</td><td>17</td><td>12</td><td>NS</td></tr><tr><td>Blood t’fusion (units)</td><td>3.0 (1.4)</td><td>3.2 (1.1)</td><td>NS</td></tr><tr><td>F2/F3</td><td>13/17</td><td>12/15</td><td>NS</td></tr></table></td><td>therapy including transfusion, fluid/electrolyte replacement, and lactulose, as necessary.

Ligation performed using the endoscopic ligating device. Ligation carried out at 1-5cm above the gastroesophageal junction. Each varix ligated with 1-3 rubber bands or until bleeding ceased. After completion of ligation, water instillation and suction used to check bleeding. Each session took about 25 mins (20-50).</td><td>therapy including transfusion, fluid/electrolyte replacement, and lactulose, as necessary.

Sclerotherapy via endoscope by intravariceal injection of mixture of 3% sodium tetradecyl sulphate and 50% dextrose in water to a total conc. of 1.5% sodium tetradecyl sulphate. During active bleeding 3-6mL of sclerosant inected just below the bleeding point. Other varices then injected circumferentiall</td><td>years</td><td>Rebleeding

Treatment failure (no initial hemostasis)

Adverse effects

Blood transfusion</td><td>stated.</td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				After initial session, repeated at 7-10 days, and then patients discharged and followed up in outpatients.	y from the gastroesophageal junction upwards, with a max. Dose of 25mL per session. Each session took about 30 mins (range 20-40 mins) After initial session, repeated at 7-10 days, and then patients discharged and followed up in outpatients.			

Results:

	Ligation (n=30)	Sclerotherapy (n=27)	p value
Mortality	25/30	23/27	Not given
Rebleeding of those whose treatment was originally successfull	11/26	8/11	<0.05
Treatment failure (no initial hemostasis)	4/30	16/27	<0.001
Adverse effects (not clear if any led to death or withdrawal from treatment)			

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Ulcers			16/30	12/27		NS		
Retrosternal pain			2/30	13/27		<0.01		
Transient dysphagia			5/30	7/27		NS		
Rectal bleeding			6/30	0/27		<0.01		
Massive variceal bleeding			0/30	1/27		NS		
ARDS			0/30	1/27		NS		
Sepsis			1/30	2/27		NS		
Spontaneous Bacterial Peritonitis			0/30	2/27		NS		
Blood transfusion (units)			1.5 (0.8)	3.9 (1.5)		<0.01		
Author's conclusions: Endoscopic banding ligation is superior to injection sclerotherapy in the management of acute esophageal variceal bleeding associated with advanced hepatocellular carcinoma.								

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Lo GH, Lai KH, Cheng JS et al. Emergency banding ligation versus sclerotherapy for the control of active bleeding from esophageal varices.	RCT, Taiwan Randomisation stated to be based on "a system of random numbers"; allocation concealment not stated	71	Inclusion: Cirrhotic paitnes with active variceal bleeding proved by emergency endoscopy within 12 hours of admission. Vasopressin 0.4 units/min + sublingual nitroglycerin for patients with history of chronic liver disease or alcoholism with upper g-I bleeding; stopped after endoscopy if bleeding stopped. After primary or secondary success, patients in both groups underwent 2nd session of treatment after 7-10 days; elective sessions at intervals of 2-3 weeks until all varices obliterated. Patients	Ligation (n=37) at or just below bleeding point; each varix ligated with 1-3 bands or until bleeding stopped	Sclerotherapy (n=34) with 1.5% sodium tetradecyl sulfate intra-variceally (3-6mL into bleeding varix; 3-4mL into other varices; total dose not	1 month	Primary success (cessation of bleeding for >72 hours by 1 treatment attempt, plus stable vital signs). Secondary success (cessation of bleeding by 2 treatment attempts within 72 hours).	not stated

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Hepatology. 1997; 25(5):1101-1104. Ref ID: 4592</td><td></td><td></td><td>with primary or secondary treatment failure received vasopressin infusion and balloon tamponade; rebleeding treated with randomised treatment.

Exclusion: bleeding already stopped; hepatocellular carcinoma; gastric variceal bleeding; encephalopathy unable to cooperate with endocopy; previous surgical or endoscopic treatment of oesophageal varices

Baseline characteristics:

<table><tr><td></td><td>Ligation</td><td>Sclero</td></tr><tr><td>Age (yr)</td><td>53 (15)</td><td>55 (13)</td></tr><tr><td>M:F</td><td>32/5</td><td>30/4</td></tr><tr><td>Aetiology n (%)
Alcoholic
Hep B
Hep C
Cryptogenic</td><td>
9 (24%)
15 (41%)
10 (27%)
3 (8%)</td><td>
11 (32%)
10 (30%)
11 (32%)
2 (6%)</td></tr><tr><td>Child-Pugh:
Class A
Class B
Class C</td><td>2 (5%)
13 (35%)
22 (60%)</td><td>3 (9%)
11 (32%)
20 (59%)</td></tr><tr><td>Size of varices F3/F2</td><td>27/10</td><td>26/8</td></tr><tr><td>Hb (g/dL)</td><td>8.7 (2.6)</td><td>9.2 (2.2)</td></tr></table></td><td></td><td>exceeding 25mL)</td><td></td><td>Rebleeding (haematemesis or melaena after 72 hours but within 1 month plus need for 2 or more transfusion units to maintain stable vital signs; bleeding source proved to be oesophageal varices by repeat endoscopy). Transfusion requirements within 7 days of treatment. Complications.

Primary endpoint of study was "treatment failure" (death related to oesophageal variceal bleeding, persistence of bleeding or rebleeding after 2 attempts at the same procedure within 1 month)</td><td></td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Blood units transfused	4.5 (2.8)	4.0 (2.5)					

Results:

	Ligation (n=37)	Sclerotherapy (n=34)	p value
Primary success:	36 (97%)	26 (76%)	0.009
Control of oozing	19/19 (100%)	16/18 (89%)	0.23
Control of spurting	17/18 (94%)	10/16 (62%)	0.012
Secondary success	-	4/6 (67%)	
Died or other treatment used	1 died (exsanguination)	2 died (massive haemorrhage) + 2 had balloon tamponade	
Rebleeding (after success)	6/36 (17%)	10/30 (33%)	0.19
Died before second attempt at endoscopy	1	1	
Control of rebleeding	4/5 (80%)	4/9 (44%)	0.23
Treatment failure at 1 month	3/37 (8%)	10/34 (30%)	0.02
Vasoconstrictors used	4 (11%)	14 (41%)	0.007
Additional therapy requirements (Balloon tamponade)	2 (5%)	7 (21%)	0.06
Blood units transfused	3.2 (1.2) range 0-6	4.5 (1.8) range 0-12	<0.01
Complications:	2 (5%)	10 (29%)	0.007
Aspiration pneumonia	0	3	
Empyema	0	1	
Adult respiratory distress syndrome	0	1	
Huge oesophageal ulcer (>1.5cm diameter)	1	3	
Bacterial peritonitis	1	2	

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Mortality at 30 days			7 (19%)	12 (35%)			0.19	
Variceal bleeding			3	6				
Hepatic failure			3	3				
Sepsis			1	3				

Author's conclusions: Ligation superior to sclerotherapy for the control of actively bleeding varices in terms of efficacy and complications.

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Masci E, Stigliano R, Mariani A et al. Prospective multicenter randomized trial comparing banding ligation with sclerotherapy of esophageal varices. Hepatogastroenterology. 1999; 46(27):1769-1773.	RCT, Italy Randomisation and allocation concealment not stated	100	Inclusion: chronic liver disease + oesophageal bleeding proved by endoscopy and initially controlled by drugs and/or balloon tamponade. Endoscopy at 1, 3, 6 and 12 months after eradication and at rebleeding. Exclusion: Age under 18 years, previous variceal sclerotherapy, haemorrhagic gastric varices, ulcers or erosions of the stomach and/or duodenum, hepatocellular carcinoma or other malignancy Baseline characteristics: Ligation: Mean age (yr), range 59.5 (26-84); M:F 36:14 Sclero: Mean age (yr), range 63.8 (28-88); M:F 39:11	Ligation (n=50) repeated every 15 days until no further varices could be taken in the bands	Sclerotherapy (n=50) intra- and peri-variceal technique with 1% polydocanol; repeated weekly until eradication (absence of visible varices); treatment withheld in case of extensive or deep ulceration.	1 year	Treatment failure (failure to control active rebleeding during and after eradication of the varices or death related to bleeding or complications or treatment different from assigned therapy).	Boston Scientific

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Aetiology:							
			Viral	41	39					
			Alcoholic	9	12					
			Other	5	2					
			Child-Pugh:							
			Class A	16	17					
			Class B	19	24					
			Class C	15	9					

Results:

	Ligation	Sclerotherapy	p value
Patients with variceal eradication n (%)	44/50 (88%)	41/50 (82%)	NS
Number of sessions to eradication (mean; range)	3.4 (1-6)	5.3 (2-11)	<0.0001
Time to eradication (mean; range days)	35 (15-60)	40 (7-20)	NS
Patients with variceal rebleeding prior to eradication n (%)	6 (12%)	21 (42%)	0.002
Post-eradication recurrence n (%)	14/44 (31.8%)	11/41 (26.8%)	NS
Time of recurrence (mean; range months)	8.9 (3-18)	13.1 (7-18)	NS
Variceal rebleeding after eradication n (%)	7/14 (50%)	4/11 (36.3%)	NS
Time of rebleeding (mean; range months)	10.3 (6-16)	11.8 (7-18)	NS
Complications:	9 (18%)	19 (38%)	
Major complications:	5 (10%)	18 (36%)	<0.005
Oesophageal stenosis	1	9	
Oesophageal ulcer	4	9	
Minor complications:	4 (8%)	1 (2%)	NS

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Fever			2	0				
Epigastric pain			1	0				
Persistent dysphagia			1	1				
Mortality:			10 (20%)	11 (22%)				
Due to variceal bleeding			2	1				
Hepatic insufficiency			6	8				
Trauma			1	0				
Sepsis			1	0				
Gastric bleeding			0	2				

Author's conclusions: Ligation is effective in elective treatment of oesophageal varices; it is better than sclerotherapy short-term because of fewer major complications and recurrences before eradication; after eradication it is no better; patients need frequent follow up to detect recurrences.

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Sarin SK, Govil A, Jain AK et al. Prospective randomized trial of endoscopic sclerotherapy versus variceal band ligation for esophageal varices:	RCT, India Randomisation and allocation concealment not stated, patients blind to treatment but not endoscopists	101	Inclusion: Patients with portal hypertension who had bled from oesophageal varices in the past or were actively bleeding at presentation (could have received balloon tamponade, vasoconstrictor or nitroglycerin therapy). If randomised treatment did not stop active bleeding or was not feasible, balloon tamponade was used. After obliteration of varices, endoscopy at 1 month then every 3 months or if bleeding occurred.	Ligation (n=51; 47 completers) 1-2cm above gastro-oesophageal junction; 1-2 bands per column around lower 4-5cm	Sclerotherapy (n=50, 48 completers) using absolute alcohol intra-variceally on a regular 7-10 day schedule (area of blanching essential for	At 4 weeks, then every 12 weeks for 4-48 weeks; mean 8.5 (4.2) months	Complications, mortality, rebleeding, hepatic failure, variceal recurrence, portal hypertensive gastropathy or gastric varices, control of	none stated

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>influence on gastropathy, gastric varices and variceal recurrence. J Hepatol. 1997; 26(4):826-832.</td><td></td><td></td><td>Exclusion: received sclerotherapy, band ligation or surgery for oesophageal or gastric varices; hepatic encephalopathy; hepatorenal syndrome; age less than 5 years; missing 3 consecutive sessions

Baseline characteristics:

<table><tr><td></td><td>Ligation</td><td>Sclero</td></tr><tr><td>Mean age (yr)</td><td>38.7 (8.6)</td><td>35.2 (11.9)</td></tr><tr><td>M:F</td><td>34:13</td><td>38:10</td></tr><tr><td>Diagnosis:
Cirrhosis
Non-cirrhotic portal fibrosis
Extra-hepatic portal vein obstruction</td><td>
34
5
8</td><td>
31
4
13</td></tr><tr><td>Child-Pugh:
Class A
Class B
Class C</td><td>
22
18
7</td><td>
24
18
6</td></tr></table></td><td>of oesophagus, at regular 7-10 day intervals until no variceal column visible or not possible to suck in a varix.</td><td>adequate sclerotherapy)</td><td></td><td>active bleeding, obliteration of varices.</td><td></td></tr>
<tr><td colspan="9">Results:

<table><tr><td></td><td>Ligation (n=47)</td><td>Sclerotherapy (n=48)</td><td>p value</td></tr></table></td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Presented with active bleeding n (%)				5 (10.6%)	7 (14.6%)			
Control of active bleed with randomised therapy				4/5 (80%)	6/7 (85.7%)		NS	
Randomised therapy achieved obliteration of varices				44	45			
Mean sessions to achieve obliteration Cirrhotic patients Non-cirrhotic patients				4.1 (1.2) 3.8 (0.91) 4.0 (2.19)	5.2 (1.8) 5.6 (1.95) 4.2 (1.40)		p<0.01	
Mean time to obliteration (weeks) Cirrhotic patients Non-cirrhotic patients				4.4 (1.3) 4.0 (1.06) 4.7 (2.37)	6.9 (3.4) 7.3 (3.6) 5.3 (2.7)		p<0.01	
Treatment failure				1/7	1/5			
Variceal ulcers				35 (74.4%)	33 (68.8%)			
Complications (some patients had more than 1): Retrosternal pain Dysphagia Throat pain Fever Oesophageal stricture				21 (44.7%) 10 9 19 3 0	24 (50%) 20 9 6 9 5		NS	
Variceal bleeding during follow up				3	10		<0.05	
Variceal recurrence				10	3		<0.05	
Portal hypertensive gastropathy: Pre-treatment Post-treatment				 5 6	 4 13		 0.02	
Gastric (lesser curve) varices: Pre-treatment Post-treatment				 10 5	 13 5			
Mortality:							NS	

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Bleeding			0		2			
Hepatic coma			2		1			
Other			1		0			

Author's conclusions: Ligation is safer than sclerotherapy and obliterates varices in a shorter time; no significant portal hypertensive gastropathy developed after ligation and strictures did not form. However, ligation is associated with more recurrences so closer monitoring of these patients is recommended.

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Shafqat F, Khan AA, Alam A et al. Band ligation vs endoscopic sclerotherapy in esophageal varices: a prospective randomized comparison. JPMA - Journal of the Pakistan Medical Association. 1998; 48(7):192-196.	RCT, Pakistan Randomisation unclear; allocation concealment adequate; 7 patients excluded due to hepatocellular carcinoma and 5 lost to follow up but not stated which groups or	70	Inclusion: Patients > 18 years old with endoscopic evidence of oesophageal variceal bleeding (active or recent). Initial treatment within 12 hours of onset of bleeding; sessions repeated every 2 weeks to eradication; follow up endoscopy every 3 months or for rebleeding. Within each group, also randomised to sucralfate or omeprazole. In case of treatment failure, alternative treatment, or other measures (e.g. Sengstaken tube, octreotide, shunt surgery) considered. Exclusion: unfit for endoscopy, oesophageal stricture, associated disease with death expected within 6 months, prior endoscopic or surgical treatment of varices.	Ligation (n=28 completers); each varix ligated at least once per treatment; larger varices twice at separate sites; no more than 10 ligations per session	Sclerotherapy (n=30 completers) with 75% alcohol para- or intra-variceally, confined to distal 8cm of oesophagus and proximal 1-2cm of stomach; not more than 20mL per session.	Mean 175 (120) days in ligation group and 150 (110) days in scleroth erapy group	Initial control of bleeding, rebleeding, variceal eradication, number of sessions required for eradication, recurrence, complications, mortality	none stated

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td>whether this was before or after treatment completion</td><td></td><td>Baseline characteristics:
<table><tr><td></td><td>Ligation</td><td>Sclero</td></tr><tr><td>Mean age (yr)</td><td>50 (13)</td><td>54 (12)</td></tr><tr><td>M:F</td><td>20:8</td><td>17:13</td></tr><tr><td>Aetiology:</td><td></td><td></td></tr><tr><td>Cirrhosis</td><td>27</td><td>30</td></tr><tr><td>Hepatitis B</td><td>5</td><td>7</td></tr><tr><td>Hepatitis C</td><td>18</td><td>21</td></tr><tr><td>Both</td><td>1</td><td>0</td></tr><tr><td>Idiopathic</td><td>2</td><td>2</td></tr><tr><td>Non-cirrhotic</td><td>1</td><td>0</td></tr><tr><td>Child-Pugh:</td><td></td><td></td></tr><tr><td>Class A</td><td>5</td><td>6</td></tr><tr><td>Class B</td><td>18</td><td>21</td></tr><tr><td>Class C</td><td>3</td><td>4</td></tr></table></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="9">Results:
<table><tr><td></td><td>Ligation</td><td>Sclerotherapy</td><td>p value</td></tr><tr><td>Active bleeding n (%)</td><td>24 (86%)</td><td>28 (93%)</td><td>NS</td></tr><tr><td>Haemostasis achieved n (%)</td><td>23 (96%)</td><td>22 (78%)</td><td>NS</td></tr><tr><td>Eradication n (%)</td><td>26 (93%)</td><td>20 (66%)</td><td><0.005</td></tr></table></td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Treatment sessions	2 (1.2)	5 (2.5)	<0.001
length of non-ICU stay (days)	4.96 (2.58); n=28	6.1 (1.7); n=30	-
Recurrent varices n (%)	5 (20%)	3 (14%)	NS
Recurrent bleeding n (%)	8 (29%)	7 (28%)	NS
Oesophageal varices n	3	4	NS
Treatment induced ulcers	4	3	NS
Undetermined	1	0	
Complications:			
Chest pain	6 (22%)	22 (73%)	<0.05
Fever	2 (7%)	9 (30%)	<0.05
Ulcer	12 (43%)	16 (49%)	NS
Bleeding ulcer	4 (14%)	3 (10%)	NS
Dysphagia	3 (11%)	4 (13%)	NS
Odynophagia	14 (50%)	0	<0.01
Encephalopathy	0	4 (13%)	<0.05
Bacterial peritonitis	0	1 (3%)	NS
Perforation	0	0	-
Stricture	0	0	-
Mortality	3 (11%; all uncontrolled bleeding within 30 days of treatment)	6 (21%; 3 uncontrolled bleeding; 2 hepatic encephalopathy; 1 bacterial peritonitis)	NS

Author's conclusions: Ligation was superior to sclerotherapy in terms of fewer sessions required for obliteration and fewer complications.

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Stiegmann GV, Goff JS, Michaeletz-Onody PA, Korula J, Lieberman D, Saeed ZA, Reveille RM, Sun JH, Lowenstein SR. Endoscopic sclerotherapy as compared with endoscopic ligation for bleeding esophageal varices. The New England Journal of Medicine 1992; 326; 1527-1532.</td><td>RCT.

Country: USA.

Randomisation in blocks of 10, with computer-generated random numbers.
4 study sites.</td><td>65 sclerotherapy and 64 ligation.</td><td>Inclusion: Active or recent bleeding from esophageal varices; >18 yrs; varices caused by cirrhosis.
Exclusion:

Exclusion: contraindication to endoscopy; previous surgical or endoscopic treatment for oesophageal varices; gastric fundal varices; intercurrent illness with death expected <12 months; symptoms of oesophageal dysfunction; current use of beta-adrenergic-antagonist agents.

Baseline characteristics:
means (sd) for continuous variables. No statistically significant differences found.

<table><tr><th></th><th>Ligation (n=64)</th><th>Sclero (n=65)</th></tr><tr><td>Age</td><td>51 (13)</td><td>53 (13)</td></tr><tr><td>M/F</td><td>53/11</td><td>51/14</td></tr><tr><td>Alcoholic cirrhosis</td><td>53</td><td>52</td></tr><tr><td>Childs A/B/C</td><td>22/30/12</td><td>20/32/13</td></tr><tr><td>Childs score</td><td>9.4 (2.1)</td><td>9.9 (2.1)</td></tr><tr><td>Previous bleeding</td><td>37</td><td>46 (71)</td></tr><tr><td>Units blood transfused for index episode</td><td>3.3 (3.2)</td><td>3.5 (3.6)</td></tr><tr><td>Serum albumin (g/l)</td><td>26.2 (5.6)</td><td>29.8 (7.0)</td></tr><tr><td>Serum total bilirubin</td><td>61 (74)</td><td>64 (85)</td></tr></table></td><td>Sedative given prior to endoscopy.

Ligation performed with endoscopic ligating device and overtube. Varices were ligated individually with a single plastic O ring, starting at or just below the gastroesophageal junction and continuing cephalad to 7cm above that junction. All varices ligated at least once per Rx. A max of 8</td><td>Sedative given prior to endoscopy.

Sclerosant was 3% sodium tetradecyl sulphate diluted with salineto a 1% solution. The varices were injected intra-variceally, and were begun at the gastroesophageal junction, and up to 2ml of sclerosant was delivered to each site. A maximum of 20 ml was used per session. Treatment</td><td>10 months</td><td>Mortality

Rebleeding (any bleeding occurring after randomisation from the upper GI tract)

Treatment failure (if bleeding did not stop completely within 24 hours of 2 sessions of Rx, or if a transfusion of 1 unit of blood/hour was necessary for >3hrs to maintain constant heamatocrit and vital signs.</td><td>Not stated</td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			(umol/l) | | Prothrombin time (sec) | 13 (2) | 14 (3) Grade of varices 2/3/4 | 8/35/21 | 9/31/25 Not stated if the groups were equivalent for site.	ligations were performed per session. Sessions were repeated as needed for recurrences of bleeding at interval sof 5-21 days until all distal esophageal varices eradicated. There were then further endoscopies (and Rxs if necessary) at 3 month intervals.	was confined to the distal 7cm of the oesophagus and the proximal 1-2 cm of the stomach. Sessions were repeated as needed for recurrences of bleeding at interval sof 5-21 days until all distal esophageal varices eradicated. There were then further endoscopies (and Rxs if necessary) at 3 month intervals.		Number of sessions required to achieve obliteration of varices. Adverse effects (not causing death or Rx withdrawal)	
Results:								

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow -up	Outcome measures	Source of funding

	Ligation (n=64)	Sclerotherapy (n=65)	p value
Mortality Survival (KM curves supplied) Based on HR p value of 0.041: HR=0.54 (0.3-0.98); lnHR=-0.61; se (lnHR)=0.30	18/64	29/65	NS 0.041
Rebleeding	23/64	31/65	0.072
Treatment failure (no initial hemostasis in those with active bleeding at index treatment)	2/14	3/13	
Number of sessions required to achieve obliteration of varices.	4 (2)	5 (2)	0.056
Adverse effects causing death Adverse effects (not stated which were those causing death or any Rx withdrawal) Esophageal stricture Bacterial peritonitis Pulmonary	1/64 1/64 0/64 0/64 1/64	4/65 15/65 8/65 8/65 4/65	NS <0.001 NS NS NS
Blood transfused per recurrence (units)	5.0 (4.2)	4.3 (3.2)	NS
Other procedures to control bleeding Operative (shunt insertion of liver transplantation) Radiologic (embolization) Endoscopic alternative (treated with the opposite to that assigned at randomisation)	 4/64 0/64 5/64	 4/65 2/65 2/65	 NS NS NS

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Author's conclusions: Patients with cirrhosis who have bleeding esophageal varices have fewer treatment-related complications and better survival rates when they are treated by esophageal ligation than when they are treated by sclerotherapy.								

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Villanueva C, Piqueras M, Aracil C et al. A randomized controlled trial comparing ligation and sclerotherapy as emergency endoscopic treatment added to somatostatin in acute variceal bleeding. J Hepatol. 2006; 45(4):560-567. Ref ID: 116	RCT, Spain Randomisation and allocation concealment adequate	168 patients (179 episodes; 11 patients included twice)	Inclusion: Haematemesis or melaena, clinical suspicion of cirrhosis, age over 18 years, oesophageal variceal bleeding confirmed on endoscopy. All had somatostatin infusion for 5 days; once infusion finished, surviving patients treated with nadolol + isosorbide mononitrate or with elective ligation for prevention of rebleeding. Therapeutic failures treated with vasoactive drugs, endoscopic treatment (up to 2 sessions), balloon tamponade, TIPS or surgery. Exclusion: bleeding from fundal varices or sources other than oesophageal varices; previous sclerotherapy or ligation within 2 weeks; previous TIPS or surgical shunt; advanced hepatocellular carcinoma; massive bleeding resulting in balloon tamponade or death before randomisation; declined consent; previous decision to avoid specific medical therapy	Ligation (n=90): each varix ligated at least once and up to 14 bands placed, starting at gastro-oesophageal junction working proximally within distal oesophagus; in actively bleeding patients, starting at site of bleeding.	Sclerotherapy (n=89) with intra-variceal 5% ethanolamine in each varix up to a total of 15-25mL; starting at gastro-oesophageal junction working proximally within distal oesophagus; in actively bleeding patients, starting at site of bleeding	42 days	Therapeutic failure (failure to control acute bleeding episode i.e. haematemesis or bloody nasogastric aspirates + systolic BP <100mmHg and/or pulse >100bpm or Hb drop of 2g/dL or more within a 6-hour period in first 24 hours; or early rebleeding i.e. criteria for failure between 24 hours and 5 days; or 5-day mortality). Complications, mortality	Fundacio Investigacio Sant Pau; Instituto de Salud Carlos III

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Baseline characteristics:					

	Ligation	Sclero
Age (yr)	62 (11)	62 (12)
M:F	62:28	69:20
Alcoholic cirrhosis	35 (39%)	36 (40%)
Previous variceal bleeding	30 (33%)	26 (29%)
Hepatocellular carcinoma	13 (14%)	7 (8%)
Child-Pugh:		
Class A	13	9
Class B	53	59
Class C	24	21
Hb (g/L)	89 (20)	94 (25)
Transfusion units before randomisation	1.2 (1.5)	1.3 (1.5)

Results:

	Ligation (n=90)	Sclerotherapy (n=89)	Relative risk (95% CI)
Complications related to therapy:			

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding	
Total			13 patients (14%) had 14 adverse effects	25 patients (28%) had 28 adverse effects			1.9 (1.1-3.5)		0.04
Major:			4 (4%)	12 (13%)			3.1 (1.1-9.1)		0.04
Aspiration pneumonia			2	4					
Bacterial peritonitis			0	1					
Empyema			0	1					
Sepsis			0	2					
Oesophageal bleeding ulcer			2	4					
Minor:			10 (11%)	16 (18%)			1.6 (0.8-3.4)		0.21
Chest pain			2	4					
Fever			2	4					
Transient arrythmias			1	2					
Transient dysphagia			1	2					
Hyperglycaemia			3	3					
Nausea			1	1					
Therapeutic failure			9 (10%)	21 (24%)			2.4 (1.1-4.9)		0.02
Failure to control acute bleeding episode			4 (4%); 2 second emergency endoscopy, 1 TIPS, 1 additional somatostatin	13 (15%); 3 balloon tamponade, 3 TIPS, 6 second emergency endoscopy, 1 additional somatostatin			3.3 (1.12-9.7)		0.02
Time admission to cessation of bleeding (hours)			6.5 (5.8)	8.4 (6.2)					0.05
Early rebleeding			4/86 (5%); 2 TIPS, 1 sclerotherapy, 1 second ligation	7/76 (9%); 1 balloon tamponade, 2 second emergency endoscopy, 3 ligation, 1 additional somatostatin			1.2 (0.6-6.5)		0.25
Late rebleeding (5-42 days)			6 (7%)	11 (12%)			1.8 (0.7-4.8)		0.21
Transfusion during trial period:									0.05
Mean (SD)			3.1 (2.3)	3.9 (3.0)					
Median (range)			3 (0-11)	3 (0-12)					

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Days in hospital (non-ICU)		13 (7)		15 (9)				0.27
Mortality								
Death within 5 days		3 (3%)		3 (3%)			1.01 (0.2-4.9)	0.72
Death within 42 days		12 (13%)		19 (21%)			1.6 (0.8-3.1)	0.17

Author's conclusions: Added ligation rather than sclerotherapy as the emergency endoscopic therapy to somatostatin for the treatment of acute variceal bleeding significantly improves efficacy and safety.

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Young MF, Sanowski RA, Rasche R. Comparison and characterisation of ulcerations induced by endoscopic ligation of esophageal varices versus endoscopic sclerotherapy. Gastrointestinal endoscopy199	RCT. Country: USA. No details of randomised sequencing method and no evidence of allocation concealment. No evidence of blinding.	10 ligation, 13 sclerotherapy.	Inclusion: Hx of variceal bleeding from esophageal ulcers. Baseline characteristics: No significance given. Ligation (n=10) / Sclero (n=13) M/F: 10/0 / 13/0 Age: 52 (range 37-71) / 58 (range 40-68) Etiology Laennec's cirrhosis: 7 / 12 Hep B: 2 / 1 Idipathic portal: 1 / 0	After sedation, ligation performed using rubber O rings. Repeated at 7-10 day intervals until obliteration of all variceal channels achieved.	After sedation, intravariceal injection of sodium tetradecyl sulphate 1.5%. Each varix injected in 2 ml increments circumferentially in the distal 5 cm beginning at the cardioesophageal junction. Repeated at 7-10 day intervals	9 months	Mortality Number of sessions required to achieve obliteration of varices Adverse effects	Not stated

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
3; 39: 119-122			hypertension				until obliteration of all variceal channels achieved.			
			Child's Pugh A/B/C	0/2/8	0/3/10					

Results:

	Ligation (n=10)	Sclerotherapy (n=13)	p value
Mortaliity	1/10	1	NS
Number of sessions required to achieve obliteration of varices.	3.6 (0.4)	6.2 (0.5)	<0.0001
Adverse effects (not stated as causing mortality or withdrawal from Rx)			
Ulcers	10/10	11/13	Not given
Esophagitis grade at 7 days post Rx	0.9	3.1	<0.001
Days for ulcers to heal	14.4 (1.4)	20.9 (1.3)	<0.0001

Author's conclusions: Ligation ....is an effective means of therapy associated with superficial ulcerations and less tissue necrosis [than sclerotherapy].

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Luz GO, Maluf-Filho F,	RCT, single centre Brazil	100 but	Inclusion: Patients > 18 years old with endoscopic evidence of oesophageal variceal	Ligation using the six shooter	Sclerotherapy injection of	6 weeks	Failure in bleeding	Departm ent of

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Matuguma SE, et al. Comparison between endoscopic sclerotherapy and band ligation for hemostasis of acute variceal bleeding. World Journal of Gastrointestinal Endoscopy 2011 May 16;3:95-100.</td><td>Randomisation adequate, allocation concealment described as being adhered to but when taken literally it is unclear</td><td>there were 17 patients with schistosomiasis (not included here) leading to N=39 sclerotherapy and N=44 band ligation</td><td>bleeding (active or recent)..

Exclusion: not directly stated.

Baseline characteristics (all patients including those with schistosomiasis) – expressed as N(%) – p-values given and smallest p was 0.29:

<table><tr><th></th><th>Ligation (N=50)</th><th>Sclero (N=50</th></tr><tr><td>Mean age (yr)</td><td>54.48</td><td>50.24</td></tr><tr><td>Male</td><td>37 (74)</td><td>35 (70)</td></tr><tr><td>Aetiology:</td><td></td><td></td></tr><tr><td>Alcohol</td><td>19 (38)</td><td>17 (34)</td></tr><tr><td>Virus</td><td>19 (38)</td><td>15 (30)</td></tr><tr><td>Schistosomiasis</td><td>6 (12)</td><td>11 (22)</td></tr><tr><td>Secondary biliary cirrhosis</td><td>4 (8)</td><td>3 (6)</td></tr><tr><td>Cryptogenic cirrhosis</td><td>1 (2)</td><td>2 (4)</td></tr><tr><td>Primary biliary cirrhos</td><td>1 (2)</td><td>2 (4)</td></tr><tr><td>Child-Pugh:</td><td></td><td></td></tr><tr><td>Class A</td><td>2 (4)</td><td>3 (6)</td></tr><tr><td>Class B</td><td>22 (44)</td><td>21 (42)</td></tr><tr><td>Class C</td><td>20 (40)</td><td>15 (30)</td></tr></table></td><td>multi-band kit. Attempts were made to ligate the varix on the rupture point while also treating the other varices with the remaining bands. Whencer the exact rupture point could not be identified ligation of all variceal tissue visible in the final 5 cm of the esophagus was performed with six elastic bands.</td><td>2.5% ethanolamine-oleate. The sclerosing solution was injected into the lumen of the hemorrhagic varix at 5 mL increments above and below the rupture point. The maximum volume used per session was 20 mL.</td><td></td><td>control (up to d 5), recurrence of bleeding (5 d and 6 weeks) eradication, complications, mortality</td><td>Gastroenterology-Gastrointestinal Endoscopy Unit, Sao Paulo University School of Medicine</td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Results:

Post treatment outcomes – excluding patients with schistosomiasis

	Ligation (N=44)	Sclerotherapy (N=39)
Failure in bleeding control	11 (25%)	6 (15.4%)
Re-bleeding	11 (25%)	6 (15.4%)
Mortality	6 (13.6%)	3 (7.7%)

Author's conclusions: Sclerotherapy and band ligation are equally efficient for the control of acute variceal bleeding.

F.7.3 TIPS for gastric varices

QUESTION In patients with confirmed gastric varices which primary treatment (endoscopic injection of glue or thrombin and / or trans-jugular intra-hepatic portosystemic shunt [TIPS]) is the most clinical and cost effective to improve outcome?

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Sanyal AJ, Freedman AM, Luketic VA et al.	RCT Country: USA Single centre	TIPS N=41; Sclerotherapy N= 39	Inclusion criteria: Patients with active variceal haemorrhage as defined as emesis of coffee-ground material or bright red blood with or	TIPS were created with Wallstents	Sclerotherapy: treatment with 2-mL intravariceal	48 months	Primary endpoints: mortality and rebleeding	National institute of health and an

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Transjugular intrahepatic portosystemic shunts compared with endoscopic sclerotherapy for the prevention of recurrent variceal hemorrhage: A randomized, controlled trial. Ann Intern Med. 1997; 126(11):849-857.	Randomisation sequence generation adequate; allocation concealment adequate Not blinded Intention to treat analysis Power analysis carried out		without melena or haematochezia, along with a decrease in haemoglobin level of at least 2 g/DL caused by bleeding varices. Bleeding was considered variceal in origin if actively bleeding varices or varices with stigmata of bleeding were seen during endoscopy and if no other lesion were noted that could explain the bleeding. Survivors of an episode of active oesophageal variceal haemorrhage were considered for inclusion if they were clinically stable and were not actively haemorrhaging (absence of haemorrhage was indicated by a stable haemoglobin level and no need for transfusions) for at least 72 hours). Exclusion: Patients who had portal venous thrombosis, ultrasonographically evident hepatoma, and end-stage cancer or systemic disease that would limit a patient's life span to less than 1 year. Baseline characteristics – no significant differences: TIPS (N=41) | Sclero (N=39)	using standard techniques. Special care was taken to ensure that only the contral portions of the right or left branches of the portal vein were used for creation of the intrahepatic tract in order to optimize haemodynamics and minimize turbulence in the stent. The stents were then dilated with an 8-mm balloon catheter. If	freehand injections of 5% Na morrhuate, for a total of 12 to 20 mL per session. Patients received sclerotherapy every 2 to 3 weeks until all varices were obliterated.		Secondary endpoints: treatment complications and rates of re-hospitalisations	award by the American College of Gastroenterology

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Age (SD) 48(8) 52(6) Male N 26 27 Child-Pugh class, n A/B/C 7/13/21 6/15/18 Causes: alc/Hep C/ Hep B/Other 16/15/3/7 17/16/2/4 Ascites, n 14 12 Encephalopathy, n 9 7 Variceal size, Grade: 1/2/3/4 0/11/16/14 1/10/17/11 Gastric varices, n 9 6	the portosystemic gradient did not decrease to less than 12 mm Hg or the completion portogram did not demonstrate excellent flow through the stent, the stent was dilated to 10 mm and pressure was again measured (could be increased to 12 mm). Parallel stents were not used in any patient. The left gastric vein				

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				was not embolized.				

Effect size

Post treatment outcomes – shaded cells highlight significant group differences:

	TIPS N=41	Sclerotherapy N=39	RR (95%CI)	p-value
Mortality	12	7		0.02
Rebleeding	10	10	0.95 (0.44-2.03)	0.95
Adverse events:				
New onset or acutely worsening encephalopathy	12	5	2.2 (0.9-5.8)	0.01
Sepsis	6	2	2.8(0.7-13.2	0.03
Haemolytic anaemia	2	0		0.2
Alcoholic hepatitis	5	5	0.95(0.29-3.03	0.2
Ascites	0	5	0.03(0.02-0.2)	0.001
Seizures	0	1	0(-0.07-0.02	0.4
Renal failure	1	2	0.47(0.04-5.03	0.3

Survival analysis was carried out for rebleeding and mortality:

Kaplan-Meier analysis results for rebleeding were presented graphically and the only statistic relating to this was >0.2; generalised Wilcoxan test.

For mortality Kaplan-Meier statistics were given as follows:

Median duration of survival in the TIPS group was 260 days (CI 118-630) and 1004 (CI 740-1173) days in the sclerotherapy group and TIPS were associated with a significantly higher risk for death (p=0.02 by generalized Wilcoxon test; p=0.03 by log rank analysis).

Authors' conclusion

Endoscopic sclerotherapy and TIPS are equivalent with respect to rebleeding developing over the long term. However, sclerotherapy may be superior to TIPS with respect to survival.

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Rössle M, Deibert P, Haag K et al. Randomised trial of transjugular-intrahepatic-portosystemic shunt versus endoscopy plus propranolol for prevention of variceal rebleeding. Lancet. 1997; 349(9058):1043-1049.</td><td>RCT multi-centre European study

Power analysis was carried out

Randomisation stratified according to Child-Pugh class and age (<60 yrs or ≥60yrs)

Unclear allocation concealment and unclear randomisation, no blinding

Intention to treat analysis</td><td>TIPS N=61 and beta blocker / EndoL N=65</td><td>Inclusion criteria: Patients with cirrhosis with variceal bleeding within 2 weeks before randomisation and age over 18 years.
Exclusion: Patients with encephalopathy grade 3 and 4; liver insufficiency with total bilirubin of more than 5mg/dL (except patients with primary biliary cirrhosis); cavernomatous portal-vein thrombosis; advanced malignancy; contraindications for propranolol (severe heart insufficiency; obstructive lung disease, severe hypotensions); and bleeding emergency.

Baseline characteristics:<table><tr><td></td><td>TIPS N=61</td><td>Propranolol/endo N=65</td></tr><tr><td>Age</td><td>54.3 (11.9)</td><td>56.6 (12.4)</td></tr><tr><td>Male</td><td>40</td><td>44</td></tr><tr><td>Aetiology (Alc/Viral/ other)</td><td>42/11/8</td><td>42/10/14</td></tr><tr><td>Child-Pugh</td><td>17/33/11</td><td>22/31/12</td></tr></table></td><td>TIPS – a catheter is introduced trans-jugularly into a hepatic vein, a puncture needle is then pushed through the catheter, and the portal vein is punctured under fluoroscopic and sonographic guidance. After predilation of the tissue tract, a stent is introduced and expanded with balloon catheters. The following stents were used: Palmaz stent (39 patients, 92 stents), Memotherm stent (16 patients 19</td><td>Endoscopic treatment consisting of either injection of polidocanol (16[SD 8] mL per session) or banding ligation (3.2 rubber bands) in intervals of 2 to 5 days until eradication of the varices was achieved or at least six treatment sessions were applied. Gastric varices were treated by intravariceal injection of bucylate/lipiodol. 33 patients were treated</td><td>1, 3 6, 9 and 12 months and then every 6 months or when needed for clinical reasons.</td><td>Clinically significant bleeding, rebleeding, failure to control bleeding, failure of endoscopic treatment (3 or more rebleedings within 1 year), hepatic encephalopathy-grade 1, clinically significant hepatic encephalopathy, refractory hepatic encephalopathy

Failure of the transjugular shunt and shunt insufficiency</td><td>Not stated</td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Class A/B/C			stents), Wallstent (6 patients, six stents). The final diameter of the stent was adjusted to achieve the desired portal venous pressure gradient (portal pressure minus inferior vena cava pressure). In 31 patients with huge varices or in whom variceal per fusion persisted after creation of the shunt, embolisation with bucrylate/lipiodol was done. Anticoagulation to prevent early thrombosis of the shunt was given.	with sclerotherapy only, 31 had a combination of sclerotherapy and band ligation, and one patient had band ligation only. Propranolol was given in dose of 63 (33) mg/day to decrease the heart rate by 25%		ALL ENDPOINTS WERE CLEARLY DEFINED	
			Previous variceal bleedings 0/1/2/>2	25/13/12/15	36/14/7/8					
			Active bleeding at randomisation	39	37					
			Oesophageal varicose	53	59					
			Transfusions before randomisation							
			0 units	7	4					
			1-2	16	19					
			3-5	17	29					
			>5	21	13					

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Effect size

Post treatment outcomes – see survival analysis results below table

	TIPS N=61	Propranolol/endo N=65
Mortality	8	8
Variceal rebleeds (episodes)	9 (episodes 11)	29 (episodes 56)
Total upper GI rebleedings (episodes)	15 (episodes 19)	33 (episodes 100)
Hospital stay (mean days (SD))	27(17)	34(28)
Hepatic encephalopathy	22	12
Clinically significant / refractory encephalopathy	16/2	7/2

Kaplan-Meier analysis:

Mortality – graph with patient at risk numbers provided; estimated 1-year rates of 90% and 89% and 2-year rates of79% and 82% for TIPS and endoscopic treatment respectively

Rebleeding – graph with patient at risk numbers provided; there was a significant difference between the groups in the time of first rebleeding from varices or from any source ($p=0.001$ for variceal and $p<0.001$ for bleeding from any sources

Encephalopathy - graph with patient at risk numbers provided; the difference between the curves of the two treatment groups was significant favouring endoscopy ($p=0.011$)

Authors' conclusion

Transjugular shunt is more effective than endoscopic treatment in prevention of variceal rebleeding but has considerable risk of hepatic encephalopathy. Survival is similar in the two groups.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Lo GH, Liang	RCT – single	TIPS N=35 and	Inclusion criteria: Patients with	TIPS – the	The injected	Median	Primary end	Grant

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
HL, Chen WC et al. A prospective, randomized controlled trial of transjugular intrahepatic portosystemic shunt versus cyanoacrylate injection in the prevention of gastric variceal rebleeding. Endoscopy. 2007; 39(8):679-685.	centre Country: Taiwan Allocation concealment adequate and randomisation sequence generation adequate Doctors evaluating the outcomes were blinded	cyanoacrylate injection N=37	cirrhosis presenting with an episode of acute gastric variceal bleeding with haematemesis and/or melena and a fall in haemoglobin level, and admitted to hospital. The endoscopic criteria for acute gastric variceal bleeding included: (i) active spurting or oozing of blood from gastric varices during endoscopy; or (ii) blood from gastric varices clot coating on gastric varices or presence of erosive spots on gastric varices, with no other potential sources of bleeding. Exclusion: (i) age <20 or >75 years; (ii) acute bleeding from oesophageal varices; (iii) presence of deep jaundice or hepatic encephalopathy; (iv) association with hepatocellular carcinoma, uraemia, or other debilitating disease; (v) history of specific treatment of gastric varices; (vi) uncontrolled acute gastric variceal bleeding; (vii) portal vein thrombosis; (viii) pregnancy; (ix) refusal to participate; or (x) death within 72 hours of admission Baseline characteristics – shaded cell:	right internal jugular vein was punctured under ultrasonographic guidance. Using the Seldinger technique, a hydrophilic 0.035-inch guide wire, a 4-Fr RC1 catheter and a 9-Fr ring transjugular intrahepatic introducer sheath were inserted into the inferior vena cava and right hepatic vein. A Superstiff guide wire	agents' consisted of n-butyl-2-cyanoacrylate 0.5 ml mixed with 1.5 ml lipiodol. The injection was aimed at the bleeding varices or with red colours signs or at the most prominent varices. This was performed at intervals of 4 weeks until there was obliteration	follow up was 33 months (range 3-46 months) in the TIPS group and 32 months in the cyanoacrylate group (range 1-50 months)	point: gastric variceal rebleeding Secondary end points: complications, blood transfusion requirements, length of hospital stay, or death.	from the participating hospital

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			See below	was exchanged into the right hepatic vein, then a 16-gauge, curved Thompson needle was used to puncture from the hepatic vein into the right portal vein. A 8-mm balloon catheter was used to dilate the liver parenchyma, followed by deployment of a 10 x 68-91-mm metallic endoprosthesis. A tipsogram				

	TIPS N = 35	Injection N= 37
Age	55(11)	52(2)
Male	25	28
Cause: Alc/hepB/ hepC/other	4/12/13/6	8/12/11/6
Serum albumin, gm/dl	2.9(0.5	3.1(0.5)
Serum bilirubin, mg/dl	1.9(1.5)	2.1(1.4)
Ascites n(%)	23(67)	19(51)
Prothrombin time, s	2.7(3.3)	2.8(2.4)
Child-Pugh Class A/B/C	9/20/6	12/19/6
Child-Pugh score	7.8(1.8)	7.6(1.7)
Blood transfused	9.3(8.4)	7.1(5.6)
Previous	20(57)	11(30)

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			history of bleeding, n(%)			was obtained and a pressure kit was used to measure the portal pressure gradient between the main portal vein and inferior vena cava.				

Effect size

Post treatment outcomes – shaded cells indicate significant group differences:

	TIPS N = 35	Injection N= 37	
Mortality	13	9	ns
Obliteration of gastric varices	7	19	<0.02
Patients with rebleeding	15 episodes 22	22 episodes 36	0.12
Patients rebleeding from gastric varices	4	14	0.01
Blood transfusion requirements mean (SD or SEM) range	3.4(2.1) (2-20)	6.2(3.3) (2-64)	<0.01
Length of hospital stay	7.2(5.3) (1-35)	8.7(6.5) (1-38)	Ns
Total n with complications	14	15	Ns
Hepatic encephalopathy	9	1	<0.01
Sepsis	3	2	Ns
Variceal bleeding	1	3	Ns
Pneumonia	1	0	Ns

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Acute renal failure			1	0		ns		

Kaplan-Meier survival analysis was carried out for proportions of patients remaining free of upper GI rebleeding (p=0.12), patients remaining free of gastric variceal rebleeding (p=0.01) and the proportion of patients surviving (p=0.17) - graphs with patients at risk given are provided, but only p-values are given.

Authors' conclusion

TIPS proved more effective than glue injection in preventing rebleeding from gastric varices with similar survival and frequency of complications.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Monescillo A, Martinez-Lagares F, Ruiz-Del-Arbol L et al. Influence of portal hypertension and its early decompression by TIPS placement on the outcome of variceal bleeding. Hepatology. 2004; 40(4):793-801.	RCT, two centre, Country: Spain Adequate allocation concealment and adequate randomisation sequence generation; no blinding and a baseline difference	N=26 TIPS group and N=26 non-TIPS group (both groups were designated a 'high risk' status based on Hepatic venous pressure gradient of more than 20 mm Hg) A low risk group was included but since it was not	Inclusion criteria: Diagnosis of liver cirrhosis by biopsy or clinical analytical, and ultrasound criteria; clinical evidence of hematemesis and/or melena in the 24-hour perod before admission; endoscopically proven bleeding from a variceal source, defined as active bleeding from a varix (jet or oozing), stigmata of recent haemorrhage, fresh blood in the stomach, and oesophageal of gastric varices without any potential bleeding lesion in the upper gastrointestinal tract; age between 18-75 years; no previous inclusion in this study. Exclusion criteria: hepatocellular carcinoma or other malignancies;	TIPS – procedural details not described	ß-blockers and/or band ligation	1 year	Primary endpoint: prospective assessment of sensitivity and specificity of HVPG cut off value (20 mm Hg) in predicting treatment failure and prospective assessment of treatment failure as well as short-and long-term survival in the 3 study groups	Redes Nacional Investigacion Gastroenterolgia y Hepatologia

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td></td><td>randomised it is not reported here.</td><td>portal vein thrombosis; patients with TIPS; HIV infection; history of cardiac failure; chronic renal failure; other concomitant important disease (e.g. neurological disease); patients without haemodynamic measurement within the first 24 hours after admission, i.e. massive bleeding and septic shock by Escherichia coli

Baseline characteristics – usually given as means (SD) or N (shaded cell group comparison p<0.05):
<table>
<tr><td></td><td>TIPS N=26</td><td>No-TIPS N=26</td></tr>
<tr><td>Age</td><td>56(12)</td><td>59(11)</td></tr>
<tr><td>Male</td><td>22</td><td>19</td></tr>
<tr><td>Aetiology Alc/HepC/ other</td><td>21/5/0</td><td>16/9/1</td></tr>
<tr><td>Previous variceal bleeding</td><td>7</td><td>4</td></tr>
<tr><td>Child-Pugh score</td><td>9.2(2.0)</td><td>9.2(2.3)</td></tr>
<tr><td>Child-Pugh class A/B/C</td><td>3/11/12</td><td>4/10/12</td></tr>
</table></td><td></td><td></td><td></td><td>Secondary endpoints: transfusion requirements; rebleeding; intensive care unit stay (n); complications during the first week of treatment mortality and causes of death during follow-up in each treatment group.</td><td></td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Bilirubin	5.8(5.3)	3.6(3.1)					
			Albumin	2.6(0.5)	2.6(0.6)					
			Prothrombin time	44(13)	47(17					
			Hepatic encephalopathy	2	4					
			Ascites	14	15					
			Mean arterial pressure	80(14)	83(18)					
			Haemoglobin	8.7(2.2)	9.4(2.0)					
			Active bleeding at endoscopy	10	8					
			Shock	6	4					
			Heart rate	101(21)	100(17)					

Effect size

Post treatment outcomes – shaded cells indicate significant group differences

	TIPS N=26	Non-TIPS N=26	p-value
Treatment failure	3	13	<0.01
In-hospital mortality	3	10	<0.02

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

6-week mortality	5	10	NS
1-year mortality	8	17	0.01
Units of blood transfused	3.1(2.6)	3.6(2.4)	NS
Intensive care unit (n)	5	4	NS
Complications	18	16	NS
Hepatic encephalopathy	8	9	NS
Injections	11	9	NS

*Non fatal: complications related to the placement of TIPS: acute pulmonary oedema, ischemic hepatitis and acute respiratory failure after sedation for TIPS insertion

Survival analysis was carried out and the No-TIPS group versus TIPS group Hazard Ratios for in-hospital and 1 year mortality were:
Given as Odds Ratios: 4.79 (95% CI 1.13-20.21) and 4.25 (95% CI 1.33-13.56)

Authors' conclusion
Early TIPS placement reduces treatment failure and mortality in high risk patients defined by haemodynamic criteria

Appendix G: Economic evidence tables

G.1 Terlipressin

G.1.1 Terlipressin vs. Octreotide or Placebo

J. Wechowski, M. Connolly, A. Woehl, A. Tetlow, P. McEwan, A. Burroughs, C. J. Currie, and A. Bhatt. An economic evaluation of vasoactive agents used in the United Kingdom for acute bleeding oesophageal varices in patients with liver cirrhosis. Curr.Med.Res.Opin. 23 (7):1481-1491, 2007.

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CUA **Study design:** Decision analytic model **Approach to analysis:** A discrete event simulation model was created with 5 health states: bleeding, no bleeding, no bleeding post transjugular intrahepatic portosystemic shunt (TIPS), post-salvage surgery, and death. **Perspective:** UK NHS **Time horizon:** 1 year	**Population:** Cirrhotic patients with acute bleeding oesophageal varices (endoscopy may or may not have been considered part of standard treatment) **Cohort settings:** Start age = 60 (50-70) M/F = NR **Interventions:** Treatment doses were based on the proceedings of the 4th Bavero International Consensus workshop recommendations [De Franchis 2006]; when the Baveno guidance differs from the licensed dosing, this was tested in the sensitivity analysis	**Total costs (mean per patient over year 1):** Intvn 1: £2623 Intvn 2: £2758 Intvn 3: £2890 **Currency & cost year:** 2005 GBP **Cost components incorporated:** Hospitalisation cost: weighted average of £746.50, considering time in intensive care (average 7.1 days) and in general ward (average 6.9 days) [NHS reference cost]; Acute vasoactive treatment cost: octreotide and terlipressin (doses costed as detailed in the intervention section). Secondary prophylaxis costs: i) endoscopic treatment (assumed average 3.5 sessions required after each bleeding episode from expert opinion; 40% annual	**Primary outcome measure:** QALYs (mean per patient) : Terlipressin produced 0.079 and 0.078 QALYs more than octreotide and placebo per patient in 1 year, respectively. **Other outcome measures (mean):** Life year gained: Treatment with terlipressin resulted in a gain of 0.107 LYG (1.3 months) over 1 year compared with octreotide and placebo; ii) There is no detectable LYG advantage for octreotide compared with placebo	**Cost-effectiveness results:** Base case (1 year): When considering cost per QALY, Terlipressin is dominant over octreotide and placebo, being more effective and less costly; - When varying the time horizon, terlipressin was dominant over octreotide from 42 days to 2 years, and was cost effective at 3 years (ICER of £356 per QALY gained) and at 5 years (£775 per QALY gained). - When varying the time horizon, terlipressin was dominant over placebo from 42 days to 3 years, and was cost effective at 5 years (£513 per QALY gained). **Probability cost-effective:** Probability of cost effectiveness at 1 year was 98.9% for terlipressin, 1.1% for octreotide, and 0.0% for placebo. At 5 years, terlipressin has also the higher probability of cost effectiveness (not reported). **Other:** Base case (1 year): When considering cost per LYG, Terlipressin is dominant over octreotide and placebo, being more effective and less costly. - When varying the time horizon, terlipressin was dominant over octreotide from 42 days to 2 years, and had an ICER of £252 per LYG at 3 years and £530 per LYG at 5 years.

J. Wechowski, M. Connolly, A. Woehl, A. Tetlow, P. McEwan, A. Burroughs, C. J. Currie, and A. Bhatt. An economic evaluation of vasoactive agents used in the United Kingdom for acute bleeding oesophageal varices in patients with liver cirrhosis. Curr.Med.Res.Opin. 23 (7):1481-1491, 2007.				
for the base-case analysis; from 42 days to 5 years in the sensitivity analysis **Treatment effect duration:** NR **Discounting:** A discount rate of 3.5% was applied to both costs and effects after 1 year	**Intervention 1:** Terlipressin 12mg/day; dose was halved after bleeding was controlled; for up to a maximum of 5 days **Intervention 2:** Octreotide Initial bolus of 50µg; followed 50µg/h; up to a maximum of 5 days **Intervention 3:** No treatment	chance of re-bleeding based on baseline risk curves); ii) treatment with b-blockers (120mg daily of propanolol, based on expert opinion and mean dose used in most RCTs); iii) 10 visits per year to a general practitioner following the initial bleed (expert opinion); iv) surgical therapies (salvage surgery and TIPS); and v) cost of death (excess cost of treatment immediately preceding death. Imputed value of £1000 considering additional ICU costs).		- When varying the time horizon, terlipressin was dominant over no treatment from 42 days to 3 years, and had an ICER of £351 per LYG at 5 years. **Subgroup analyses:** NA **Analysis of uncertainty:** A univariate sensitivity analysis and a probabilistic sensitivity analysis were performed. All parameters were varied in the univariate sensitivity analysis, using extremes values. Terlipresssin remained cost effective versus octreotide and placebo in all scenarios. Some scenarios showed octreotide being not cost effective compared to placebo.
Data sources				
Health outcomes: Baseline outcomes in cirrhotic patients during bleeding and non-bleeding were sources from observational studies with long term follow-up for survival, control of bleeding, and re-bleeding rates [2 3]. Curves were fitted for each treatment based on published data [3,4 5]. Efficacy data on survival, re-bleeding and control of bleeding were obtained from RCTs meta-analyses reported in 2 Cochrane reviews for terlipressin and octreotide [6,7] . Trials for somatostatin and its analogue octreotide were not pooled separately. It was assumed that the relative risks versus placebo for the 3 analysed end points were identical for the 2 drugs. **Quality-of-life weights:** The baseline utility score for non-bleeding patient of 0.75 was obtained based on previous studies [8]. In the model, from expert opinion, a disutility of 25% from baseline was applied for each bleeding episode and for TIPS intervention, and 50% from baseline was applied for salvage surgery. Reduction from baseline following TIPS and salvage surgery were based on observations by Rubenstein 2004[9]. All estimates of utility were varied in the probabilistic sensitivity analysis ±25%. **Cost sources:** Costs were obtained from published UK sources [NHS reference cost database; BNF; PSSRU].				
Comments				
Source of funding: The study was supported by Ferring Pharmaceuticals, St Prex, Switzerland; **Limitations:** The effects of treatments integrated in this economic evaluation were taken from RCTs (high quality studies) comparing terlipressin and octreotide with placebo. Some trials comparing terlipressin and octreotide directly were not used in this economic analysis, as these studies were graded of low quality (not double-blinded) in the Cochrane review by (Loannou 2003[6]) **Other:**				
Overall applicability*: Directly Applicable **Overall quality**: Minor Limitations**				

Abbreviations: BNF = British National Formulary; CI = confidence interval; CUA = cost-utility analysis; d/a deterministic analysis ICER = incremental cost-effectiveness ratio; GBP = Great Britain Pound; LYG = Life-Year Gained; NA = Not applicable; NHS = National Health Service; NR = not reported; PSSRU = Personal Social Services Research Unit; QALY = Quality-Adjusted Life-Years; RCT = Randomised Controlled Trial; TIPS = Transjugular Intrahepatic Portosystemic Shunt; UK = United Kingdom.

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious Limitations / Very serious limitations*

G.2 Timing of endoscopy

G.2.1 Table 1

J. G. Lee, S. Turnipseed, P. S. Romano, H. Vigil, R. Azari, N. Melnikoff, R. Hsu, D. Kirk, P. Sokolove, and J. W. Leung. Endoscopy-based triage significantly reduces hospitalization rates and costs of treating upper GI bleeding: a randomized controlled trial. Gastrointest.Endosc. 50:755-761, 1999.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Comparative cost analysis developed part of a RCT **Study design:** RCT **Perspective:** US Medicare **Time horizon:** 30 days **Treatment effect**	**Population:** Patients with nonvariceal upper GI bleeding and stable vital signs; n=110. **Cohort settings:** There were no statistically significant differences between the 2 groups for baseline demographic and clinical characteristics. **Intervention 1:** Early endoscopy was undergone in the emergency department within 1 to 2 hours, and patients were triaged based on the endoscopic findings (n=56); Patients with low-risk findings on early endoscopy were discharged directly from the	**Total costs [Median (interquartile range)]:** Intvn 1: $2068 (928-3960) Intvn 2: $3662 (2473-7280), p=0.00006 **Currency & cost year:** USD; year NR; assumed that cost were in 1999 USD. **Cost components incorporated:** Units of transfusion required; hospital stay (including readmissions); endoscopic procedures (including repeat endoscopy); surgical procedures; and unplanned visit to any physician. The overall hospitalisation stay (main cost component) was	**Outcome measures:** The key clinical outcomes were favouring early endoscopy, but were not statistically different between groups. **Recurrent hemorrhage (median, IQR):** Intvn 1: 2 (3.6) Intvn 2: 3 (5.6) P=.63 **Deaths (no, %):** Intvn 1: 0/56 Intvn 2: 2/48 [c] P=.54 Both deaths in the late group were unrelated to GI bleeding or endoscopy. **Adverse events:** 26 of the 56 patients (46%) in the early group were discharge directly from the emergency	**Cost-effectiveness results:** NA **Probability cost-effective:** NA **Subgroup analyses:** NA **Analysis of uncertainty:** No sensitivity analysis was performed; results of the cost analysis are presented with interquartile ranges.

J. G. Lee, S. Turnipseed, P. S. Romano, H. Vigil, R. Azari, N. Melnikoff, R. Hsu, D. Kirk, P. Sokolove, and J. W. Leung. Endoscopy-based triage significantly reduces hospitalization rates and costs of treating upper GI bleeding: a randomized controlled trial. Gastrointest.Endosc. 50:755-761, 1999.				
duration: NR **Discounting:** NA	emergency department. **Intervention 2:** Late endoscopy was undergone for elective patients within 1 to 2 days of admission (n=48).	significantly shorter for the early group because of the 46% of patients discharge directly from the emergency department, and because of a significant shorter stay in the medical ward (1.3 days for early vs 1.5 for late, p=0.0004), however, the number of days spent in the intensive care unit and the intermediate care unit did not differ significantly.	department, and none of them suffered an adverse outcome (recurrent bleeding, underwent repeat endoscopy, or died). **Unplanned physician visits during follow up:** Unplanned visit to the physician during the 30-day follow-up period was significantly lower for the early group.	
Data sources				
Health outcomes: Collected as part of the RCT. **Quality-of-life weights:** NA **Cost sources:** Cost data were obtained for the 30 day period using the hospital financial software, and were independent of hospital charges.				
Comments				
Source of funding: Supported in part by grants from the American Digestive Health Foundation and the Hibbard E. Williams Research Award from the University of California, Davis Health System **Limitations:** Results of the cost analysis were presented with a median (interquartile range); analysis developed from a US perspective (not directly applicable to the UK NHS); 30-day time horizon (a longer time horizon might capture additional effects from compared interventions). **Other:**:				
Overall applicability*: Partially Applicable Overall quality: Minor Limitations**				

Abbreviations: CI = confidence interval; CUA = cost-utility analysis; GI =gastro intestinal; IQR = Interquartile Range; ICER = incremental cost-effectiveness ratio; n = number of patients in study; NR = not reported; NA = Not applicable; pa = probabilistic analysis; QALY = Quality-Adjusted Life-Years; LYG = Life-Year Gained; NHS = National Health Service; RCT = Randomised Controlled Trial; US = United States; USD= United states dollar;

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious Limitations / Very serious limitations*

G.2.2 Table 2

NCGC Economic Model: Timing of Endoscopy. 2011				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA **Study design:** Decision analytic model **Approach to analysis:** Markov model was created with 9 health states: In hospital (pre endoscopy); In hospital (post endoscopy which was undertaken 0-4 hours post admission); In hospital (post endoscopy which was undertaken 4-12 hours post admission); In hospital (post endoscopy which was undertaken 12-24 hours post admission); In hospital (post endoscopy which was undertaken 24-48 hours post admission); In hospital (post	**Population:** Non elective patients who had experienced an acute upper gastrointestinal bleed presenting either as a new admission or as an inpatient. Included patients with and without suspected variceal bleeding **Cohort settings:** Start age = NR M/F = NR **Intervention 1:** Weekday access to endoscopy: endoscopy staff onsite weekdays 8am-5pm.; assumed to allow access to endoscopy within a similar time interval observed in hospitals that do not have an on call service **Intervention 2:** Everyday access to endoscopy: endoscopy staff onsite on weekdays 8am-5pm and on site on weekends 8am-12pm;	**Total costs (mean per patient):** Intvn 1: £3382 Intvn 2: £3428 Intvn 3: £3999 Intvn 4: £4012 Incremental (2-1): £ 46 (95%CI:-£306; £430; p=NR) [Intervention 3 and 4 were dominated] **Total cost per 1000 patients:** Intvn 1: £3,381,936 Intvn 2: £ 3427889 Intvn 3: £3,999,356 Intvn 4: £4,011728 **Currency & cost year:** 2010 UK GBP **Cost components**	**Primary outcome measure:** **QALYs (mean per patient)** Intvn 1: 0.051 Intvn 2: 2: 0.052 Intvn 3: 0.051 Intvn 4: 0.051 Incremental (2-1): 0.0013 (95%CI:0.0006;0.0019; p=NR) [Intervention 3 and 4 were dominated] **Other outcome measures:** **Death (mean per 1000 patients)** Intvn 1: 110 Intvn 2: 91 Intvn 3: 98 Intvn 4: 108	Intervention 3 and 4 were dominated strategies. **Primary ICER (Intvn 2 vs Intvn 1):** ICER: £ 36,590 per QALY gained (pa) Probability Intervention 1 was cost-effective: 53% Probability Intervention 2 was cost-effective: 47% **Subgroup analyses:** Disaggregated results were presented by pre-endoscopy Rockall score, however as implementation costs were not assigned cost effectiveness was not assessed. **Analysis of uncertainty:** Sensitivity analyses were run probabilistically. In all analyses either Intvn. 1 or 2 was recorded as the most or second most optimal strategy. Throughout all of the sensitivity analyses, the probability that Intvn. 3 or 4 being optimal was zero. Parameters tested in univariate analyses included utility assigned to the in and out of hospital states, cost of endoscopy, number of presentations per year; proportion of low and high risk patients in cohort; with the later showing a change in results from intvn. 1 being optimal to intvn. 2 becoming optimal. The results were most sensitive to change in the number presentation a provider expected in a year. The optimal strategy is only certain when the number of presentations per year is 50 or below; where intvn 1 is the most cost effective option. Intvn 1 is more likely to be more cost

NCGC Economic Model: Timing of Endoscopy. 2011				
endoscopy which was undertaken 48-72 hours post admission); In hospital (post endoscopy which was undertaken more than 72 hours post admission); discharged and at home; dead. **Perspective:** UK, NHS **Time horizon:** 28 days **Treatment effect duration:** NR **Discounting:** NA – due to short time horizon	assumed to allow endoscopy within 24 hours of presentation **Intervention 3:** Extended everyday access to endoscopy: endoscopy staff onsite everyday 8am-5pm, and on call everyday 5pm-12am; assumed to allow endoscopy within 12 hours of presentation **Intervention 4:** Continuous access to endoscopy: endoscopy staff on site everyday 8am-5pm, and on call everyday 5pm-8am; assumed to allow endoscopy within 4 hours of presentation	**incorporated:** Endoscopy consultant and nurse, Endoscopy procedure (consumables and maintenance), hospital stay	**Average length of stay (days):** Intvn 1: 9.0 Intvn 2: 7.9 Intvn 3: 8.4 Intvn 4: 8.3	effective than intvn 2 if a provider is expecting less than 330 presentations per year, with decreasing certainty that this is the most cost effective option as the number of presentations increase. For more than 330 presentations per year, intvn 2 is more likely to be optimal, with increasing certainty that this is the optimal option as the number of presentations increase. Results were also sensitive to a change in the cost of hospital stay. Where the same cost for hospital stay was applied to the pre and post endoscope states, the number of presentations needed for intvn 2 to be more cost effective to intvn 1 decreased. An exploratory threshold analysis showed that the patient needs to have at least 20 days of full health post the time horizon (at no additional cost to the NHS) for Intvn 2 to become cost effective with an ICER of £19,715 when compared to intvn 1 (under the base case assumption of 300 presentations per year).
Data sources				
Health outcomes: Health outcomes were derived from statistical analysis of prospective national audit, as reported by Hearnshaw SA, Logan RF, Lowe D et al. Use of endoscopy for management of acute upper gastrointestinal bleeding in the UK: results of a nationwide audit. Gut. 2010; **Quality-of-life weights:** Derived from UK patient level data (n=57) collected using the EQ5D as reported by Leontiadis GI, Sreedharan A, Dorward S et al. Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding. Health Technol Assess. 2007; 11(51):iii-126. **Cost sources:** NHS reference costs 2009-2010 as reported by: Department of Health. NHS reference costs 2009-2010: Appendix NSRC04: NHS trust and PCT combined reference cost schedules.				
Comments				
Source of funding: NA; **Limitations:** Based on prospective observational patient level data collected as part of a national UK audit in 2007. Causal assumptions regarding link between timing of endoscopy and death and discharge rate, however this was considered reasonable and appropriate by expert clinical opinion. Both deterministic and probabilistic sensitivity analysis was performed allowing assessment of uncertainty. A 28 day horizon was used, potentially limiting the analysis by not capturing downstream costs and benefits. Analysis assessed quality of life and calculated QALYs.; **Other:**				

NCGC Economic Model: Timing of Endoscopy. 2011
Overall applicability*: Direct Applicability Overall quality: Potentially serious limitations**

Abbreviations: CUA = cost-effectiveness analysis; CI = confidence interval;; d/a deterministic analysis; GBP = Great British Pounds; ICER = incremental cost-effectiveness ratio; NHS = National Health Service; NR = not reported; pa = probabilistic analysis; UK = United Kingdom
** Directly applicable / partially applicable / Not applicable; ** Minor limitations /potentially serious Limitations / Very serious limitations*

G.3 Management of non-variceal bleeding

G.3.1 PPI

G.3.1.1 Table 1

G. I. Leontiadis, A. Sreedharan, S. Dorward, P. Barton, B. Delaney, and C. W. Howden. Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding. Health Technol.Assess. 11(51):1-164, 2007.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis (28-day time horizon) and cost-effectiveness analysis (lifetime horizon) **Study design:** Decision-analytic model **Approach to analysis:** An individual sampling model which constructed a large number of virtual patient histories. Events assessed by the model were: Waiting for endoscopy (endoscopies available at 9:00am 7 days per week); endoscopy with or without therapy; re-bleeding; surgery; death; inpatient post-endoscopy; discharge home;	**Population:** Haemodynamically stable patients after an episode of bleeding peptide ulcer **Cohort settings:** Start age = NR M/F = NR **Interventions** 12 strategies were compared from combinations of treatments before endoscopy, at endoscopy, and after endoscopy. After strategies subject to dominance and extended dominance were excluded, 5 strategies can be included in incremental analysis. Strategy 1: Oral PPI, EHT [a], Fixed [b] Strategy 2: Nothing, EHT, Fixed Strategy 3: Nothing, EHT, Variable [c]	**Mean total cost (Incremental cost to subsequent option in brackets):** Strategy 1: £868 (£12) Strategy 2: £856 (£28) Strategy 3: £827 (£3) Strategy 4: £825 (£10) Reference: £814 **Currency & cost year:** UK GBP, 2007 **Cost components incorporated:** Therapeutic and	**QALDs - 28 day horizon (incremental effect to subsequent option in brackets)** Strategy 1: 17.51(0.18) Strategy 2: 19.30 (0.48) Strategy 3: 18.31(0.08) Strategy 4: 18.71 (0.91) Reference: 17.81 **Life years – lifetime horizon**	**Cost-effectiveness results:** The results presented below are those after excluding cases of dominance and extended dominance. **ICER vs subsequent option: 28 days / lifetime:** <u>Strategy 1 vs strategy 2:</u> £24,300 per QALY gained (22,200 – 26,800) / £140 per LY gained (127 – 157) <u>Strategy 2 vs strategy 3:</u> £21,300 per QALY gained (20,200 – 22,600) / £111 per LY gained (104 – 118) <u>Strategy 3 vs strategy 4:</u> £13,000 per QALY gained (10,700 – 16,600) / £75 per LY gained (61 – 97)

G. I. Leontiadis, A. Sreedharan, S. Dorward, P. Barton, B. Delaney, and C. W. Howden. Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding. Health Technol.Assess. 11(51):1-164, 2007.				
terminate (patients alive at 28 days). **Perspective:** UK NHS **Time horizon:** 28-day time horizon and a lifetime analysis. **Discounting:** NA - No cost applied after 28 days	Strategy 4: IV PPI, EHT, Variable Reference: IV PPI, EHT, Fixed [a] EHT – Endoscopic haemostatic therapy offered to patients with major stimata of recent haemorrhage (SRH). [b] Fixed – Patients received the same treatment as before endoscopy, except patients who were receiving no treatment received oral PPI. All patients received oral PPI at discharge. [c] Variable – For patients with detected major SRH, IV PPI for 72 hours then oral PPI; oral PPI for other patients. All patients remained on oral PPI at discharge.	diagnostic procedures (Endoscopy; Endoscopy therapy; Surgery), time in hospital, drug treatments (Oral PPI; IV PPI).	Strategy 1: 9.58 (0.08) Strategy 2: 10.36 (0.26) Strategy 3: 9.84 (0.04) Strategy 4: 10.06 (0.48) Reference: 9.58	<u>Strategy 4 vs Reference:</u> £4120 per QALY gained (3830 – 4460) / £22 per LY gained (20 – 23) **Probability cost-effective:** NR – visual inspection of the CEAC presented suggested a 0.7 to 0.95 probability the "Oral PPI – Fixed" strategy was cost effective, depending on the comparator. **Subgroup analyses:** NA **Analysis of uncertainty:** For the 28-days analysis, the sensitivity analysis showed that there is a non-negligible probability that other strategies are superior than 'Oral PPI + endoscopic haemostatic therapy for patients with major SRH + Oral PPI'. However, this strategy is strongly favoured in the lifetime analysis.
Data sources				
Health outcomes: Baseline risks: Baseline risk rates of re-bleeding and death were breakdown by Rockall score as proposed by Vreeburg and colleagues (Vreeburg EM, Terwee CB, Snel P, Rauws EA, Bartelsman JF, Meulen JH, et al. Validation of the Rockall risk scoring system in upper gastrointestinal bleeding. Gut 1999; 44:331–5). Treatment effect and probabilities: The effect of therapies on risks of re-bleeding and death; risk rates for re-bleeding and death after discharge; probability that re-bleeding requires surgery; mortality at surgery. The model used data from the HTA review and from various published sources. Life expectancy following discharge: Life expectancy among survivors was obtained by applying a RR of 2.1 (95% CI 1.7 to 2.6) (Vreeburg and colleagues) to general population life-tables (Government Actuary's Department). Vreeburg and colleagues: Vreeburg and colleagues: Vreeburg EM, Terwee CB, Snel P, Rauws EA, Bartelsman JF, Meulen JH, et al. Validation of the Rockall risk scoring system in upper gastrointestinal bleeding. Gut 1999; 44:331–5. **Quality-of-life weights:** The EuroQoL EQ-5D was given to 57 consecutive patients surviving a UGI bleed. The questionnaire was given at discharge or 7 days after the GI				

G. I. Leontiadis, A. Sreedharan, S. Dorward, P. Barton, B. Delaney, and C. W. Howden. Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding. Health Technol.Assess. 11(51):1-164, 2007.
bleed. This indicated the immediate deterioration in QoL after a GI bleed. A further follow-up questionnaire at 4 weeks was completed by all patients. These data were used to represent QoL at home and in hospital: QoL at home - 0.78 (0.70; 0.85); Qol in hospital - 0.45 (0.34; 0.57). **Cost sources:** NHS reference cost 2007; PSSRU 2007; BNF 51 (2006)
Comments
Source of funding: Developed from the Health Technology Assessment programme, a part of the National Institute for Health Research (UK). **Limitations:** No cost was applied after 28-days for the lifetime analysis. Results of the lifetime analysis were not presented in cost per QALY gained. **Other:**
Overall applicability*: Directly Applicable Overall quality: Minor limitations**

Abbreviations: BNF = British National Formulary; CEAC = cost effectiveness acceptability curve; CI = confidence interval; EHT = Endoscopic Haemostatic Therapy; GBP = Great Britain Pound; HTA = Health Technology Assessment; ICER = Incremental Cost-Effectiveness Ratio; IV = Intravenous; LY = Life-Year; NHS = National Health Service; NR = not reported; PSSRU = Personal Social Services Research Unit; PPI = Proton Pump Inhibitors; QALD = Quality-Adjusted Life-Days; QALY = Quality-Adjusted Life-Years; QoL = Quality of Life; RCT = Randomised Controlled Trial; SRH = Stimata of Recent Haemorrhage; UGI = Upper Gastrointestinal; US = United States; UK = United Kingdom;
** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious Limitations / Very serious limitations*

G.3.1.2 Table 2

B. M. Spiegel, G. S. Dulai, B. S. Lim, N. Mann, F. Kanwal, and I. M. Gralnek. The cost-effectiveness and budget impact of intravenous versus oral proton pump inhibitors in peptic ulcer hemorrhage. Clinical Gastroenterology and Hepatology 4 (8):988-997, 2006.

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: Cost-utility analysis **Study design:** Decision-analytic model **Approach to analysis:** TreeAge software was used to develop the economic model. To calculate QALYs, utilities for 4 health states were incorporated to the model: dyspepsia; ulcer hemorrage without surgery; ulcer hemorrhage or ulcer perforation with surgery; and death.	**Population:** Patients with high-risk peptic ulcer haemorrhage (active bleeding or non-bleeding visible vessel) in whom successful endoscopic haemostasis was performed **Cohort settings:** Start age = NR M/F = NR **Interventions:** All interventions received upper endoscopy within 24 hours and received	**Total cost (base case):** - Oral PPI: $6864 - IV PPI: $8009 - IV H2RA: $9250 (taken from a figure) **Currency & cost year:** 2005 USD **Cost components**	**Quality-Adjusted Life-Year s (QALY):** - Oral PPI = 0.9767 QALYs - IV PPI = 0.9783 QALYs - IV H2RA: 0.9670 QALYs (taken from a figure)	**Base-case analyses ICER:** - IV H2RA is dominated by PPI strategies, being less effective and more costly - ICER IV PPI vs oral PPI = $708,735 per QALY gained **Probability cost-effective:** Probability of IV PPI to be cost effective with a threshold of $50k = 8%; $100k = 12%; $200k = 22% **Subgroup analyses:** NA **Analysis of uncertainty:** Method

B. M. Spiegel, G. S. Dulai, B. S. Lim, N. Mann, F. Kanwal, and I. M. Gralnek. The cost-effectiveness and budget impact of intravenous versus oral proton pump inhibitors in peptic ulcer hemorrhage. Clinical Gastroenterology and Hepatology 4 (8):988-997, 2006.				
Perspective: US third-party payer **Time horizon:** Not explicitly mentioned, but seems to be 30 days according to probabilities used in the model **Discounting:** NA - All cost were applied during the first year	haemostatic interventions for active bleeding or nonbleeding visible vessels, then: Intervention 1: Oral PPI 48 hrs hospital stay with high dose oral PPI then discharge if no complication; 8-week course of oral PPI therapy after discharge; if recurrent haemorrhage after discharge, readmission and IV PPI therapy. Intervention2: IV PPI Equivalent of 80mg bolus injection of omeprazole followed by a continuous infusion of 8mg/h over 72 hours; 8-week course of oral PPI therapy after discharge; if recurrent haemorrhage after discharge, readmission and IV PPI therapy. Intervention 3: IV H2RA Equivalent of a 50mg bolus injection of ranitidine followed by a continuous infusion of 13.3mg/h over 72 hours; 8-week course of oral PPI therapy after discharge; nothing specified if readmission.	**incorporated:** - Drug treatment cost (including IV tubing and pump when IV treatment); - Interventions cost (endoscopy, surgery); - Hospital stay; - Inpatient and outpatients consultations; - Cost for treating complicated and uncomplicated ulcer haemorrhage (Medicare DRG cost).		- A multivariable sensitivity analysis (tornado analysis) was performed. - Then a one-way sensitivity analysis was undertaken on the most influential variables: 72-hour rebleed rate with oral PPI; 72-hour rebleed rate with IV PPI; and hospital length of stay with IV PPI. - Finally, a probabilistic sensitivity analysis was performed. <u>Results</u> - IV PPI became dominant when the rebleed rate with oral PPI > 24% (base case = 13%; range from the review = 2%-27%) - IV PPI became dominant when the hospital length of stay for patients on IV PPI without rebleeding decrease to less than 3 days (base case = 4 days) - Oral PPI became dominant when the rebleed rate with IV PPI > 13% (base case = 6%; range from the review = 6%-24%). - ICER when using the drug acquisition costs from the Veterans Administration = $477,114 per QALY gained
Data sources				
Health outcomes: Probability estimates were derived from systematic reviews of RCTs and expert opinion elicited using the delphi technique. **Quality-of-life weights:** Derived from a range of published studies including Groeneveld et al, Ebell et al, Sonnenberg et al **Costs and resource use:** i) Costs for endoscopic and surgical procedures and physician services: from the 2005 American Medical Association Current Procedural Terminology codebook, and the 2005 Medicare Fee Schedule				

B. M. Spiegel, G. S. Dulai, B. S. Lim, N. Mann, F. Kanwal, and I. M. Gralnek. The cost-effectiveness and budget impact of intravenous versus oral proton pump inhibitors in peptic ulcer hemorrhage. Clinical Gastroenterology and Hepatology 4 (8):988-997, 2006.
ii) Base-case pharmaceutical costs: from the average wholesale process listed in the 2005 Red Book. iii) Sensitivity analysis pharmaceutical costs (lower acquisition cost for large buying consortiums): Veteran's Administration iv) Inpatient resource use was included under the standard Medicare Diagnostic-Related Group reimbursement for upper GI bleeding and were prorated by hospital length of stay v) Average length of stay as reported by the Center for Medicare and Medicaid Services
Comments
Source of funding: Supported by Veterans Administration Health Services Research and Development awards; by a National Institute of Health K23 Award; and by an American Association for the Study of Liver Diseases Advanced Hepatology Fellowship Award. **Limitations:** This is not clear from the publication how the relative risks of mortality were considered using compared strategies; This analysis being developed from a US perspective, the applicability of the results to the UK NHS is questionable. **Other:**
Overall applicability*: Partially Applicable Overall quality: Potentially serious limitations**

Abbreviations: BNF = British National Formulary; CEAC = cost effectiveness acceptability curve; CI = confidence interval; DRG =diagnostic related group; ICER = Incremental Cost-Effectiveness Ratio; IV = Intravenous; LY = Life-Year; NR = not reported; NA = not applicable; PSSRU = Personal Social Services Research Unit; PPI = Proton Pump Inhibitors; M/F = Male to Female ratio; QALD = Quality-Adjusted Life-Days; QALY = Quality-Adjusted Life-Years; QoL = Quality of Life; RCT = Randomised Controlled Trial; SRH = Stimata of Recent Haemorrhage; UGI = Upper Gastrointestinal; US = United States; USD = United states dollar UK = United Kingdom;

* Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious Limitations / Very serious limitations

G.3.2 Treatment options after first/failed endoscopy

B. M. R. Spiegel, J. J. Ofman, K. Woods, and N. B. Vakil. Minimizing recurrent peptic ulcer haemorrhage after endoscopic haemostasis: the cost-effectiveness of competing strategies. Am.J.Gastroenterol. 98 (1):86-97, 2003.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CEA **Study design:**	**Population:** Patients with peptic ulcer haemorrhage in whom successful endoscopic haemostasis was performed	**Total costs (mean per patient):** Intvn 1: $7943 Intvn 2: $7412 Intvn 3: $8856	**Primary outcome measure:** The effectiveness was defined as the proportion of	Selective second look endoscopy at 24hrs only in patients at high risk for rebleeding (as identified by the Baylor Bleeding Score) is the base case dominant strategy, being more effective and less

B. M. R. Spiegel, J. J. Ofman, K. Woods, and N. B. Vakil. Minimizing recurrent peptic ulcer haemorrhage after endoscopic haemostasis: the cost-effectiveness of competing strategies. Am.J.Gastroenterol. 98 (1):86-97, 2003.				
Decision analysis model. **Approach to analysis:** Based on reviews of literature. When there was a range of data available from the literature, the model was bias favouring clinical follow-up (second look endoscopy only in patients with evidence of rebleeding). **Perspective:** US Medicare **Time horizon:** 30 days after hospital discharge **Discounting:** N/A	**Cohort settings:** Start age = NR; M/F = NR **Intervention 1: Clinical follow-up:** Follow patients clinically after haemostasis and repeat endoscopy only in patients with evidence of rebleeding. Probability of rebleeding in patients with clinical follow-up was 18.8% (in literature: 4-40%) **Intervention 2: Clinical follow-up + PPI:** Administer iv PPI after haemostasis and repeat endoscopy only in patients with clinical signs of rebleeding. The probability of rebleeding in patients with clinical follow-up + PPI was 13.2% (0-29%) **Intervention 3: Second look for all patients:** Perform second look endoscopy at 24hrs in all patients with successful endoscopic haemostasis. Patients found to have subclinical bleeding or a nonbleeding visible vessel underwent retreatment of the lesion. The probability of rebleeding when all patients undergo a second look endoscopy was 11% (7-21%) **Intervention 4: Selective second look:** Perform selective second look endoscopy at 24hrs only in patients at high risk for rebleeding as identified by the Baylor Bleeding Score. Retreatment as for intervention 3. The probability of rebleeding in patients with low-risk Baylor Bleeding Scorewas 5% (0%), compared to a probability of rebleeding	Intvn 4: $7262 **Currency & cost year:** 2001 US dollars **Cost components incorporated:** Inpatient resource use for complicated (6 days hospital stay) and uncomplicated (3 days hospital stay) ulcer haemorrhage (blood transfusions, laboratory costs, medication costs, and intensive care unit monitoring). IV PPI cost (medication and iv tubing and pump) Cost of upper endoscopy (consultation and procedure) Cost of surgical ulcer or perforation repair (inpatient resource use for bowel perforation; consultation, surgeon's fee & anaesthesiologist's fee) Cost of inpatient gastroenterologist or surgical follow-up visit	patients with prevented rebleeding, surgery, or death. Intvn 1: 81% Intvn 2: 87% Intvn 3: 89% Intvn 4: 91%	costly than others. Probability cost-effective: N/A **Subgroup analyses:** N/A **Analysis of uncertainty:** A one-way sensitivity analyses, two-way sensitivity analyses, and a probabilistic sensitivity analysis (2nd order Monte Carlo) were performed. Clinical follow-up dominates when the probability of rebleeding is <10% Clinical follow-up + PPI dominates when its probability of rebleeding <9% Clinical follow-up + PPI dominates when the probability of complications from endoscopy >3% Large variations on the cost of PPI and endoscopy can change the conclusion of the analysis

B. M. R. Spiegel, J. J. Ofman, K. Woods, and N. B. Vakil. Minimizing recurrent peptic ulcer haemorrhage after endoscopic haemostasis: the cost-effectiveness of competing strategies. Am.J.Gastroenterol. 98 (1):86-97, 2003.				
	in patients with high-risk Baylor Bleeding Score was 12% (0%). The Proportion of patients with high-risk Baylor Bleeding Score was 56% Patients with rebleeding after discharge were readmitted to receive repeat upper endoscopy (10% of rebleeding happened after 72 hours according to literature; assumed after discharge). Patients with recurrent bleeding despite endoscopic retreatment received surgical oversewing of the bleeding ulcer. Patients with endoscopy-induced perforation underwent surgical repair of the lesion.	Based on data from the Center for Medicaid and Medicare Services, it was assumed an average hospital stay of 3 days post treatment for uncomplicated cases, and 6 days for complicated cases. Assumed daily gastroenterologist follow-up when patient hospitalised. Also assumed that patients requiring surgery received an initial surgical consultation followed by a daily follow-up visit by the surgeon while hospitalised		(favouring Clinical follow-up + PPI) Clinical follow-up + PPI preferred when the proportion of high-risk patients >66% Variations in cost of PPI + proportion of high-risk patients varied the conclusion favouring or selective second look or Clinical follow-up + PPI Variations in cost of endoscopy + probability of rebleeding on iv PPI varied the conclusion favouring selective or second look or Clinical follow-up + PPI
Data sources				
Health outcomes: Taken from a reviews of literature. The key probabilities used are listed above in Population and Intervention. **Quality-of-life weights:** N/A **Cost sources:** Costs for endoscopic and surgical procedures and physician services were obtained from the 2001 American Medical Association Current Procedural Terminology codebook and the 2001 Medicare Fee Schedule. Inpatient resource use, including blood transfusions, laboratory costs, medication costs, and intensive care unit monitoring were included under the standard Medicare Diagnosis Related Group (DRG) reimbursement for upper GI haemorrhage. The cost of iv PPI therapy was the average pharmacy cost of buying consortiums from 6 institutions (equivalent of 80mg bolus followed by 8mg/h for 72 hours).				
Comments				
Source of funding: NR; **Limitations:** US study; no quality of life assessment; no PPI use in options Second look for all patients and Selective second look (Clinical follow-up + PPI being the usual care in current UK practice); **Other:**				

B. M. R. Spiegel, J. J. Ofman, K. Woods, and N. B. Vakil. Minimizing recurrent peptic ulcer haemorrhage after endoscopic haemostasis: the cost-effectiveness of competing strategies. Am.J.Gastroenterol. 98 (1):86-97, 2003.				
Overall applicability*: Partially Applicable	**Overall quality**: Potentially serious limitations**			

Abbreviations: CEA = cost-effectiveness analysis; CI = confidence interval; NR = not reported pa = probabilistic analysis; M/F=male/female; PPI= Proton Pump Inhibitor; US = United States; GI = Gastrointestinal; UK = United Kingdom; iv = Intravenous; N/A not applicable

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious Limitations / Very serious limitations*

G.4 Primary prophylaxis

T. Ben-Menachem, B. D. McCarthy, R. Fogel, R. M. Schiffman, R. Patel, V, B. J. Zarowitz, D. R. Nerenz, and R. S. Bresalier. Prophylaxis for stress-related gastrointestinal hemorrhage: a cost effectiveness analysis. Crit.Care Med. 24 (2):338-345, 1996.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CEA **Study design:** Decision analytic model **Approach to analysis:** A decision tree, using data from a systematic review, comparing immediate effects of prophylaxis and no prophylaxis on the reduction of stress related haemorrhage in ICU patients. **Perspective:** US healthcare payer perspective (Hospital based) **Time horizon:**	**Population:** ICU patients at risk (high or low) of stress related haemorrhage Two prophylactic interventions were compared; assumed to have equal efficacy (as no published data suggested the contrary). Mortality rate was assumed to be unaffected as shown in published literature. **Intervention 1:** No Prophylaxis: average 7 days (median of identified studies) **Intervention 2:** Cimetidine (H2-receptor antagonist): Continuous infusion for 7 days (900mg) (The study also reported on Sucralfate	**Total costs (mean per patient):** Intvn 1: $595 Intvn 2, Cimetidine : $839 Sucralfate: $647 (Nosocomial pneumonia carries an added cost of $10,062 but baseline risk is 0% - sensitivity analysis varied this estimates for sucralfate only) **Currency & cost year:** US dollars	**Primary outcome measure:** Bleeding episode averted (base case) **Intvn 1:** 6 episodes per 100 patients **Intvn 2:** (cimetidine or sucralfate): 3 episodes per 100 patients	**Primary ICER (Intvn 2 vs Intvn 1):** ICER: •Cimetidine vs no prophylaxis: $7,538 per episode averted (Sucralfate vs no prophylaxis: $1,144 per episode averted) **Subgroup analyses: NR** **Analysis of uncertainty:** The paper states that even with increased effectiveness of Cimetidine, Sucralfate remains the cost effective option, therefore all the sensitivity analyses were carried out on Sucralfate (which is not under consideration in the review question). Deterministic sensitivity analyses were carried

T. Ben-Menachem, B. D. McCarthy, R. Fogel, R. M. Schiffman, R. Patel, V, B. J. Zarowitz, D. R. Nerenz, and R. S. Bresalier. Prophylaxis for stress-related gastrointestinal hemorrhage: a cost effectiveness analysis. Crit.Care Med. 24 (2):338-345, 1996.				
Immediate (7 days – based on the average ICU length of stay and the assumption that length of stay was not affected by interventions). Some authors reported longer ICU stays for patients with stress-related haemorrhage, however, this additional length of stay is thought to be due to underlying diseases and not directly attributable to the haemorrhage **Discounting:** N.A. due to short time horizon.	as a third comparator at 1g every 6hrs for 7 days, however this intervention is not part of the review question) **Probabilities incorporated to the analysis:** •Base-case frequency (risk) of stress-related haemorrhage among ICU patients not receiving prophylaxis: 6% - median rate among study included from the systematic review. •Base-case probability of risk reduction from prophylaxis: 50% reduction – based on a meta-analysis of stress-related haemorrhage prophylaxis •The base-case analysis assumed that prophylaxis did not alter the frequency of nosocomial pneumonia given the uncertainty of published estimates	Cost year NR (assumed 1996 – year of publication) **Cost components incorporated:** Prophylactic medications Esophagogastroduod enoscopy Serial hematocrit determinations Cimetidine/sucralfate therapy Blood transfusions Treatment of Nosocomial Pneumonia (for sensitivity analysis performed for sucralfate only)		out on: Risk of haemorrhage - Prophylaxis more cost effective with higher risk Risk reduction with prophylaxis - Prophylaxis more cost effective with higher efficacy Risk of Nosocomial Pneumonia - Increase of incidence leads to a decrease in cost effectiveness (1% increase leads to ICER of $4,497)
Data sources				
Health outcomes: Systematic review **Quality-of-life weights:** N.A. **Cost sources:** Henry Ford Hospital (Detroit, US)				
Comments				
Source of funding: Henry Ford Hospital Research and Education Funds **Limitations:** Sensitivity analyses did not consider Cimetidine, No probabilistic sensitivity analysis, No QoL, No Mortality, US focussed study, costs from US hospital not from national sources;				
Overall applicability*: Partially applicable Overall quality: Potentially serious Limitations**				

Abbreviations: CEA = cost-effectiveness analysis; ICER = incremental cost-effectiveness ratio; NR = not reported

** Directly applicable / partially applicable / Not applicable; ** Minor limitations /potentially serious Limitations / Very serious limitations*

G.5 Management of variceal bleeding

G.5.1 TIPS

S. Mahadeva, M. C. Bellamy, D. Kessel, M. H. Davies, and C. E. Millson. Cost-effectiveness of n-butyl-2-cyanoacrylate (N-butyl-2-cyanoacrylate glue injections versus transjugular intrahepatic portosystemic shunt in the management of acute gastric variceal bleeding. Am.J.Gastroenterol. 98 (12):2688-2693, 2003.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CEA **Study design:** The retrospective review included 20 patients who had TIPS between January 1995 and December 1999; and 23 patients who had glue injection between January 2000 and October 2001 **Approach to analysis:** Retrospective review using clinical records for cases during a six month period. **Perspective:** NHS, UK.	**Population:** Patients with confirmed bleeding gastric varices on upper GI endoscopy **Cohort settings:** **Start age** Intvn 1: 55 (±3) Intvn 1: 52(±3) **M/F** Intvn 1: 15/8 Intvn 1: 13/7 No significant differences between the 2 groups in terms of patient characteristics, transfusion requirement, and gastric variceal anatomy **Intervention 1:** Endoscopic cyanoacrylate glue injection: At endoscopy, N-butyl-2-cyanoacrylate was diluted with Lipiodol and injected as a bolus of 1 to 2 ml, according to the variceal size. Most patients had a plain abdominal x-ray postendoscopy to evaluate opacification of varices. Follow-	**Total costs (mean per patient):** The final median cumulative cost for the follow-up period of 6 months (or until death / until liver transplant) was: Intvn 1: $4,138 (IQR – 1,618-25,325); Intvn 2: TIPS: $11,906 (IQR – 6,850-38,110) p<.0001 Incremental:- $7768 **Currency & cost year:** USD; year not specified, but assumed 2001 **Cost components incorporated:** • Cost of TIPSS (including all equipments, time of medical and radiologic staffs, medication, and 2 hrs for general anaesthesia) • Cost of endoscopic cyanoacrylate injection (including all equipments, time of medical nursing staffs, and the use of the endoscopy unit)	**Primary outcome measure**: **Mortality** No significant difference in the overall mortality rate between groups (figures not reported – Kaplan-Meier curves for survival show additional life-years for TIPS); see appendix below for the **Other outcome measures:** **Initial rebleeding rate:** Glue injection: 30% TIPSS: 15% p=.005 Incremental: 15% **Inpatient stay** Glue injection: 13 ± 1 day TIPS: 18 ± 2 day p=.05	**Primary ICER (Intvn 2 vs Intvn 1):** Incremental results were not reported. The results show that glue injection is less costly than TIPS. The significant higher cost of TIPS was mainly related to the cost of the procedure together with the increased length of hospitalisation. **Subgroup analyses:** NR **Analysis of uncertainty:** No uncertainty analysis was performed.

S. Mahadeva, M. C. Bellamy, D. Kessel, M. H. Davies, and C. E. Millson. Cost-effectiveness of n-butyl-2-cyanoacrylate (N-butyl-2-cyanoacrylate glue injections versus transjugular intrahepatic portosystemic shunt in the management of acute gastric variceal bleeding. Am.J.Gastroenterol. 98 (12):2688-2693, 2003.				
Time horizon: 6 months **Discounting:** N/A	up post-index endoscopy was arranged within 48 hrs, then on a weekly or monthly basis, depending on the degree of variceal obliteration. **Intervention 2:** TIPS TIPS was performed under general anaesthesia. After stent insertion, routine Doppler ultrasound scanning was performed after 2 days and after 2 weeks, and then on an every-3-month basis to assess stent patency. If shunt dysfunction was suspected on Doppler scan, angiography was performed.	• The inpatient stay (including nursing staff costs, administrative and clerical staff costs, consumables, equipments, overhead, and capital costs). • It was assumed no difference in ward staff fee, routine blood investigations, standard vasoactive drugs, and basic radiology between the 2 groups • Days in hospital for the first stay and further hospitalisations for rebleeding or complications of treatment were recorded as the cost of the therapeutic procedures	Incremental 5 days	
Data sources				
Health outcomes: Retrospective analysis from patient records identified via hospital databases. **Quality-of-life weights:** N/A **Cost sources:** All costs were based on the Healthcare Resource codes (National Health Service, United Kingdom) of St. James's University Hospital (Leeds, United kinkdom) over April 2000 to March 2001 financial period.				
Comments				
Source of funding: NR; **Limitations:** No quality of life assessment; short time horizon; median costs presented as results; no sensitivity analysis performed **Other:**				
Overall applicability*: Partially applicable Overall quality**: Minor limitations				

Abbreviations: CEA = cost-effectivenesse analysis; ICER = incremental cost-effectiveness ratio; IQR = Inter-Quartile Range; GI = Gastrointestinal; NR = not reported, NHS = National Health Service, TIPS = Transjugular Intrahepatic Portosystemic Shunt; UK = United Kingdom; USD = United States Dollars;
** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious Limitations / Very serious limitations*

G.5.2 Antibiotics

A. Pauwels, N. Mostefa-Kara, B. Debenes, E. Degoutte, and V. G. Levy. Systemic antibiotic prophylaxis after gastrointestinal hemorrhage in cirrhotic patients with a high risk of infection. Hepatology 24(4):802-806, 1996.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-consequence analysis **Study design:** Comparative cost analysis developed as part of a RCT **Approach to analysis:** Trial based analysis **Perspective:** Presumed to be from provider perspective. **Time horizon:** (The duration of the study period was similar in both groups: 11.3 ± 0.7 days (range, 6-24 days) for the prophylaxis antibiotic group; and 10.7 ± 0.6 days (range, 4-18 days) for the control group. **Discounting:** NA (short time horizon)	**Population:** Cirrhotic patients after gastrointestinal haemorrhage with Child-Pugh's class C and/or a rebleeding (Child-Pugh's class A-B with rebleeding), admitted to a French Liver Intensive Care Unit, between December 1989 and March 1992. These patients are judge having a high risk of infection. Patients with proven infection on admission, patients who died within the first 12 hours after admission and patients who underwent surgery within the first 24 hours after admission, were excluded from analysis of results. **Cohort settings:** For patient characteristics please refer to table 1 in appendix. **Intervention 1: Antibiotic prophylaxis** (n=30): Patients received antibiotic prophylaxis with amoxicillin and clavulanic acid 1g/200mg three times daily and ciprofloxacin 200mg twice daily. This therapy was given from admission or rebleeding to 3 days after cessation of the haemorrhage. It was administrated first intravenously and then orally 24 hours after cessation of the bleeding. In patients with serum	**Total costs (mean per patient):** Intvn 1: $167 ± 42 Intvn 2: $208 ± 63(p=<0.05) Incremental: - $48 **Currency & cost year:** USD, year not reported (assumed 1996, year of publication) **Cost components incorporated:** Cost of antibiotic treatment only.	**Mortality at 4 weeks** Intvn 1: 4(13.3%) Intvn 2: 8 (23.5%) (not significant) **Patients with infections** Intvn 1: 4(13.3%) Intvn 2: 18 (52.9%) P<.001 **Patients with sepsis** Intvn 1: 2(6.6%) Intvn 2: 12 (35.3%) P<.01 **Length of stay in ICU (days)** Intvn 1: 6.5 ± 0.9 Intvn 2: 7.4 ± 1.1 (not significant)	Prophylaxis antibiotic therapy dominates no antibiotic prophylaxis, being more effective and less costly. **Analysis of uncertainty:** No sensitivity analysis was undertaken.

A. Pauwels, N. Mostefa-Kara, B. Debenes, E. Degoutte, and V. G. Levy. Systemic antibiotic prophylaxis after gastrointestinal hemorrhage in cirrhotic patients with a high risk of infection. Hepatology 24(4):802-806, 1996.				
	creatinine level >200mmol/L, doses were reduced to amoxicillin plus clavulanic acid 500mg/100kg twice daily and ciprofloxacin 200mg once daily. In case of rebleeding during the study period, the prophylaxis was restarted for the same duration. When an infection was suspected, the initial empiric antibiotic treatment was ciprofloxacin and a combination of vancomycin and ceftazidime. The duration of antibiotic prophylaxis was 4.35 ± 0.4 days (range, 1-10 days); intravenous administration: 2.7 ± 0.4 days, orally: 1.65 ± 0.2 days). **Intervention 2: Placebo** (n=34): No prophylaxis antibiotic treatment. When an infection was suspected, the initial empiric antibiotic treatment was ciprofloxacin and a combination of amoxicillin and clavulanic acid.			
Data sources				
Health outcomes: From one RCT **Quality-of-life weights:** NA **Cost sources:** NR				
Comments				
Source of funding: NR **Limitations:** Short time horizon and limited cost analysis means key costs may not have been included. Unclear if best source for cost and treatment effects was used. No sensitivity analysis. No quality of life assessment; **Other:**				
Overall applicability*: Potentially serious Limitations Overall quality: Partially applicable**				

Abbreviation; NA=not applicable; NR = not reported; RCT= randomised control trial

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious Limitations / Very serious limitations*

G.5.3 Band Ligation

I. M. Gralnek, D. M. Jensen, T. O. G. Kovacs, R. Jutabha, G. A. Machicado, J. Gornbein, J. King, S. Cheng, and M. E. Jensen. The economic impact of esophageal variceal hemorrhage: cost-effectiveness implications of endoscopic therapy. Hepatology 29:44-50:44-50, 1999 (ref ID 358)				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CEA **Study design:** Economic analysis developed using patient-level data from a randomised controlled trial (Feb 1990 to April 1994) **Perspective:** US Medicare **Time horizon:** 1 year **Discounting:** Not applicable	**Population:** All patients with active or recent severe upper GI haemorrhage from oesophageal varices requiring hospitalization (N=66) **Subgroup 1:** patients with active bleeding at index endoscopy (emergency treatment); **Subgroup 2:** patients with clean varices or stigmata of recent haemorrhage at index endoscopy (elective treatment) Index endoscopy was performed within 24 hours from the time of presentation with upper GI haemorrhage **Cohort settings:** Sclerotherapy: n=31; Mean Age: 50;M/F:26/5 Ligation: n=35; Mean Age: 54; M/F:26/9 **Intervention 1: Endoscopic sclerotherapy:** the actively bleeding varix or varix with stigmata of recent haemorrhage was injected intravariceally with TES solution (3% tetradecyl sulfate mixed in equal volumes with absolute ethanol and normal saline) up to 2 mL per injection using a 5-mm, 25-gauge sclerotherapy needle. All remaining oesophageal varices were then similarly injected intravariceally. **Intervention 2: Endoscopic ligation:** the actively bleeding varix or varix with the stigmata of recent haemorrhage was initially ligated using a single-shot endoscopic ligating device. All remaining oesophageal	**Total costs (mean per patient):** **All patients:** Intvn 1:$16,893 Intvn 2: $16,388 Median (IQR): Intvn 1:$13,197 (6,122-21,842) Intvn 2: $ 9,696 (2,978-24,044); p=0.46 **Subgroup 1:** Intvn 1: (n=9): $19,015 Intvn 2 (n=12):$17,232 Median (IQR): Intvn 1: (n=9): $17,016 (7,556-25,515) Intvn 2 (n=12): $12,035 (3,278-26,506); p=0.68 **Subgroup 2:** Intvn 1: (n=22): $16,025 Intvn 2 (n=23): $15,948 Median (IQR): Intvn 1: (n=22): $12,650 (6,122-18,703) Intvn 2 (n=23): $9,969 (2,978-21,854); p=0.56 **Currency & cost year:** 1995-96 US dollars	**Primary outcome measure:** Patient Survival post 1 year **All patients:** Intvn 1: 22/31 (71%) Intvn 2: 21/35 (60%) **Subgroup 1:** Intvn 1: 6/9 (67%) Intvn 2: 4/12 (33%) **Subgroup 2:** Intvn 1y: 16/22 (73%) Intvn 2: 17/23 (74%) **Other outcome measures**: Other differences in clinical outcomes recorded were non-significant with the exception of the percentage of surgical shunts (more	**Cost per additional survival was calculated using reported outcomes.** In the analysis of all patients, sclerotherapy led to a higher survival and to additional costs. The cost per additional 1% in survival was calculated to be $46. **Subgroup analyses:** In patients with active haemorrhage (emergency treatment), sclerotherapy led to a higher survival and to additional costs. The cost per additional 1% in survival was calculated to be $52. In patients with clean varices or stigmata of recent haemorrhage (elective treatment), ligation led to a 1% higher survival and to savings of

I. M. Gralnek, D. M. Jensen, T. O. G. Kovacs, R. Jutabha, G. A. Machicado, J. Gornbein, J. King, S. Cheng, and M. E. Jensen. The economic impact of esophageal variceal hemorrhage: cost-effectiveness implications of endoscopic therapy. Hepatology 29:44-50:44-50, 1999 (ref ID 358)				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
	varices were then ligated. Before endoscopy, most patients with active or presumed active variceal bleeding were empirically treated by the ICU physicians with vasopressin ± nitroglycerin or octreotide. Follow-up endoscopic treatments were performed 5 to 7 days, 3 to 4 weeks, 7 to 8 weeks, and then monthly after the index endoscopy until all oesophageal varices were obliterated. Following endoscopic treatment sessions, all patients were treated with H2 receptor antagonists and antireflux measures. After variceal obliteration was achieved, endoscopic examinations were performed every 3 months for the first year, then yearly or if there was any episode of rebleeding thereafter. If varices reappeared after obliteration, endoscopic treatment was repeated using the originally assigned form of endoscopic therapy.	**Cost components incorporated:** All diagnostic and therapeutic endoscopies including endoscopist fees; all surgical shunt procedures including surgeon and anaesthesiologist professional fees; all TIPS procedures including radiologist and technical fees; all hospital days inclusive of ICU and non-ICU days; and all blood product transfusions (packed red blood cells, fresh frozen plasma, and platelets). The cost of orthotopic liver transplantation undergone after random assignment was not included.	used in intvn. 1); number of failures in treatment (more in intvn. 2) and number of esophageal strictures (more in intvn.1).	$77 per patient. **Analysis of uncertainty:** No sensitivity analysis was performed.
Data sources				
Health outcomes: From the prospective randomised trial **Quality-of-life weights:** Not applicable **Cost sources:** Professional reimbursement for medical-surgical services and procedures was estimated using the American Medical Association 1996 Physicians' Current Procedural Terminology (CPT) codes and the corresponding Medicare Fee Schedule				
Comments				
Source of funding: The clinical trial was supported in part by NIH NIDDK 41301 (Human Studies Core), General CRC M01-RR00865-23, and NIH R01 DK 33273 (Dr. Jensen). The economic analysis was funded in part by a 1995 American Society for Gastrointestinal Endoscopy (ASGE) Outcomes and Effectiveness Award and a 1997 American Digestive Health Foundation (ADHF) Wilson-Cook Endoscopic Research Scholar Award (Dr. Gralnek); **Limitations:** US perspective; assessment of the cost effectiveness not adequate; one-year time horizon; no sensitivity analysis was performed; small cohort size which led to low power of the study;				
Overall applicability*: Partially applicable **Overall quality**: Potentially serious limitations**				

Abbreviations: CEA = cost effectiveness analysis; ICER = incremental cost-effectiveness ratio; US = United States; GI = Gastrointestinal; ICU = Intensive Care unit; TIPS = transjugular intrahepatic portosystemic shunt; IQR = Inter-Quartile Range; USD = United States Dollars. NR = not reported.

**Directly applicable / Partially applicable / Not applicable; ** Minor limitations / potentially serious limitations / very serious limitation*

Appendix H: Forest Plots

H.1 Initial Management and resuscitation

H.1.1 Blood Products

Figure 1: Mortality (30 day follow-up)

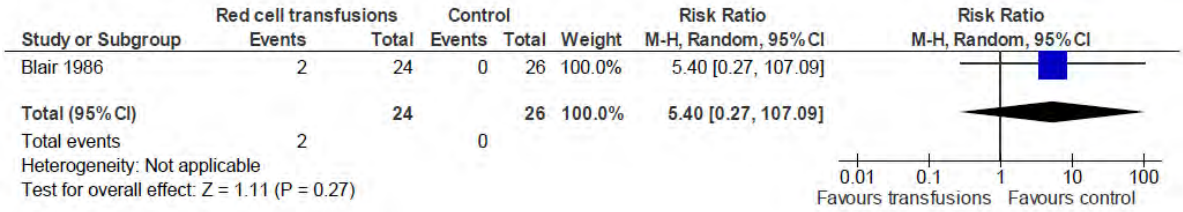
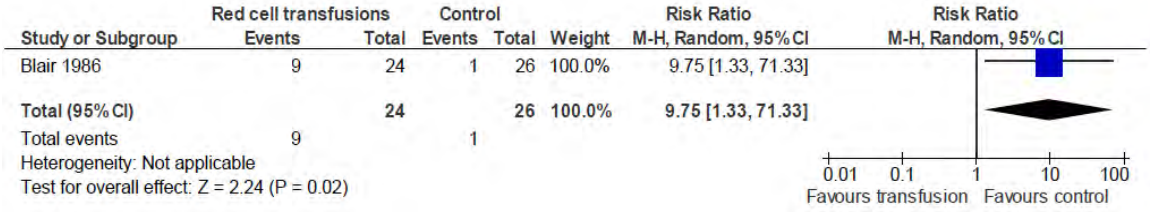


Figure 2: Re-bleeding (30 day follow-up)



H.1.1.1 rFVIIa vs. placebo all patients

Figure 3: Mortality (5 day follow-up)

Figure 4: Mortality (42 day follow-up)

Figure 5: Failure to control bleeding

Figure 6: Failure to control rebleeding

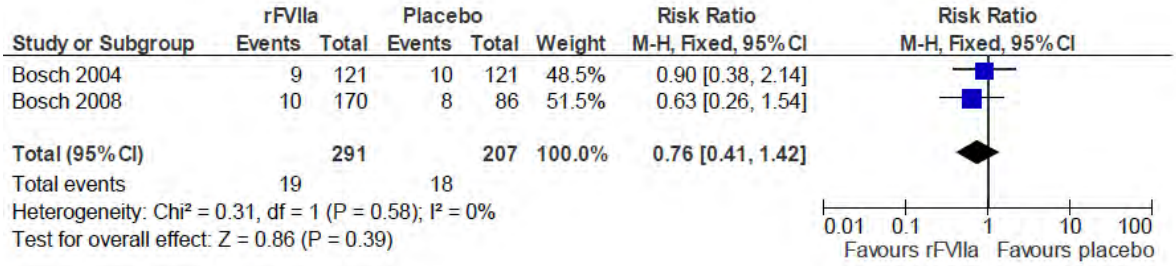


Figure 7: Emergency procedures at day 5

Figure 8: Red blood cell transfusion (24 hrs) – divided by dose of rFVIIa

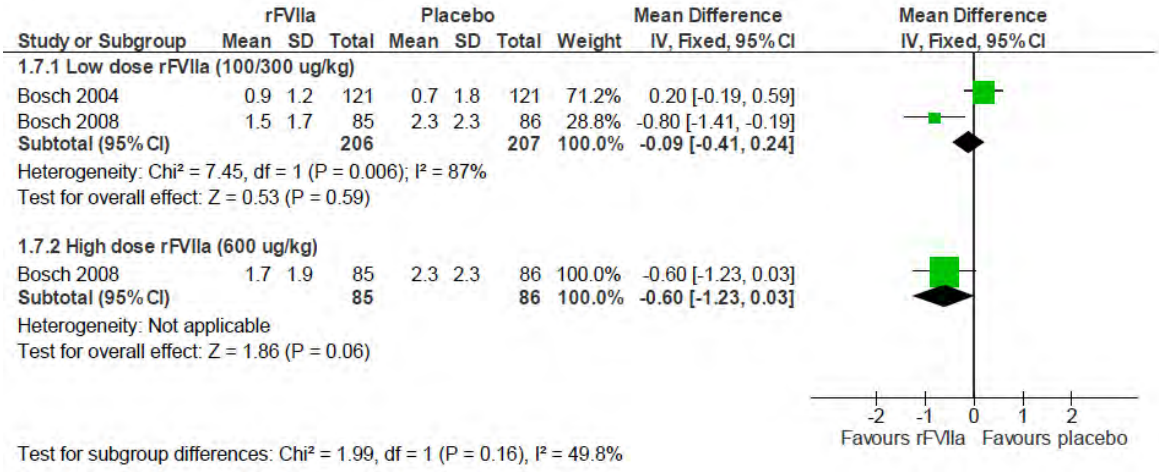


Figure 9: Red blood cell transfusion (5 days) – divided by dose of rFVIIa

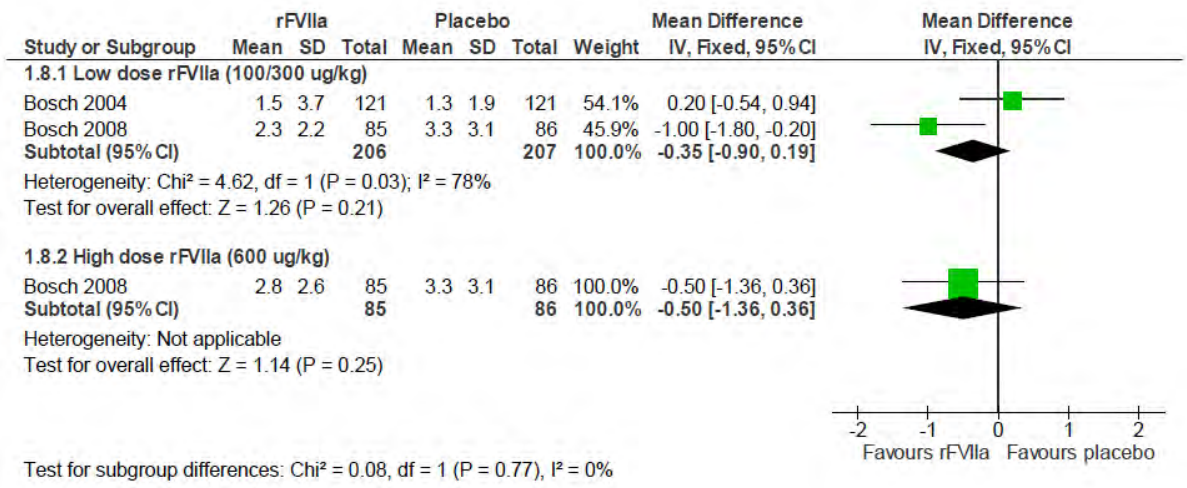


Figure 10: Serious adverse events (mainly thromboembolic events, such as portal vein thrombosis, arterial thromboembolic events) – by day 42

Figure 11: Fatal adverse events by day 42

H.1.1.2 rFVIIa vs Child-Pugh Grade B/C

Figure 12: Mortality (5 day follow-up) divided by dose of rFVIIa – moderate to severe cirrhosis

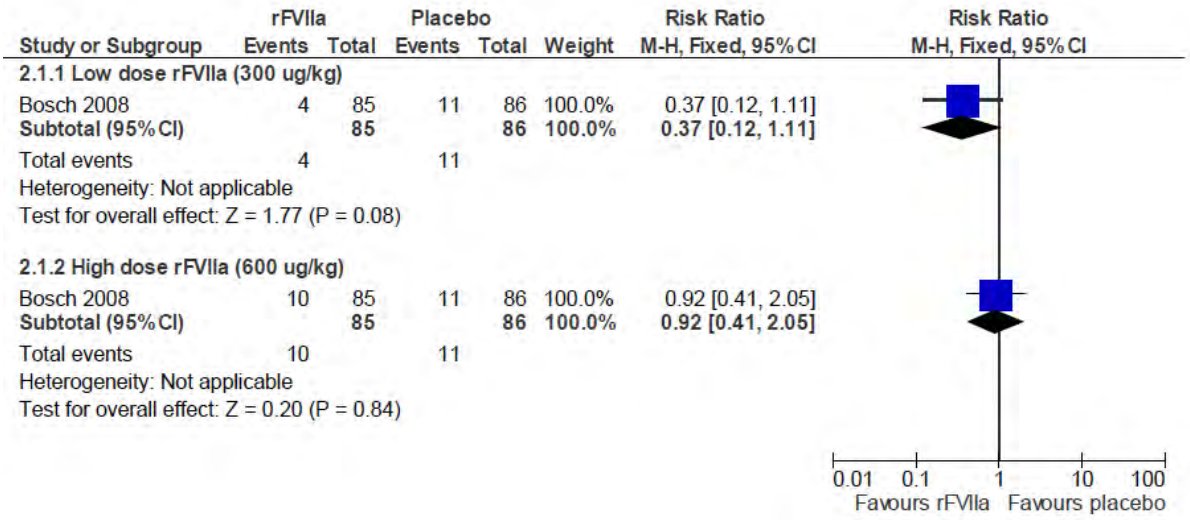


Figure 13: Mortality (42 day follow-up) divided by dose of rFVIIa – moderate to severe cirrhosis

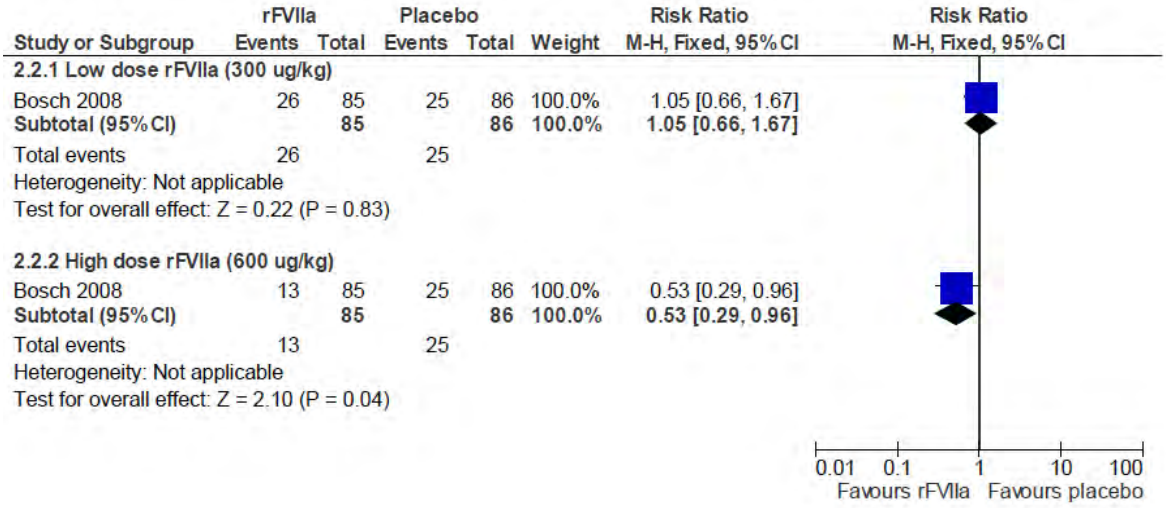


Figure 14: Failure to control bleeding by dose of treatment – moderate to severe cirrhosis

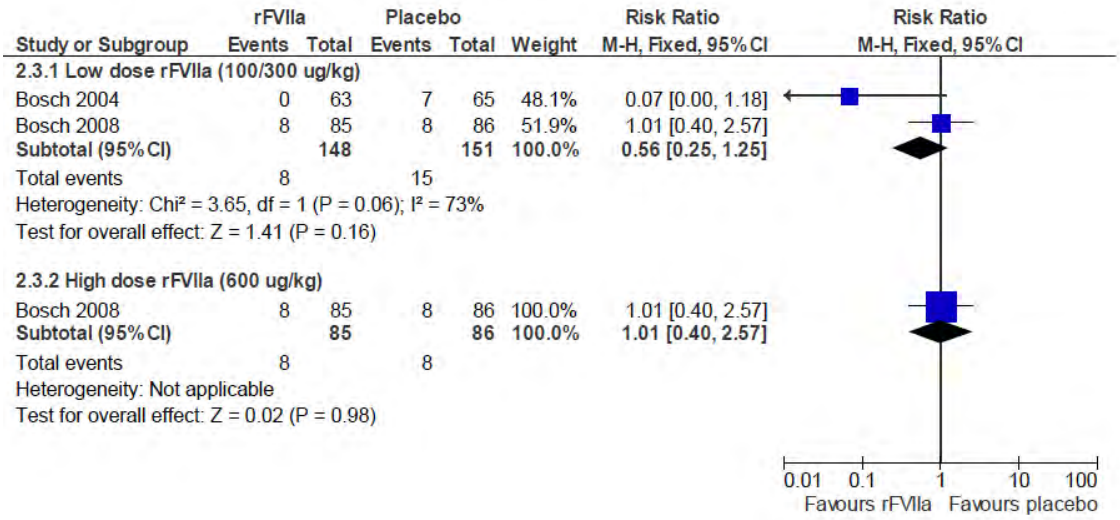


Figure 15: Failure to control rebleeding by dose of treatment – moderate to severe cirrhosis

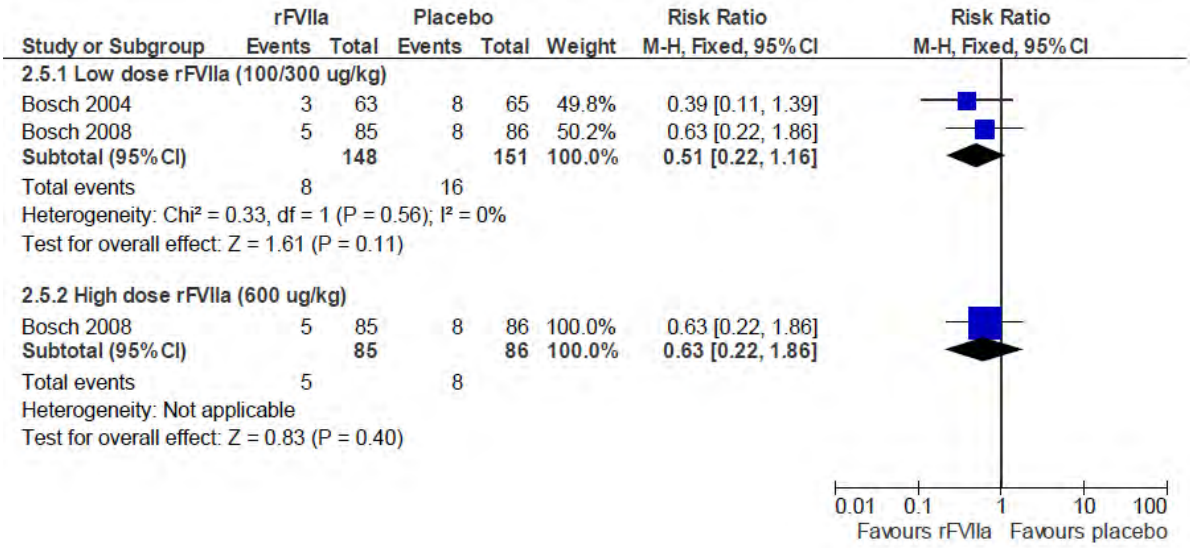


Figure 16: Emergency procedures at day 5 by dose of rFVIIa – moderate to severe cirrhosis

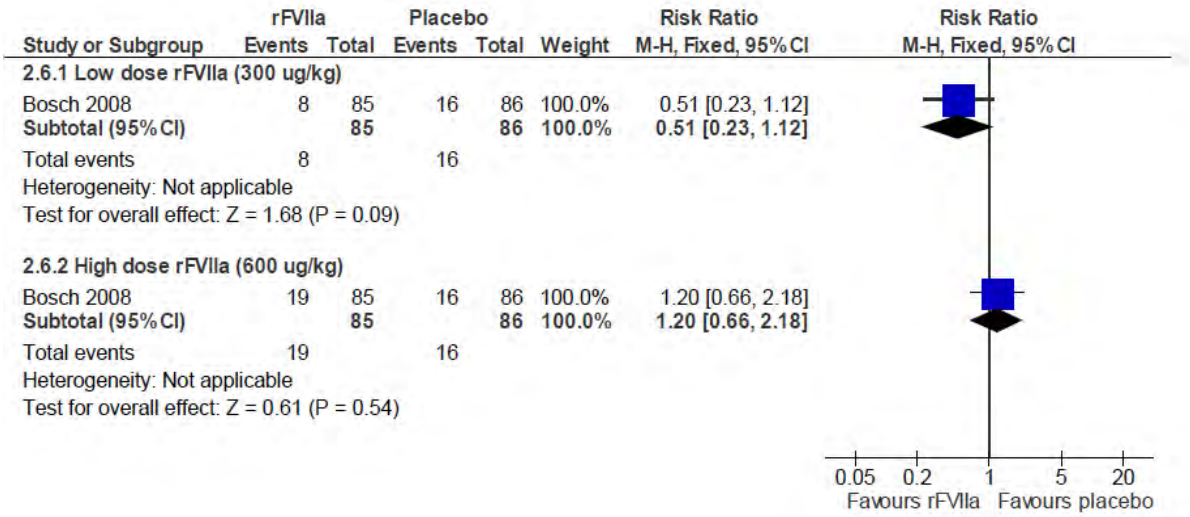


Figure 17: Red blood cell transfusion (24 hrs) by dose of rFVIIa – moderate to severe cirrhosis

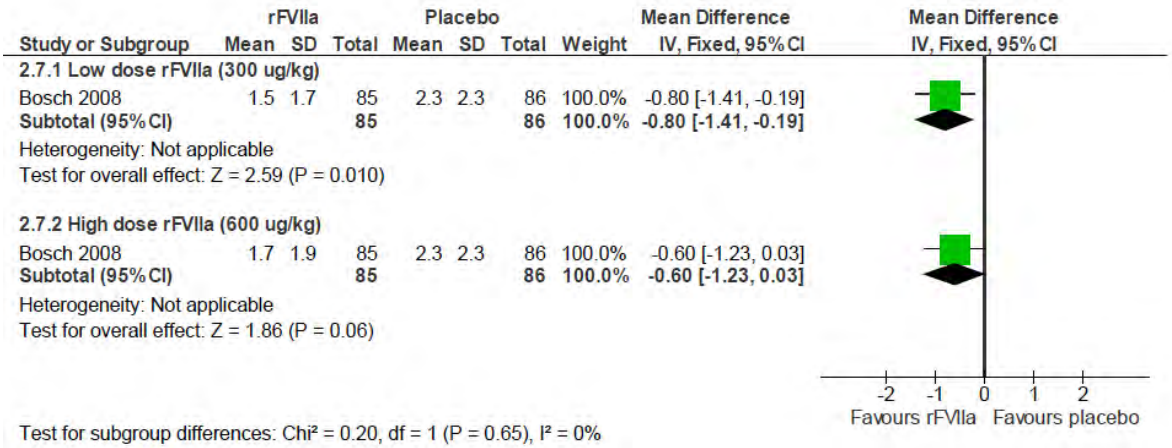


Figure 18: Red blood cell transfusion (5 day) by dose of rFVIIa – moderate to severe cirrhosis

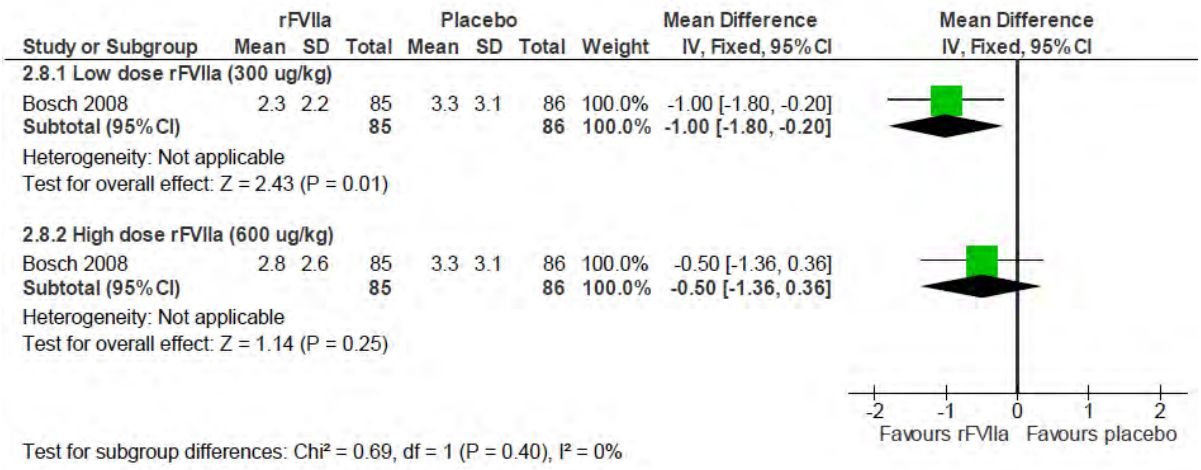


Figure 19: Serious adverse events (mainly thromboembolic events, such as portal vein thrombosis, arterial thromboembolic events) by day 42 – moderate to severe cirrhosis

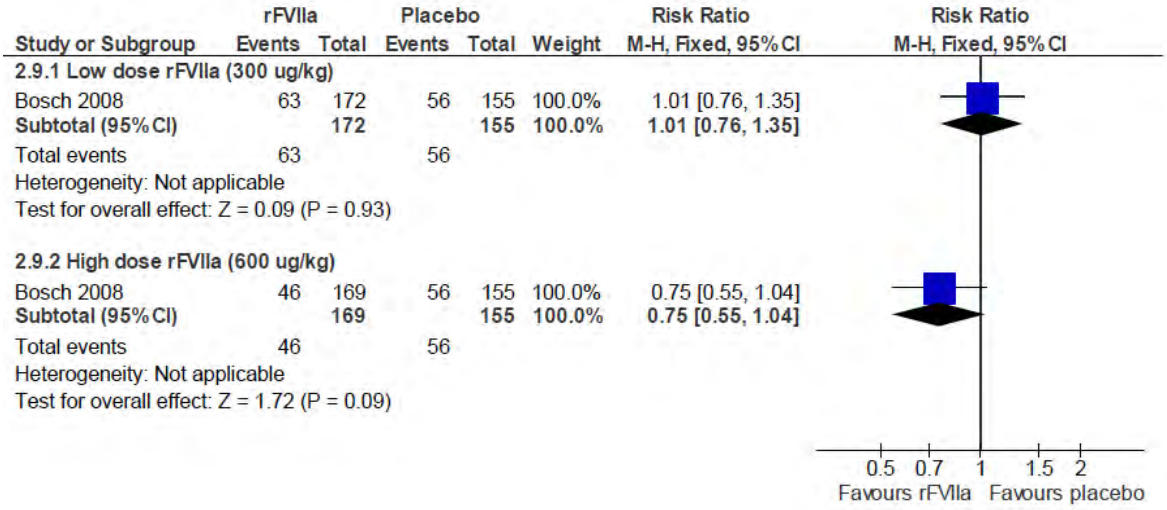
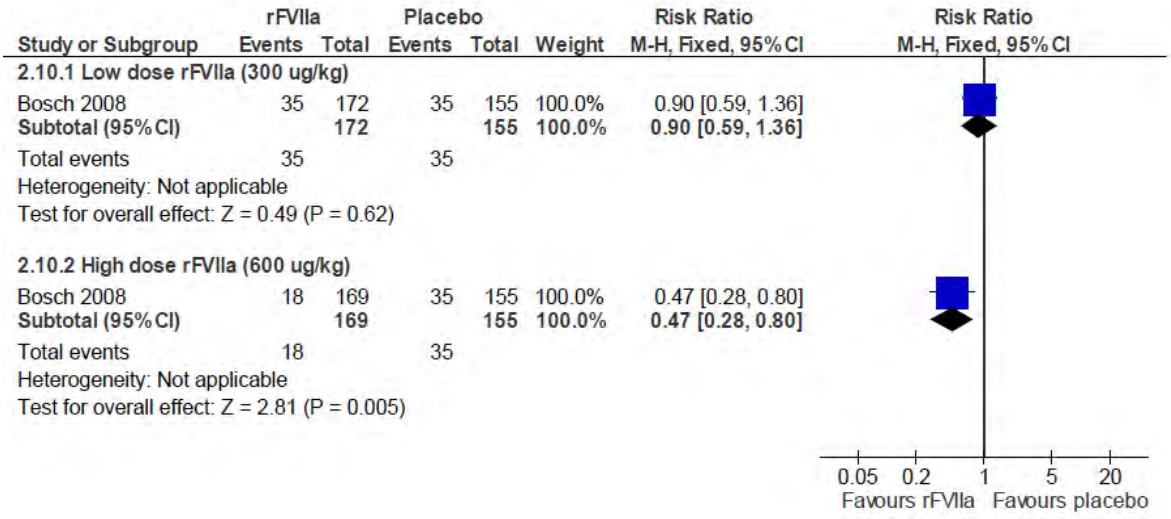


Figure 20: Fatal adverse events by day 42 – moderate to severe cirrhosis



H.1.2 Terlipressin

H.1.2.1 Terlipressin vs Placebo

Figure 21: Mortality within 6 weeks

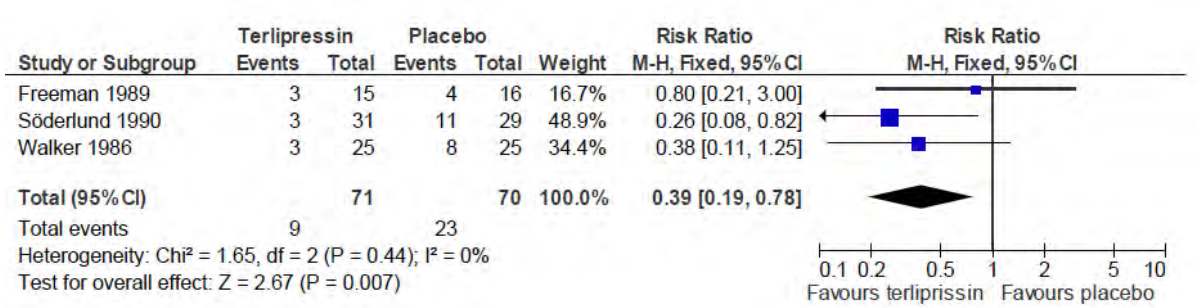


Figure 22: Failure to achive initial hemostasis

Figure 23: Rebleeding

Figure 24: Number of patients needing additional procedures required for uncontrolled bleeding / rebleeding

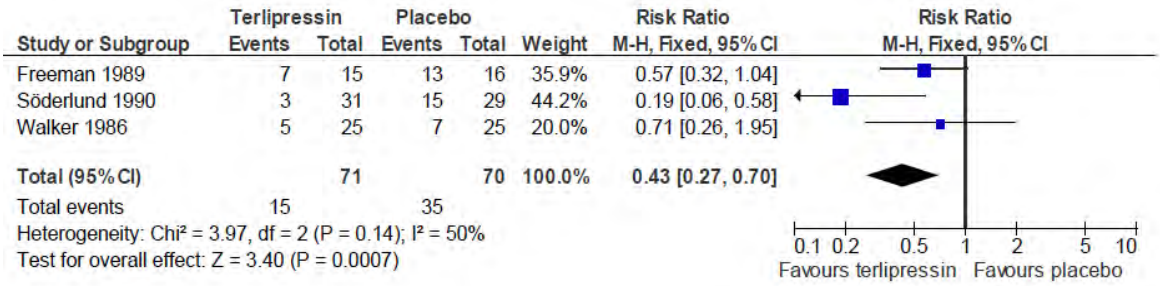


Figure 25: Blood transfusion requirements

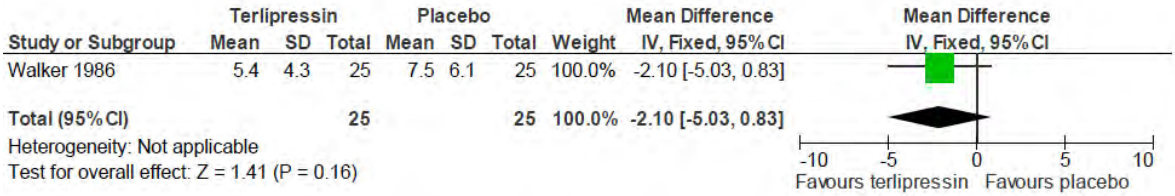


Figure 26: Adverse events causing withdrawal from treatment

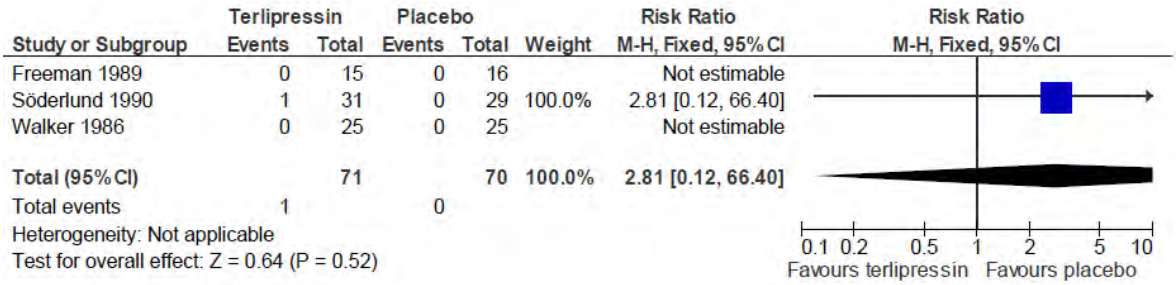


Figure 27: Fatal adverse events

H.16.1.1 Terlipressin vs Octreotide

Figure 28: Mortality within 6 weeks

Figure 29: Failure to achieve initial hemostasis

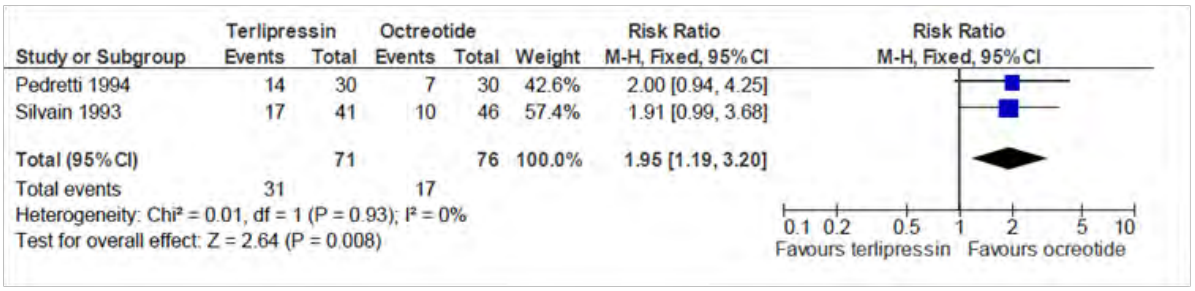


Figure 30: Rebleeding

Figure 31: Number of patients needing additional procedures required for uncontrolled bleeding / rebleeding

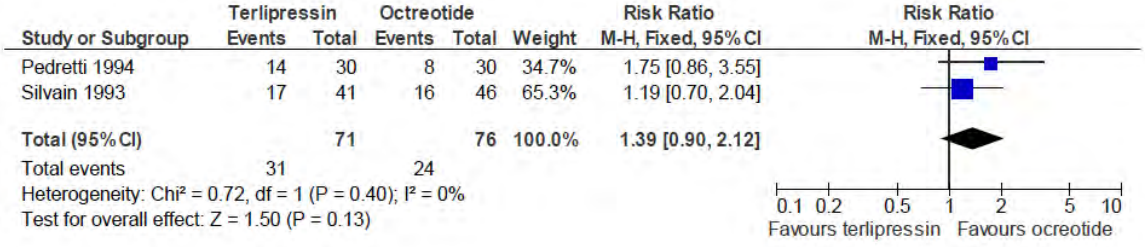


Figure 32: Blood transfusion requirements

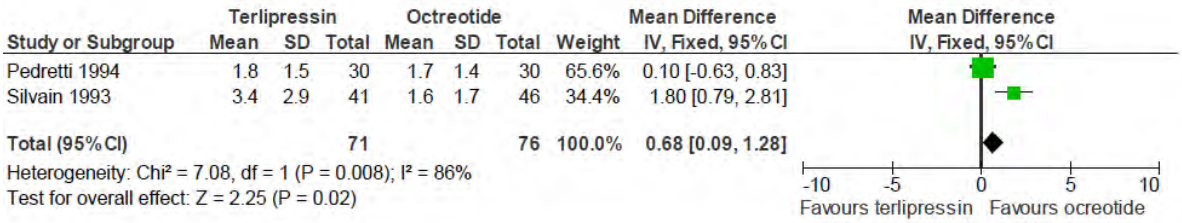


Figure 33: Adverse events causing withdrawal from treatment

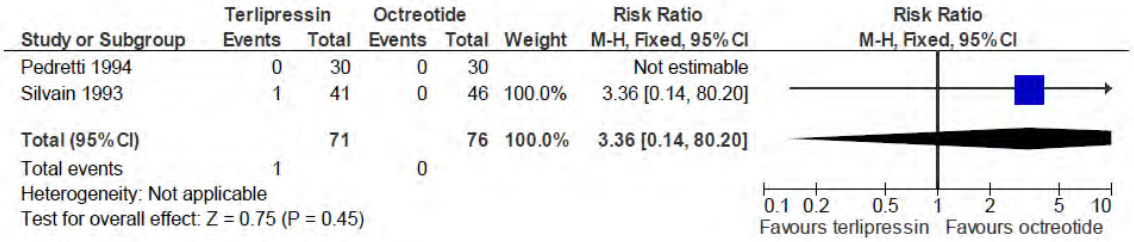
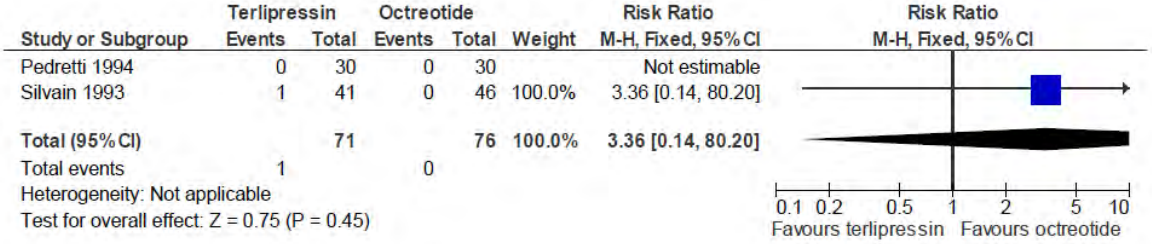


Figure 34: Fatal adverse events



H.29.1.1 Terlipressin vs somatostatin

Figure 35: Mortality within 6 weeks

Figure 36: Number of patients failing to achieve initial hemostasis

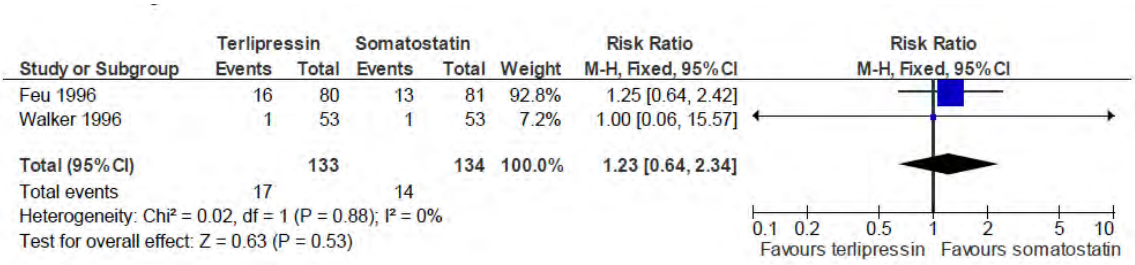


Figure 37: Rebleeding

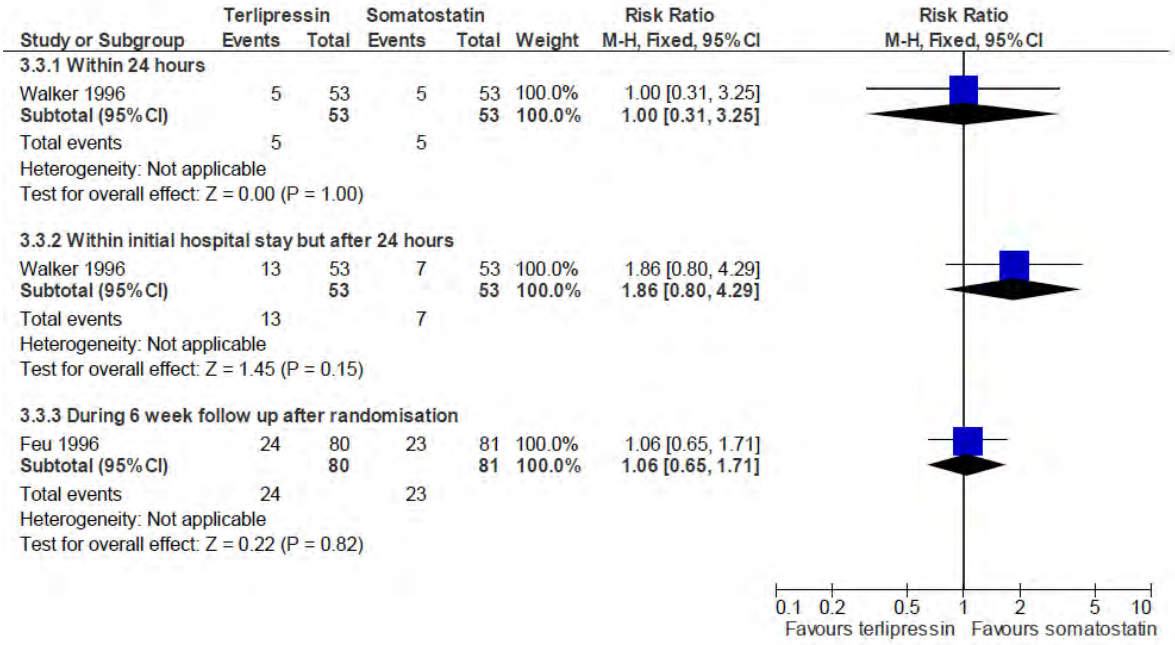


Figure 38: Number of patients needing additional procedures required for uncontrolled bleeding / rebleeding

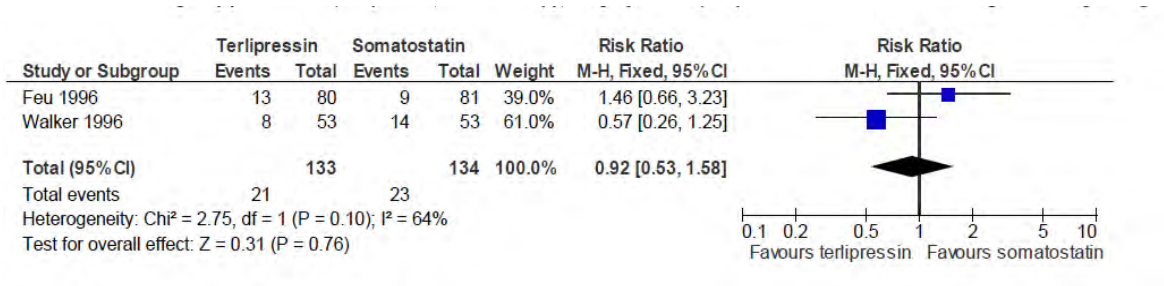


Figure 39: Blood transfusion requirements (units of fresh frozen plasma)

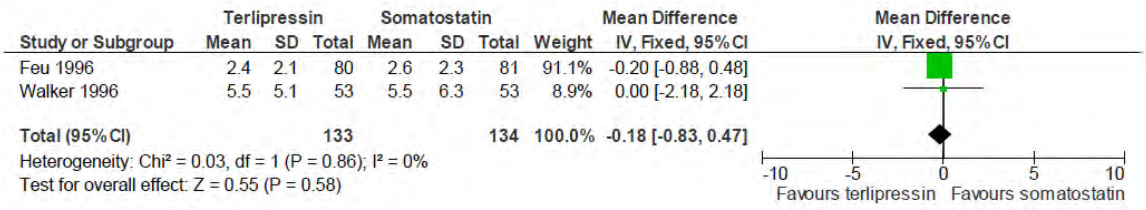


Figure 40: Length of hospital stay

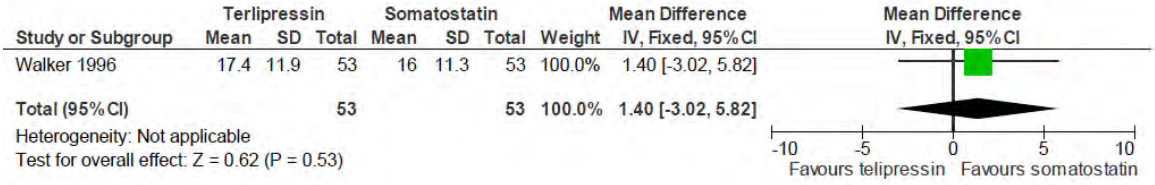


Figure 41: Adverse events causing withdrawal from treatment

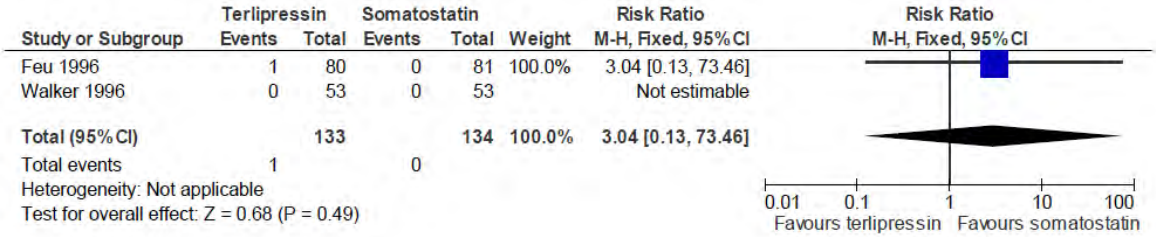


Figure 42: Fatal adverse events

H.45.1.1 Most effective duration of terlipressin treatment

Figure 43: Mortality within 6 weeks

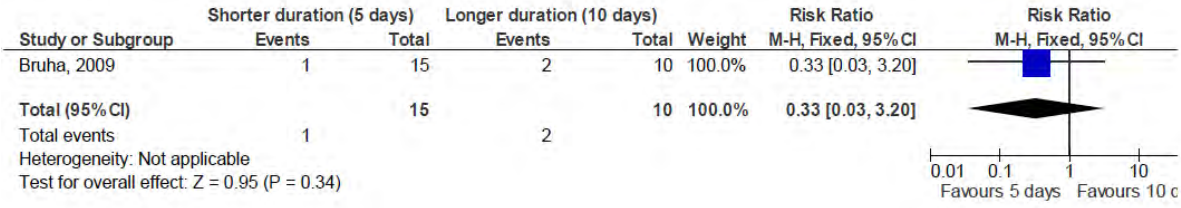


Figure 44: Rebleeding within 6 weeks

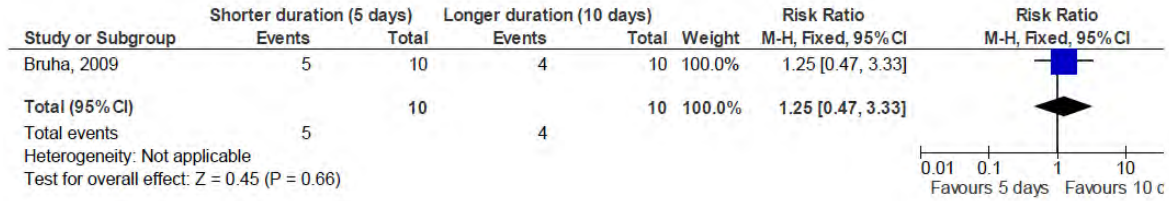


Figure 45: Transfusion needs (fresh frozen plasma)

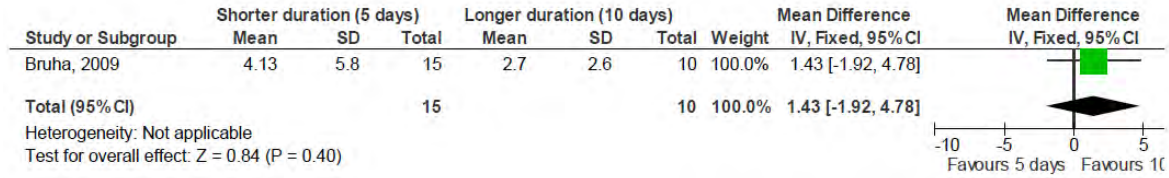


Figure 46: Transfusion needs (packed red cells)

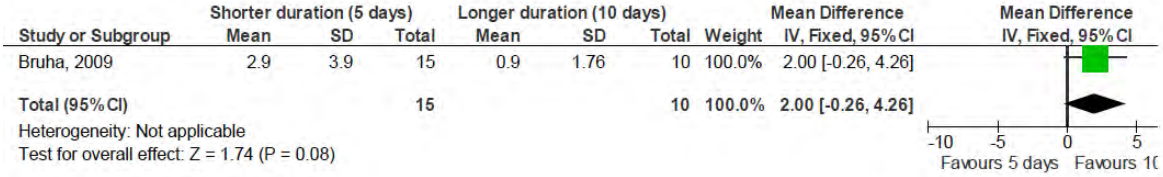


Figure 47: Adverse events causing withdrawal from treatment

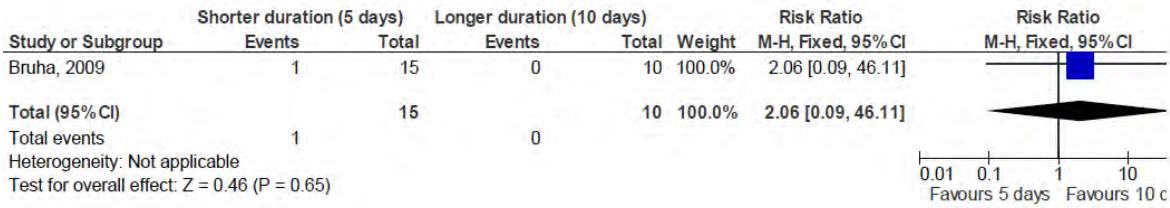
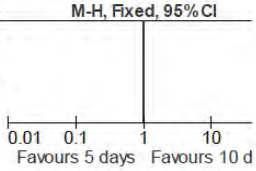


Figure 48: Fatal adverse events

Study or Subgroup	Shorter duration (5 days) Events	Total	Longer duration (10 days) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bruha, 2009	0	15	0	10		Not estimable
Total (95% CI)		15		10		Not estimable
Total events	0		0			

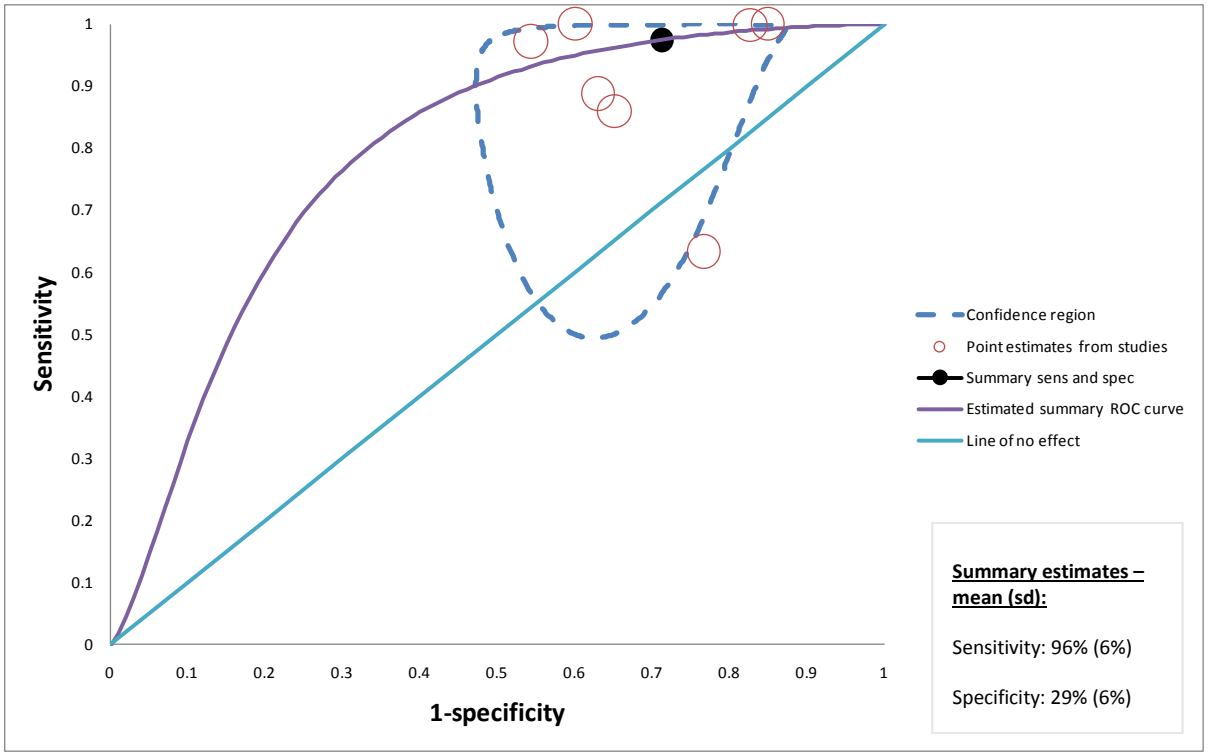
Heterogeneity: Not applicable
Test for overall effect: Not applicable



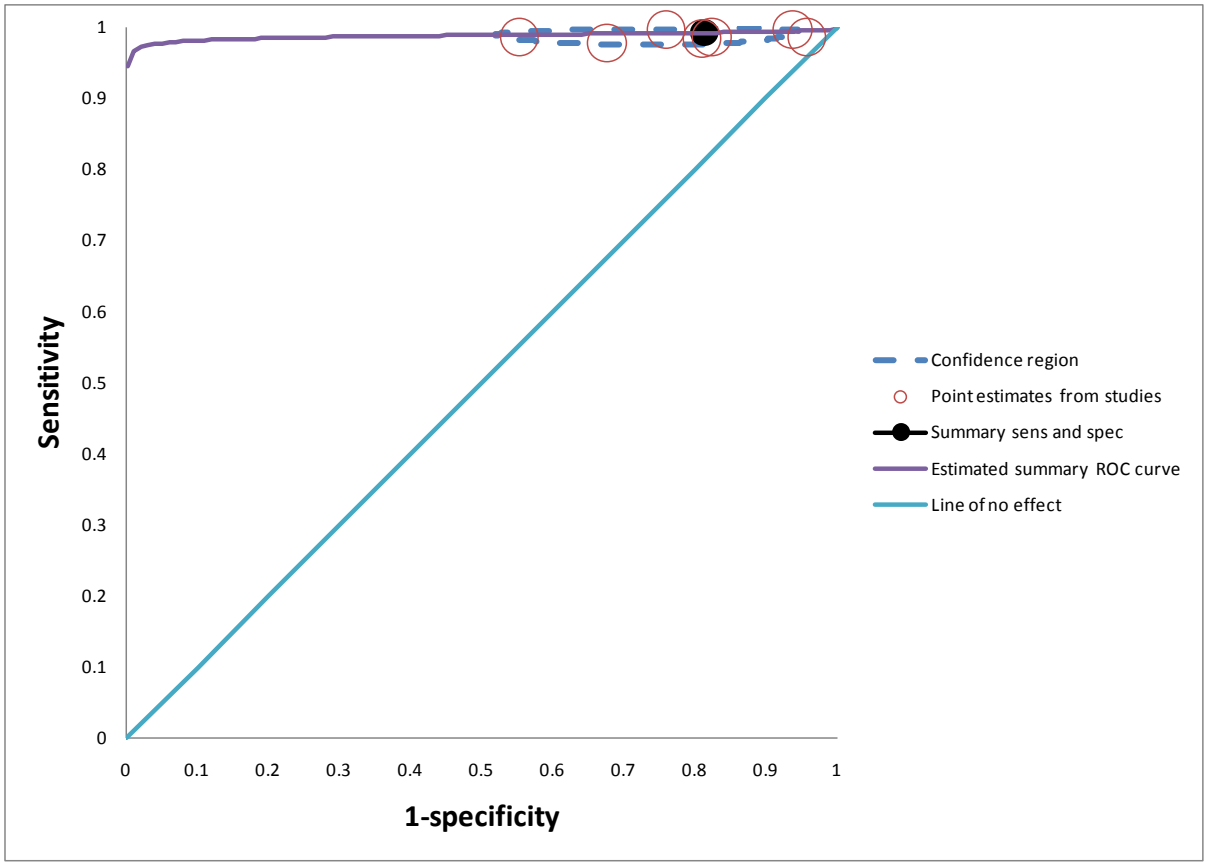
H.63 Assessment of risks

H.63.1 Diagnostic test accuracy plots

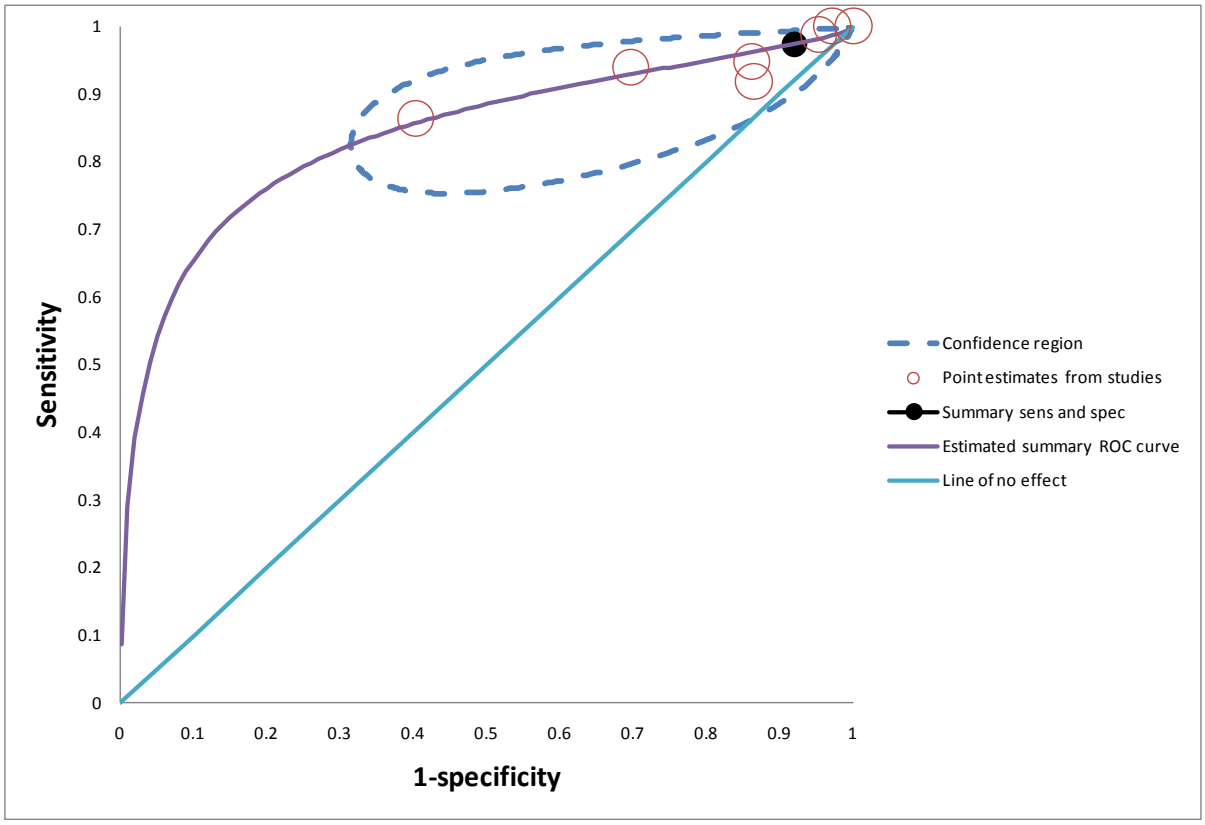
H.63.1.1 Diaganostic test accuracy plot for the pre endoscopy Rockall for all outcomes combined (need for intervention, mortality and rebleeding). See legend for the different aspects of the graph. Sensitivity and specificity summary statistics are presented in the grey box.



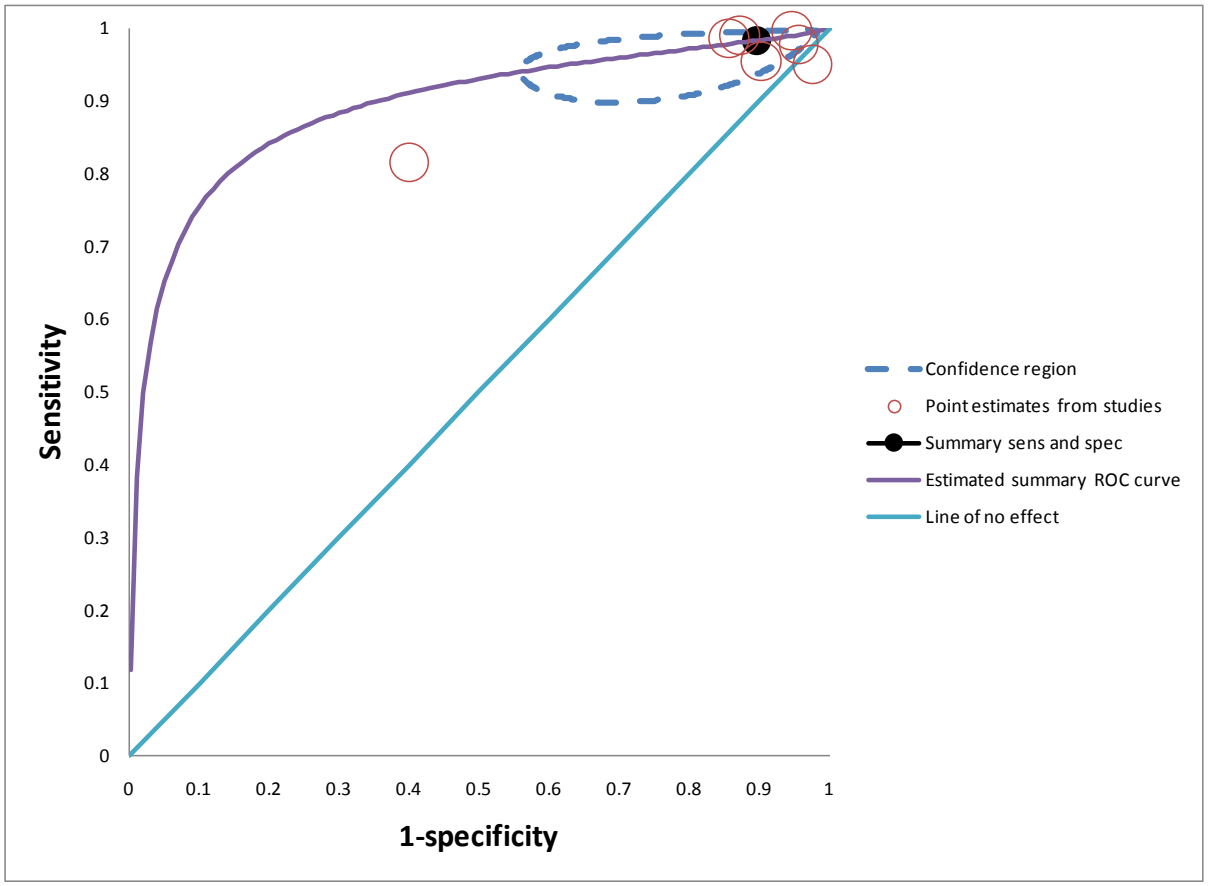
H.63.1.2 Diaganostic test accuracy plot for the Blatchford scale for need for intervention. See legend for the different aspects of the graph. Sensitivity and specificity summary statistics are presented in the grey box.



H.63.1.3 Diaganostic test accuracy plot for the post endoscopy Rockall scale for rebleeding. See legend for the different aspects of the graph. Sensitivity and specificity summary statistics are presented in the grey box.



H.63.1.4 **Diaganostic test accuracy plot for the post endoscopy Rockall scale for mortality. See legend for the different aspects of the graph. Sensitivity and specificity summary statistics are presented in the grey box.**



H.64 Timing of endoscopy

H.64.1 Early vs delayed endoscopy

Figure 49: Mortality (30 day or less follow-up)

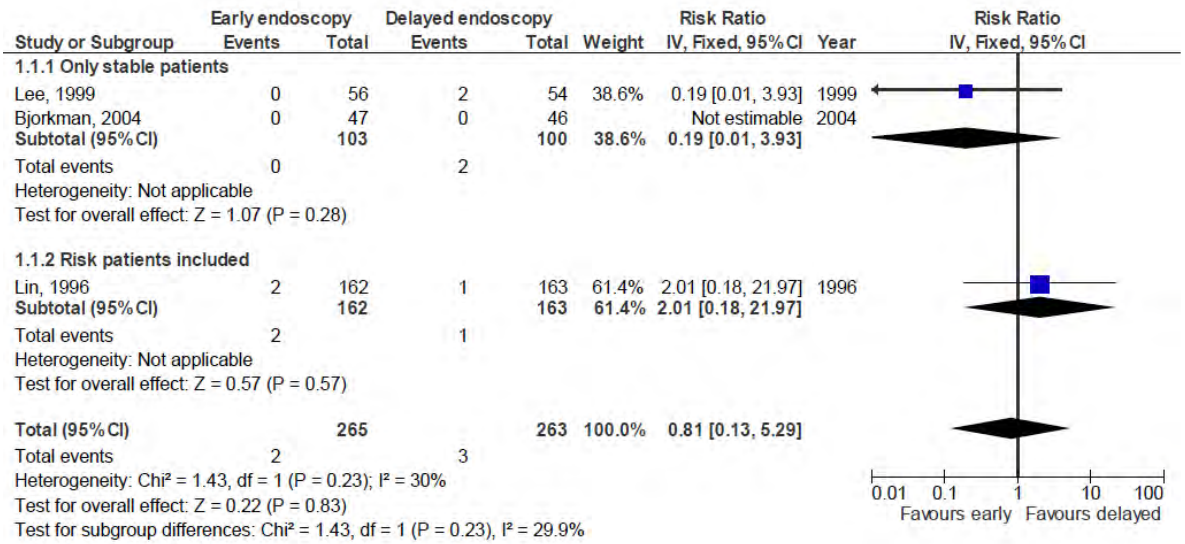


Figure 50: Rebleeding (30 day or less follow-up)

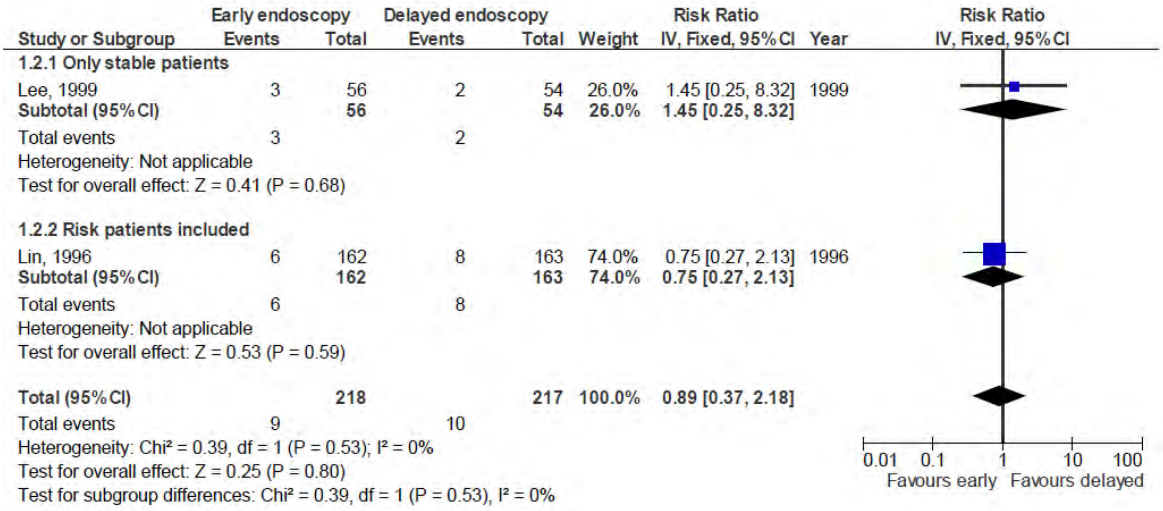


Figure 51: Surgery for continued bleeding

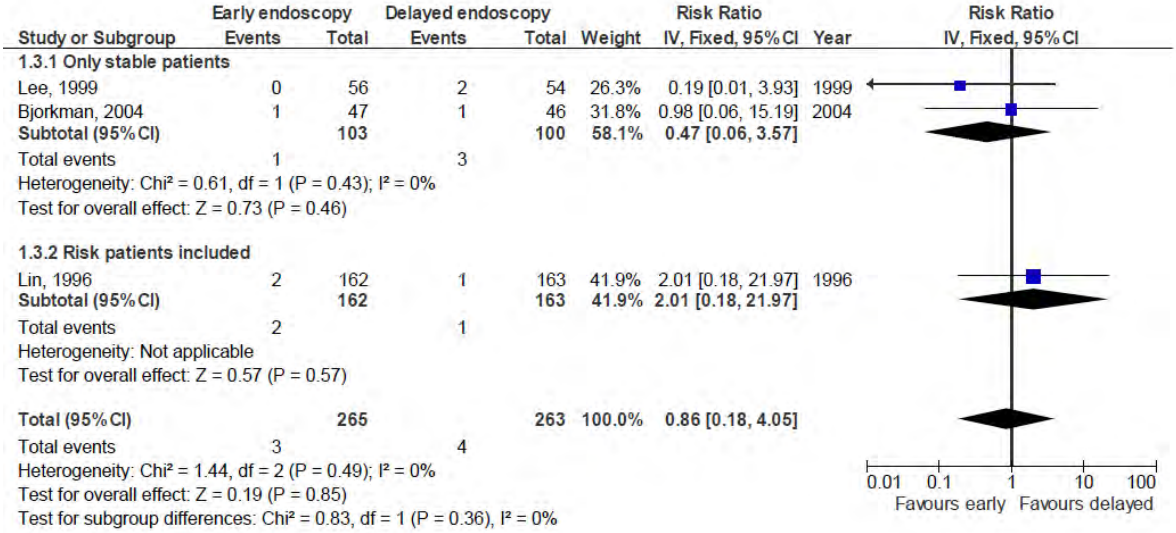


Figure 52: Mean units of blood transfused (mean units of blood transfused)

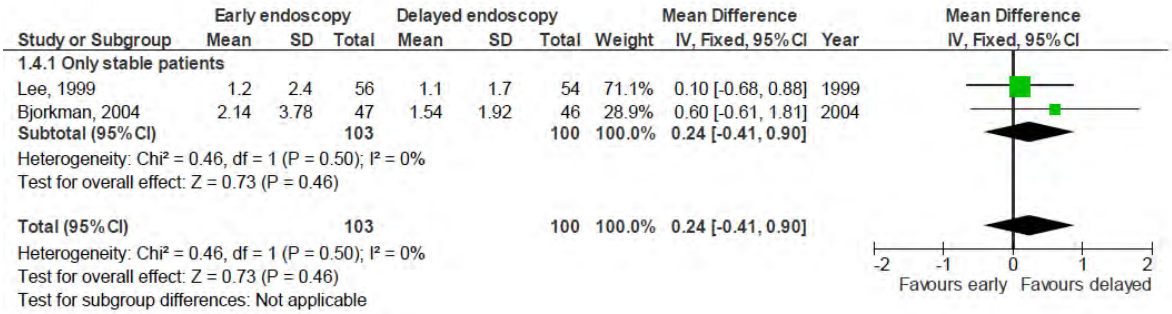
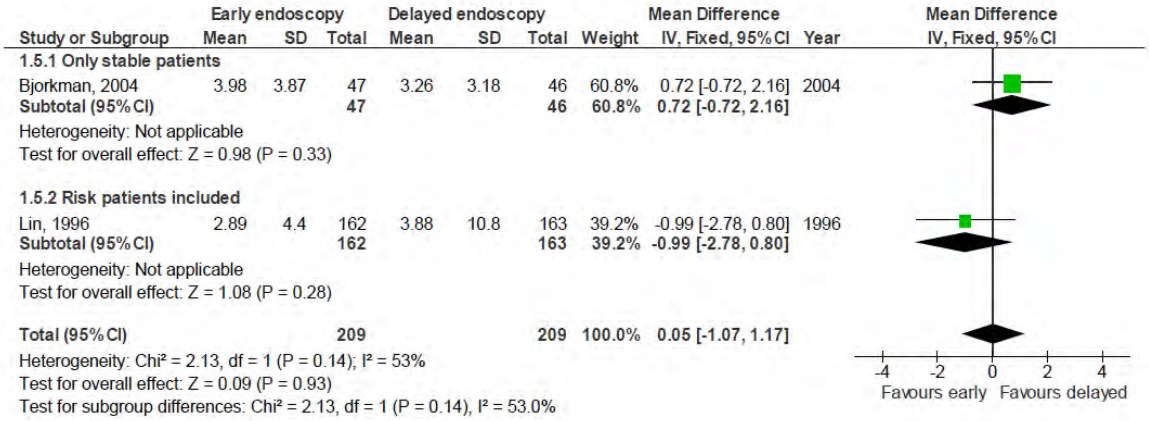


Figure 53: Length of hospital stay (mean days)



H.65 Management of non-variceal bleeding

H.65.1 Combination treatments

H.65.1.1 Combination vs adrenaline alone

Figure 54: Mortality divided by type of combination (30 day or less follow-up)

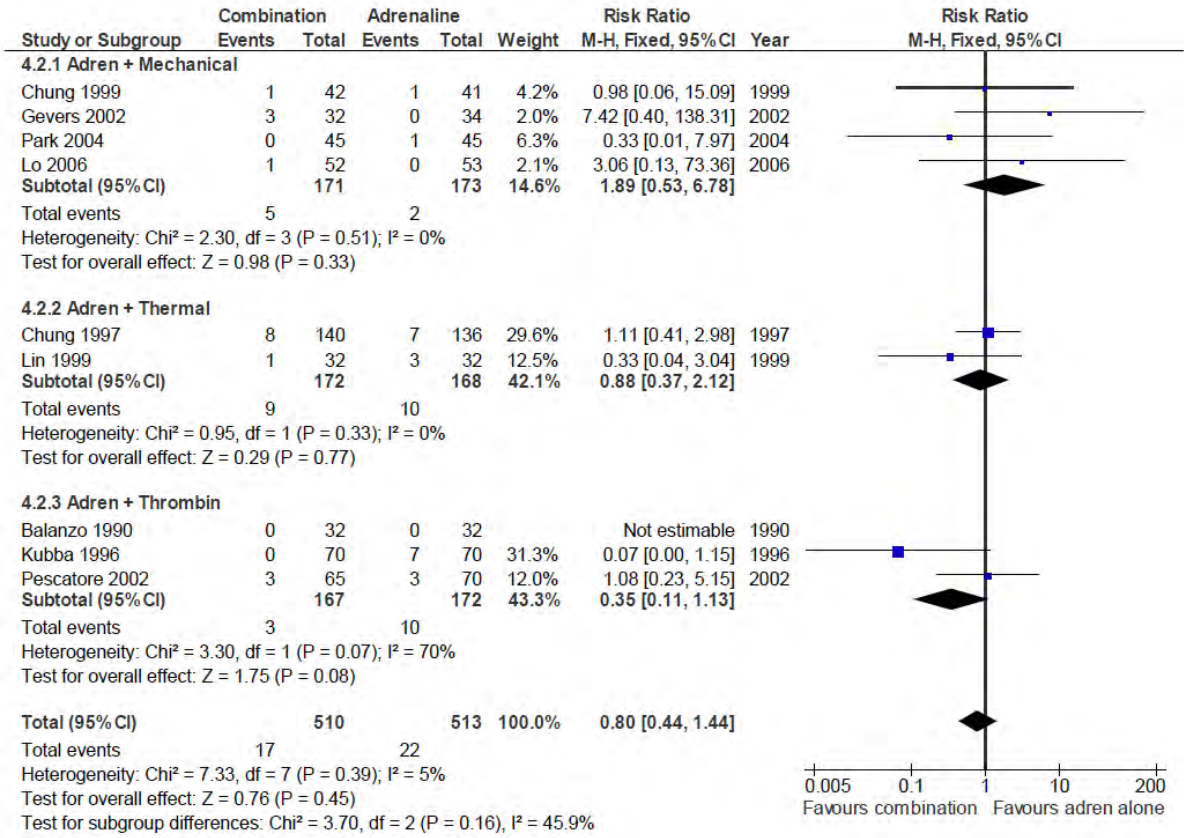


Figure 55: Rebleeding divided by type of combination (30 day or less follow-up)

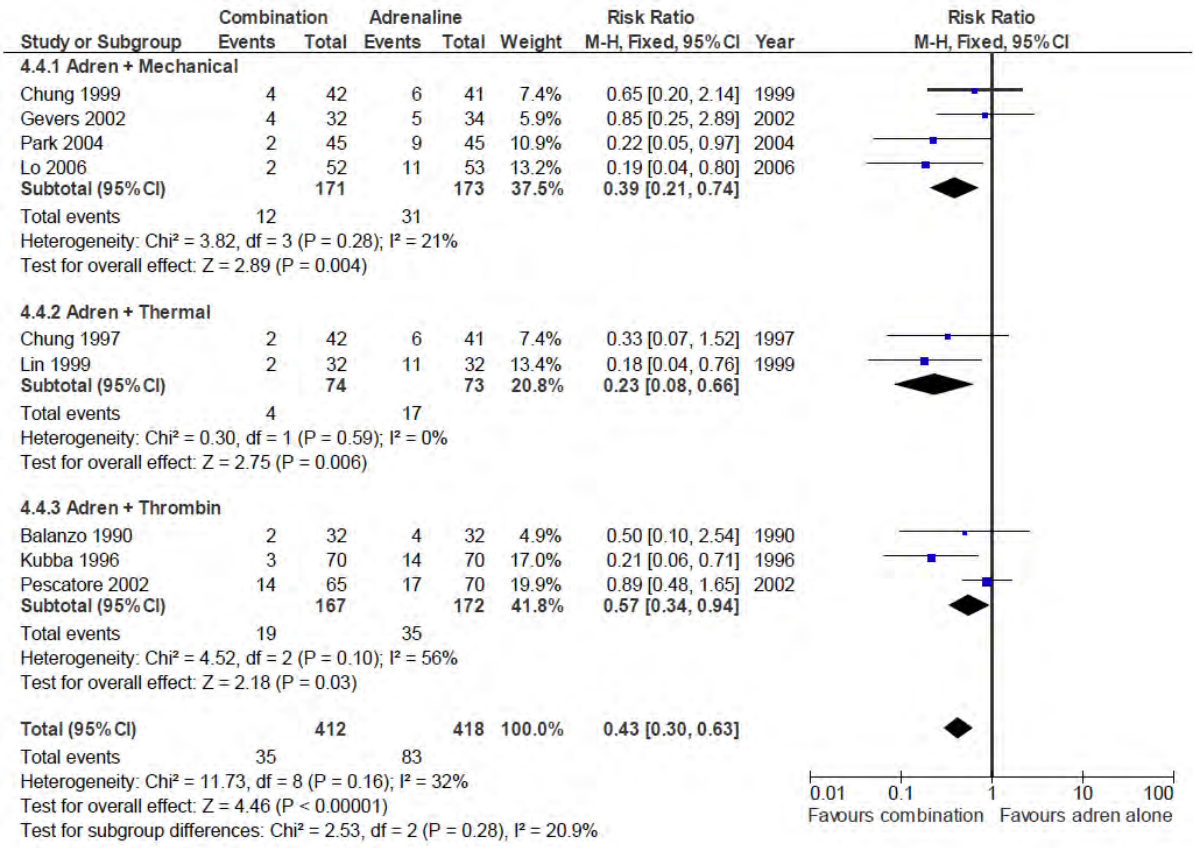


Figure 56: Failure to achieve hemostasis divided by type of combination treatment

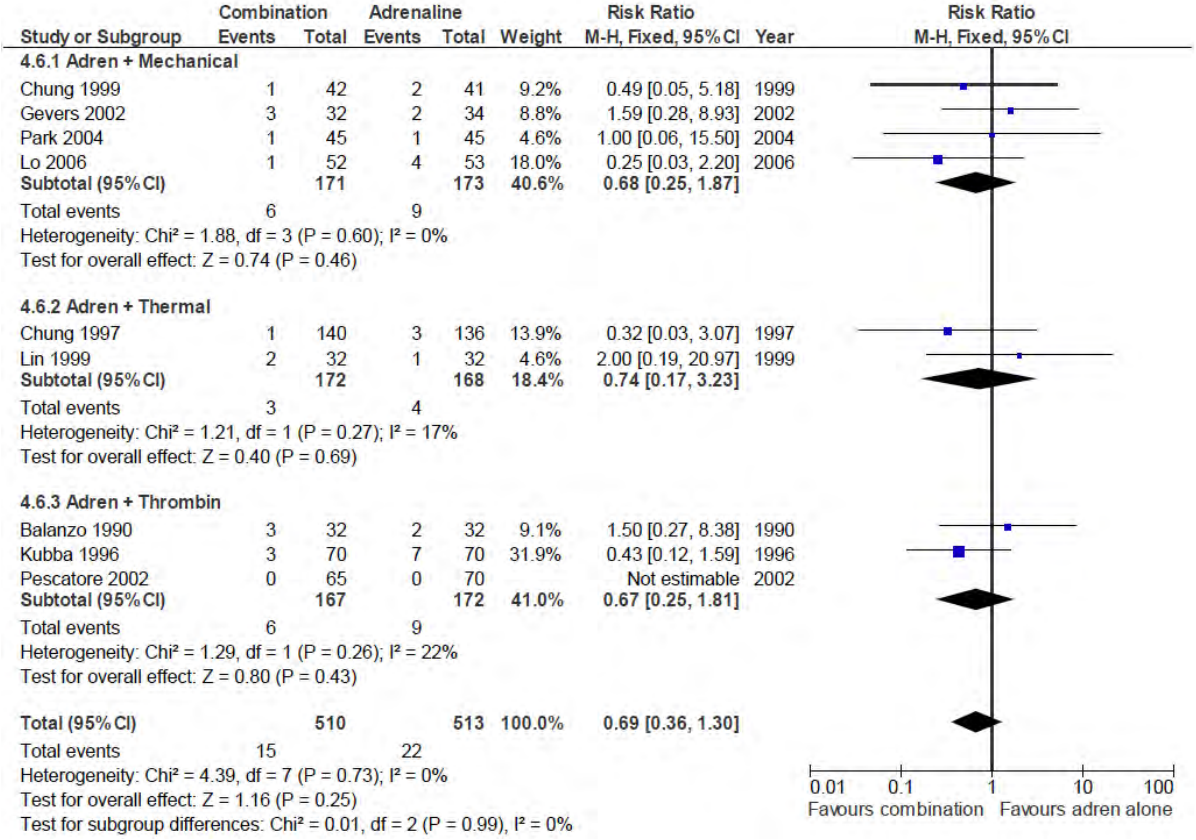


Figure 57: Emergency surgery

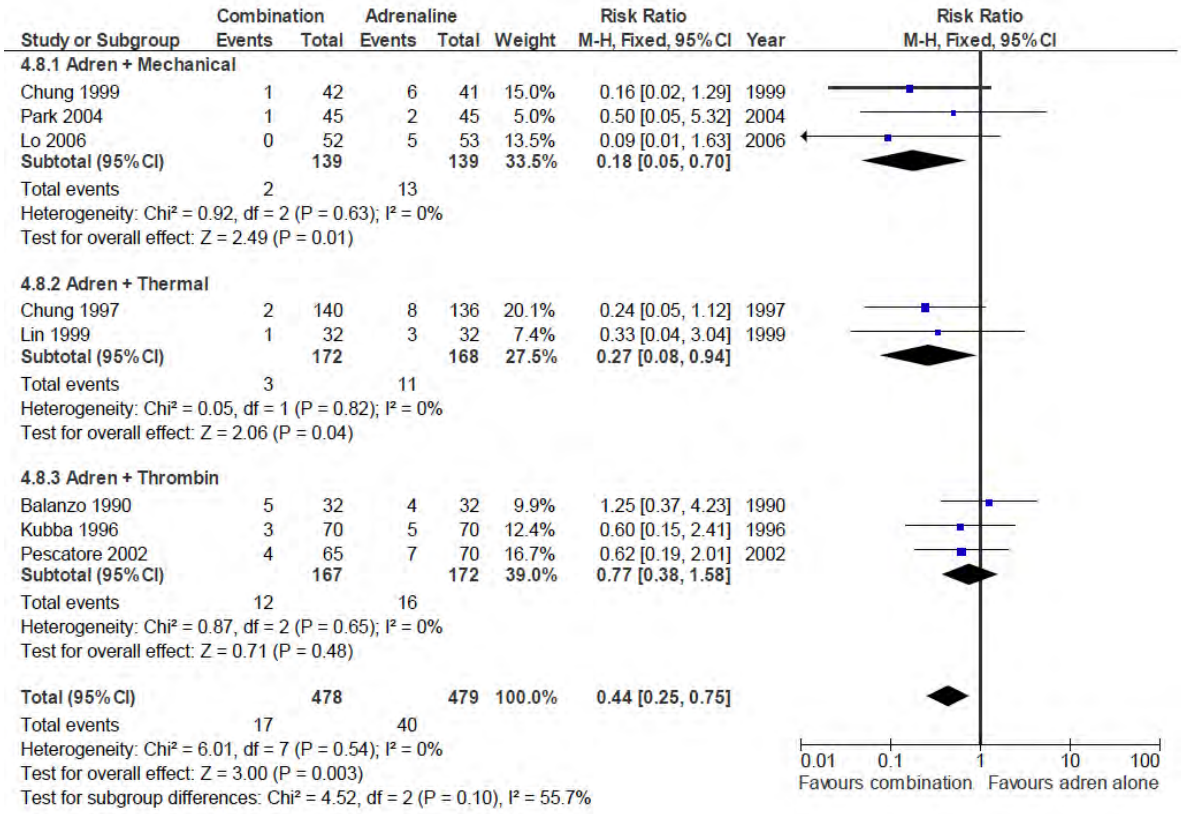


Figure 58: Blood transfusion requirements

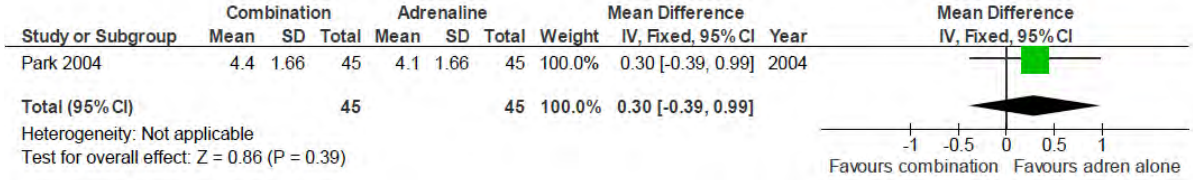
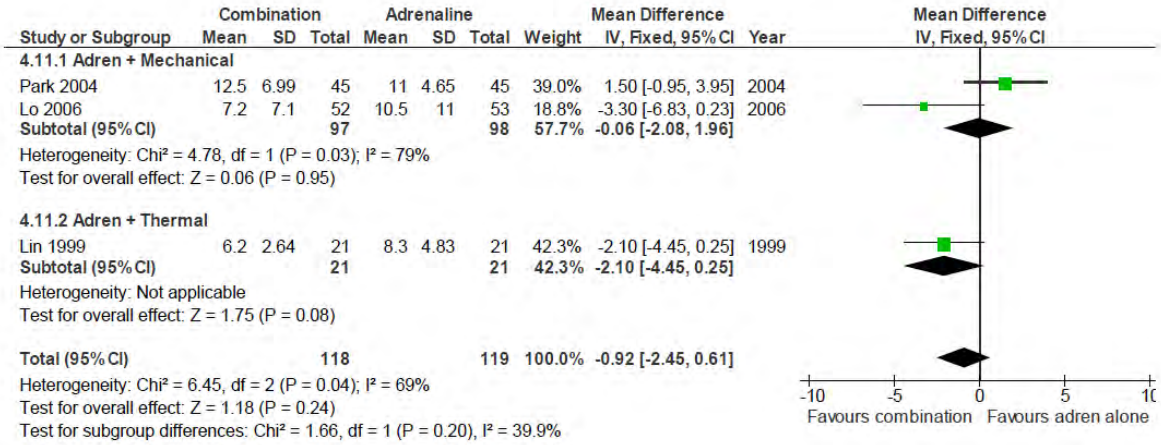


Figure 59: Length of hospital stay by type of combination



H.65.1.2 Adrenaline plus thermal vs adrenaline plus mechanical

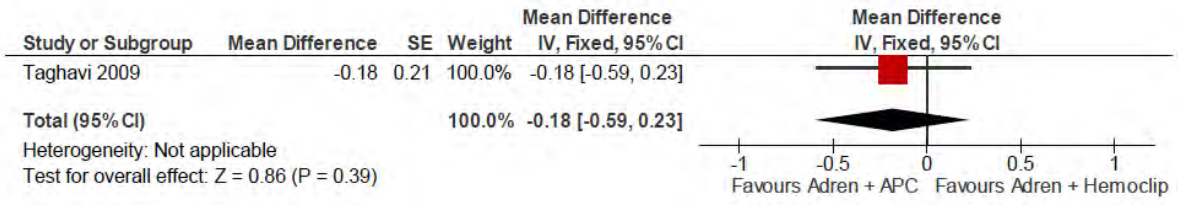
Figure 60: Mortality (30 day follow-up)

Figure 61: Rebleeding (30 day follow-up)

Figure 62: Failure to achieve hemostasis

Figure 63: Emergency procedures

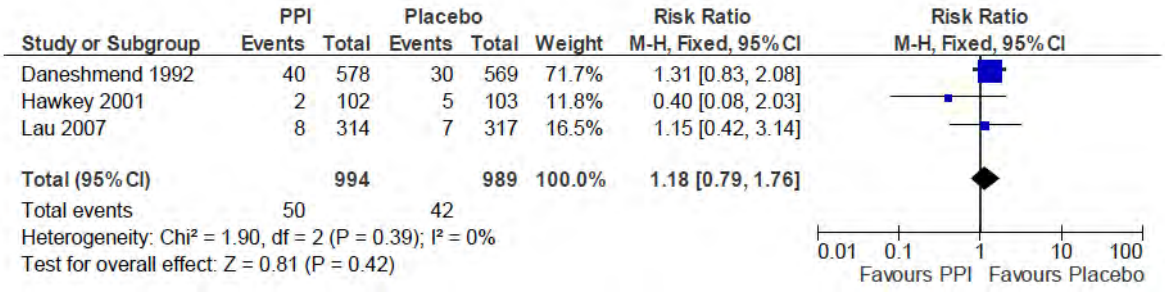
Figure 64: Length of hospital stay



H.65.2 PPIs

H.65.2.1 PPI vs placebo pre endoscopy

Figure 65: Mortality within 30 days



Source: <Insert Source text here>

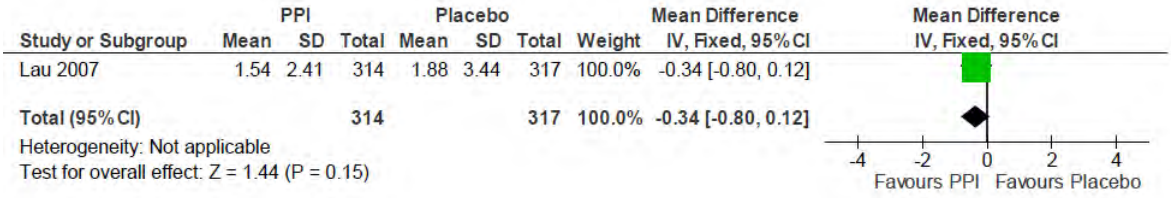
Figure 66: Rebleeding within 30

Source: <Insert Source text here>

Figure 67: Surgery for continued or recurrent bleeding

Source: <Insert Source text here>

Figure 68: Blood transfusion requirements

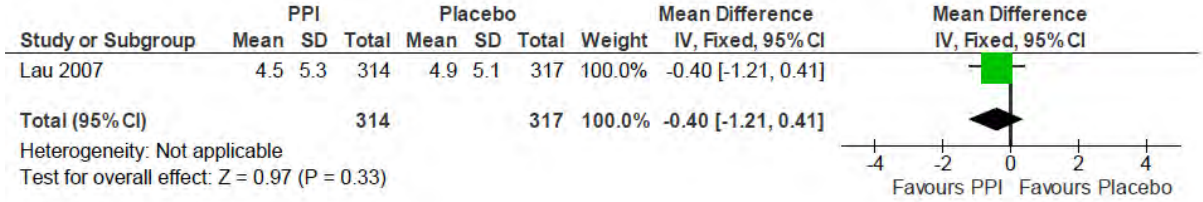


Source: <Insert Source text here>

Figure 69: Rate of patients needing blood transfusions

Source: <Insert Source text here>

Figure 70: Length of hospital stay



Source: <Insert Source text here>

H.65.2.2 PPI vs H2RAs Pre endoscopy

Figure 71: Mortality within 30 days

Source: <Insert Source text here>

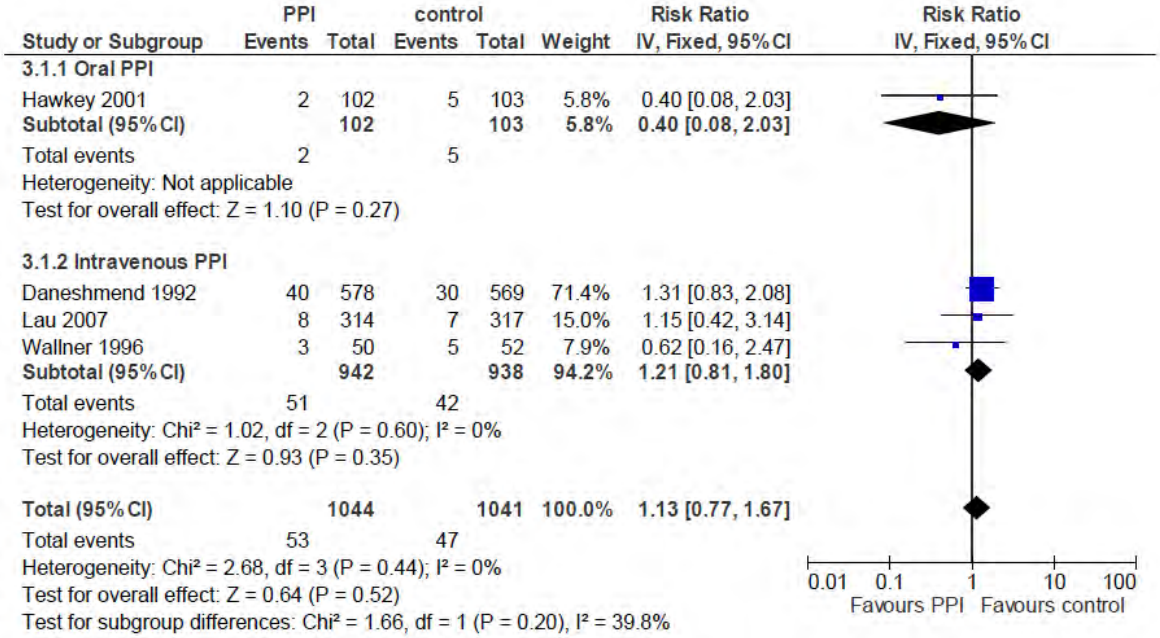
Figure 72: Surgery for continued or recurrent bleeding

Figure 73: Patients requiring blood transfusions

Source: <Insert Source text here>

H.65.2.3 PPI – route of administration (i.v vs p.o) Pre endoscopy (indirect comparison)

Figure 74: Mortality within 30 days



Source: <Insert Source text here>

Figure 75: Rebleeding within 30 days

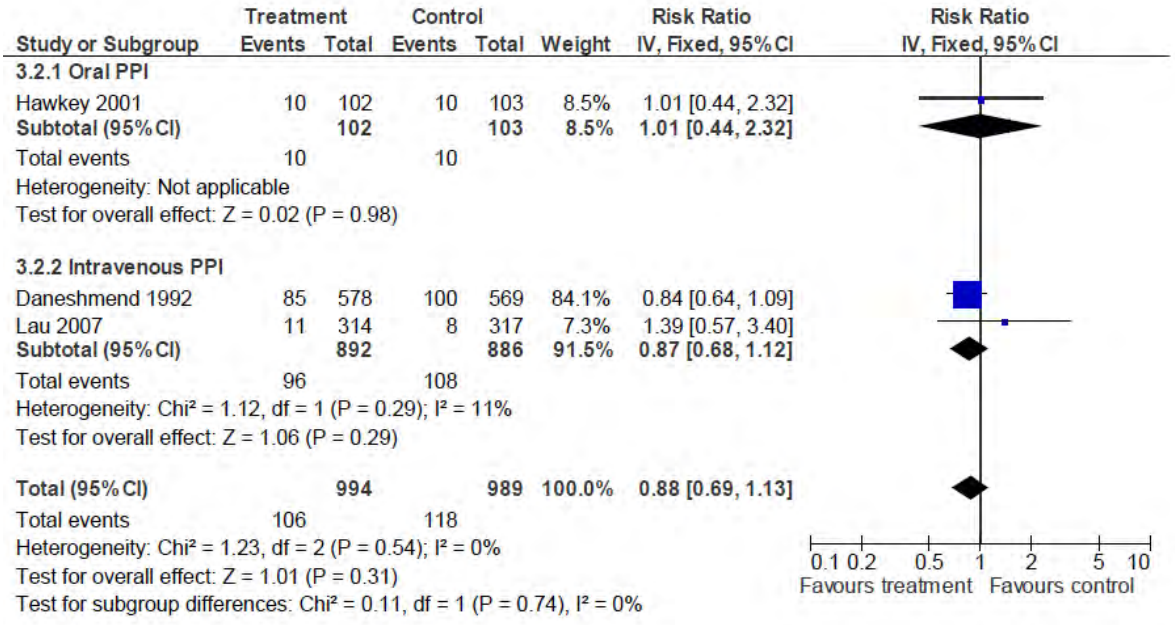
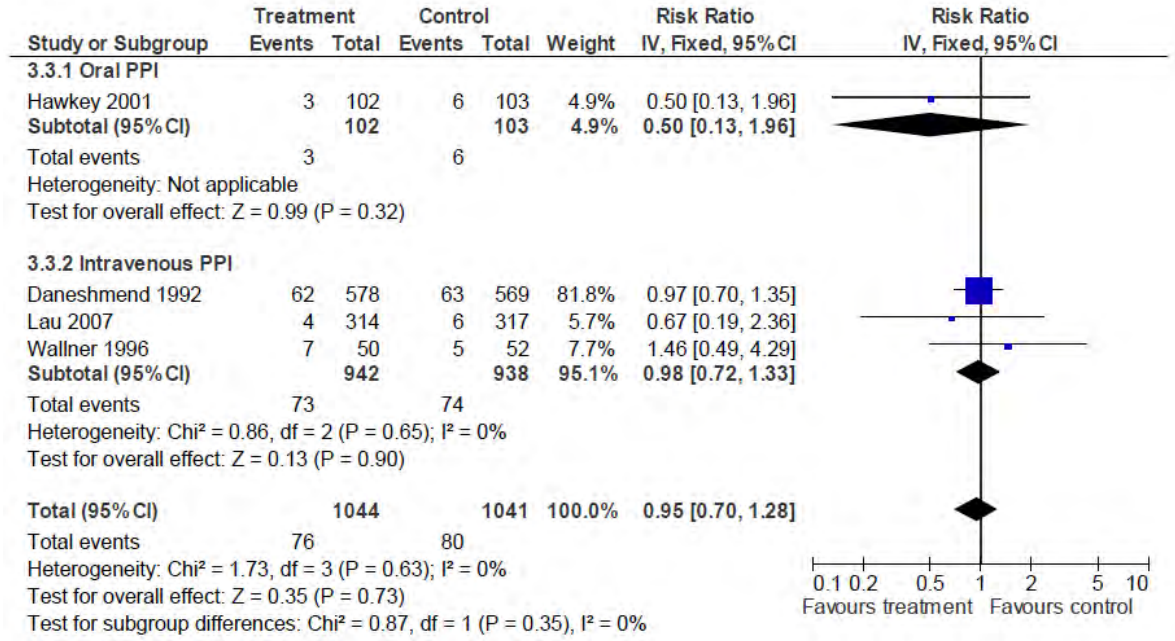


Figure 76: Surgery for continued or recurrent bleeding



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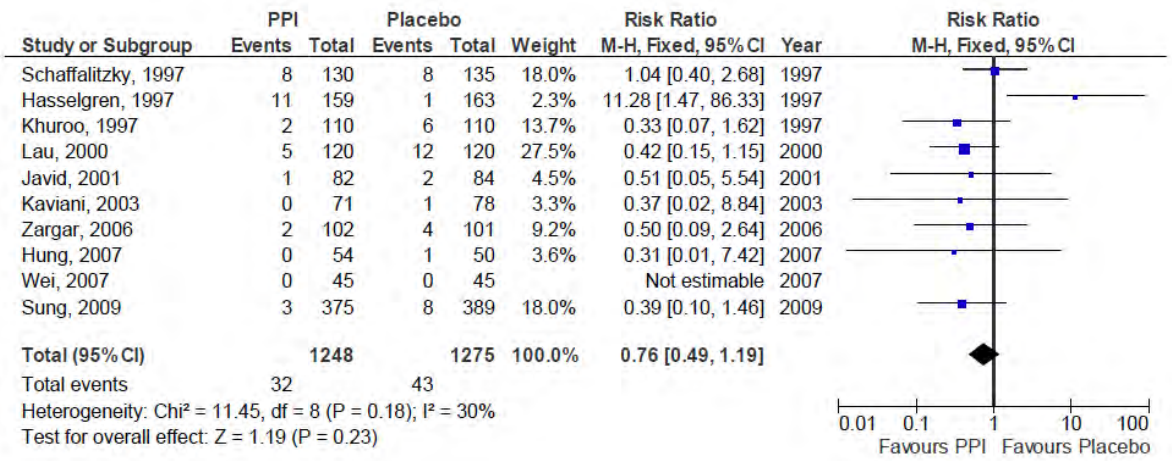
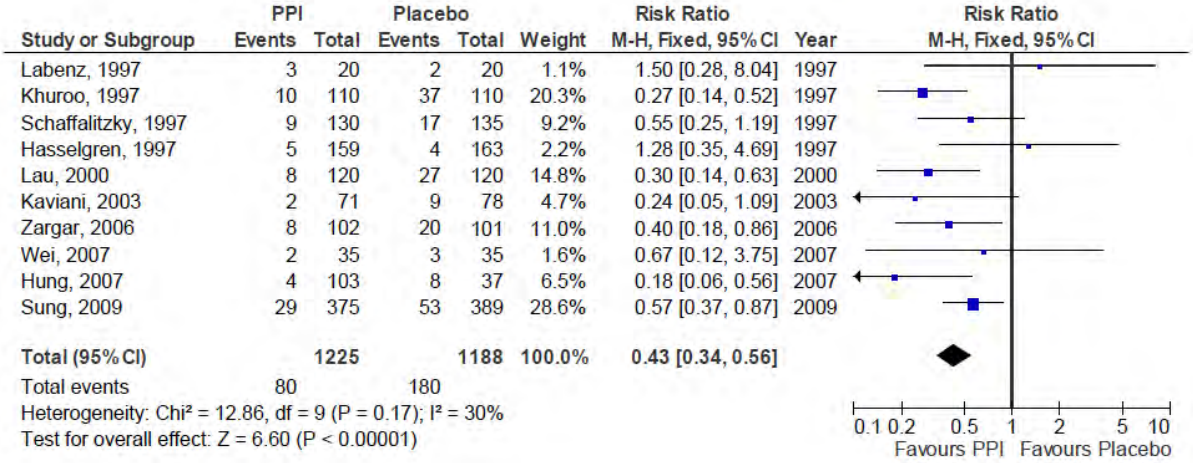
H.65.2.4 PPI vs placebo post endoscopy

Figure 77: Mortality within 30 days



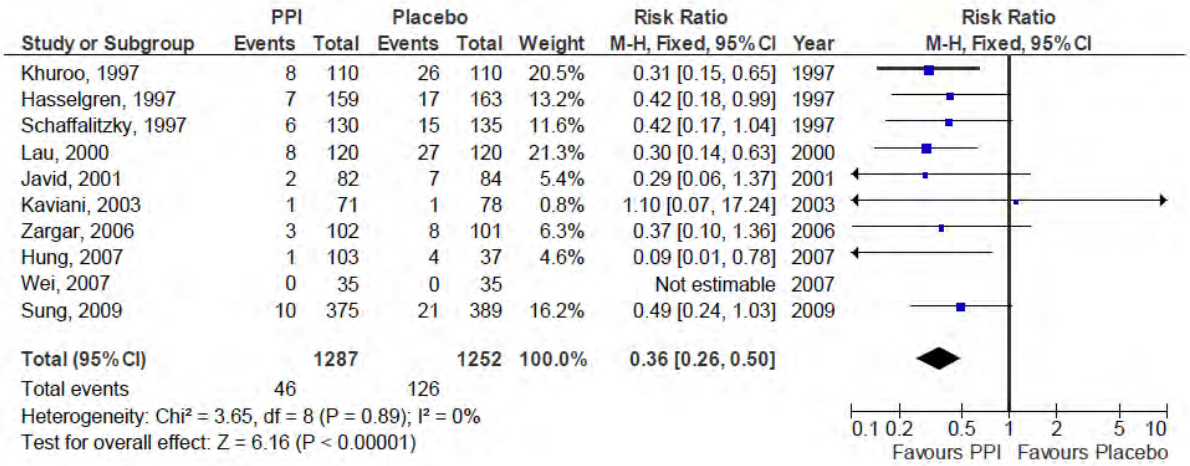
Source: *<Insert Source text here>*

Figure 78: Rebleeding within 30



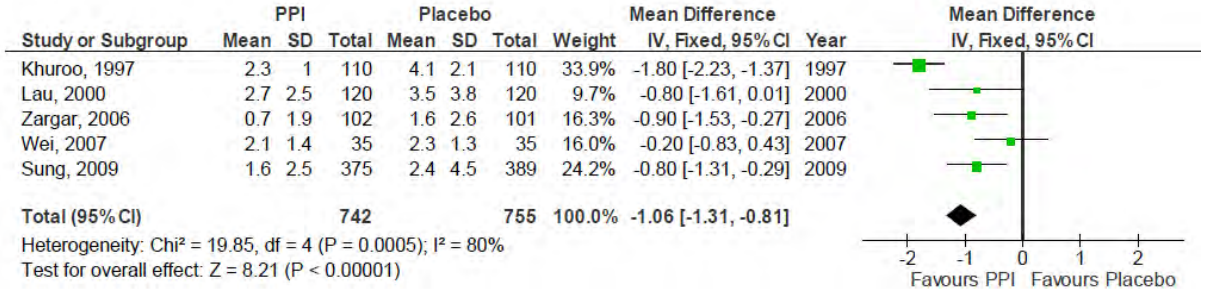
Source: *<Insert Source text here>*

Figure 79: Surgery for continued or recurrent bleeding



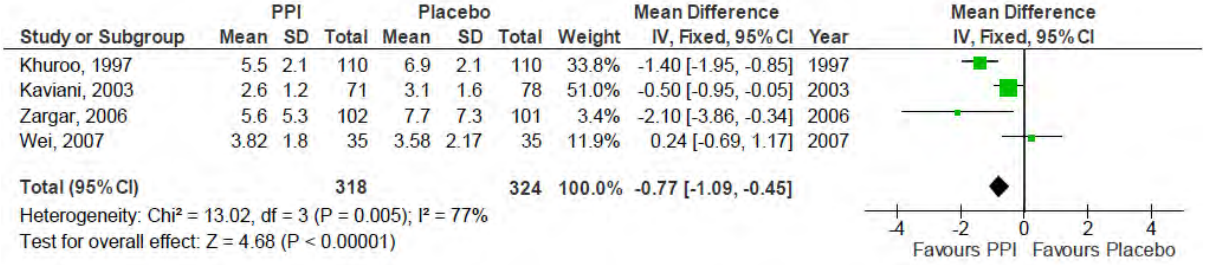
Source: <Insert Source text here>

Figure 80: Length of hospital stay – days



Source: <Insert Source text here>

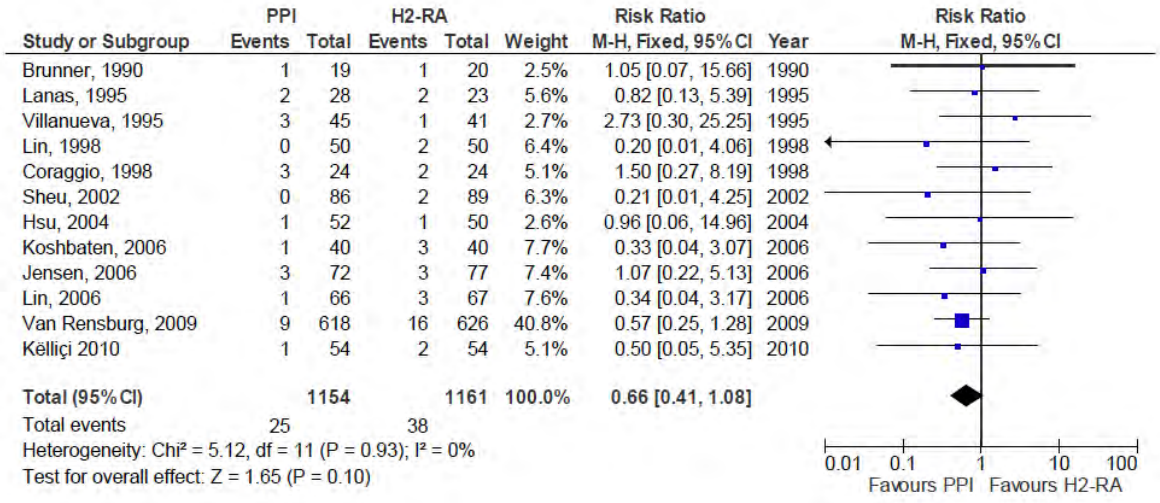
Figure 81: Blood transfusion requirements – in ml



Source: <Insert Source text here>

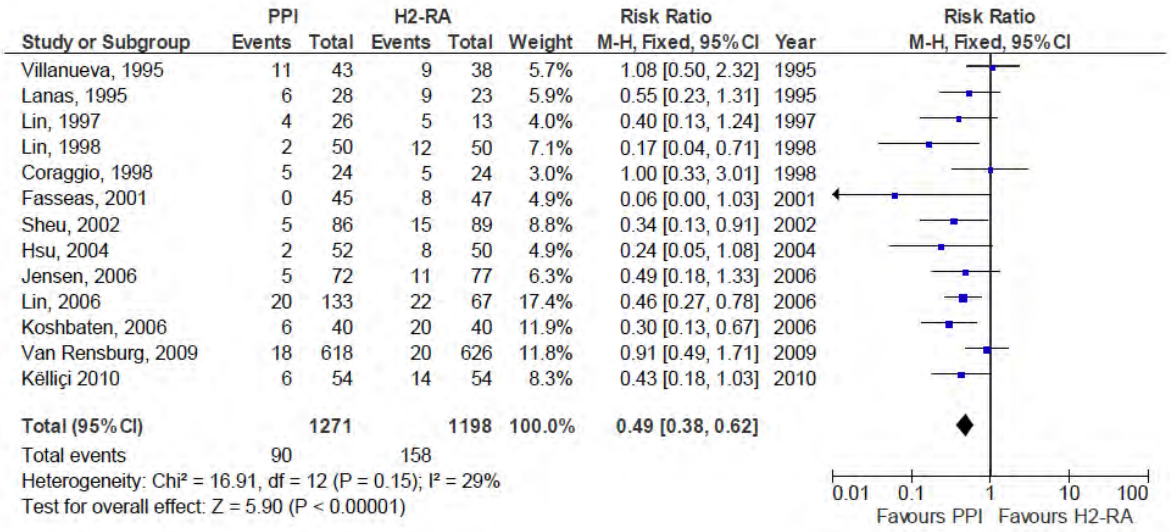
H.65.2.5 PPI vs H2RAs post endoscopy

Figure 82: Mortality within 30 days



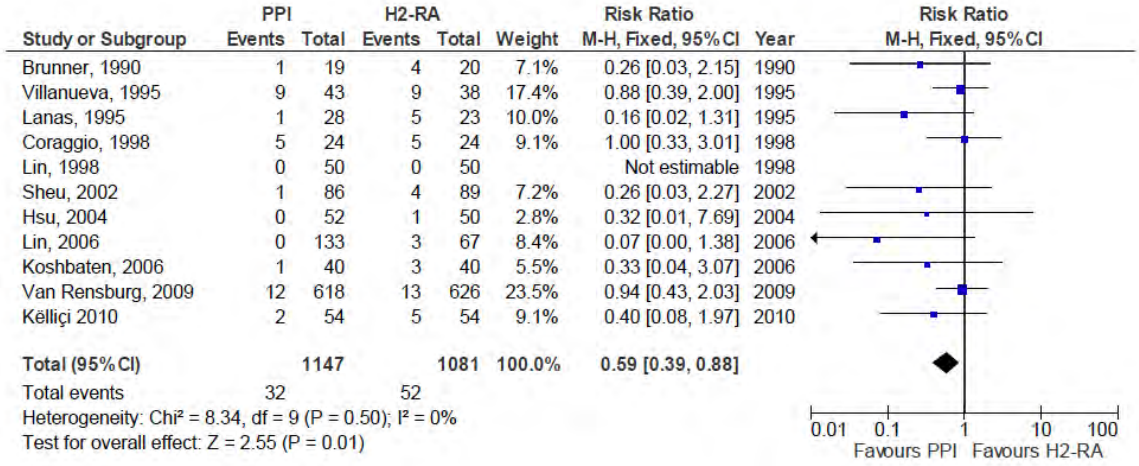
Source: <Insert Source text here>

Figure 83: Rebleeding within 30



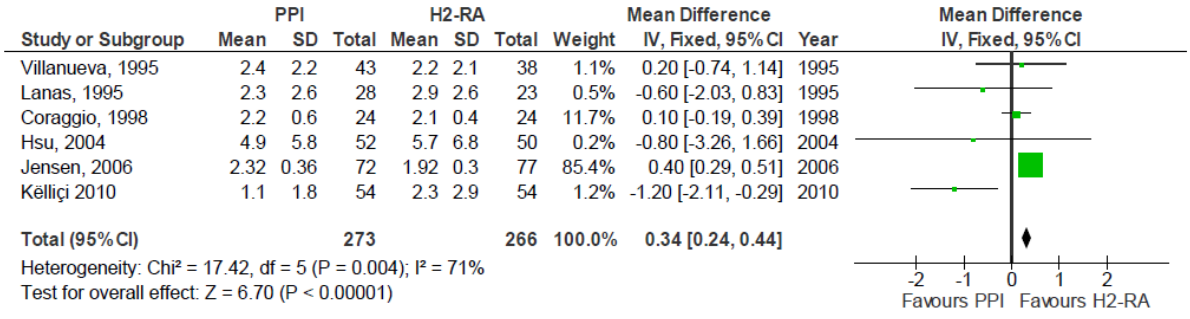
Source: <Insert Source text here>

Figure 84: Surgery for continued or recurrent bleeding



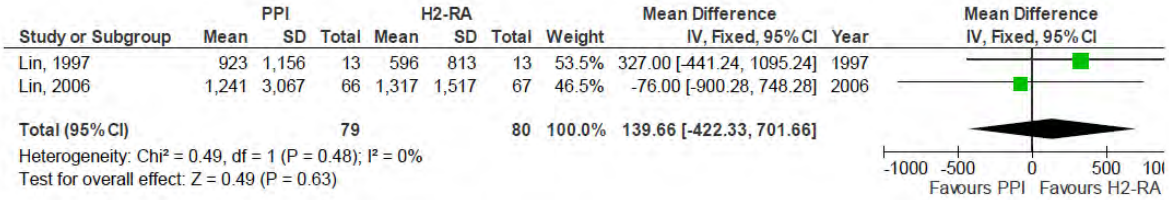
Source: <Insert Source text here>

Figure 85: Blood transfusion requirements – mean units of blood



Source: <Insert Source text here>

Figure 86: Blood transfusion requirements – in ml

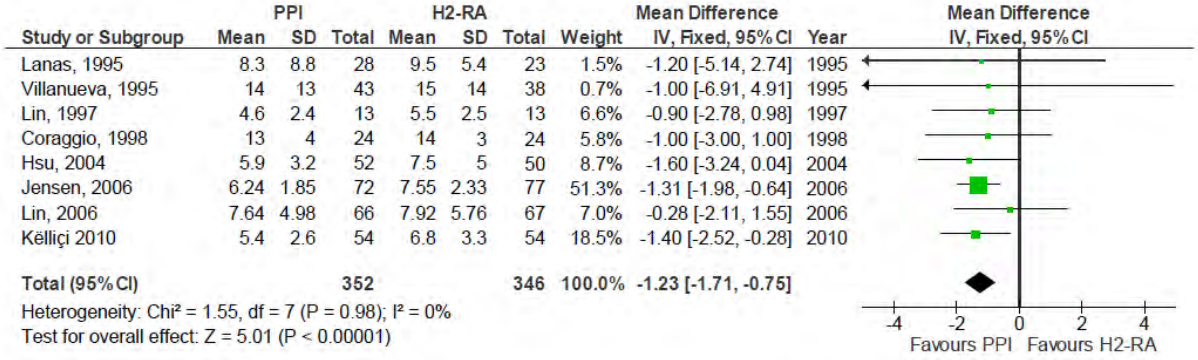


Source: <Insert Source text here>

Figure 87: Patients requiring blood transfusions

Source: <Insert Source text here>

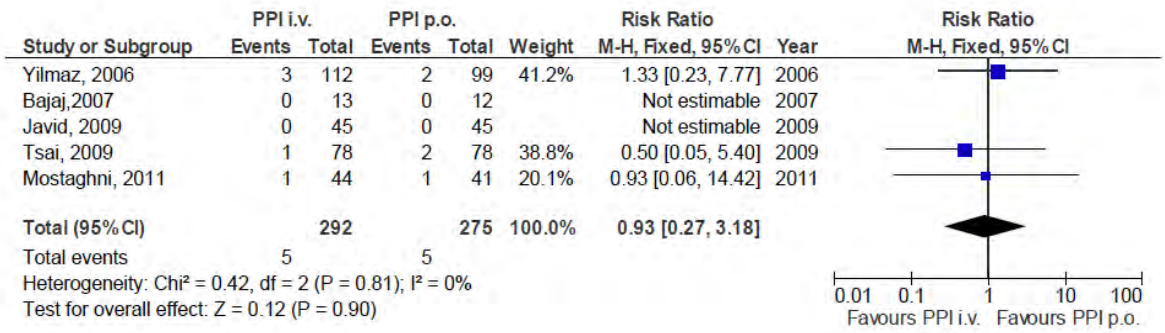
Figure 88: Length of hospital stay



Source: <Insert Source text here>

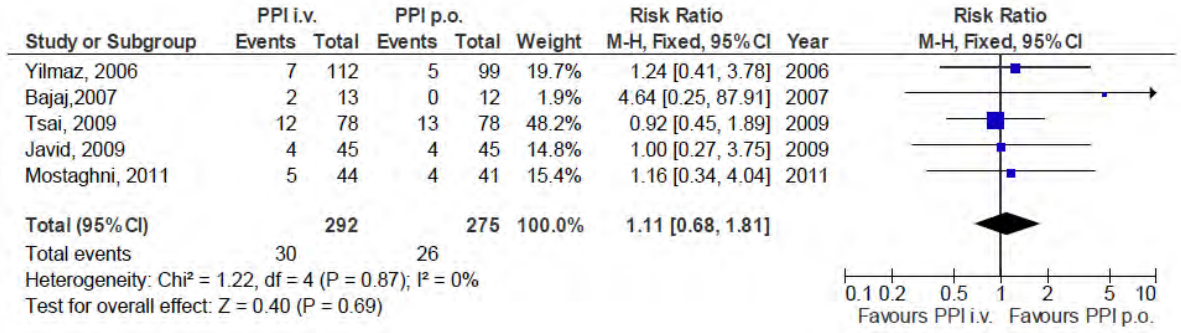
H.65.2.6 PPI – route of administration (i.v. vs p.o.) post endoscopy (direct comparison)

Figure 89: Mortality within 30 days



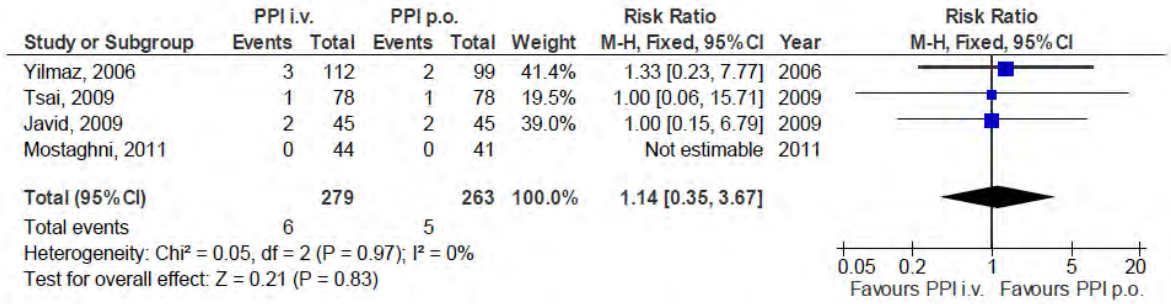
Source: <Insert Source text here>

Figure 90: Rebleeding within 30



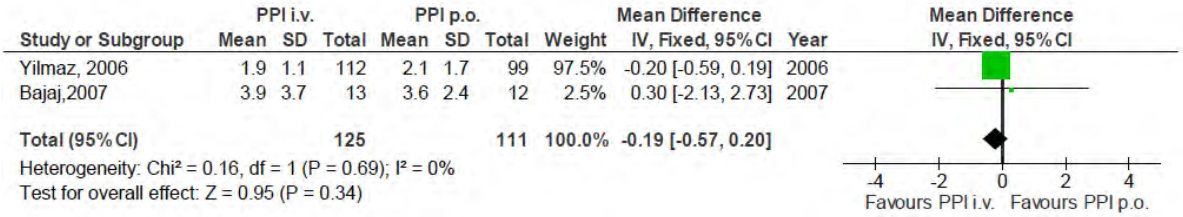
Source: <Insert Source text here>

Figure 91: Surgery for continued or recurrent bleeding



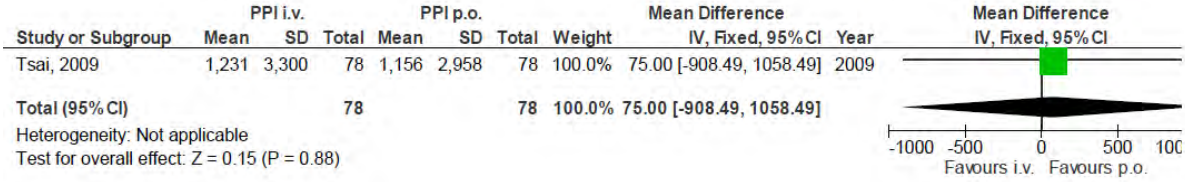
Source: <Insert Source text here>

Figure 92: Blood transfusion requirements – mean units of blood



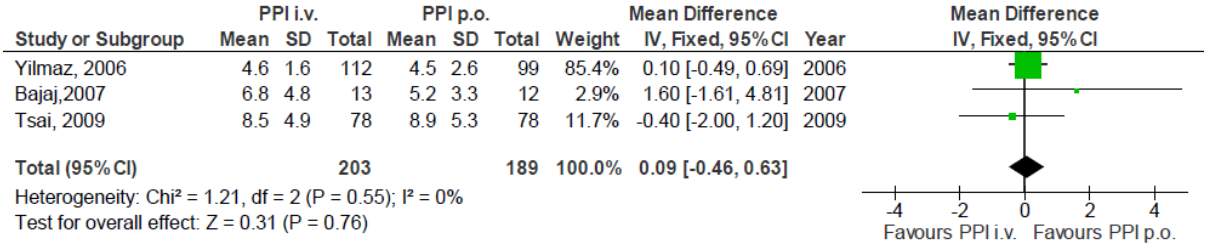
Source: <Insert Source text here>

Figure 93: Blood transfusion requirements – in ml



Source: *<Insert Source text here>*

Figure 94: Length of hospital stay - days

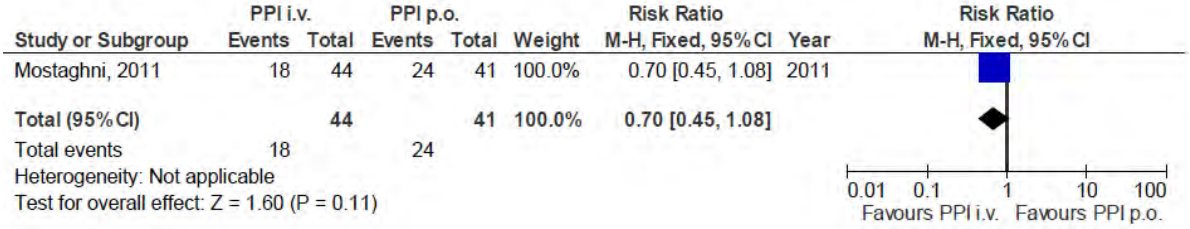


Source: *<Insert Source text here>*

Figure 95: Patients needing blood transfusions

Source: *<Insert Source text here>*

Figure 96: Patients requiring second endoscopy



Source: *<Insert Source text here>*

H.65.3 Treatment options after first/failed endoscopy

H.65.3.1 Routine second look vs routine follow up

Figure 97: Mortality

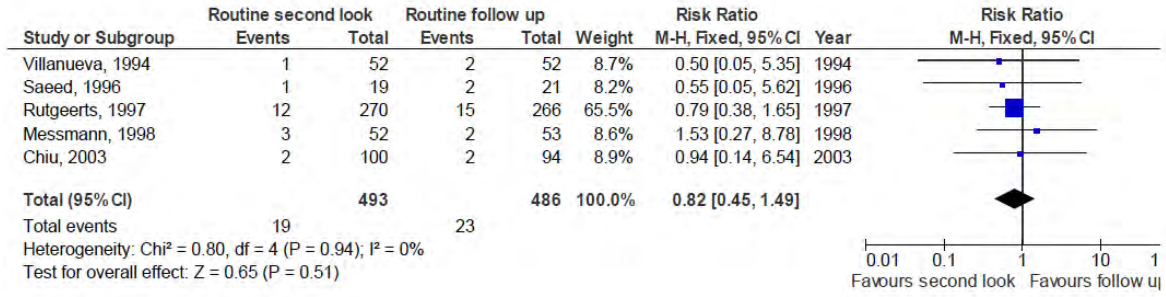


Figure 98: Rebleeding (with length of follow up)

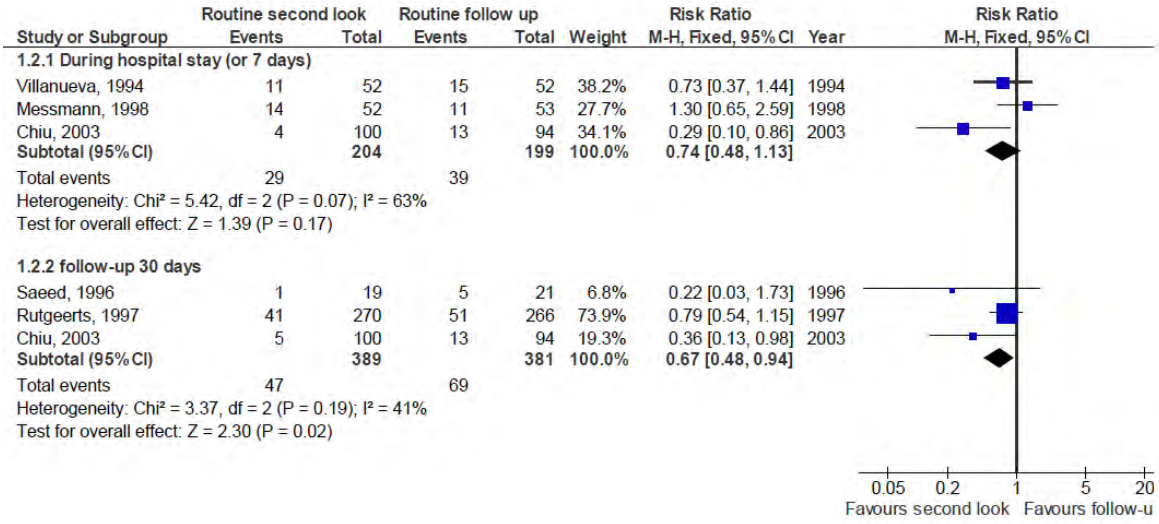


Figure 99: Surgery for continued bleeding

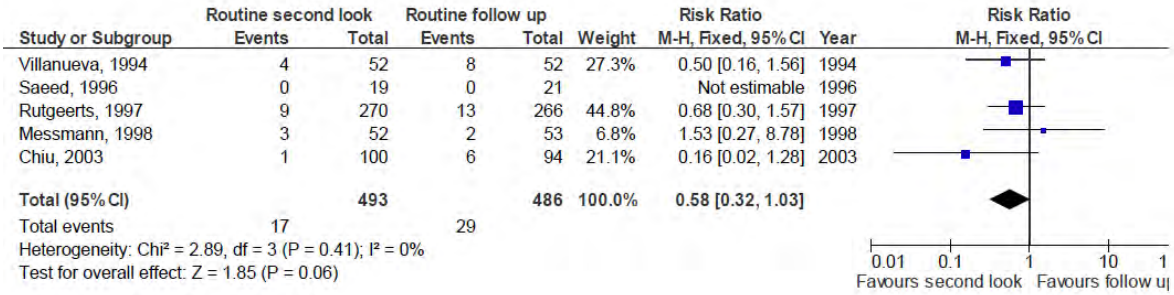


Figure 100: Length of hospital stay (mean difference of days spent in hospital)

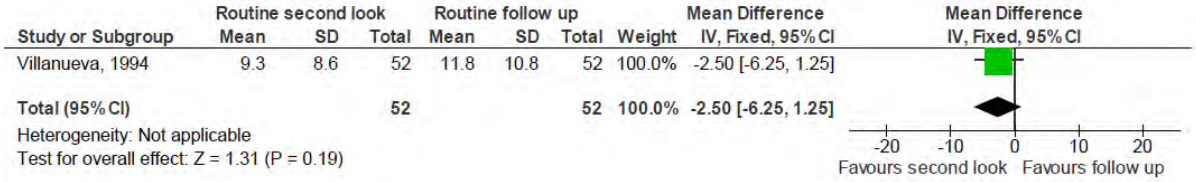
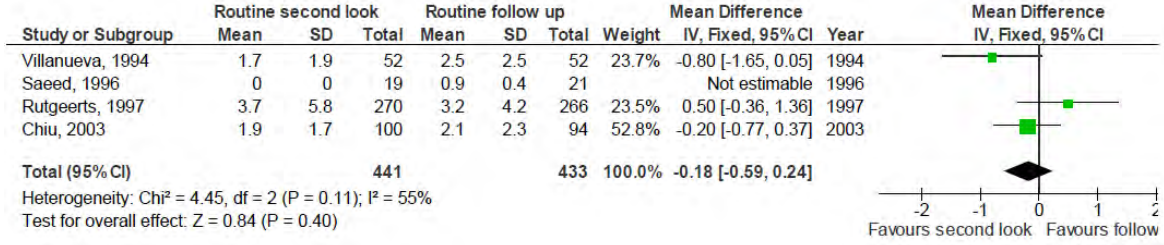


Figure 101: Blood transfusion requirements (mean difference of units transfused)



H.65.3.2 Endoscopic treatment vs surgery (in patients who rebleed)

Figure 102: Mortality (30 days or less)

Figure 103: Rebleeding (30 days or less)

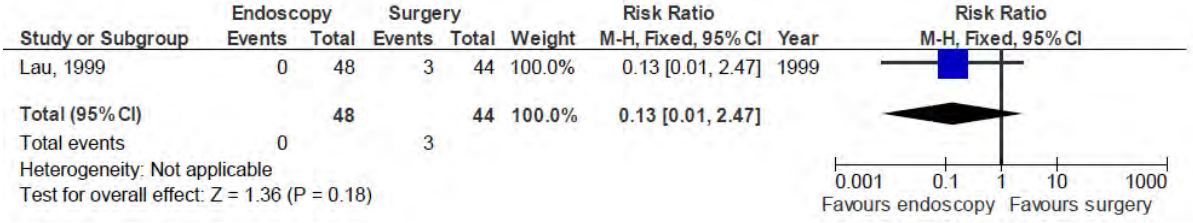


Figure 104: Salvage surgery

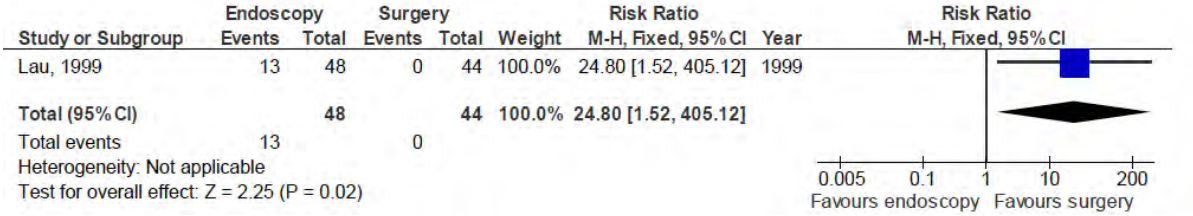


Figure 105: Failure to achieve haemostasis

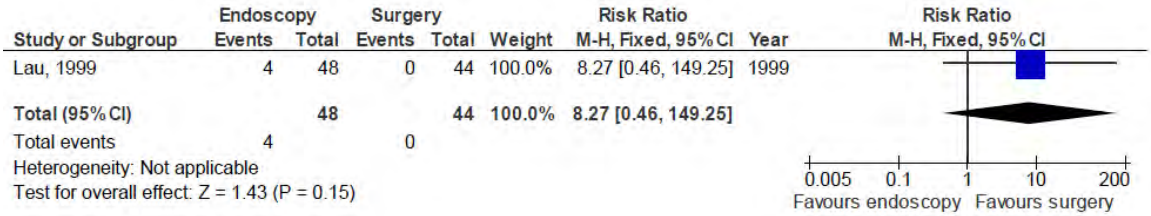
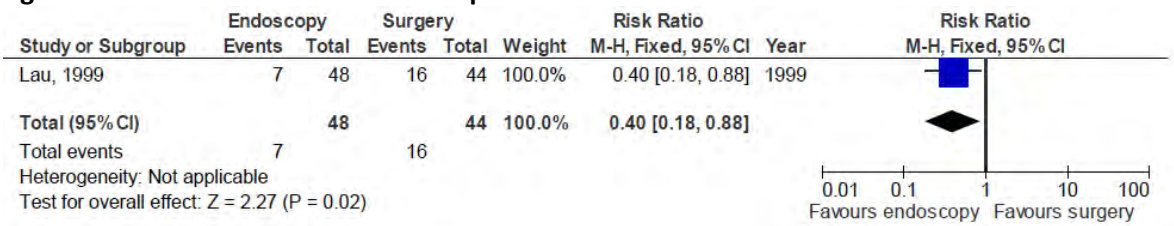


Figure 106: Rate of treatment complications



H.65.3.3 When first line treatment fails (embolisation vs surgery)

Figure 107: Mortality

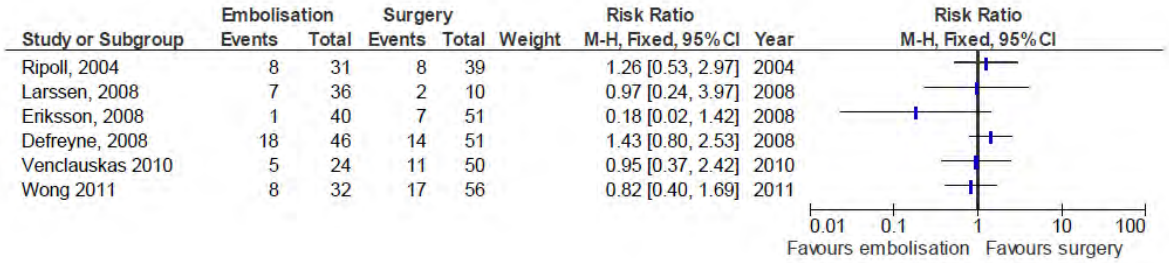


Figure 108. Failure to achieve haemostasis

Figure 109: Rebleeding (by follow up)

Figure 110: Salvage treatment (usually surgery)

Figure 111: Length of hospital stay (mean difference of days spent in hospital)

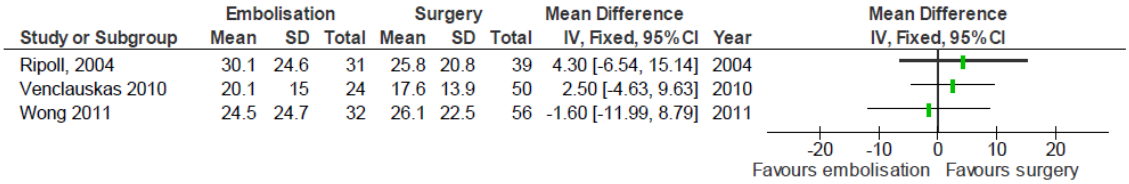


Figure 112: Blood transfusion requirements (mean difference of units transfused)

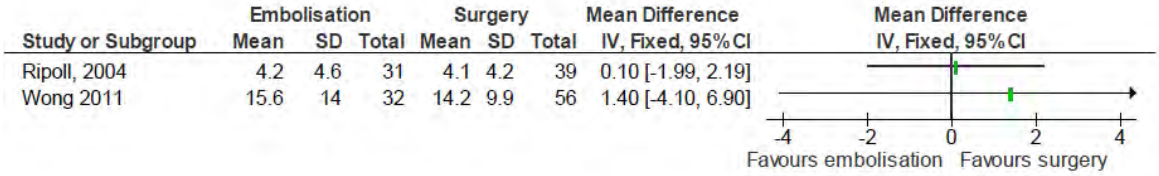
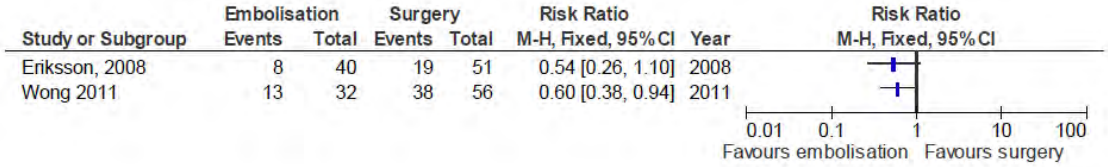


Figure 113: Adverse events – treatment complication



H.66 Control of bleeding and prevention of rebleeding

Figure 114: Longer and shorter term mortality

Figure 115: Confirmed rebleeding (30 day follow up)

Figure 116: Surgery

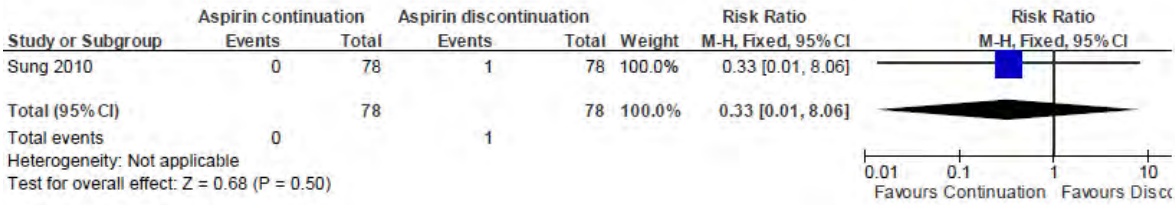
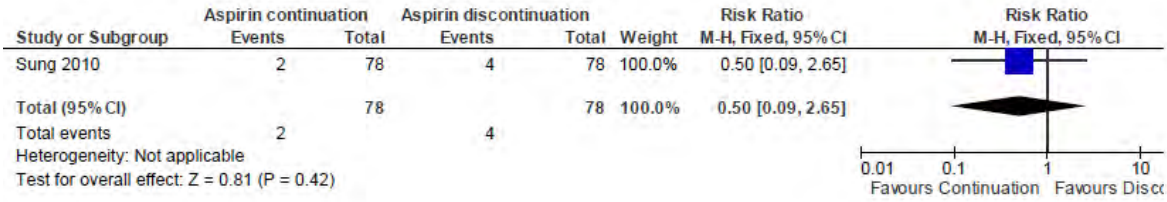


Figure 117: Adverse events (serious nonfatal)



H.67 Primary prophylaxis

H.67.1 PPI vs Placebo

Figure 118: Mortality

Figure 119: Bleeding

Figure 120: Nosocomial pneumonia

Figure 121: Length of ICU stay

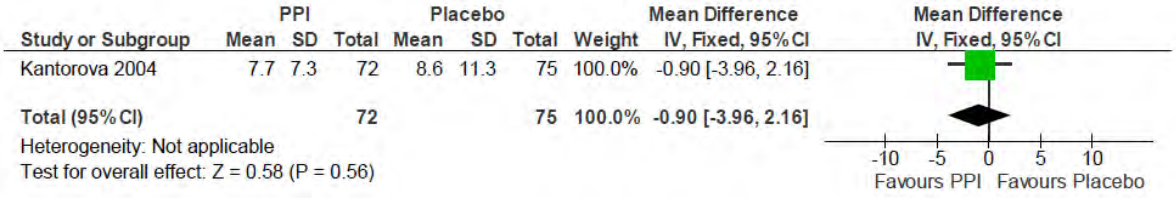
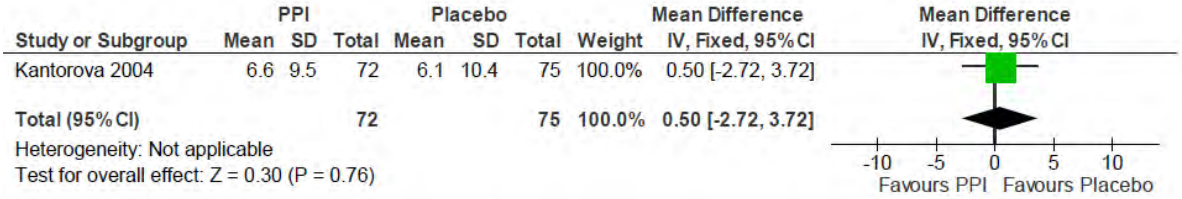


Figure 122: Days on ventilator



H.67.2 H2RA vs Placebo

Figure 123: Mortality by risk group

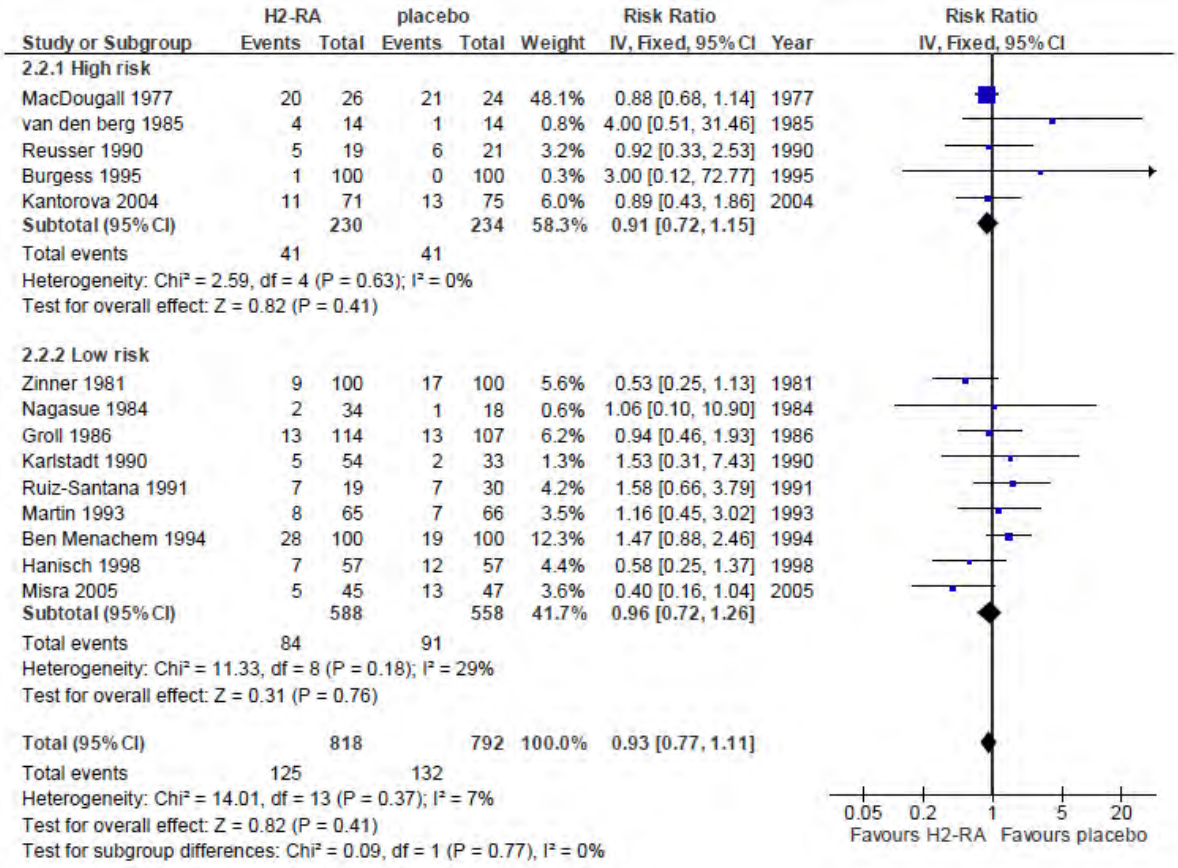


Figure 124: Bleeding by risk group

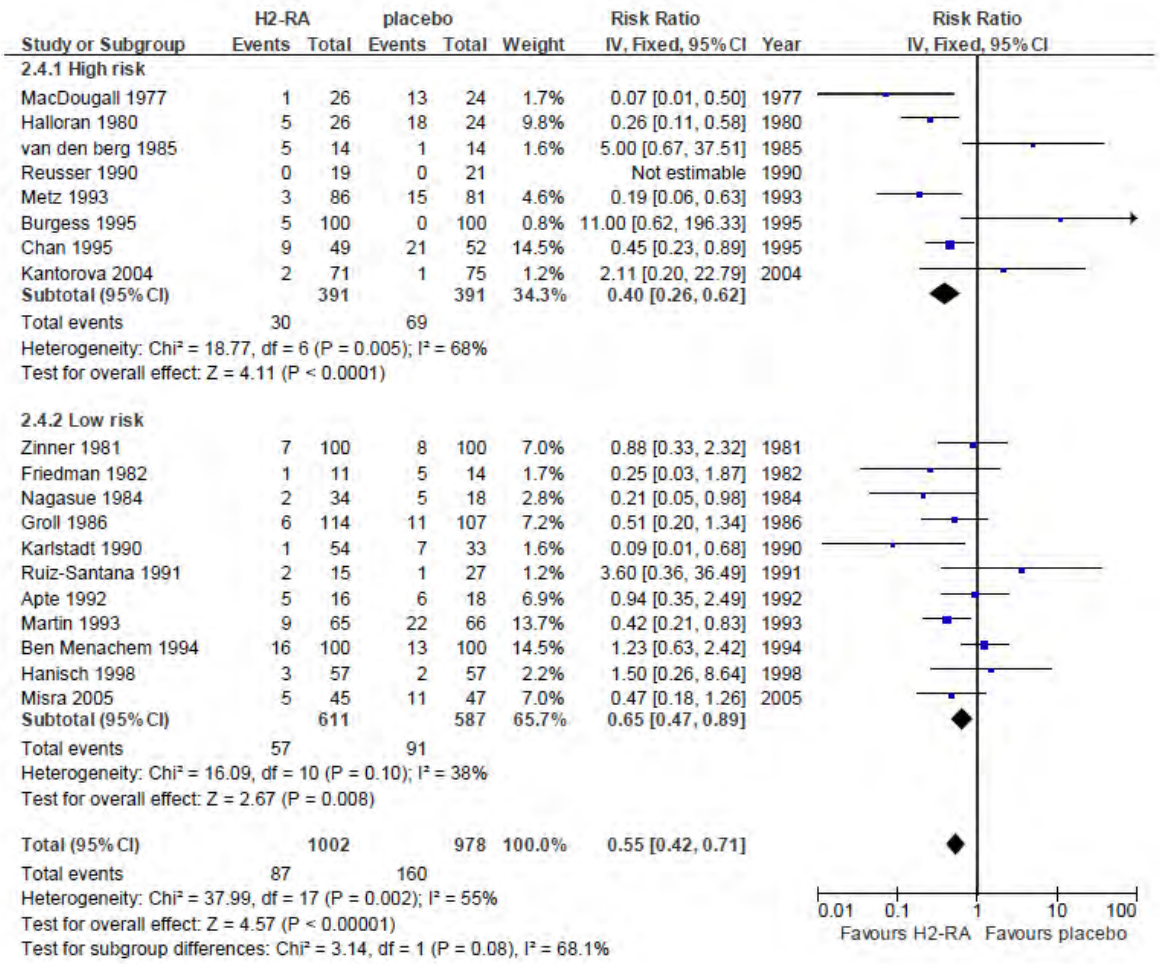


Figure 125: Nosocomial Pneumonia

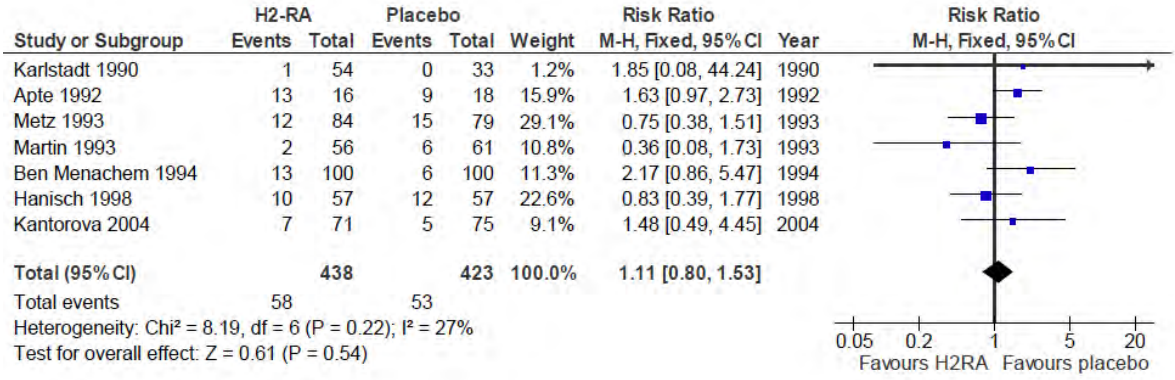


Figure 126: Length of ICU stay

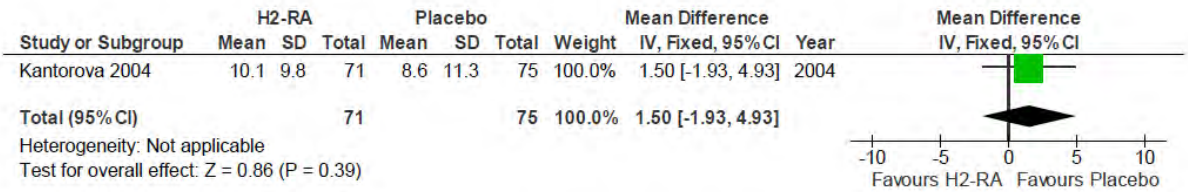


Figure 127: Days on ventilator

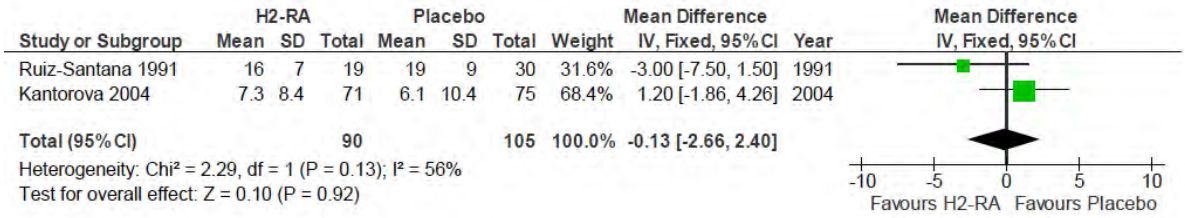


Figure 128: Transfusion requirements (units transfused)

Figure 129: Need for transfusions (patients who need transfusions)

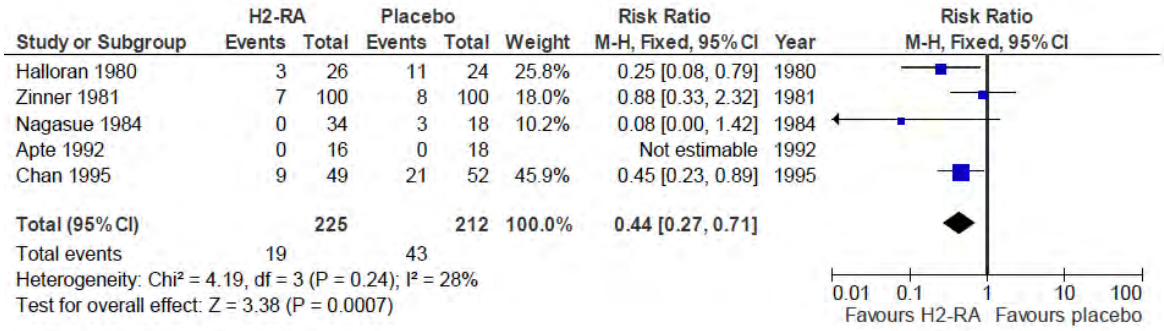
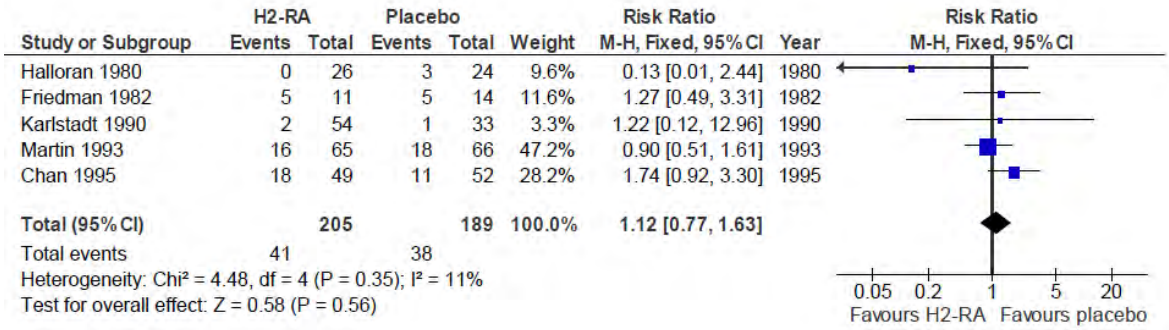


Figure 130: Adverse events



H.67.3 PPI vs H2RAs

Figure 131: Mortality

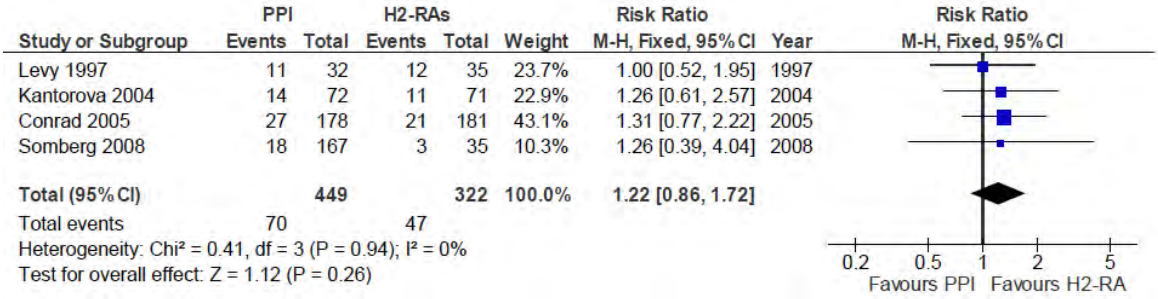


Figure 132: Bleeding

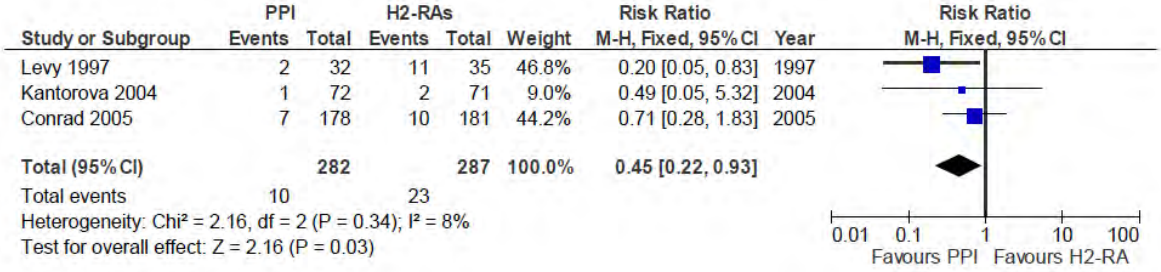


Figure 133: Any overt bleeding

Figure 134: Nosocomial Pneumonia

Figure 135: Length of ICU stay

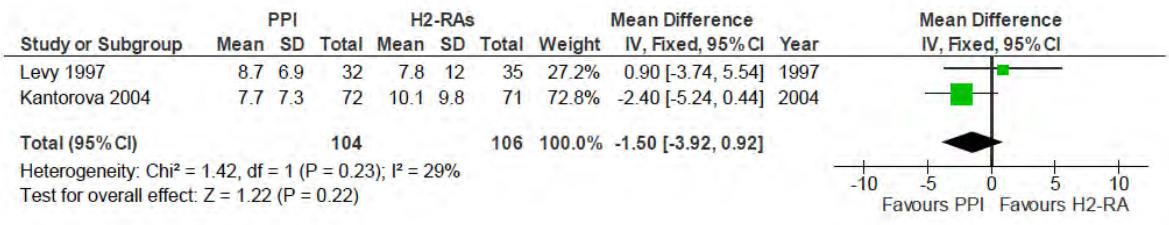


Figure 136: Days on ventilator

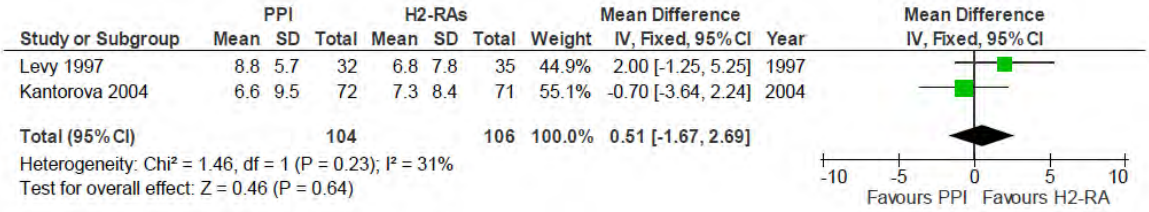


Figure 137: Serious adverse events

H.68 Management of variceal bleeding

H.68.1 TIPS

Figure 138: Mortality (variable follow-up to 50 months)

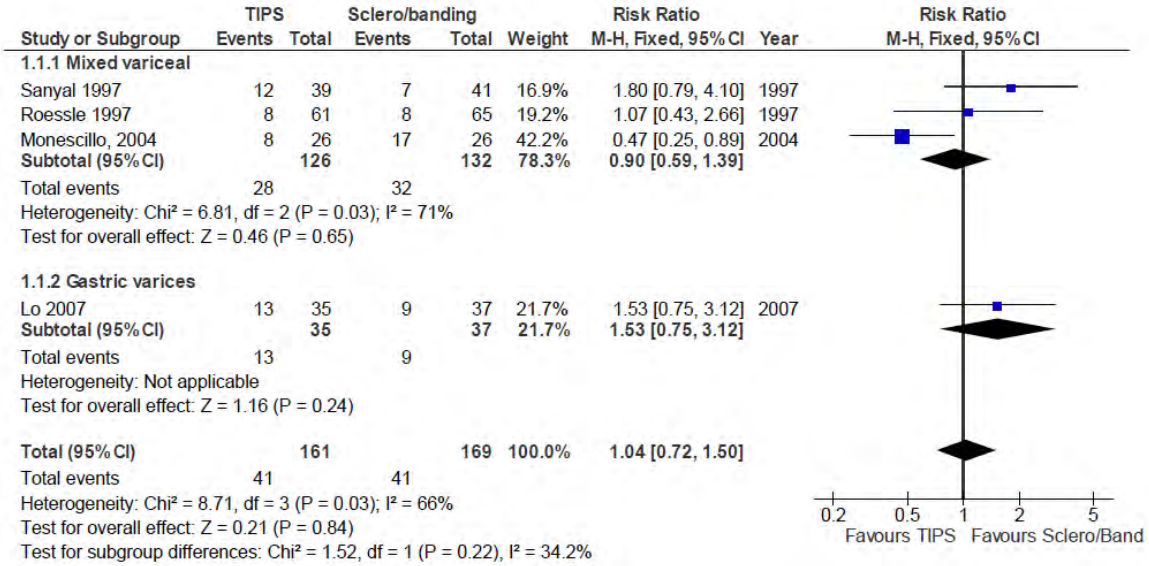


Figure 139: Rebleeding (variable follow-up to 50 months)

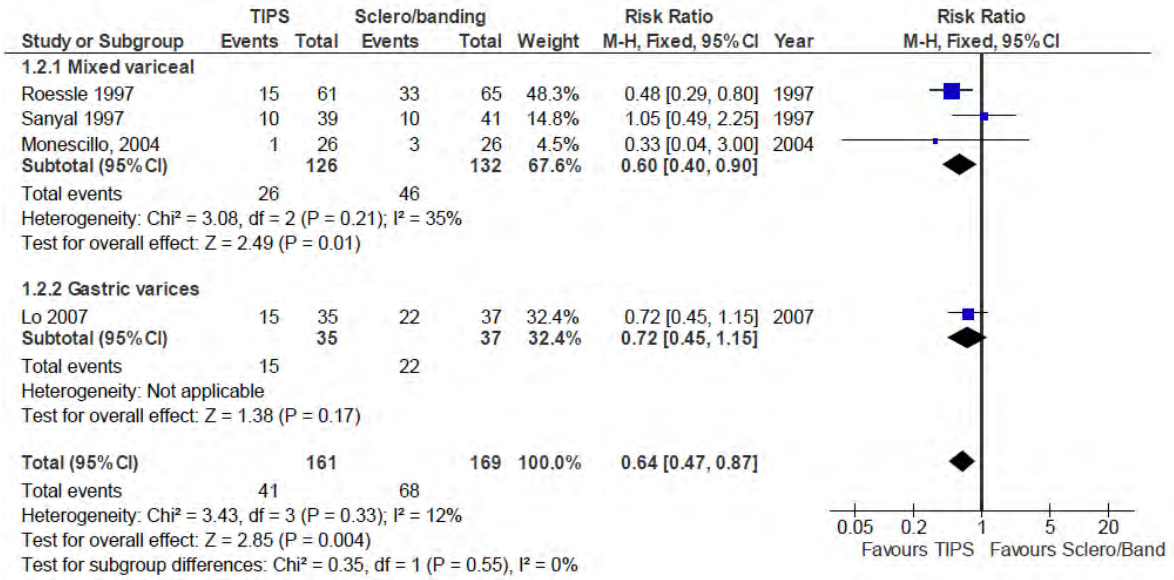


Figure 140: Blood transfusion requirements

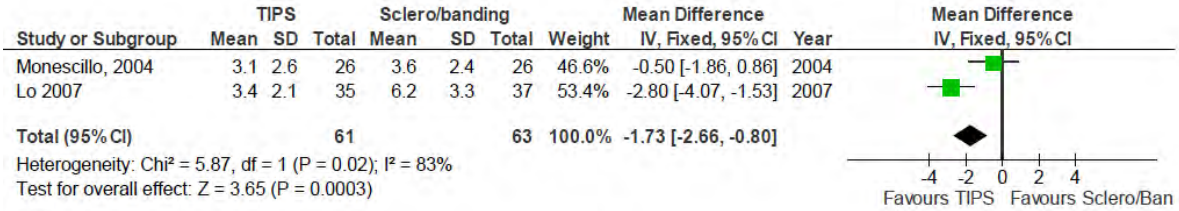


Figure 141: Length of hospital stay

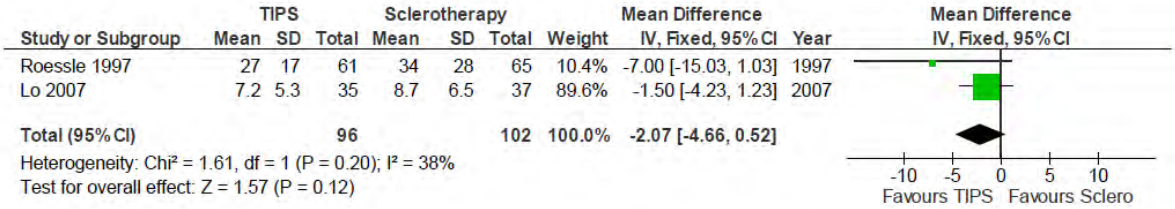


Figure 142: Treatment failure

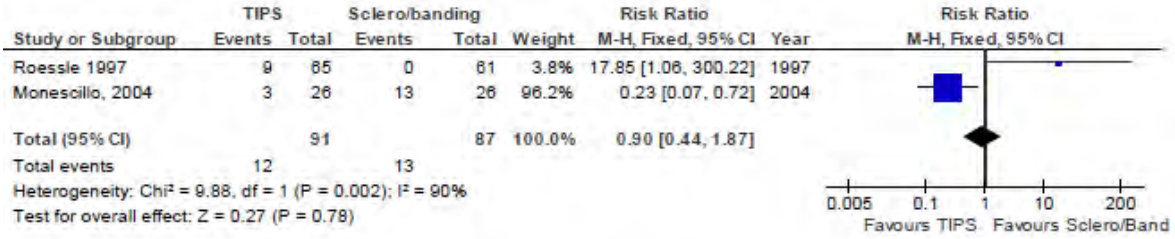


Figure 143: Adverse events – Hepatic encephalopathy

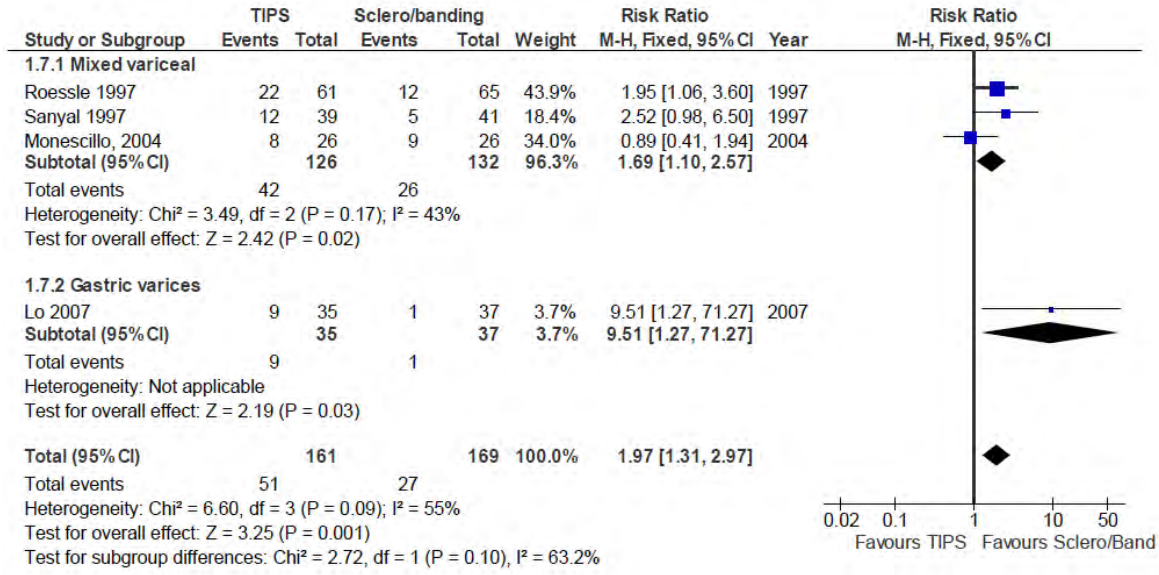
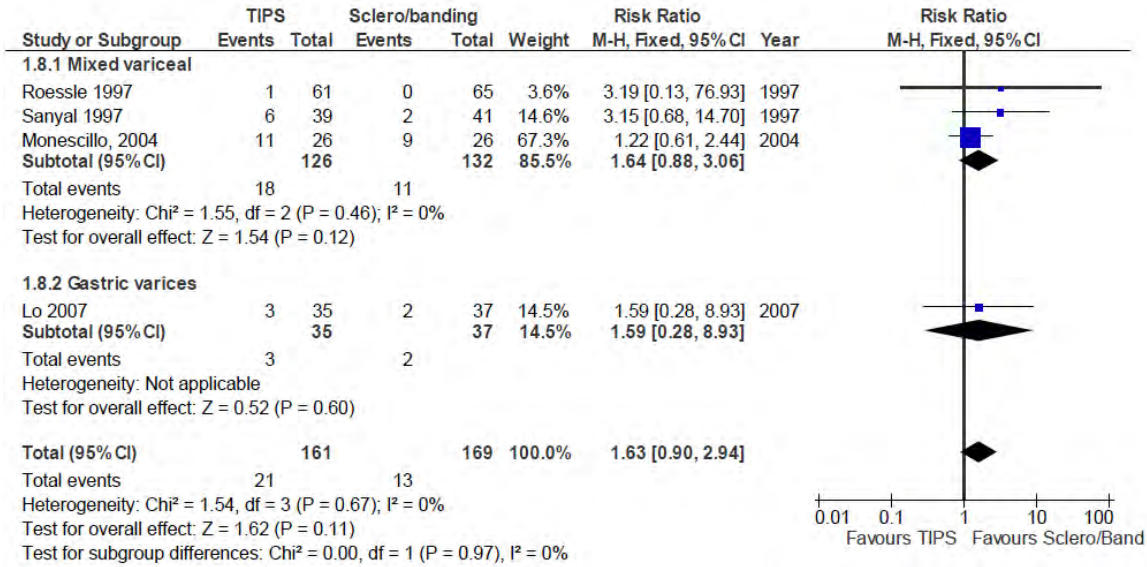


Figure 144: Adverse events - Sepsis



H.68.2 Antibiotics

Figure 145: All cause mortality (variable follow-up to 22 months)

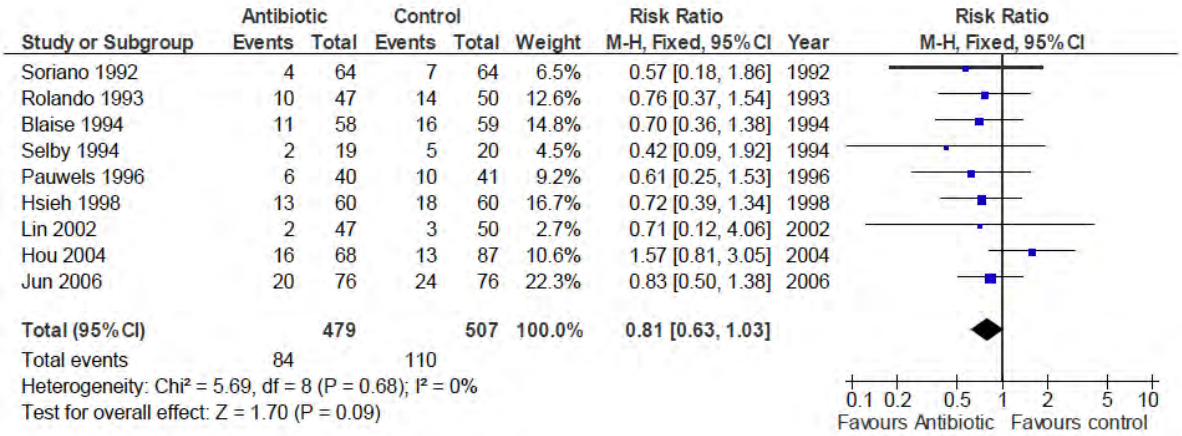


Figure 146: Short, medium and long mortality follow-up

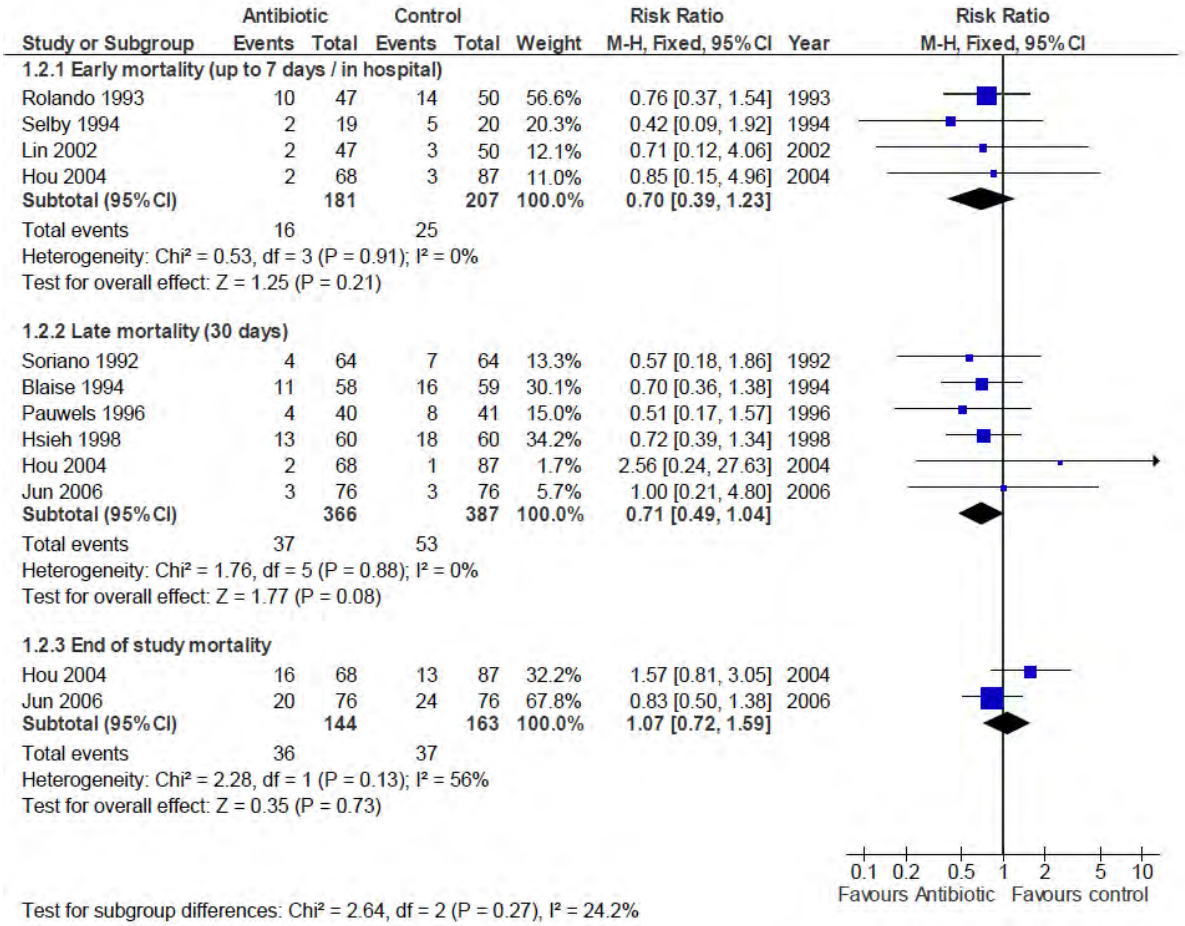


Figure 147: Infection related mortality

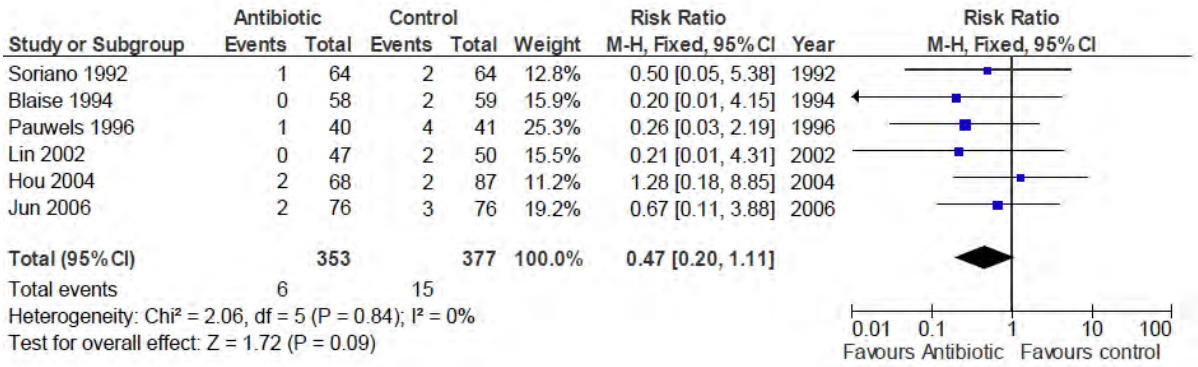


Figure 148: Rebleeding by length of follow up

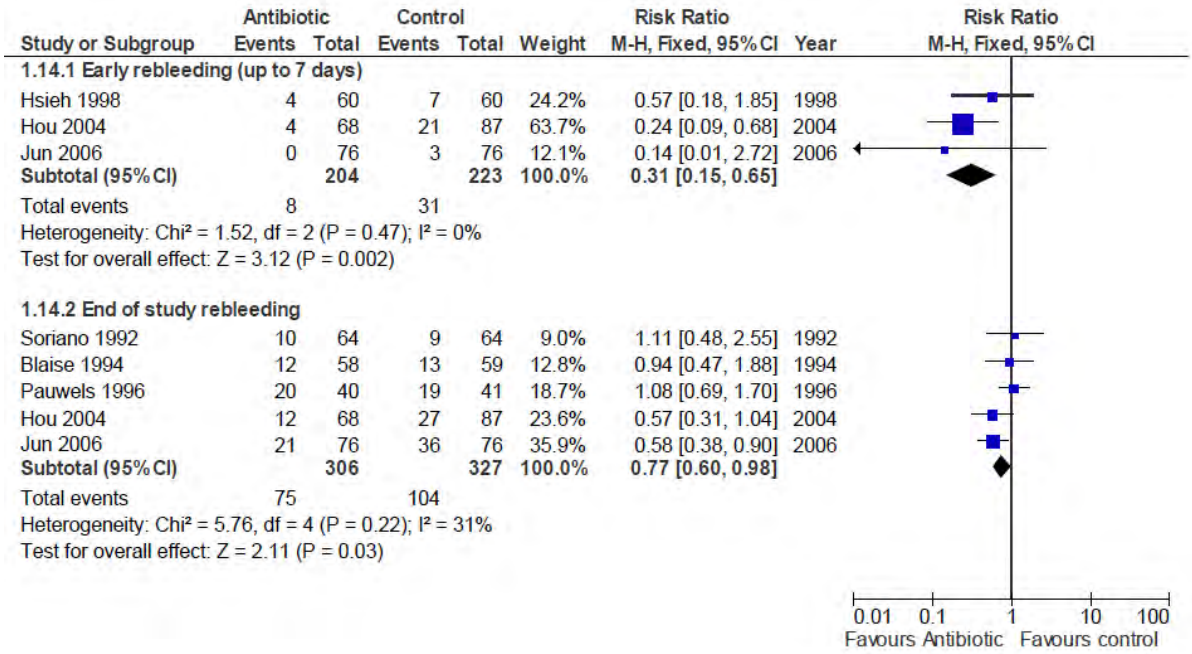


Figure 149: Blood transfusion requirements

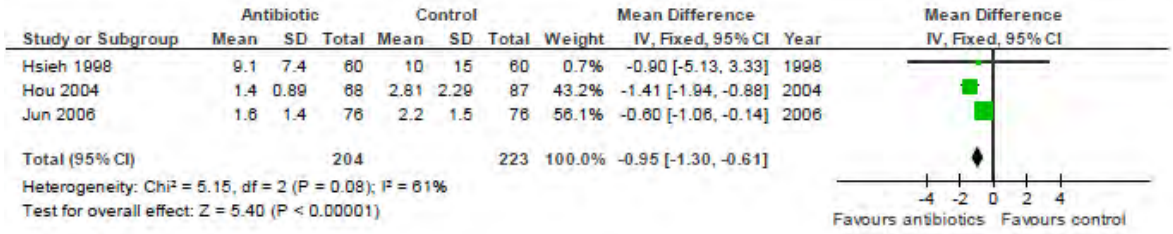


Figure 150: Length of hospital stay

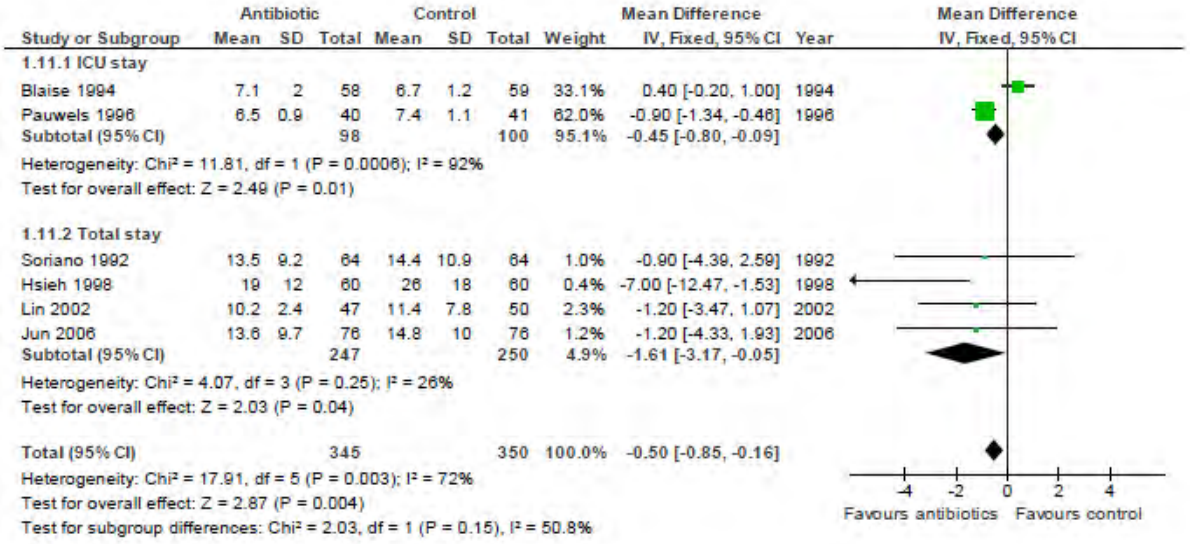


Figure 151: Any infections

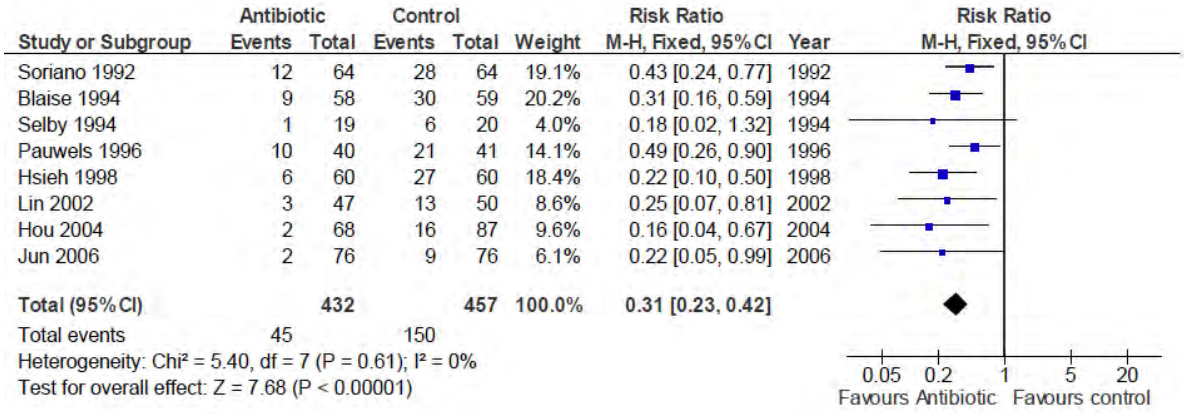


Figure 152: Bacteraemia

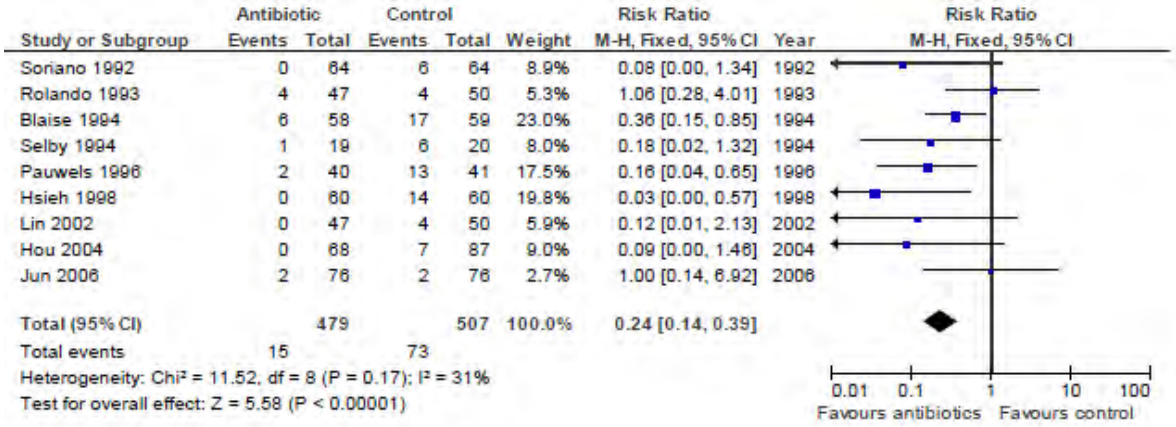


Figure 153: Spontaneous bacterial peritonitis

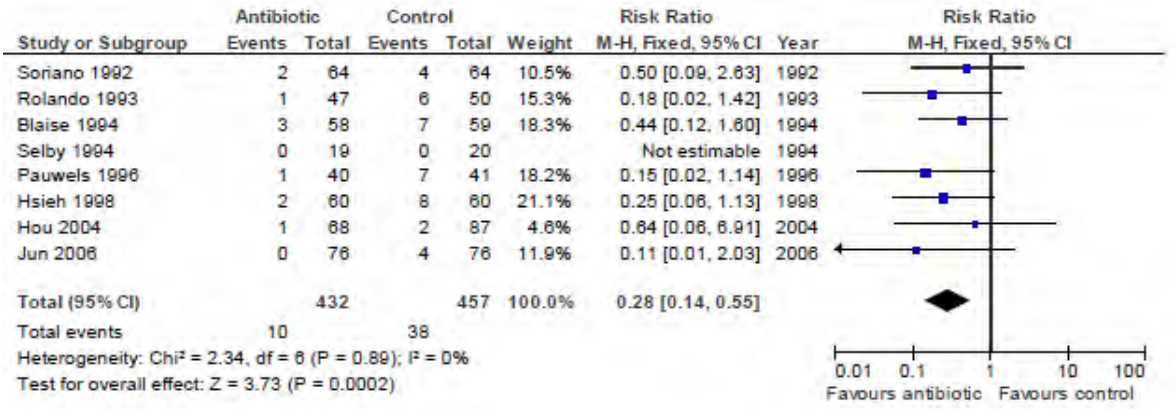
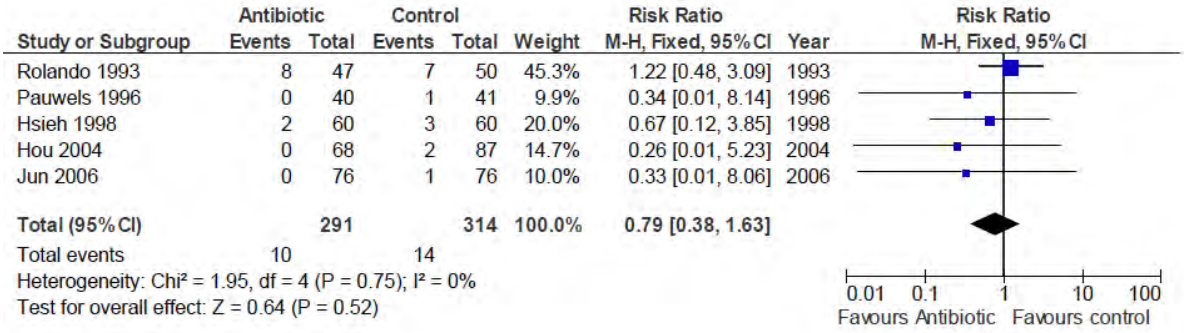
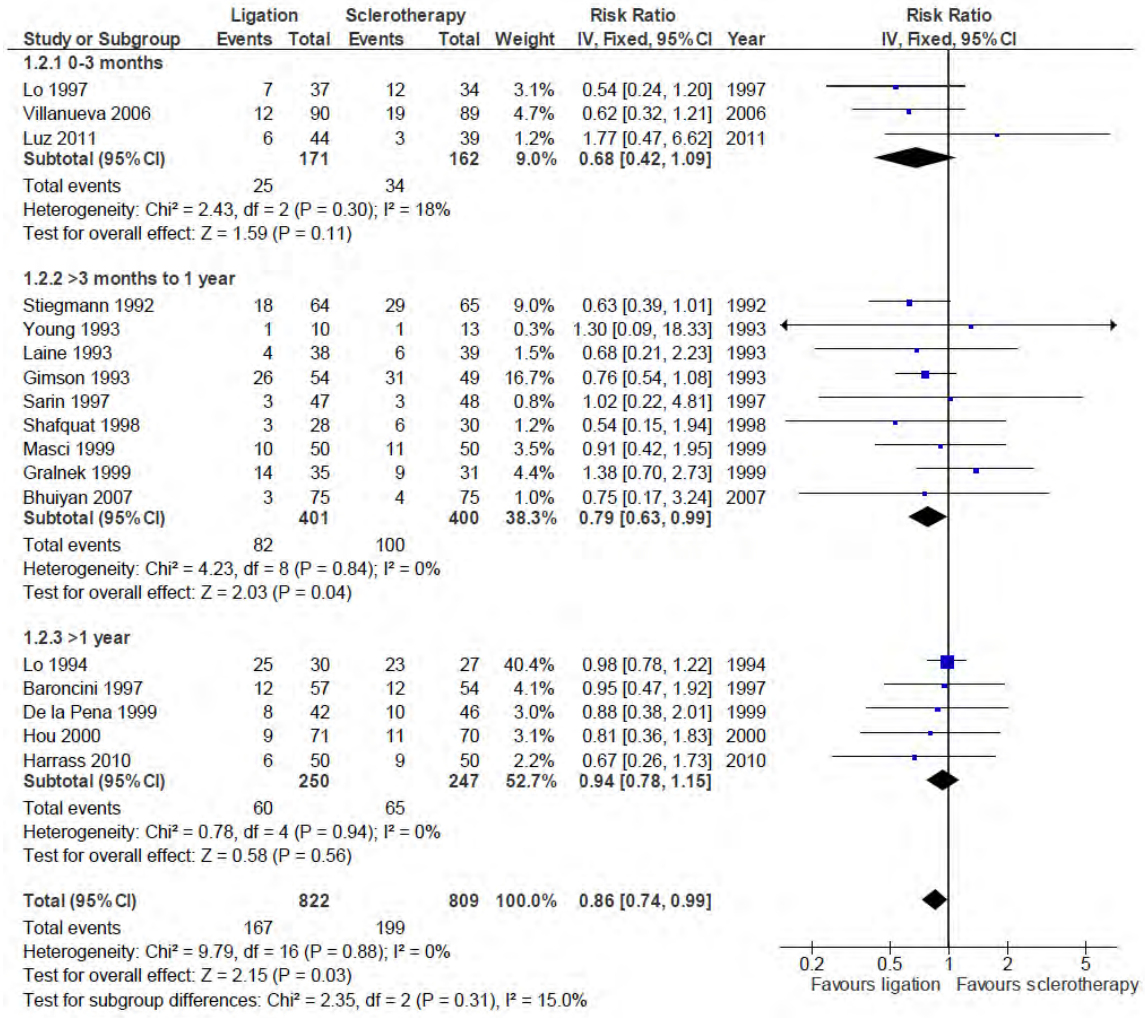


Figure 154: Pneumonia



H.68.3 Banding ligation

Figure 155: Mortality by follow-up period



igure 156: Rebleeding (variable follow-up length up 30 to 1840 days~)

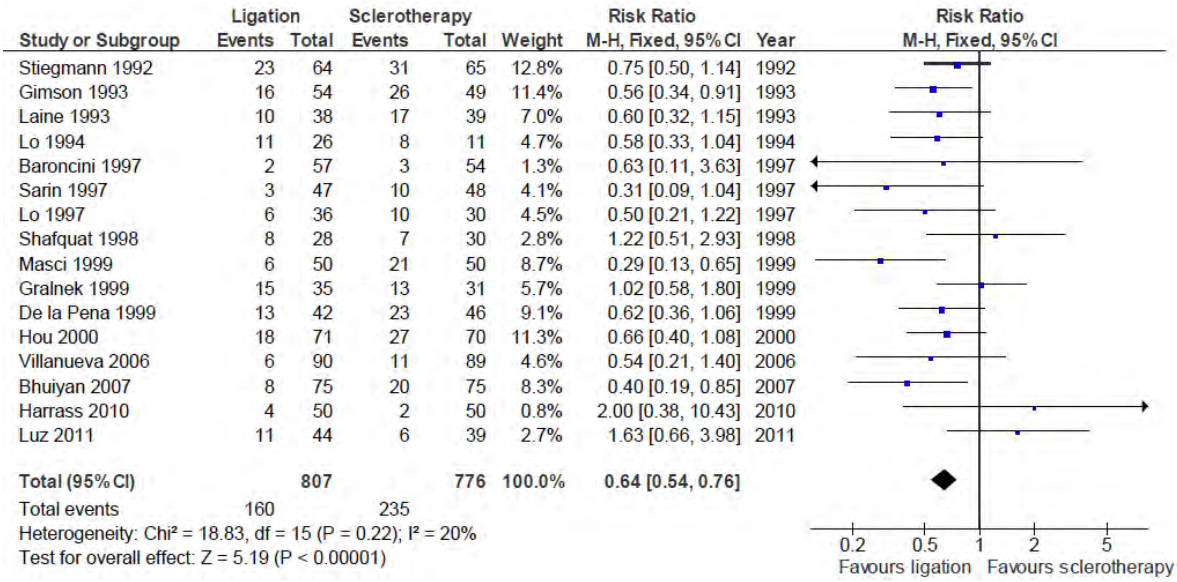


Figure 157: Treatment failure (no initial haemostasis) by severity of cirrhosis

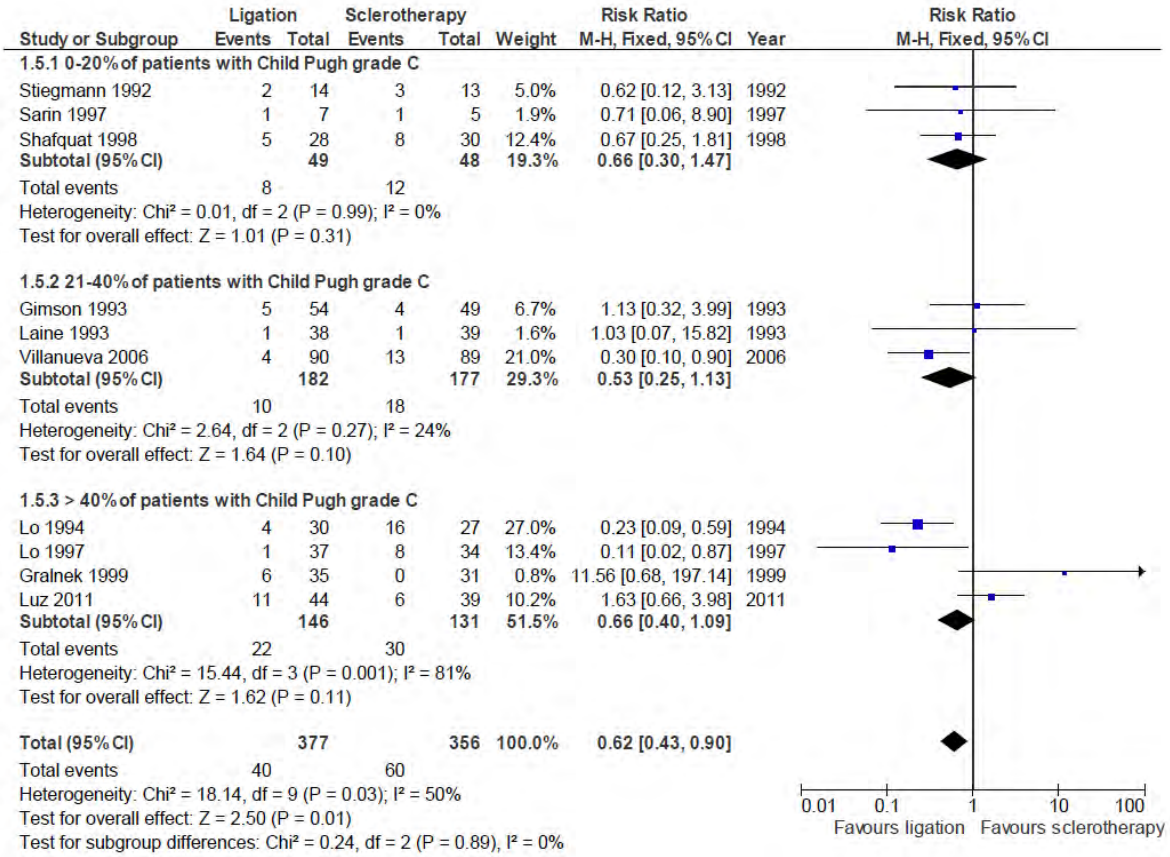


Figure 158: Number of sessions to eradication, by severity of cirrhosis

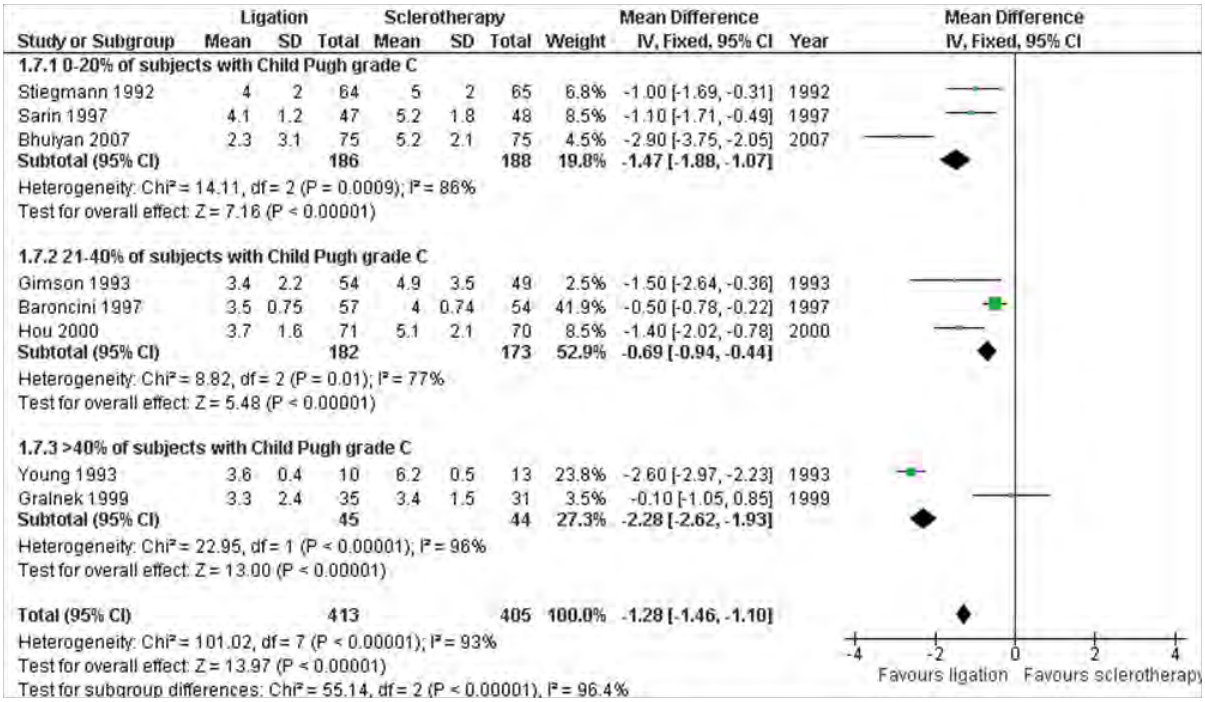


Figure 159: Units of blood transfused, by cirrhosis severity

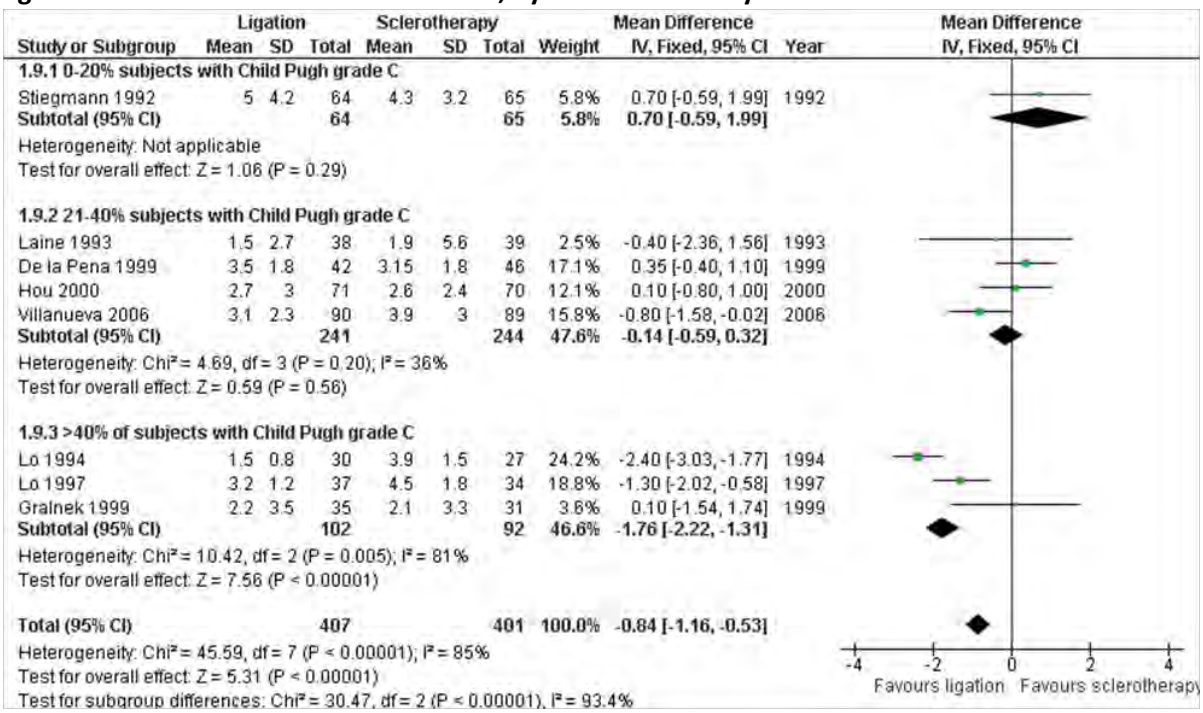


Figure 160: Need for additional treatments

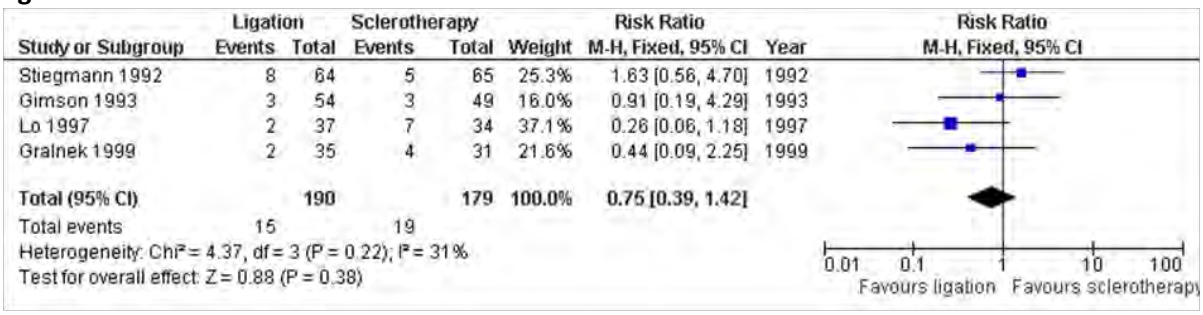


Figure 161: Adverse events leading to death

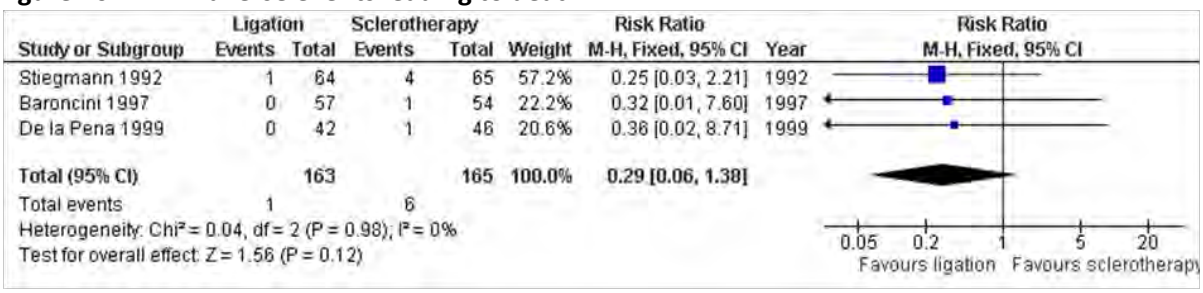


Figure 162: Adverse events - stricture

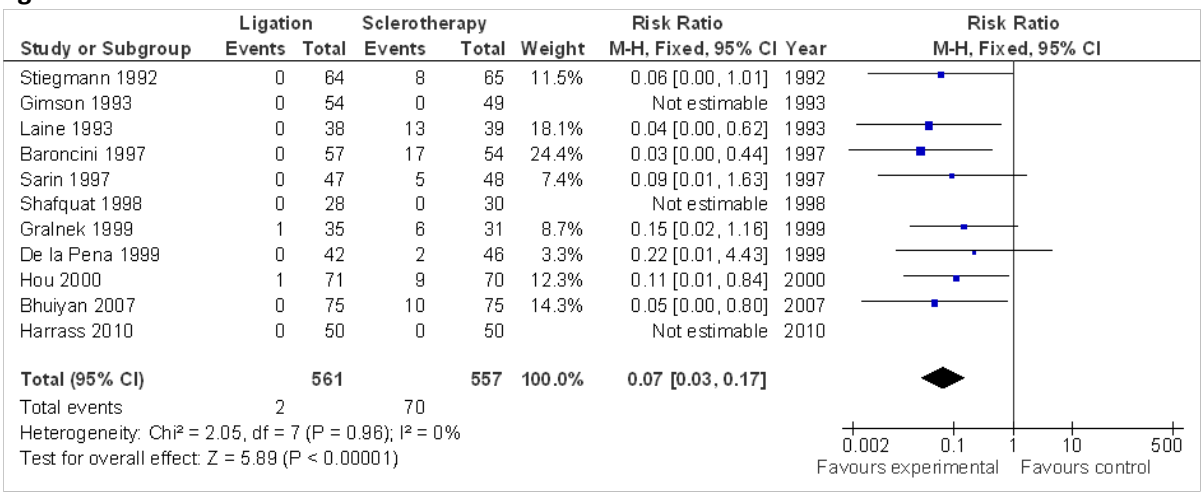


Figure 163: Length of ICU stay

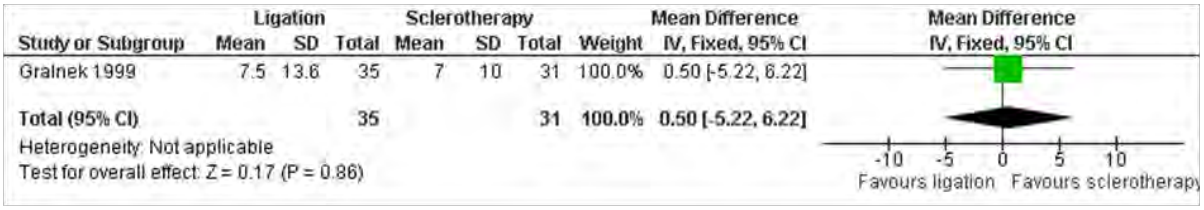


Figure 164: Length of hospital stay outside of ICU

Appendix I: A cost effectiveness model comparing early and late endoscopy in people with acute upper gastrointestinal bleeding

I.1 Introduction

An economic model was developed to assess the cost-effectiveness of four different endoscopy services assumed to facilitate endoscopy within different time limits after presentation of a patient with an acute upper gastro-intestinal bleed.

The clinical review included 3 Randomised Control Trials (RCTs) assessing this question (Table 1). Two of these [10,11] were conducted on stable patients with low-risk, nonvariceal upper GI bleeding. The other [12] was conducted on all patients with nonvariceal upper GI bleeding, including low- and high-risk patients (20% of the patients included in the trial were in shock at baseline). The clinical trials showed no difference in health outcomes (mortality) using early endoscopy compared to late endoscopy in the assessed populations and subpopulations of patients (Table 2).

Table 1: Randomised Control Trials assessing timing to endoscopy.

Study	Population	Early endoscopy	Late endoscopy
Bjorkman 2004 (N=93)	Stable patients with non-variceal UGI bleeding (low-risk)	Within 6 hours of initial evaluation	Within 48 hours of initial evaluation
Lee 1999 (N=110)	Stable patients with non-variceal UGI bleeding (low-risk)	Within 1-2 hours of admission (in the emergency department)	Within 1-2 days of admission
Lin 1996 (N=325)	Patients with peptic ulcer bleeding (low- and high-risk)	Within 12 hours of arrival at the emergency room	More than 12 hours of arrival at the emergency room

Table 2: Mortality outcomes from studies assessing timing to endoscopy

Study	Early endoscopy	Late endoscopy	P Value
Lee 1999	0/56	2/48	P=.54
Bjorkman 2004	0/47	0/46	NS
Lin 1996 (Clear; Coffee ground; Bloody nasogastric aspirates)	0/109; 2/38; 0/15	0/109; 0/39; 1/15	NS

The assessment by Lee 1999 and Bjorkman 2004 of the resource use associated with early versus late endoscopy in low-risk patients showed conflicting results: Bjorkman 2004 concluded that there was no resource use advantage by having earlier endoscopy compared to later endoscopy, and Lee 1999 showed that earlier endoscopy was less costly than later endoscopy (due to the significant reduction in length of hospital stay –Table 3). The reason for this contradiction could be due to the specifics of the methodology used in the trials: in Bjorkman 2004, the decision for discharge after early endoscopy was taken by the attending physician whereas it was the investigator endoscopist in Lee 1999. Therefore, during the Bjorkman 2004 trial, only 9% of patients were discharged by the attending physician compared to the proposed 40% by the investigator endoscopist (in the same trial), and 46% during the Lee 1999 trial. Additionally, in the Lee 1999 trial, unplanned healthcare attendances during the 30-day follow-up period were significantly lower for the early endoscopy

group, and no patients discharged directly from the emergency department suffered an adverse outcome.

Table 3: Lee 1999 resource use (stable patients with nonvariceal upper GI bleeding)

Resource use	Early endoscopy (n=56)	Late endoscopy (n=48)	P Value
Transfusion requirement (units)	1.2 ± 2.4	1.1 ± 1.7	0.44
Hospital stay (median, IQR)	1 (0-3)	2 (2-3)	0.0001
Repeat endoscopy (No, %)	4 (7.1)	4 (7.4)	0.98
Surgery (No, %)	2 (3.6)	1 (1.9)	0.99
Readmission (No, %)	4 (7.1)	8 (14.8)	0.21
Unplanned visits to any physician (No, %)	5 (8.9)	13 (24.5)	0.031

Table 4: Lin (1996): resource use (subgroup of nonvariceal upper GI bleeding patients with bloody nasogastric aspirates; 60% in shock)

Resource use	Early endoscopy (n=15)	Late endoscopy (n=15)	P Value
Rebleeding after endoscopy therapy (assumed as repeat endoscopy) (No, %)	0 (0)	2 (13)	NS
Endoscopy therapy (No, %)	5 (33)	11 (73)	NS
Emergency operation (No, %)	1 (7)	4 (27)	NS
Blood transfusion (ml)	450 ± 465	666 ± 548	<0.001
Days in hospital (Mean)	4 ± 3.5	14.5 ± 10.8	<0.05

Lin 1996 reported results by subgroups of patients (established before randomisation): patients with clear nasogastric aspirates (early n=109, late n=109); patients with coffee-ground nasogastric aspirates (early n=38, late n=39); and patients with bloody nasogastric aspirates (early n=15, late n=15). The proportion of patients in shock per cohort was the following: clear 11%; coffee-ground 36%; bloody 60%. No resource use advantage was shown in patients with a clear or coffee ground aspirate. However, in patients with bloody nasogastric aspirates, early endoscopy resulted in a significantly lower blood transfusion requirement and shorter hospital stay (Table 4).

Current provision of endoscopic services in England means that patients presenting with acute upper gastrointestinal bleed receive an endoscopy more than 24 hours after presentation [13]despite current recommendations by the British Society of Gastroenterologists that endoscopy take place within the first 24 hours [13]. Recommending early endoscopy would involve substantial service reorganisation and the cost of implementing and sustaining an earlier access to endoscopy could be signficant.

The Guideline Development Group (GDG) proposed there could be an economic advantage of early endoscopy; however, considered it was necessary to build an economic model to formally evaluate the trade-offs between clinical outcomes and costs of implementing strategies that would allow a patient to have endoscopy more quickly after an acute upper gastrointestinal bleed. We decided to develop an economic evaluation comparing early versus late endoscopy to assess the potential economic advantage of early endoscopy for the National Health Service (NHS).

I.2 Methods

I.2.1 Model overview

A cost-utility analysis was undertaken where costs and quality-adjusted life-years (QALYs) were considered from a UK NHS and personal social services perspective.

The following general principles were adhered to:

- The GDG was consulted during the construction and interpretation of the model.
- When published data was not available we used unpublished data and expert opinion to populate the model.
- Model assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model employed a cost-effectiveness threshold of £20,000 per QALY gained in the base case.
- The model was systematically checked by an experienced health economist at the NCGC.

A summary of the key assumptions are listed in section I.2.6, and detailed in full in the subsequent sections of this appendix.

I.2.2 Time Horizon and discounting

The time horizon of 28 days was chosen on the pragmatic basis of the data available for the model.

Given that the available evidence presented in the clinical review did not suggest a significant difference in mortality, the time horizon was thought sufficient to capture the incremental costs and benefits associated with each comparator. However, potential limitations of this structural assumption are discussed alongside an exploratory threshold sensitivity analysis in this report. Due to the short time frame neither costs nor QALYs were discounted.

I.2.3 Comparators

A nationwide audit of current practice demonstrates that endoscopy staff are typically available during the working week (9am-5pm) with on-call services at night and the weekend variable. Median time to endoscopy for hospitals without on-call endoscopy services is 25 hours (IQR 14-60), whereas for those with an on-call service it was 22 hours (IQR 10-47) [13].

Based on this information and clinical expert opinion, four implementation strategies were devised to allow for provision of endoscopy within certain timeframes after presentation with an acute upper gastrointestinal bleed:

- **Weekday access to endoscopy:** In this strategy endoscopy staff are on-site on weekdays 8am-5pm. This is assumed to allow access to endoscopy within a similar time interval observed in hospitals that did not record an on-call service in a nationwide UK audit undertaken in 2007.
- **Everyday access to endoscopy:** In this strategy endoscopy staff are on-site on weekdays 8am-5pm and weekends 8am-12pm. This is assumed to allow endoscopy to occur within 24 hours of admission or start of inpatient bleed.
- **Extended everyday access to endoscopy:** In this strategy endoscopy staff are on-site everyday 8am-5pm, and are on call everyday 5pm-12am. This is assumed to allow endoscopy to occur within 12 hours of admission or start of an inpatient bleed
- **Continuous access to endoscopy:** In this strategy endoscopy staff are on site everyday 8am-5pm, and are on call everyday 5pm-8am. This is assumed to allow endoscopy to occur within 4 hours of admission or start of an inpatient bleed

I.2.4 Population

The population entering the model comprised of patients who had experienced an acute upper gastrointestinal bleed presenting either as a new admission or as an inpatient. This group included patients with and without suspected variceal bleeding.

I.2.5 Subgroups

Our estimates of mortality and discharge rate are determined by Rockall score group (see Appendix B) The Rockall score is a tool validated to predict risk of mortality [14,15]. The Rockall score is composed of points given for age, existence of co morbidities and level of shock as detailed in Table 5. We define low risk as having a pre-endoscopy Rockall score of 0-2 and high risk as having a pre-endoscopy Rockall score of 3-7.

Table 5: Components of the Pre Endoscopy Rockall Score

Risk factor	0 points	1 Point	2 points	3 points
Age	<60 years	60-79 years	>80 years	
Level of shock	No shock (SBP≥100mmHG, pulse <100/min)	Tachycardia (SBP≥100mmHG, pulse ≥100/min)	Hypotension (SBP<100mmHG)	
Co morbidity	No major co morbidity		Cardiac failure, IHD or any other major co morbidity	Renal or Liver failure, disseminated malignancy

We present costs and QALYs for each of the strategies for 7 subgroups as defined by Rockall score (Rockall score 0; Rockall score 1; Rockall score 2; Rockall score 3; Rockall score 4; Rockall score 5; Rockall score 6 or 7). However, as the implementation cost of different service structures would cover all Rockall groups we have analysed cost-effectiveness only at the whole population level (and not by subgroup). The evaluation of cost-effectiveness, which did include the implementation cost, was undertaken by aggregating the results for the subgroups, taking into account the proportion of patients you would expect to find with each Rockall score.

I.2.6 Summary of Key Assumptions in the Economic Model

The following is a list of the key assumptions detailed in the below methods sections [ϕ=related sensitivity analyses performed – see I.2.10 for details].

- Increasing staffing level will allow endoscopy to occur earlier as outlined in section I.2.2. ϕ
- The differences in mortality and discharge observed in **Error! Reference source not found.** are determined only by Rockall score, time since endoscopy and time since admission. The timeframe of 28 days is sufficient to capture key differences in resource use associated with different timings of endoscopy subsequent to a presentation of an acute upper gastro-intestinal bleed [see section I.2.7.1]
- Timing of endoscopy does not significantly affect mortality beyond 28 days ϕ [see sectionI.2.7.1]
- Once discharged there is no probability of mortality or further resource use within 28 days [see section I.2.7.1]

  Both death and discharge can take place before endoscopy [see section I.2.7.1].
- We identified the cost of additional staffing as the key differential implementation cost of the four strategies [see section I.2.8.11)

- One medical consultant and one staff nurse (band 5) would need to be available in order to provide endoscopy, which was assumed to take 3 hours to complete while on call (taking into account the time needed to prepare for the endoscopy and travel) [see section 1.2.8.11)
- There would be 8 consultants and 6 nurses on the on call rota, with both members of staff expected to return to site [see section I.2.8.11]

I.2.7 Approach to Modelling

I.2.7.1 Model Structure

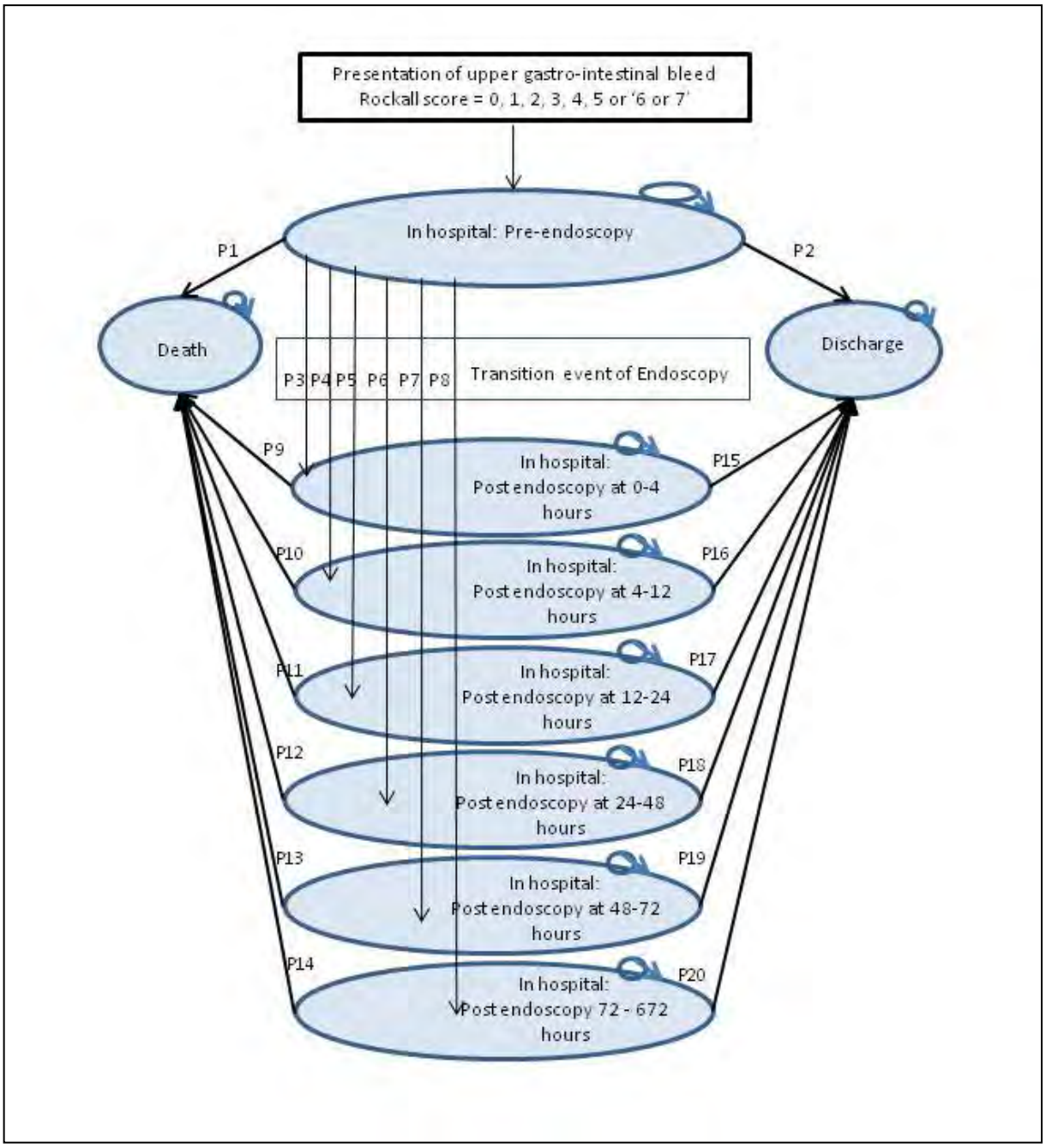
A Markov model was constructed to calculate resource use costs and Quality Adjusted Life Years (QALYs) for each subgroup in each compared strategy over a time horizon of 28 days.

In a Markov model a set of mutually exclusive health states are defined that describe what can happen to the population of interest over time. People in the model can only exist in one of these health states at a time. Possible transitions are defined between each of the health states and the probability of each transition occurring within a defined period of time (a cycle) is assigned to each possible transition.

The number of patients entering the Markov model for each subgroup was in accordance to the proportion the subgroup assumed in the population. In order to assess the cost-utility of implementing the compared strategies for a population, the implementation cost (taking into account the number of patients in the population) was added to the resource costs summed for all subgroups. This total cost was compared to the total number of QALYs achieved by all subgroups.

Figure 1 illustrates the health states in the model and possible transitions between them in each cycle. Note that this is a simplified illustration as it does not show the time dependency associated with each transition probability. Each transition probability is also dependent on Rockall subgroup

Figure 165: Markov model – simplified transition state diagram



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Notes on the transition probabilities (see section I.2.9for further detail): Transition probabilities P1 to P8 are dependent on time elapsed since presentation of the acute upper gastrointestinal bleed and the Rockall score of the subgroup. Transition probabilities (p9 to p20) are dependent on time elapsed to and since endoscopy and the Rockall score of the subgroup.

P1: Probability of discharge before endoscopy dependent on time since admission.

P2: Probability of death before endoscopy dependent on time since admission.

P3 –P8: Probability of having an endoscopy. These are the only transition probabilities that are dependent on the strategy being compared.

P9-P14: Probability of discharge after an endoscopy. These probabilities are conditional on the time to endoscopy and the time elapsed since endoscopy.

P15-P20: Probability of death after an endoscopy. These probabilities will be conditional on the time to endoscopy and the time elapsed since endoscopy.

A one hour cycle duration was used in this model to reflect the potentially quick movement between states assumed possible with having continuous access to endoscopy. All the probabilities, costs

associated with hospital stay and health utilities inputted into the model were converted to reflect the one hour cycle length in the model.

The model was run for repeated cycles, and the time spent in each health state was calculated. By attributing costs and quality of life weights to the time spent in each health state, total resource costs and QALYs can be calculated. Secondary outcomes recorded in the model were mortality, number of endoscopies, number of discharges, length of stay in hospital and time at home. The model was run for 672 cycles in order to calculate costs and QALYs over the 28 day horizon.

From the first cycle until the cycle in which a patient has an endoscopy, a patient may die, be discharged, continue to wait in hospital in a pre-endoscopy state, or have an endoscopy and thereby move to a post endoscopy state. It was assumed that whilst death and discharge could occur throughout a cycle. Patients could only move to a post endoscopy state at the end of the cycle, thereby allowing death and discharge to occur within the first hour before endoscopy. Once a patient has moved to a post endoscopy state; each cycle thereafter patients may either die, be discharged or continue to stay in hospital.

A one off cost is associated with each patient that has an endoscopy. The cost of performing the endoscopy is not assumed to change in regard to its timing or to the risk level of the patient. A different cost is applied to the length of stay in hospital before endoscopy and after endoscopy. This is reflective of the different expected resource use, as recorded by NHS reference costs. Time spent in hospital before and after endoscopy is associated with the same quality of life. In case of death, the patient remains in the dead health state which is associated with no cost and a Health Related Quality of Life (HRQoL) equal to 0. In the case of discharge, the patient is assumed to go home and live for the remainder of the time horizon at no cost, but with a higher HRQoL score than if they were in hospital.

For each strategy the expected healthcare resource costs and expected QALYs were calculated by estimating the costs and quality adjusted hour for each state and then multiplying them by the proportion of patients who would be in that state as determined by the differing transition probabilities associated with the strategy taken. Quality adjusted hours were converted into quality adjusted life years.

The basecase analysis assumed 300 patients would present with acute upper gastrointestinal bleeding per year, which equates to a mean of 23 patients presenting in any 28 day period. The accrued QALYs and costs associated with length of stay and endoscopy throughout the model were summed. The cost of the level of staffing required to implement each strategy for 28 days was added to this subtotal. The total costs and QALYs for a strategy were divided by the number of patients in the model, allowing an average cost and QALY per patient to be calculated. Comparing these results allows us to identify which strategy is the most cost-effective.

I.2.7.2 Uncertainty

The model was built probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run repeatedly – 10,000 times for the base case and 5000 times for each sensitivity analysis – and results were summarised. The number of simulations used was chosen considering the Monte Carlo error of the incremental costs, QALYs and net monetary benefit using methods as described by Koehler et al[16]. It was set to ensure that the Monte Carlo error was not more than 5% of the standard error for each of these outcomes in all analyses, with the base case having an improved accuracy due to the greater number of simulations.

The way in which distributions are defined reflects the nature of the data, so for example costs were given a gamma distribution, which is bounded by zero and positively skewed (reflecting that costs are not negative, and have the potential to be very high in a few cases). All of the variables that were probabilistic in the model and their distributional parameters are detailed in Table 6 and in the relevant input summary tables in section I.2.8.1.

Table 6: Description of the type and properties of distributions used in the probabilistic sensitivity analysis

Parameter	Type of distribution	Properties of distribution
Death and discharge transition rates		Derived from statistical model. Poisson distributions were assumed for the number of deaths and discharges over the time periods in the statistical model.
Costs of length of stay.	Gamma	Bounded at 0, positively skewed. Derived from mean and its standard error. Alpha and Beta values were calcaulated as follows: $Alpha = (mean/SE)^2$ $Beta = SE^2/Mean$
Utility	multivariate lognormal distribution	Bounded at 0 and capped at 1. Derived from log of the utility score and its standard error. Cholesky decomposition keeps correlation between utility applied in hospital and at home
Probability of being in a particular subgroup / presenting at a particular time	Dirichlet;	Fitted to multinomial data. Represents a series of conditional distributions, bounded on 0-1 interval.
Probability of having a therapeutic or diagnostic endoscopy	Beta	Bounded between 0 and 1. Derived by the number of patients in the sample and the number of patients having therapeutic endoscopy.

For simplicity the following variables, were left deterministic (i.e. were not varied in the probabilistic analysis): cost-effectiveness threshold (which was deemed to be fixed by NICE), probability of endoscopy (which was assumed dependent upon strategy), the number of expected presentations per year, the cost of endoscopy, and the time and cost of staff required to implement each strategy.

In addition, various deterministic sensitivity analyses were undertaken to test the robustness of model assumptions and data sources. In these one or more inputs were changed and the model rerun to see the impact on results (see I.2.10 for more detail)

I.2.8 Model Inputs

I.2.8.1 Summary table of model inputs

Model inputs were based on a statistical analysis of national registry data, national reference cost data and supplemented by additional sources as required. Model inputs were validated with clinical members. A summary of the model inputs used in the base-case (primary) analysis is provided in Table 7. More details about sources, calculations, probability distributions and rationale for selection can be found in the sections following this summary table.

Table 7: Summary of base case model inputs (ϕ= parameter subject to sensitivity analysis)

Parameter	Deterministic value	Distribution	Source
Cohort Settings			
Probability of presenting with a pre-endoscopy Rockall score of ϕ:			
Rockall score 0	0.18	Dirichlet	Patient-level data from audit
Rockall score 1	0.16		
Rockall score 2	0.14		
Rockall score 3	0.16		
Rockall score 4	0.19		
Rockall score 5	0.11		
Rockall score 6 or 7	0.06		
Number of expected upper GI bleeds per year ϕ:	300	n/a	Expert opinion, provider data
Probability that an upper GI bleed patient will present in the following times:			
Weekday: 12am - 6am	12%	Dirichlet	Patient-level data from audit
Weekday: 6am - 7am	2%		
Weekday: 7am - 8am	1%		
Weekday: 8am - 5pm	37%		
Weekday: 5pm -7pm	8%		
Weekday: 7pm - 8pm	4%		
Weekday: 8pm -12 am	11%		
Saturday: 12 am - 8am	3%		
Saturday: 8am – 12pm	2%		
Saturday: 12pm – 5pm	3%		
Saturday: 5pm - 12am	3%		
Sunday: 12 am - 8am	3%		
Sunday: 8am – 12pm	2%		
Sunday: 12pm – 5pm	4%		
Sunday: 5pm - 12am	5%		
Utility Weights ϕ			
Applied to time spent in hospital subsequent to GI bleed	0.60	multivariate lognormal	[17]
Applied to time spent at home subsequent to GI bleed	0.80		[17]
Percentage of patients assumed to have had therapeutic intervention at endoscopy (the compliment of which were assumed to have diagnostic endoscopy only)			
Rockall 0	11%	beta	Patient-level data from audit
Rockall 1	18%	beta	Patient-level data from audit

Parameter	Deterministic value	Distribution	Source
Rockall 2	22%	beta	Patient-level data from audit
Rockall 3	25%	beta	Patient-level data from audit
Rockall 4	25%	beta	Patient-level data from audit
Rockall 5	36%	beta	Patient-level data from audit
Rockall 6 and 7	39%	beta	Patient-level data from audit
Costs associated with health states and transition events [NB: these costs vary depending on Rockall subgroup, for information the proportion of diagnostic and therapeutic procedures used here is the average across all Rockall scores] **ϕ**.			
Cost applied to health states in first 24 hours of hospital stay			
Pre-endoscope state	£403.29	gamma	Calculated from NHS reference cost[18]
Post endoscope states	£372.25	gamma	Calculated from NHS reference cost[18]
Daily cost applied to health states in after 24 hours of hospital stay			
Pre-endoscopy state (Rockall Score 3-7)	£283.98 (£206.79 applied as excess bed day)	gamma	Calculated from NHS reference cost[18]
Pre-endoscopy state (Rockall Score 0-2)	£256.56 (£211.21 applied as excess bed day)	gamma	Calculated from NHS reference cost[18]
Post endoscope states	£353.23 (£238.16 applied as excess bed day)	gamma	Calculated from NHS reference cost[18]
Cost of endoscopy ϕ			
Endoscopy (all Rockall scores)	£100.85	n/a	Calculated from NHS reference cost[18]
Implementation costs (annual)			
Weekday access (Weekdays 8am-5pm):	£184,211	n/a	Calculated from values given in [19]
Extended access to endoscopy (Weekdays 8am-5pm, Weekends 8am-12pm)	£234,248	n/a	
Extended access to endoscopy (everyday 8am-5pm onsite, 5pm-12am on call),	£368,896	n/a	
Continuous access to endoscopy (everyday 8am-5pm onsite, 12am-8am and 5pm-12am on call)	£387,478	n/a	
Staff resource use and costs			
Allowance for sickness and	20% of basic	n/a	Assumed

Parameter	Deterministic value	Distribution	Source
holidays	salary		
Time required to complete on call endoscopy	3 hours of nursing time, and 1 programmed activity of consultant time.	n/a	Expert opinion
Nurses			
Normal working hours per week	37.5	n/a	[19]
Band 5 - median annual salary	£24,700	n/a	[19]
NHS staff percentage enhancements for all time on Saturday (midnight to midnight) and any week day after 8pm and before 6am	1.3	n/a	[20]
NHS staff percentage enhancements for all time on Sunday and public holidays.	1.6	n/a	[20]
Number of nurses (band 5) on the rota	6	n/a	Expert opinion
Annual salary percentage enhancement for on call agreement	4.5%	n/a	[20]
Percentage enhancement for time worked whilst on call	1.5	n/a	[20]
Consultants			
Normal working hours per week	40	n/a	[19]
Median annual salary	£89,400	n/a	[19]
Percentage enhancement for work in premium time	Programmed activity costed at 3 hours	n/a	[21]
Number of consultants on the rota	8	n/a	Expert opinion
Annual salary percentage enhancement for on call agreement	5%	n/a	[21]
Transition probabilities			
Transition probabilities to death state	Time dependent and stratified by subgroup – please see Appendix J.3 for tables of rates applied.	Numbers of death and discharges assume a Poisson distribution in a competing risks model	Patient-level audit data
Transition from pre-endoscope states to post endoscope states ϕ	Time dependent and stratified by subgroup – please see	n/a	Patient-level audit data and assumptions inherent in

Parameter	Deterministic value	Distribution	Source
	section I.2.9.2		strategies compared.

I.2.8.2 The UK Comparative Audit of Upper Gastrointestinal Bleeding and the use of Blood.

Many of the model inputs, including the rates of mortality, discharge, endoscopy, and baseline population characteristics were informed by data collected by a national prospective audit sponsored by The British Society of Gastroenterologists and the National Blood Service.

The estimates used in the economic model were calculated directly from the patient-level dataset, which was provided in full and initially analysed in PASW Statistics 18 (SPSS) 2009. In total, details for 6750 patients were recorded, each with a Rockall score which was either assigned prospectively or retrospectively calculated by a clinician. Details of the audit population and method have been previously reported [13, 22]. The manner in which the audit was used to inform selected model parameters is given in the relevant sections below. Details of data selection and the methods used to calculate the rates of death and discharge is reported in Appendix J.

I.2.8.3 Probability of presenting with a certain pre-endoscopy Rockall score

The probability of presenting with a specific pre-endoscopy Rockall score was estimated using all the records in the national UK registry data. This was calculated by dividing the total number of patients in the audit with a particular Rockall score by the total number of patients in the audit. The number of patients in the model population was multiplied by the probability to give an estimate of the mean number of patients you would expect to present in each subgroup per year, and this was converted to the number you would expect in 28 days. Table 8 details the number of patients for each subgroup entering the model in the base case given 300 presentations of acute upper GI bleed expected in 28 day time horizon of the model.

Table 8: Proportion of patients in each subgroup, as determined by the proportion of patients in the audit with each Rockall score.

Subgroup	Number of patients in audit.	Deterministic Probability	No. of expected presentations per 28 days in the base case.
Rockall 0	1240	0.18	4.23
Rockall 1	1065	0.16	3.63
Rockall 2	946	0.14	3.23
Rockall 3	1088	0.16	3.71
Rockall 4	1257	0.19	4.29
Rockall 5	757	0.11	2.58
Rockall 6 or 7	397	0.06	1.35
Total	6750		23.01

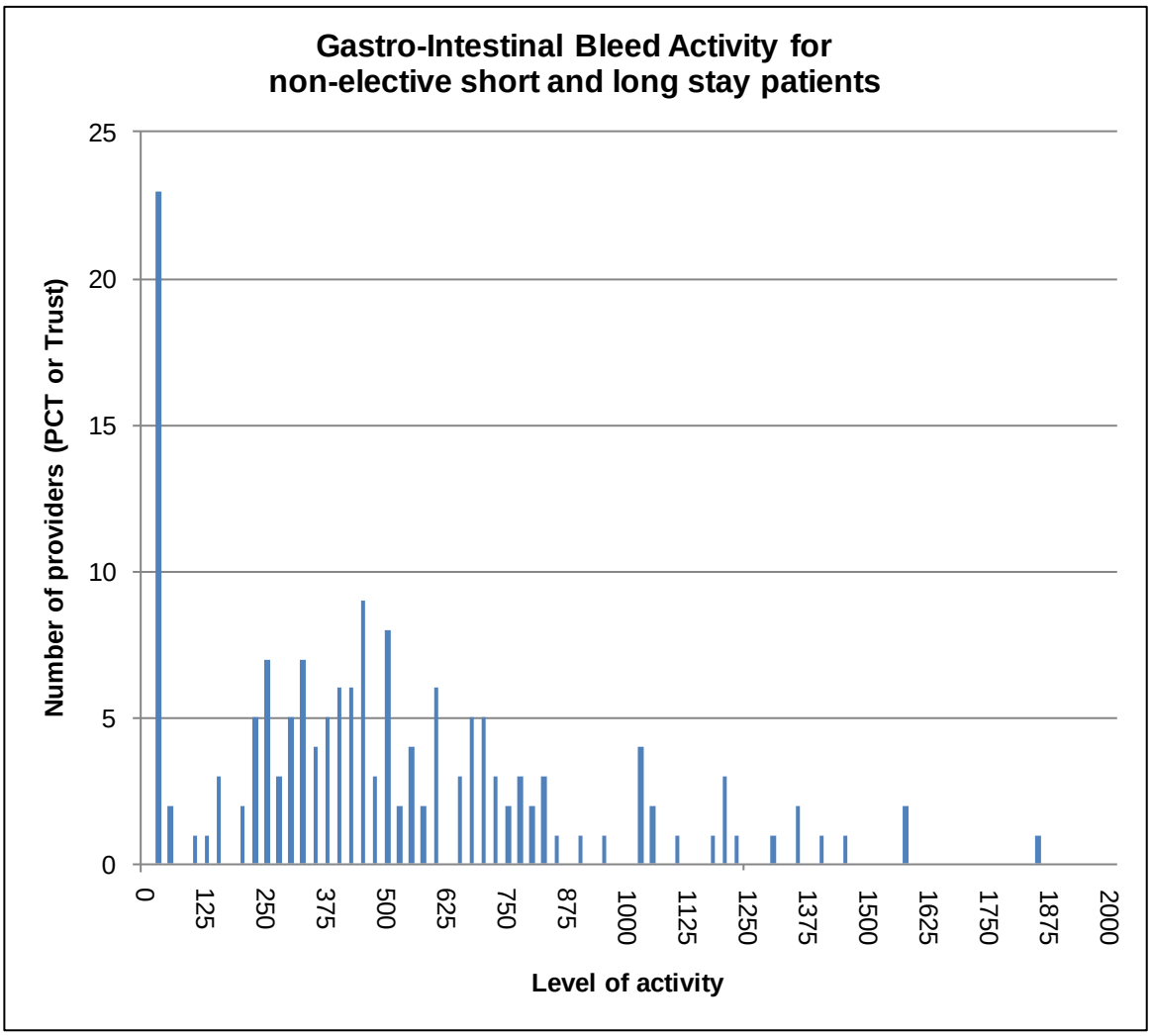
In the probabilistic analysis, a Dirichlet distribution was fitted using the expected proportion of patients presenting in any one subgroup. This parameter was explored in a sensitivity analysis by altering the number of expected patients in each subgroup.

I.2.8.4 The number of upper GI admissions requiring endoscopy.

As the national registry did not require the participating providers to report on more than 60 presentations in a three month period, NHS reference cost activity data was consulted to estimate the relevant level of activity per provider, per year[23].

The NHS reference cost database identified 165 healthcare providers of gastro- intestinal services reporting 78195 units of activity. These were identified using the HRG codes of FZ30Z, FZ290Z, FZ308 DE&F, but only considering non-elective inpatient activity (i.e. excluding activity associated with outpatient procedures). The mean level of activity per provider per year was 480 and the median was 434. Figure 2 shows that the level of activity associated with gastrointestinal bleeding per provider has a large range, with many of the providers having less than 50 gastrointestinal bleed related admissions per year. However, other providers report much greater activity levels, with 32 providers reporting over 750 units of activity per year.

Figure 166: Frequency of Gastro-Intestinal Bleed Activity Level experienced by Health Providers



Source: NHS reference costs 2009-2010 appendix: DBRC organisation-specific reference cost data[23]

Given that not all of the reported activity will be an acute upper gastrointestinal bleed, for example the HRG codes used also include lower gastrointestinal bleed, the base case assumed that an average provider might expect 300 presentations of acute upper gastrointestinal bleed per year. This was supported by an estimate based on admission data collected by ORMIS as well as a local audit of services provided in the Royal Bolton Hospital.

Given the large range of activity level per provider, to explore the impact of a provider's activity level on the cost effectiveness of the four strategies, the number of expected patients presenting with an acute upper GI bleed was examined in a sensitivity analysis.

I.2.8.5 The time of presentation of patients with an acute upper gastrointestinal bleed.

It was assumed that the time of presentation followed the same distribution as recorded by the national audit data registry. All records that gave a time of presentation were used. This allowed an estimation of the mean number of presentations requiring endoscopy that fell out of the normal working day (8am-5pm), as outlined I Table 9. The time periods presented in Table 9 are categorised according to unsocial hours or premium time, as determined by NHS and consultant terms, conditions and contracts (see section I.2.8.12) In the probabilistic analysis, a Dirichlet distribution was fitted using the expected proportion of patients presenting in any one time frame.

Table 9: The number and time of an upper gastrointestinal bleed activity requiring endoscopy.

Time period	Number of upper GI bleeds (audit)	%
Weekday		
Between 12am and 6am	762	12%
Between 6am and 7am	123	2%
Between 7am and 8am	86	1%
Between 8am and 5pm	2346	37%
Between 5pm and 7pm	502	8%
Between 7pm and 8pm	231	4%
Between 8pm and 12am	717	11%
Total number of upper GI bleeds occurring on a weekday	**4767**	**75%**
Saturday		
Between 12am and 8am	163	3%
Between 8am and 12pm	142	2%
Between 12pm and 5pm	200	3%
Between 5pm and 12am	215	3%
Total number of upper GI bleeds occurring on a Saturday	**720**	**11%**
Sunday		
Between 12am and 8am	172	3%
Between 8am and 12pm	151	2%
Between 12pm and 5pm	277	4%
Between 5pm and 12am	303	5%

Time period	Number of upper GI bleeds (audit)	%
Total number of upper GI bleeds occurring on a Sunday	**903**	**14%**

I.2.8.6 Quality of Life (utilities)

The Quality Adjusted Life Year (QALY) is a measure of a person's length of life weighted by a valuation of their Health Related Quality of Life (HRQoL) over that period. Utilities are a measurement of the preference for a particular health state, with a score ranging from 0 (death) to 1 (perfect health).

Determining the quality of life associated with an acute condition can be difficult as it may involve a state worse than death, and therefore is also controversial. To inform the utility of the time spent in the model; a search of the economic and quality of life literature identified utilities and disutilities which have been used in previous economic evaluations regarding acute upper GI bleeding. The findings from this search are presented in Table 10.

Table 10: Estimates of utilities associated with upper GI bleeding

Clinical Event	Utility of health state (0-1)	Notes	Source
Non Variceal Bleeding			
QoL at home after acute gastrointestinal bleed	0.78 (0.70 – 0.85)	Quality of Life based on the EuroQol 5 Dimension questionnaire scores of 57 UK patients surviving a UGI bleed, the majority of whom had Proton Pump Inhibitor administered. The questionnaire was given at discharge or a maximum of 7 days post the gastrointestinal bleed, and a follow up questionnaire was administered at 4 weeks. Patients with oesophageal variceal bleeding or critically ill were excluded. The female to male ratio of respondents was 22:35	17
QoL in hospital after acute gastrointestinal bleed	0.45 (0.34 – 0.57)		
Acute gastrointestinal bleed caused by peptic ulcer(a)	0.27 (based on 5 days with a disutility of -0.01 (95% CI:0-0.01) (b)	Utilities elicited from USA patients on chronic acid suppression for peptic ulcer or ulcer like dyspepsia (n=73). The value of health events such as perforation or gastronintestinal bleed were determined by calculating the number of QALYs a patient would exchange to avoid one adverse event. Distributions for event disutilities were highly skewed with 32% of patients unwilling to trade any life expectancy to avoid complication. Fewer than half of the patients had experienced a complication from a previous ulcer. Among the remaining patients the number of QALYs a patient would give up to avoid a GI bleed ranged between 0.01-12.41 QALYS. The median disutility associated with GI bleeding was 0.01 (95% Confidence Interval: 0-	24
Inpatient treatment for uncomplicated ulcer haemorrhage	0.49 (based on 2 days with a disutility of -0.003)		24-26
Inpatient treatment for complicated ulcer haemorrhage	0.46 (based on 8 days with a disutility of -0.01)		24-26
Inpatient treatment for ulcer haemorrhage and surgery	0.46 (based on 11 days with a disutility of -0.016)		24-26

Clinical Event	Utility of health state (0-1)	Notes	Source
		0.01).	
- Upper endoscopy - Gastrointestinal haemorrhage requiring hospitalisation - Inpatient treatment of complicated ulcer - Inpatient treatment of complicated ulcer requiring surgery	0.5675 0.5 0.4902 0.4642	Utilities used for an economic evaluation exploring Proton Pump Inhibitors in acute peptic ulcer bleeding Utilities quoted from a USA source – Teng and Wallace. One thousand health related quality of life estimates. Med care 2000:38:583-637	27
Major upper GI bleed episode	0.39	Derived from evidence which main focus was on atrial fibulation or stroke rather than gastrointestinal bleeding	28
Variceal Bleeding			
Decompensated cirrhosis with variceal bleeding	0.24 – 0.440	Utilities elicited from USA cirrhotic patients (n=114) and hospital staff (n=83). The questionnaire was based on the time trade off method. The utility doctors assigned to this health state ranged between 0.24-0.28. The utility patients assigned this health state ranged between 0.35-0.44	29
Patients with no bleeding oesophageal varices During bleeding episode Post TIPS Post salvage therapy	0.75 0.56 0.56 0.375	Based on Younossi et al. (2001) and determined by patients with chronic liver disease. Based on expert opinion	30
Baseline TIPS (1 year) Baseline Distal splenorenal shunt (1 year)	0.64 (0.61-0.68) 0.62 (0.58-0.65)	Used SF6D. Reported a lower QoL score for those who died (0.56 and 0.57).	31
Variceal haemorrhage in cirrhotic patients	25% utility toll (0%-80%)	Via consensus.	9
Bleeding episode of variceal bleed Post bleed no TIPS required Post TIPS no re-bleeding	0.30 (0.20-0.50) 0.63(0.50 – 0.75) 0.6 0(0.50-0.7)	Estimated from published sources.	32

Abbreviations: TIPS = Transjugular intrahepatic portosystemic shunt; QoL = Quality of life

(a) A gastrointestinal bleeding event was described as having the following characteristics: Vomiting blood prompts emergency room visit, Blood transfusion and endoscopy performed, two days in intensive care unit, nasogastric tube for 2 days, 3 days in regular hospital bed with restricted diet, daily medication for at least 2 months.

(b) The utility is based on 5 days in hospital associated with the GI bleed as described above (2 days in intensive care and 3 days in regular hospital bed).It was calculated from the presented disutility using the following formula: disutility in QALYs = (1-utility in health state)(duration of health state in days)/365 days*[25]

The preferred method for determining utilities for NICE economic evaluations is the EuroQoL (EQ-5D) questionnaire[33]. The EQ-5D comprises five dimensions of health: mobility, ability to self-care,

ability to undertake usual activities, pain and discomfort, and anxiety and depression. For the NICE reference case, preferences from the general public should be used.

In keeping with the NICE reference case, quality of life weights (utilities) applied to patients in the model were based on the findings from Leontiadis et al.2007[17]. These authors used the EQ-5D questionnaire to ascertain a quality of life score for 57 UK patients that had experienced an upper gastrointestinal bleed. The questionnaire was given to patients at discharge or at 7 days (which ever was sooner) and at 4 weeks follow up. The authors provide details of the method and the patient-level data in an appendix.

In the deterministic analysis, the model uses the mean value of the data presented by Leontiadis et al [17] at seven days or at discharge for the utility weight applied to patients in hospital, and the mean value of the data presented at 4 weeks follow up for the utility weight applied to patients who have been discharged and are at home. Quality of life weights (utilities) were applied to each hour a patient was in hospital or at home and are detailed in Table 11. A sensitivity analysis explored the impact putting the upper and lower extreme values found in the literature would have on results (i.e. the greatest difference found in the quality of life between being in hospital and at home. The impact of having half the quality of life in hospital than at home , as well as having no difference and full quality of life at home and in hospital (a utility of 1 applied to all states), was also explored.

For the probabilistic analysis, the correlation between the utility scores given in hospital and post discharge were preserved by sampling from a multivariate lognormal distribution, using a Cholesky decomposition[34]. A cholesky decomposition is a standard method for sampling values from a multivariate lognormal distribution by generating independent random normal samples and inducing correlations using covariance estimates. To calculate the parameters of the multivariate lognormal distribution, all the utilities for pre and post utility scores were transformed to the natural log scale, and their mean, standard error of the mean and covariance were calculated in Microsoft Excel. If any utility value was missing from a pair of values recorded for a patient, both the pre and post discharge utility for that patient was excluded from the covariance and correlation calculations. In total 3 of 56 utility pairs were excluded. The sample was capped at 1 to ensure all selected utilities were bounded between 0 and 1. As there were several utility values recorded as 1.0, we were unable to derive a distribution for utility decrements as per standard methods[34] and therefore had to sample from a distribution of the utilities.

Table 11: Utility weights applied in the model (Source: Leontiadis et al.2007[17])

Event	Deterministic	Distribution	Characteristics of the dataset used to generate values for the probabilistic sensitivity analysis.			
			Mean	Variance	Covariance	Correlation
Time spent **in hospital** subsequent to GI bleed	0.60	multivariate lognormal distribution using a Cholesky decomposition	0.62 [a]	0.058	0.026	0.722
Time spent **at home** subsequent to GI bleed	0.80		0.80	0.023		

(a) Note that the full dataset was used to calculate the mean which was used in the deterministic base case analysis. Missing utility for time spent at home for some patients meant that the dataset used for the Cholesky decomposition was smaller, hence a different mean is reported for this smaller dataset.

I.2.8.7 Resource Use and Costs

Costs are associated with the health states (in hospital pre endoscopy, in hospital post endoscopy), transitional events (endoscopy) and with the strategy employed (staff required to implement the strategy). Both the cost of being in a health state and the cost of the procedure itself were estimated from NHS reference costs[18]. NHS reference costs are reported for different Health Resource Groups (HRGs), with each HRG covering clinically similar diagnoses or procedures thought to also have similar resource use and costs. In some cases, there will be a different expected resource use for the same HRG code depending whether or not the patient has a complication or comorbidity (CC), for which different unit costs are reported.

The HRG code, description and associated unit cost used in the analysis are detailed in Table 13. For all health state costs, the estimated cost was converted into an hourly cost before being applied in each hourly cycle in the model.

The cost of the first day in hospital is greater than days thereafter, with the average daily cost in hospital decreasing with increasing length of stay. To reflect this, three costs for the length of stay were applied. For the first 24 cycles (hours) of the model, the average hourly cost was derived from the non elective patient short term stay data (length of stay of 1 day). Thereafter non-elective patient long term stay data was used to derive the average hourly cost from 24 hours until the NHS trim point[a] had been achieved. In order not to double count the first day in hospital, the duration and cost of the first day were subtracted from the average length of stay and unit cost before the average cost per hour was calculated. This method ensured that the average of the NHS reference cost was applied for the average length of stay reported for the NHS reference cost code. The cost of the excess bed day for the relevant code was applied from the trim point until discharge, death or the completion of the time horizon as appropriate.

In the probabilistic analysis, a gamma distribution was fitted to all the NHS reference unit costs by manually adjusting the standard error of the mean until the interquartile range of the distribution best matched that reported for the unit cost. A gamma distribution was chosen so that the distribution was constrained at zero (to avoid negative costs) and reflect the positive skew normally seen in cost data. The unit cost selected at random from the gamma distribution then fed into the calculations detailed below

The cost of the endoscopy procedure itself was applied with each transition from a pre-endoscope state to a post-endoscope state. This cost remained fixed throughout all analyses.

The cost of the strategy implementation was estimated using sources such as the PSSRU, and NHS employer handbooks and contracts [19-21]. It was assumed that the key implementation cost would arise due to the additional staff hours required to implement the strategies. More detail is provided in section I.2.8.11.

I.2.8.8 Cost of being in hospital prior to endoscopy (the pre-endoscope state)

Reference cost data is available from patients who have had a gastro-intestinal bleed and have not had a procedure (HRG code FZ38). Non elective short term stay data (hospital stay 1 day or less) was was applied to all patients in pre-endoscope states for the first 24 hours (cycles)(FZ38F).

Where these pre-endoscope patients stay for two days or more, reference cost data is collected and provided separately for patients with and without complications and comorbidities (CC), as there is

[a] Elective and non-elective inpatient NHS reference costs exclude the costs of bed days that fall outside nationally set lengths of stay, known as trim points. (NB These are different to the trimpoints used for the Payment by Results tariff) . Costs beyond the trim point are separated and their mean is the average cost of an excess bed day. The trimpoint is calculated as follows: Upper Quartile + (1.5 * Inter Quartile Range) [35]

expected to be differential resource use in these subgroups.As one could expect a patient with Rockall score 3 and above to have at least one major co morbidity, costs derived from the HRG code FZ38D (with CC) were applied to the preendoscope state for patients with Rockall scores 3-7. Costs derived from the HRG code FZ38E (without CC) were applied to the pre endoscope state for patients with Rockall scores 0-2. These costs were applied from 24 hours until the NHS reference cost trim point was reached (18 days for code FZ38D and 10 days for FZ38E[36]), with the cost of the excess bed day being applied thereafter.

I.2.8.9 Cost of Endoscopy

The cost of endoscopy was estimated by subtracting the unit cost of a day for a patient without having had a procedure from the unit cost of one day for a patient who did have a procedure for a gastrointestinal bleed using code FZ29Z. The cost of endoscopy therefore was estimated at £100.85. This was felt be a reasonable estimate of the associated cost of consumables and maintenance (i.e. disinfection) of equipment that would be incurred with each endoscopy. The cost of endoscopy was applied as a one off cost each time a patient moved from a pre-endoscope state to a post endoscope state. In the model, a patient only undergoes one endoscopy; however the procedure costs would be higher if a follow up endoscopy was needed. Therefore the influence of the cost of the endoscopy on results was assessed in a sensitivity analysis. This parameter was not made probabilistic.

I.2.8.10 Cost of being in hospital after an endoscopy (the post-endoscope states)

The reference costs provide separate data for diagnostic (code FZ309) and therapeutic procedures (code FZ29Z) for an upper gastrointestinal bleed. The cost of endoscopy (£100.84) was subtracted from both of these unit costs to avoid double counting of this cost. The registry data was used to estimate the proportion of patients that were expected to have had a therapeutic procedure and was stratified by Rockall score. The data was prepared as detailed in Appendix B. Only records which gave a definitive indication of whether a therapeutic procedure was given or not at endoscopy were included in the calculation of the percentage of patients expected to have therapy or not (thereby excluding 59 of 4812 records). A beta distribution was fitted to the binomial data by setting $\alpha=r$ (where r was the number of patients having therapy) and $\beta= n-r$ (where n was the total number of patients with and without therapy).

Table 12: Percentage of each subgroup undertaking therapeutic and diagnostic endoscopy.

Subgroup	Percentage reported having therapy	Percentage assumed to have diagnostic endoscopy only	α	β
Rockall 0	11%	89%	81	639
Rockall 1	18%	82%	142	633
Rockall 2	22%	78%	155	550
Rockall 3	25%	75%	211	640
Rockall 4	25%	75%	222	677
Rockall 5	36%	64%	199	347
Rockall 6 and 7	39%	61%	99	158
Total	23%	77%	1109	3644

In order to account for the different proportions of patients undertaking diagnostic and therapeutic procedures in each subgroup, a respective weighted average unit cost was calculated. This was done by multiplying cost for Major or Therapeutic Endoscopic Procedures for Gastrointestinal Bleed (FZ29Z) by the proportion of patients having a therapeutic procedure and multiplying the cost of Diagnostic Endoscopic or Intermediate Procedures for Gastrointestinal Bleed (FZ30Z) by the proportion of patients not having a therapeutic procedure. Both HRG codes were associated with a

similar length of stay. To keep consistency, the average length of stay was also adjusted by multiplying the average length of stay for the HRG code by the respective proportion of patients having a therapeutic or diagnostic procedure. The weighted unit cost per day was calculated by dividing the weighted cost by the adjusted length of stay. Please refer to Table 13 and Table 14 for details of calculations.

The weighted unit cost for a non elective short term stay (length of stay of 1 day) was applied to any cycles spent in a post endoscope state within the first 24 hours of the model. Subsequently the average daily cost of a non elective long term stay was applied until the trim point (10 days[36]) had been achieved. In order not to double count the first day in hospital, the cost and duration of the first day was subtracted from this unit cost before the average cost per day was calculated. The excess bed stay cost (weighted according to proportion of patients expected to have had therapy) was applied thereafter until discharge, death or the completion of the time horizon as appropriate.

Table 14 gives the calculations used in the model using the NHS reference costs. Note that the average daily cost is highest on the first day, falls from day 2 and then falls further after the trim point. Also, note for each cost the standard error of the mean (not presented) is relatively large and therefore the uncertainty surrounding these unit costs is substantial.

Table 13: NHS reference costs for gastro-intestinal bleed.

Code	Intervention	Average length of stay(days)	Trim point (days)	Mean unit cost¥	LQR	UQR	SEM
Non elective short term stay							
FZ29Z	Major or Therapeutic Endoscopic Procedures for Gastrointestinal Bleed	1.00	N/A	£504 [a]	£308	£600	225
FZ30Z	Diagnostic Endoscopic or Intermediate Procedures for Gastrointestinal Bleed	1.00	N/A	£464 [b]	£296	£519	170
FZ38F	Gastrointestinal Bleed with length of stay 1 day or less	1.00	N/A	£403 [c]	£284	£480	148
Non elective long term stay							
FZ29Z	Major or Therapeutic Endoscopic Procedures for Gastrointestinal Bleed	4.50	10	£1,682 [d]	£1,215	£2,007	644
FZ30Z	Diagnostic Endoscopic or Intermediate Procedures for Gastrointestinal Bleed	4.91	10	£1,863 [e]	£1,042	£2,366	1116
FZ38D	Gastrointestinal Bleed with length of stay 2 days or more with Major CC	6.42	18	£1,944 [f]	£1,496	£2,183	622
FZ38E	Gastrointestinal Bleed with length of stay 2 days or more without Major CC	4.34	10	£1,261 [g]	£998	£1,413	367
Non elective long term stay -Excess bed day							
FZ29Z	Major or Therapeutic Endoscopic Procedures for Gastrointestinal Bleed			£229 [h]	£162	£263	92
FZ30Z	Diagnostic Endoscopic or Intermediate Procedures for Gastrointestinal Bleed			£241 [j]	£200	£292	58
FZ38D	Gastrointestinal Bleed with length of stay 2 days or more with Major CC			£207 [k]	£155	£249	72

Code	Intervention	Average length of stay(days)	Trim point (days)	Mean unit cost¥	LQR	UQR	SEM
FZ38E	Gastrointestinal Bleed with length of stay 2 days or more without Major CC			£211 [l]	£156	£251	76

Abbreviations: LQR = lower quartile range; UQR = Upper quartile range; SEM = Standard Error of the mean; CC= with complications or co morbidities;

¥ These are mean per stay or mean per excess bed day. Note that the letters in this column are in reference to the table of calculations which follows.

Source: NHS Reference Costs 2009-2010 [18 36]

Table 14: Costs applied to health states and the transition event of endoscopy in the Markov model.

Parameter description	Daily cost	Hourly cost	Cycles in which hourly cost applied	Notes on calculation of daily cost in reference to Table 13
Endoscopy (all Rockall scores)	£100.85 [n]	n/a	n/a	= a - c
First day in state				
Pre-endoscopy (all Rockall scores)	£403.29[m]	£16.80	0 until 24	= c
Post endoscopy (all Rockall Scores) §	£372.25 [o]	£15.51	0 until 24	= (a*[% having therapy]) + (b*[% not having therapy]) – n
After first day in state, until trim point achieved.				
Pre-endoscopy - High risk patients with Rockall Score 3-7	£283.98	£11.83	24 until 432	= (f - c) / (6.52-1)
Pre-endoscopy - Low risk patients with Rockall Score 0-2	£256.56	£10.69	24 until 240	= (g – c) / (4.34-1)
Post endoscopy (all Rockall scores) §	£353.23	£14.72	24 until 240	=((a*[% having therapy])+ (b*[% not having therapy])-[o]) / (4.91 - 1)
After trim point has been surpassed.				
Pre-endoscopy – High risk patients with Rockall Score 3-7	£206.79	£8.62	432 until 672	= k
Pre-endoscopy - Low risk patients with Rockall Score 0-2	£211.21	£8.80	240 until 672	= l
Post endoscopy (all Rockall scores) §	£238.16	£9.92	240 until 672	=(h*[% having therapy])+ (j*[% not having therapy])

Note: *§= A separate cost was calculated for each Rockall subgroup using the proportion having therapy from Table 12. The daily cost and hourly cost presented here are the weighted average across all Rockall subgroups. But it is the costs for the individual subgroups that are used in the model.*

The cost for hospital stay in the first 24 hours is based on NHS Reference short term stay data, thus reflective of the costs accrued by patients who left hospital within 24 hours of endoscopy. The data shows that, once the cost of endoscopy has been subtracted, costs are higher for patients who did not have the procedure. This may be reflective of the need for active management in these patients during the first 24 hours. The unit cost of hospital stay after 24 hours (as reported in Table 13) is highest for those patients still waiting for endoscopy that have co morbidities (i.e. Rockall score 3-7) and lowest for those waiting for endoscopy without co morbidities (i.e. Rockall score 0-2).

Although the cost estimates for hospital stay derived from NHS reference costs may be reflective of those incurred in current practice, we do not know how these costs they may change with a change of practice in timing of endoscopy. In three of the assessed strategies patients are endoscoped earlier than they would be in current UK practice, resulting in a greater proportion of patients being endscoped and fewer being discharged without endoscopy. This would change the casemix of patients and associated cost that informs the NHS reference cost for each HRG. For example, the unit cost for an endoscopic procedure under a strategy of earlier endoscopy may be more heavily influenced by the hospital stay costs of a patient that would otherwise been discharged without endoscopy.

To explore the impact of using different costs pre and post endoscopy further, asensitivity analysis is conducted where thesame cost for hospital stay is applied to both the pre and post endoscopy states. In one analysis the costs derived from patients who never had endoscopy are applied for hospital stay both pre and post endoscopy, but still according to Rockall score. In the other analysis the cost derived from patients who had therapeutic or diagnostic endoscopy is applied to both the pre and post endoscope states.

I.2.8.11 Overview of the approach taken to cost the implementation of the strategies.

Clinical experts identified the cost of additional staffing as the key differential implementation cost of the four strategies. Clinical experts agreed that one medical consultant and one staff day nurse (band 5) would need to be available in order to provide endoscopy, which was assumed to take 3 hours to complete on-call (taking into account the time needed to prepare for the endoscopy and travel). Where hours of work are onsite and cover the lunchtime period, an hour has been subtracted from working time per day to take this into account. No time was subtracted for rest breaks if the personnel were on-call.

Staff costs were estimated in line with the terms outlined in the NHS Terms and Conditions Service Handbook [20] and the 2003 Consultant Contract[21]. Salary percentage and time enhancements were applied to the basic median salary and employer's on-cost as reported by PSSRU[19]. The implementation costs of the strategies which involve on call services (i.e. the extended everyday service and the continuous access service) varied depending on how many presentations of acute upper gastrointestinal bleeding were expected.

The implementation (staff) cost for each strategy was added to the total resource cost estimated by the model for all subgroups. It was assumed that the nurse and consultant needed to implement the strategies would be employed to do only endoscopies, and were additional to the staff already costed within the NHS reference costs used to estimate length of stay costs.

It was not possible to provide an accurate costing of current practice as the registry did not provide specific information on the staff contractual arrangements. Additionally, clinical experts provided anecdotal evidence that even where no formal on-call arrangements are in place, out of hour services are still often provided on the good will of the medical staff.

I.2.8.12 Staff contractual arrangements, hours and pay for on-call and out of hours work

Nurses

The nurse could be employed under three distinct types of on call availability, as in line with NHS on-call implementation guidance:

- At home ready to be called out or to undertake work at the work place

- At work ready to undertake work
- Sleeping in at a work place.

It is recognised that there are three types of payment types for this availability

- Flat rate available for all staff
- Flat rate by grade
- Percentage of salary

Although on-call pay agreements are set locally, the model assumes it is set based on a percentage of salary. The payment enhancement is determined by the frequency that on call cover is expected, as set out in Table 15. In the model we assume that the nurse has a frequency of on call of 1 in 6 or more but less than 1 in 3, attracting a payment enhancement of 4.5% of basic salary, and that time taken (including travel) to complete an endoscopy whilst on call will be 3 hours.

For work done (including travel time) as a result of being called out, the nurse can take time off in lieu or be paid at time and a half, with the exception of work done on public holidays which is paid at double time. These contractual arrangements as well as other possible locally arranged alternatives are detailed in annex A3 of the NHS Terms and Conditions Service Handbook. For simplicity the model assumes the nurse is paid at time and a half and does not take into account public holidays.

Table 15: Nurse salary percentage enhancements for on call working hours, as determined by the frequency of expected on call periods.

Maximum number of nurses on rota	Frequency of on-call	Value of enhancement as percentage of basic pay
3	1 in 3 or more frequent	9.5%
6	1 in 6 or more but less than 1 in 3	4.5%
9	1 in 9 or more but less than 1 in 6	3.0%
12	1 in 12 or more but less than 1 in 9	2.0%
	Less frequent than 1 in 12	by local agreement

The NHS Terms and Conditions Service Handbook also stipulates that NHS staff must be reimbursed for working unsociable hours[20]. As Table 16 outlines, a staff nurse (band 5) should be paid time plus a third for hours worked on Saturday, and hours between 8pm and 6am on weekdays, and time and two thirds for hours worked on a Sunday or Public Holiday. For simplicity, public holidays were not accounted for.

Table 16: NHS staff percentage enhancements for worked unsocial hours.

Pay Band	All time on Saturday (midnight to midnight) and any week day after 8pm and before 6am	All time on Sundays and Public Holidays (midnight to midnight)
1	1.5	2
2	1.44	1.88
3	1.37	1.74
4 – 9	1.3	1.6

Source: The NHS Terms and Conditions Service[20]

Consultants

The Consultant 2003 Contract states that if a consultant is required to participate in an on-call rota, he or she shall be paid a supplement in addition to basic salary, in recognition of his or her availability to work during on-call periods[21]. The availability supplement should be reflective of the frequency and the type of work that the on-call consultant undertakes, as set out in Table 17.

A gastroenterologist would normally fall under category B, under the assumption that adequate trainee cover allows for the on call consultant to advise remotely and return to site later[37]. However, conflicting results between [11] and [10] suggested that resource savings were more likely if the endoscopy was undertaken by a lead which could facilitate discharge decisions. Further, in the UK context it has been shown that such on-call cover only reduces length of wait to endoscopy by a median of 2 hours [13]. Therefore in the scenarios modelled we conservatively assume that the consultant would fall under category A as the consultant would be typically required to return immediately to site when called. Clinical experts informed that there will typically be a 1 in 8 frequency of commitment, and thereby attract a 5% on-call supplement to their basic salary.

The 2003 Consultant Contract also refers to premium time, which is defined as any time that falls outside the period 07:00 to 19:00 Monday to Friday, and any time on a Saturday or Sunday, or public holiday [21]. Premium time rates are applied where staff are expected to be contracted on site and for the hours undertaken on call (which is assumed at least in part to fall in premium time).

Normally a consultant is expected to draw up a work plan that averages 10 programmed activities (PAs) of 4 hours per week. In cases where a PA is agreed in premium time, it will last for 3, rather than 4, hours (Schedule 7, [21]). Alternatively, if a premium time PA be additional to that drawn up in the work plan, the consultant can be paid for the extra PA at an additional 10% of their basic salary ([38], Schedule 14.7, [21]). Three hours of unpredictable emergency work done whilst on-call should be treated as one programmed activity, and has the same cost as a programmed activity in premium time, plus the enhancement to basic salary is applied on an annual basis.

Clinical experts informed that typically 2-3 hours is needed for each on-call endoscopy which occurs in the on call period. Taking the maximum time required, we assume each out of hour endoscopy is equivalent to one unit of a programmed activity in premium time.

Table 17: Consultant percentage enhancements for on call working hours, as determined by the frequency of expected on call periods

Maximum number of consultants on rota	Frequency of on-call	Value of enhancement as percentage of basic pay	
		Category A	Category B
4	High Frequency: 1in 1 to 1in 4	8.0%	3.0%
8	Medium Frequency: 1 in 5 to 1 in 8	5.0%	2.0%
	Low Frequency: 1 in 9 or less frequent	3.0%	1.0%

Source : The 2003 Consultant Contract [21]

I.2.8.13 Reference costs for endoscopy staff

The annual unit cost of the relevant cadre of staff for hours in the normal working week (8am-5pm) were established using those reported by PSSRU (2010) [19]. Where necessary these costs were recalculated to obtain the unit cost based on the basic salary, which is not inclusive of earnings made by overtime pay.

Table 18 details the mean basic salary, the mean earnings, median basic salary and salary oncosts for each cadre of staff. As the median is considered a more robust indicator of 'typical' pay, it is the median basic salary that has been used in calculating the implementation cost[19]. A breakdown of the

data used in the estimation of the implementation cost in the base case is provided in Table 19, with notes on the calculations provided in footnotes.

Table 18: Unit costs for endoscopy personnel

Cadre	Mean Basic Salary[a]	Median basic salary[b]	Mean Earnings [c]	Salary oncosts [d]	Normal working hours per week
Staff nurse, band 5, day ward	£24,300	£24,700	£29,300	£5,888	37.5
Consultant - medical	£90,400	£89,400	£120,200	£31,482	40

Source: PSSRU (2010)[19]

(a) Mean basic salary is calculated by dividing the total amount of basic pay earned by staff in the group by the total worked FTE for those staff.
(b) The median is calculated by ranking individuals FTE basic pay, and taking the midpoint. It is considered a more robust indicator of 'typical' pay than the mean
(c) Calculated as mean basic salary, but for all earnings. This includes basic salary, plus hours related pay, overtime, occupation payments, location payments and other payments including redundancy pay or payment of notice periods.
(d) This is the sum of the relevant salary oncosts such as employers National Insurance and 14% of salary for employers' contribution to superannuation.

Table 19: Implementation staff costs

Staffing details [a]	Hours worked per week with time enhancement added as appropriate [b]	Staff number (WTE) [c]	Annual salary plus [d] employer's on cost [e]	Annual cost for staff number[f]	Allowance for holidays & sickness 20% [g]	Total annual cost [h]
Weekday strategy						**£184,211**
Consultant - weekday	40	1.00	£120,882	£120,882	£24,176	£145,058
Nurses - weekday	40	1.07	£30,588	£32,627	£6,525	£39,153
Everyday strategy						**£217,324**
Consultant - weekday	40	1.00	£120,882	£120,882	£24,176	£145,058
Consultant - weekend	10.67	0.15	£120,882	£18,132	£3,626	£21,759
Nurses - weekday	40	1.07	£30,588	£32,627	£6,525	£39,153
Nurses – weekend	11.6	0.31	£30,588	£9,462	£1,892	£11,354
Extended everyday strategy						**£368,006**
Consultant - weekday	40.00	1.00	£120,882	£120,882	£24,176	£145,058
Consultant - weekend	21.33	0.53	£120,882	£64,470	£12,894	£77,364
Nurses - weekday	40.00	1.07	£30,588	£32,627	£6,525	£39,153

Staffing details [a]	Hours worked per week with time enhancement added as appropriate [b]	Staff number (WTE) [c]	Annual salary plus [d] employer's on cost [e]	Annual cost for staff number[f]	Allowance for holidays & sickness 20% [g]	Total annual cost [h]
Nurses – weekend	23.20	0.62	£30,588	£18,924	£3,785	£22,709
Consultant - on call supplement		8.00	£6,044	£48,353		£48,353
Consultant - on call PAs	6.88	0.17	£120,882	£20,796		£20,796
Nurse - on call supplement		6.00	£1,376	£8,259		£8,259
Nurse - on call work	7.74	0.21	£30,588	£6,315		£6,315
Continuous access strategy						**£387,478**
Consultant - weekday	40.00	1.00	£120,882	£120,882	£24,176	£145,058
Consultant - weekend	21.33	0.53	£120,882	£64,470	£12,894	£77,364
Nurses - weekday	40.00	1.07	£30,588	£32,627	£6,525	£39,153
Nurses - weekend	23.20	0.62	£30,588	£18,924	£3,785	£22,709
Consultant - on call supplement		8.00	£6,044	£48,353		£48,353
Consultant - on call Pas	11.82	0.30	£120,882	£35,732		£35,732
Nurse - on call supplement		6.00	£1,376	£8,259		£8,259
Nurse - on call work	13.30	0.35	£30,588	£10,850		£10,850

(a) Weekday= any scheduled work done 7am to 7pm Monday to Friday for consultants and any scheduled work done 6am-8pm for nurses. Weekend = any work done on Saturday or Sunday.

(b) Note that for nurses Saturday and Sunday attracts a different supplement for time worked Note that to account for lunch, 1 hour was subtracted from the daily total hours in a given strategy if staff were costed as on site. No hours for lunch were given if the staff were on-call.

(c) WTE = working time equivalent = number of hours worked per week divided by the number of normal contracted hours per week. Note that WTE includes any applicable time enhancement. The number of consultants and nurses on the rota are as determined by the provider. In the model it is assumed there are 8 consultants on the rota and 6 nurses, with one of each on call at any one time.

*(d) The median annual salary as reported by PSSRU (2010). The additional salary for on call supplement = Median salary * percentage enhancement (i.e. 4.5% for nurses or 5% for consultants)*

*(e) Employer oncost as reported by PSSRU. The additional oncost for on call supplement = employers' oncost * percentage enhancement (i.e. 4.5% for nurses or 5% for consultants)*

(f) Annual cost for staff number = [b][e]*

*(g) Allowance for sickness and holiday = 20% * [f]*
(h) Total cost = [f]+[g]

I.2.9 Transition probabilities

I.2.9.1 Probability of death and discharge

Transition probabilities for death and discharge from all states were derived from rates calculated by a statistical model of registry data, where admission and endoscopy and the date of death or discharge were recorded. Details of the statistical model and its results are given in Appendix B. Discharge and mortality rates were estimated separately for different Rockall scores, within set time periods since admission and for different endoscopy groups. The method employed aimed to separate subgroups with different risks of death or discharge as well as accounting for the time at risk pre- and post-endoscopy for the same individual. Poisson distributions were assumed for the number of deaths and discharges.

The statistical model generated 3000 simulated values for each hourly death and discharge rate. In the deterministic cost-effectiveness analysis, the mean of the 3000 values was used. In the probabilistic cost-effectiveness analysis, for each simulation the rate was selected at random from one of the 3000 values.

Hourly rates were converted into an hourly probability before inputting into the Markov model. This was done using the formula:

$$P=1-e^{-Rt}$$

Where R=selected rate and t=1 (hour)

The probability of mortality and discharge before scoping was determined by the rate of these events for all patients in the audit still waiting for endoscopy. The probability of mortality and discharge after endoscopy was determined by the rate of these events in audit patients that had an endoscope within a particular time period.

I.2.9.2 Probability of endoscopy (transition probabilities from pre endoscope states to post endoscope states).

In the Markov model, endoscopy is viewed as an event which allows transition from pre-endoscopy states to post endoscopy states (this differs from the statistical model detailed inAppendix B in which endoscopic procedure was viewed as a risk). The probability that a patient would have an endoscopy was informed by rates calculated from the registry data and *dependent on assumptions* regarding the feasibility of providing endoscopy in the compared strategies. The probability of having an endoscopy per time period for each Rockall score in each strategy is given in Table 20, and the resulting frequency at which patients are scoped in a time period post presentation for each strategy is given in Table 21.

The strategies assumed that by increasing staff availability, the probability of a patient being scoped would also increase. The probability of being scoped before a certain time limit was set below 1 to reflect the reality that it may not be possible to scope all patients within the time limit set regardless of the staff available to undertake the procedure, i.e. the requirement to have nil by mouth or the need to stabilise the patient. The strength of the assumption that the increased staffing levels associated with each strategy will increase the probability of having an endoscope by a certain time period was tested in sensitivity analyses (see section I.2.10).

The probability of endoscopy for a given time period.

The registry data was used to calculate the rate of endoscopy in current practice where there is variable on call services. The data was prepared as outlined in Appendix J.2. The rate of endoscopy was calculated by dividing the number of endoscopies within a given time period since admission by the hours at risk in the pre-endoscope state for that time period. This was done for each Rockall score; with Rockall score 6 and 7 aggregated together. These rates were converted into hourly probabilities which fed into the Markov model.

The probability of endoscopy for a given time period for the Weekday strategy

In order to estimate the potential rate of endoscopy where no on call services are available, we derived the frequency of endoscopy in each time period using audit data for providers which had not recorded an on call service. The probability of endoscopy calculated by using all records in the audit dataset (i.e. variable on-call services)was manually adjusted (i.e. decreased or increased) until the frequency of endoscopy in each time period calculated by the model matched that found in the audit for providers which had not recorded an on-call service. The weekday strategy assumed these adjusted probabilities of endoscopy which reflected the lower probability of early endoscopy with less service provision. The hourly probabilities calculated in this process fed into the Markov model assessing the weekday strategy.

The probability of endoscopy for a given time period for the Everyday strategy

Access to endoscopy everyday (onsite on8am-5pm on Weekdays and 8am-12pm on Weekends) is assumed to allow endoscopy to occur within 24 hours of admission or start of inpatient bleed. Therefore in the base case, the model assumed that, as services were available on the weekend, the probability of being endoscoped would be the same as that observed in current practice for the first 12 hours, and a probability of 0.9 of being scoped between 12-24 hours was set to ensure the majority of patients were scoped in the first 24 hours. The probability of being scoped in every subsequent time period was set to 0.98.

The probability of endoscopy for a given time period for the Extended Everyday strategy

Extended access to endoscopy (onsite everyday 8am-5pm, on call everyday 8pm-12am) is assumed to allow endoscopy to occur within 12 hours of admission or start of an inpatient bleed. Using the same logic as described above, the probability of being endoscoped was the same as that observed in current practice for the first 4 hours, and a probability of 0.9 of being scoped between 4-12 hours was set to ensure the majority of patients were scoped in the first 12 hours. The probability of being scoped in every subsequent time period was set to 0.98.

The probability of endoscopy for a given time period for the Continuous strategy

Continuous access to endoscopy (onsite everyday 8am-5pm, on call everyday 5pm-8am) is assumed to allow endoscopy to occur within 4 hours of admission or start of an inpatient bleed. In the base case, the probability of having an endoscope within the first 4 hours is set to 0.9 for each time period, and 0.98 for each subsequent time period.

Table 20: Probability of endoscopy in each time period.

	TIME SINCE ADMISSION (HOURS)									
Risk Factor	0-4	4-12	12-24	24- 48	48 –72	72-120	120 - 240	240-360	360-480	480-672
Current practice (variable on call services)										

Risk Factor	TIME SINCE ADMISSION (HOURS)									
	0-4	4-12	12-24	24- 48	48 –72	72-120	120 - 240	240- 360	360- 480	480- 672
Rockall 0	0.03	0.10	0.26	0.37	0.52	0.35	0.59	0.29	0.00	0.00
Rockall 1	0.03	0.12	0.31	0.37	0.50	0.37	0.60	0.11	0.13	0.17
Rockall 2	0.04	0.13	0.28	0.31	0.45	0.34	0.52	0.16	0.13	0.02
Rockall 3	0.06	0.12	0.27	0.31	0.42	0.34	0.60	0.14	0.17	0.07
Rockall 4	0.04	0.11	0.22	0.26	0.29	0.29	0.35	0.15	0.17	0.02
Rockall 5	0.09	0.14	0.25	0.25	0.41	0.17	0.24	0.15	0.12	0.05
Rockall 6 and 7	0.06	0.18	0.22	0.22	0.39	0.19	0.24	0.09	0.00	0.00
Weekday strategy (8am-5pm week days – no on call service)										
Rockall 0	0.03	0.08	0.26	0.29	0.45	0.25	0.30	0.00	0.00	0.00
Rockall 1	0.03	0.10	0.30	0.34	0.45	0.30	0.40	0.00	0.00	0.00
Rockall 2	0.03	0.10	0.23	0.29	0.40	0.30	0.35	0.10	0.00	0.00
Rockall 3	0.03	0.11	0.23	0.27	0.35	0.30	0.34	0.00	0.00	0.10
Rockall 4	0.02	0.09	0.21	0.21	0.25	0.25	0.30	0.10	0.17	0.02
Rockall 5	0.07	0.10	0.22	0.20	0.35	0.17	0.20	0.15	0.12	0.20
Rockall 6 and 7	0.03	0.11	0.15	0.18	0.40	0.25	0.15	0.00	0.00	0.00
Extended access strategy (Weekdays 8am-5pm, Weekends on-call 8am-5pm)										
Rockall 0	0.03	0.10	0.90	0.98	0.98	0.98	0.98	0.98	0.98	0.98
Rockall 1	0.03	0.12	0.90	0.98	0.98	0.98	0.98	0.98	0.98	0.98
Rockall 2	0.04	0.13	0.90	0.98	0.98	0.98	0.98	0.98	0.98	0.98
Rockall 3	0.06	0.12	0.90	0.98	0.98	0.98	0.98	0.98	0.98	0.98
Rockall 4	0.04	0.11	0.90	0.98	0.98	0.98	0.98	0.98	0.98	0.98
Rockall 5	0.09	0.14	0.90	0.98	0.98	0.98	0.98	0.98	0.98	0.98
Rockall 6 and 7	0.06	0.18	0.90	0.98	0.98	0.98	0.98	0.98	0.98	0.98
Extended access strategy (everyday 8am-12am)										
Rockall 0	0.03	0.90	0.98	0.98	0.98	0.98	0.98	0.98	0.98	0.98
Rockall 1	0.03	0.90	0.98	0.98	0.98	0.98	0.98	0.98	0.98	0.98
Rockall 2	0.04	0.90	0.98	0.98	0.98	0.98	0.98	0.98	0.98	0.98
Rockall 3	0.06	0.90	0.98	0.98	0.98	0.98	0.98	0.98	0.98	0.98
Rockall 4	0.04	0.90	0.98	0.98	0.98	0.98	0.98	0.98	0.98	0.98

Risk Factor	TIME SINCE ADMISSION (HOURS)									
	0-4	4-12	12-24	24- 48	48 –72	72-120	120 - 240	240- 360	360- 480	480- 672
Rockall 5	0.09	0.90	0.98	0.98	0.98	0.98	0.98	0.98	0.98	0.98
Rockall 6 and 7	0.06	0.90	0.98	0.98	0.98	0.98	0.98	0.98	0.98	0.98
Continuous access strategy (everyday 12am-12am)										
Rockall 0	0.90	0.98	0.98	0.98	0.98	0.98	0.98	0.98	0.98	0.98
Rockall 1	0.90	0.98	0.98	0.98	0.98	0.98	0.98	0.98	0.98	0.98
Rockall 2	0.90	0.98	0.98	0.98	0.98	0.98	0.98	0.98	0.98	0.98
Rockall 3	0.90	0.98	0.98	0.98	0.98	0.98	0.98	0.98	0.98	0.98
Rockall 4	0.90	0.98	0.98	0.98	0.98	0.98	0.98	0.98	0.98	0.98
Rockall 5	0.90	0.98	0.98	0.98	0.98	0.98	0.98	0.98	0.98	0.98
Rockall 6 and 7	0.90	0.98	0.98	0.98	0.98	0.98	0.98	0.98	0.98	0.98

Table 21: Frequency of endoscopy in a time period post presentation.

Strategy	TIME SINCE PRESENTATION (HOURS)										% of cohort scoped
	0-4	4-12	12-24	24-48	48 – 72	72-120	120 - 240	240-360	360-480	480-672	
Weekday	3%	9%	19%	15%	8%	7%	5%	1%	0%	0%	68%
Everyday	5%	11%	71%	7%	0%	0%	0%	0%	0%	0%	95%
Extended Everyday	5%	84%	9%	0%	0%	0%	0%	0%	0%	0%	98%
Continuous	90%	10%	0%	0%	0%	0%	0%	0%	0%	0%	100%

I.2.10 Sensitivity analysis

A range of sensitivity analyses were completed to test the robustness of the results to changes in key inputs and assumptions. These are outlined in Table 22

Table 22: Sensitivity Analysis description and inputs

ID	Sensitivity analysis description	Value used in the sensitivity analysis
Base case value for number of presentations (for comparison):		**300**
SA1:Presentations (25)	Due to a large range of reported activity data for upper GI bleeds, the expected annual number of patients presenting with an acute upper GI bleeds was varied in the sensitivity analysis.	25
SA2: Presentations (50)		50
SA3: Presentations (100)		100
SA4: Presentations (150)		150
SA5: Presentations (200)		200
SA6: Presentations (400)		400
SA7: Presentations (500)		500
SA8: Presentations (750)		750

ID	Sensitivity analysis description	Value used in the sensitivity analysis
SA9: Presentations (1000)		1000
SA10: Presentations (1500)		1500
SA11: Presentations (2000)		2000
Base case values for number of expected patients in each subgroup (for comparison):		**Rockall score 0: 1052 (18%)** **Rockall score 1: 899 (16%)** **Rockall score 2: 785 (14%)** **Rockall score 3: 909 (16%)** **Rockall score 4: 1071 (19%)** **Rockall score 5: 648 (19%)** **Rockall score 6 or 7:338 (11%)**
SA12: Rockall Subgroup (Uniform)	This sensitivity analysis altered the number of expected patients in each subgroup so that there was an equal proportion in each.	Rockall score 0: 800 (14%) Rockall score 1: 800 (14%) Rockall score 2: 800 (14%) Rockall score 3: 800 (14%) Rockall score 4: 800 (14%) Rockall score 5: 800 (14%) Rockall score 6 or 7:800 (14%)
SA13: Rockall Subgroup (low risk)	This sensitivity analysis altered the number of expected patients in each subgroup so that there was a positive skew towards lower Rockall scores in the distribution of patients	Rockall score 0: 1000 (20%) Rockall score 1: 900 (18%) Rockall score 2: 800 (16%) Rockall score 3: 700 (14%) Rockall score 4: 600 (12%) Rockall score 5: 500 (10%) Rockall score 6 or 7: 400 (8%)
SA14: Rockall Subgroup (high risk)	This sensitivity analysis altered the number of expected patients in each subgroup so that there was a positive skew towards higher Rockall scores in the distribution of patients	Rockall score 0: 400 (8%) Rockall score 1: 500 (10%) Rockall score 2: 600 (12%) Rockall score 3: 700 (14%) Rockall score 4: 800 (16%) Rockall score 5: 900 (18%) Rockall score 6 or 7: 1000 (20%)
Base case value for the utility weights (for comparison):		**0.6 for time in hospital, 0.8 for time spent at home**
SA15: Utility (full utility)	These analyses explore the scenarios where there is no difference in utility between time in hospital and at home.	1
SA16: Utility (extreme values)	Lowest utility found in the literature applied for time in hospital, and highest utility found applied for time at home (greatest difference in utility expected between states)	0.24 for time in hospital and 0.85 for time at home
Base case value for the cost of endoscopy (for comparison):		**£100.85**
SA17: Cost of endoscopy (£175)	The cost of endoscopy was subject to a sensitivity analysis should the estimated cost rise in the near future. In addition results of this	£175
SA18: Cost of endoscopy		£250

ID	Sensitivity analysis description	Value used in the sensitivity analysis
(£250)	analysis should give an indication whether the strategies are likely to be cost effective should a repeat endoscopy be required for all patients undergoing endoscopy.	
SA19: Cost of endoscopy (£500)		£500
Base case value for the cost of length of stay (for comparison)		**Please refer to Table 14**
SA20: LOS cost pre endoscopy assumes same cost as post endoscopy base case value	The cost of length of stay in the base case is different for pre and post endoscopy, as per the NHS reference cost. In this set of sensitivity analyses the same cost of length of stay is applied pre and post endoscopy; first by assuming the cost for length of stay is that derived by the NHS costs for patients that had endoscopy, and secondly by assuming the cost for length of stay is that derived by NHS costs for patients that had not had endoscopy. A deterministic sensitivity analysis is also conducted using these costs with the number of expected presentations detailed in analyses SA1-SA10.	First day =£372.25 Daily cost from day one to trim point =£353.23 Daily cost beyond trim point (excess bed day) = £238.16
SA21: LOS cost post endoscopy assumes same cost as pre endoscopy base case value		First day =£403.29 Daily cost to trim point = £259.56 (Rockall score 0-2), £283.98 (Rockall score 3-7) Daily cost beyond trim point (excess bed day) = £211.21 (Rockall score 0-2), £206.79 (Rockall score 3-7)
Base case values for the probability of mortality (for comparison):		**Various - See Error! Reference source not found.**
SA22: No mortality	In this sensitivity analysis all mortality probabilities are set to 0 so length of stay in hospital is only determined by the probability of discharge.	0
Base case value for the time horizon (for comparison):		**28 days (672 hours)**
SA23: Extended time horizon	This was an exploratory threshold analysis to examine the impact that the time horizon of 28 days may have on results.	5 years (with discount factor of 3.5% applied) 20 days
Base case values for the annual cost of implementing the weekday and everyday strategies (for comparison):		**Weekday: £184,211** **Everyday: £234,248**
SA24: Adding an on-call rota for emergency patients	In this sensitivity analysis the model was rerun deterministically, with an on call rota added to both the weekday and everyday strategy, with 1 emergency on call endoscopy per week for both of these strategies.	Weekday: £256,581 Everyday: £306,618

I.2.11 Computations

The model was constructed in Microsoft Excel and was evaluated by cohort simulation. Time dependency was built in by cross referencing the number of the cycle to an upper time limit associated with each transition probability and cost. There was no time dependency associated with utility.

Due to the model size and speed of computation, each subgroup was evaluated independently and results aggregated for a population analysis. For each subgroup analysis, the number of patients in the subgroup entering the model was recorded, alongside key results such as QALYs per patient and

resource cost per patient. Note that implementation costs were not accounted for in the subgroup analyses.

In the deterministic population analysis, the total number of QALYs and resource costs accrued by each subgroup was recorded. These subtotals were summed across all subgroups to ascertain the total number of patients in the population and the total QALYs and resource costs accrued for the population. The implementation cost for the population was added to the total resource cost accrued, before dividing the costs and QALYs by the number of patients in the population to calculate a cost per patient and cost per QALY.

In the probabilistic analysis, the simulation was rerun for each subgroup independently with key results of each simulation copied and stored to aggregate for population totals. Random numbers that selected the value from the Dirichlet distributions for the time of presentation and the proportion of patients in each subgroup took the same starting seed for each rerun of the simulation. This ensured that when the totals for the subgroups were aggregated, each iteration across the subgroups referred to the same distribution of patients within each Rockall group and the same number of expected on-call endoscopies, and therefore the correct implementation costs for the population were applied. Key results of the simulation for each subgroup were recorded and aggregated.

I.2.11.1 Calculating cost effectiveness

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with two alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$ Where: Costs/QALYs(X) = total costs/QALYs for option X	• Cost-effective if: ICER < Threshold

When there are more than two comparators, as in this analysis, options must be ranked in order of increasing cost then options ruled out by dominance or extended dominance before calculating ICERs excluding these options.

It is also possible, for a particular cost-effectiveness threshold, to re-express cost-effectiveness results in term of net monetary benefit (NMB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the total costs (formula below). The decision rule then applied is that the comparator with the highest NMB is the most cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost.

$$Net\ Benefit(X) = \left(QALYs(X) \times \lambda\right) - Costs(X)$$ *Where: Costs/QALYs(X) = total costs/QALYs for option X; λ = threshold*	• Cost-effective if: highest net benefit

Both methods of determining cost effectiveness will identify exactly the same optimal strategy. For ease of computation NMB was used to identify the optimal strategy in the probabilistic analysis simulations.

The probabilistic analysis was run for 10,000 and 5000 simulations for the basecase and sensitivity analyses respectively. Each simulation, total costs and total QALYs were calculated for each strategy. Net benefit was also calculated and the most cost-effective option identified (that is, the one with

the highest net benefit), at a threshold of £20,000 per QALY gained. The results of the probabilistic analysis were summarised in terms of mean costs, mean QALYs and mean net benefit for each treatment option, where each was the average of the simulated estimates. The option with the highest mean net benefit (averaged across the simulations) was the most cost-effective at the specified threshold. The percentage of simulations where each strategy was the most cost-effective gives an indication of the strength of evidence in favour of that strategy being cost-effective.

Results are also presented graphically where mean total costs and mean total QALYs for each treatment options are plotted. Comparisons not ruled out by dominance or extended dominance are joined by a line on the graph where the slope represents the incremental cost-effectiveness ratio, the magnitude of which is labelled.

I.2.12 Interpreting Results

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

I.2.13 Validation

The model was developed by the health economists in consultation with the rest of the GDG; model structure, inputs and results were presented to and discussed with the GDG to assess face validity and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The model was also peer reviewed by an experienced health economist from the NCGC; this included systematic checking of the model calculations.

I.3 Results

Detailed results are presented over the next few pages for the base case and various sensitivity analyses including an exploratory threshold analysis to explore the potential impact having a short time horizon. As the results of the deterministic and probabilistic analysis were comparable, all results reported below are means from the probabilistic analysis unless otherwise specified.

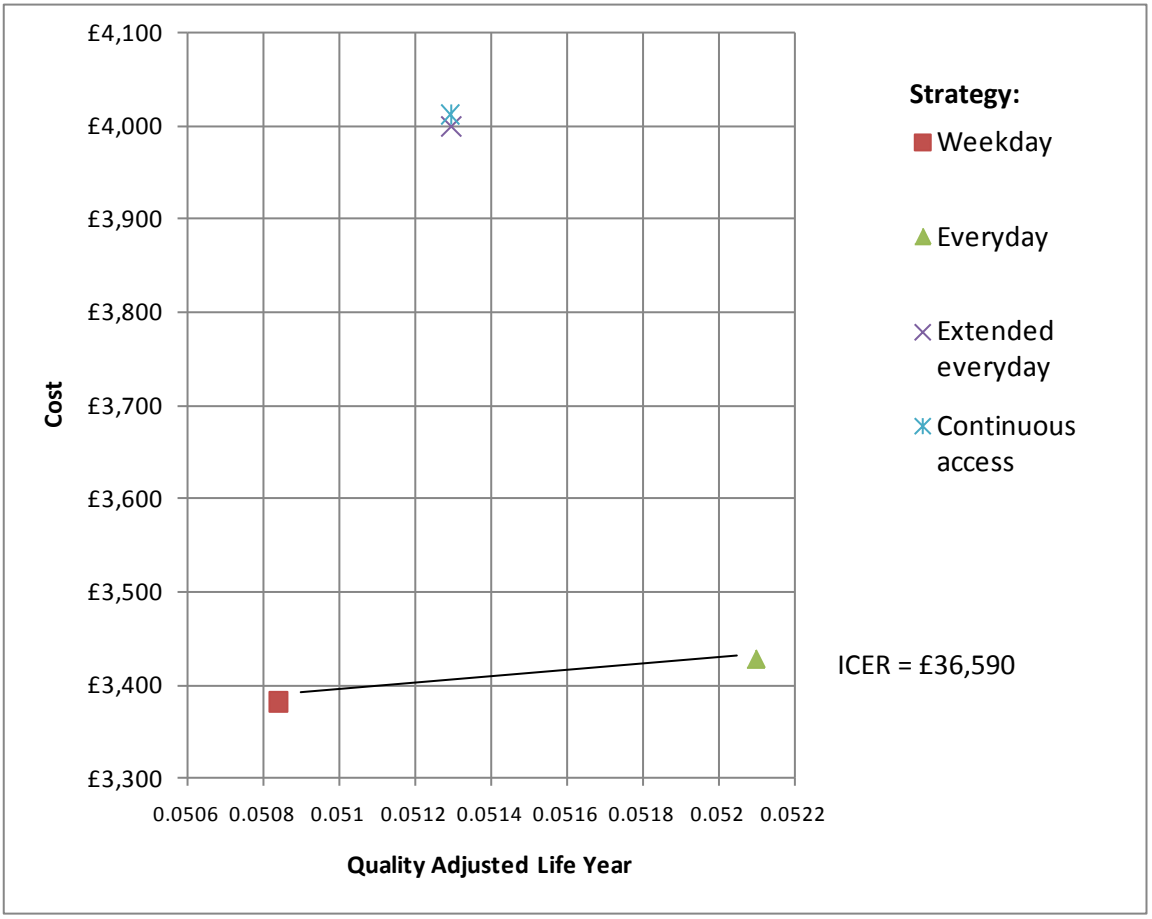
I.3.1 Base Case

Table 23 and Figure 3 show the mean QALYs and cost per patient of each strategy in the base case. Both the Extended everyday strategy (assumed to allow endoscopy within 12 hours) and the Continuous strategy (assumed to allow endoscopy within 4 hours) were dominated strategies as they provided less QALYS at increased cost when compared to the Everyday strategy. As these strategies are dominated, they are not further considered in the incremental analysis and the ICER is not calculated – see Figure 3.

Table 23: Results for the Base Case – probabilistic analysis

Strategy	Mean per Patient		Net Monetary Benefit at threshold of:		Rank at threshold of:		At £20k per QALY, the percentage of times that the strategy ranked:			
	QALY	Cost	20K	30K	£20K	£30K	1st	2nd	3rd	4th
Weekday	0.051	£3,382	-£2,365	-£1,857	1	1	53%	47%	0%	0%
Everyday	0.052	£3,428	-£2,386	-£1,865	2	2	47%	53%	0%	0%
Extended everyday	0.051	£3,999	-£2,973	-£2,460	3	3	0%	0%	62%	38%
Continuous	0.051	£4,012	-£2,986	-£2,473	4	4	0%	0%	38%	62%

Figure 167: Cost effectiveness plane showing mean cost and QALY per patient expected with each strategy (Base Case – probabilistic analysis).



In the base case analysis, the strategy that provided the most QALYs was the everyday strategy, where endoscopy was assumed to occur within 24 hours. However, this came at additional cost to the weekday strategy. Using the mean costs and QALYs generated over the probabilistic sensitivity analysis, the ICER of the everyday strategy when compared to the weekday strategy is £36,590, which is above the NICE threshold of £20,000 per QALY.

However, the probabilistic sensitivity analysis also indicted there was great uncertainty in whether the weekday strategy was optimal once the potential error in the mean values used was accounted for. At a £20,000 per QALY threshold, the probability that the weekday strategy is the most cost

effective is 0.53, and the probability that the Everyday strategy is cost effective is 0.47. Upper and lower confidence intervals for the incremental costs and QALYS for the non dominated strategies are presented in Table 24.

Table 24: Incremental costs and effects of the everyday strategy vs. the weekday strategy

	Incremental cost	LCI	UCI	Incremental QALY	LCI	UCI
Everyday vs. Weekday	£46	-£306	£430	0.0013	0.0006	0.0019

LCI = Lower end of 95%confidence interval; UCI = Upper end of 95% confidence interval

Table 25 and Table 26 give secondary outcomes and a breakdown of costs from the base case probabilistic analysis. These show that the everyday strategy has the lowest length of stay and associated cost of all the strategies. It also has the least number of deaths expected.

Table 25: Secondary clinical outcomes (base case – probabilistic analysis)

Strategy	Average length of stay (days)	Clinical outcome per 1000 patients		
		Number of deaths	Number remaining in hospital at 28 days	Number of endoscopies
Weekday access	9.00	110	122	677
Everyday access	7.91	91	95	948
Extended everyday access	8.35	98	102	983
Continuous access	8.27	108	108	995

Table 26: Breakdown of costs (base case – probabilistic analysis)

Strategy	Cost per 1000 patients of:			
	Hospital stay	Endoscopy	Staff	Total
Weekday access	£2,699,585	£68,315	£614,037	£3,381,936
Everyday access	£2,551,474	£95,590	£780,825	£3,427,889
Extended everyday access	£2,670,602	£99,106	£1,229,647	£3,999,356
Continuous access	£2,619,788	£100,362	£1,291,579	£4,011,728

NB: 300 presentations are expected annually in the base case, therefore these costs would accrue over 3.33 years.

It was unexpected that the extended everyday strategy (where most patients are endoscoped in the 4-12 time period) and continuous access strategy (where most patients are endoscoped in the 0-4 hour period) results in less QALYs, a higher number of deaths and a greater length of stay than the everyday strategy (where most patients are endoscoped in the 12-24 hours time period). However, these results are reflective of the mortality and discharge rates calculated from patient level data in the national audit (please refer to Appendix J)

There are several examples of higher rates of discharge and lower rates of mortality for those endoscoped between 12-24 hours than those endoscoped in an earlier timeframe. This is particularly the case for rates calculated from patients with a Rockall score of 2 or higher. In the Everyday

strategy, the majority of patients are scoped between 12-24 hours, therefore it is this strategy that sees the highest QALY gain, and lower length of stay.

For example, compare the mortality rates presented in Table 41 (Appendix section J.3) for patients with Rockall score 6 or 7. In the post admission time periods 12-24 hours, and 120-240 hours, the mortality rate for those scoped in 4-12 hour time period was higher than those scoped later in the 12-24 hour time period. In the post admission time periods 0-24 hours and 48-240 hours, the mortality rates for those scoped in the 0-4 hour time period were higher than those scoped later in the 12- 24 hour time period.

Higher discharge rates for those endoscoped in the time period 12-24 hours can also be seen in the Rockall scores above 2. For example, in score Rockall 4 (Table 39) in all time periods with the exception of 12-24 hours, the discharge rate for the patients scoped for 12-24 hours was higher than for those patients endoscoped between 0-12 hours.

There is not an identical pattern across all Rockall scores and all time periods, and only a few of the examples are outlined here, but the overall effect is that there are more deaths, a lower QALY gain and a greater length of stay associated with the extended everyday and continuous access strategies than there is for the everyday strategy. This results in the extended everyday and continuous access strategy being dominated by the Everyday strategy.

I.3.2 Subgroup analysis

Disaggregated results for each Rockall score subgroup are given in Table 27, Table 28 and Table 29. To note, no implementation costs have been added.

Table 27: Disaggregated results by Rockall Score subgroup (Base Case - Probabilistic)

Strategy / Subgroup by Rockall score	Mean QALYs per patient				Mean Costs per patient (not inc. implementation cost)				Net Monetary Benefit at £20,000 threshold (not inc. implementation cost)			
	Weekday	Everyday	Extended everyday	Continuous	Weekday	Everyday	Extended everyday	Continuous	Weekday	Everyday	Extended everyday	Continuous
0	0.058	0.058	0.059	**0.059**	£1,455	£1,481	£1,268	**£1,110**	-£297	-£324	-£96	**£68**
1	0.056	**0.057**	0.056	0.057	£2,162	£1,914	£2,148	**£1,316**	-£1,037	-£771	-£1,029	**-£180**
2	0.052	**0.054**	0.053	0.053	£3,089	**£2,759**	£3,124	£3,150	-£2,044	**-£1,682**	-£2,056	-£2,081
3	0.052	**0.053**	0.052	0.052	£3,130	**£2,725**	£2,889	£3,106	-£2,094	**-£1,664**	-£1,857	-£2,071
4	0.047	**0.048**	0.046	0.045	**£3,336**	£3,397	£3,614	£3,634	**-£2,395**	-£2,429	-£2,699	-£2,726
5	0.044	0.046	**0.047**	0.046	£3,620	**£3,554**	£3,568	£4,204	-£2,736	-£2,639	**-£2,620**	-£3,278
6 and 7	0.033	**0.038**	0.035	0.034	**£3,315**	£3,671	£3,760	£3,712	**-£2,655**	-£2,916	-£3,054	-£3,022

Table 28: Disaggregated costs by Rockall Score subgroup (Base case- Probabilistic)

Strategy / Subgroup by Rockall Score	Cost of hospital stay per 1000 patients				Cost of endoscopies per 1000 patients			
	Weekday	Everyday	Extended	Continuous	Weekday	Everyday	Extended	Continuous
0	£1,398,922	£1,393,651	£1,171,936	**£1,010,879**	**£55,957**	£87,465	£96,328	£99,583
1	£2,088,124	£1,819,275	£2,049,589	**£1,215,705**	**£74,157**	£95,278	£98,736	£100,242
2	£3,015,027	**£2,662,427**	£3,024,981	£3,049,706	**£74,408**	£96,860	£99,186	£100,359
3	£3,055,405	**£2,626,471**	£2,788,986	£3,005,189	**£74,177**	£98,251	£100,065	£100,633
4	**£3,266,729**	£3,297,849	£3,513,237	£3,532,979	**£68,677**	£98,702	£100,466	£100,764
5	£3,550,450	**£3,455,540**	£3,467,821	£4,103,412	**£69,716**	£98,613	£100,213	£100,672
6 and 7	**£3,257,719**	£3,575,293	£3,660,833	£3,611,055	**£56,840**	£95,867	£99,540	£100,509

Table 29: Disaggregated secondary clinical outcomes, by Rockall score subgroup (Base case - Probabilistic)

Strategy/ Subgroup by Rockall Score	Average length of stay (days)				Number of deaths per 1000 patients				Number remaining in hospital at 28 days per 1000 patients				Number of endoscopies per 1000 patients				Number of discharges per 1000 patients			
	WD	ED	E-ED	C	WD	ED	E-ED	C	WD	ED	E-ED	C	WD	ED	E-ED	C	WD	ED	E-ED	C
0	4.5	4.1	3.3	**2.9**	4	12	2	**0**	32	39	5	**0**	555	867	955	**987**	964	950	994	**1000**
1	6.9	5.5	6.3	**3.6**	18	**14**	31	65	82	48	67	**8**	735	945	979	**994**	899	**937**	902	927
2	10.3	**8.2**	9.6	9.7	62	46	39	**38**	172	**96**	170	179	738	960	984	**995**	766	**858**	790	783
3	10.1	**8.1**	8.6	9.4	**75**	67	97	84	137	94	**80**	113	736	974	992	**998**	788	**839**	823	803
4	10.9	**10.3**	11.1	11.2	185	**144**	186	191	144	133	**133**	133	681	979	996	**999**	671	**723**	681	676
5	11.9	**11.0**	11.0	13.5	230	202	**152**	195	171	**143**	146	229	564	951	987	**997**	600	655	**702**	576
6 and 7	**11.1**	11.6	12.1	12.0	437	**336**	348	359	189	**187**	213	214	564	951	987	**997**	375	**477**	439	428

I.3.3 Sensitivity Analysis

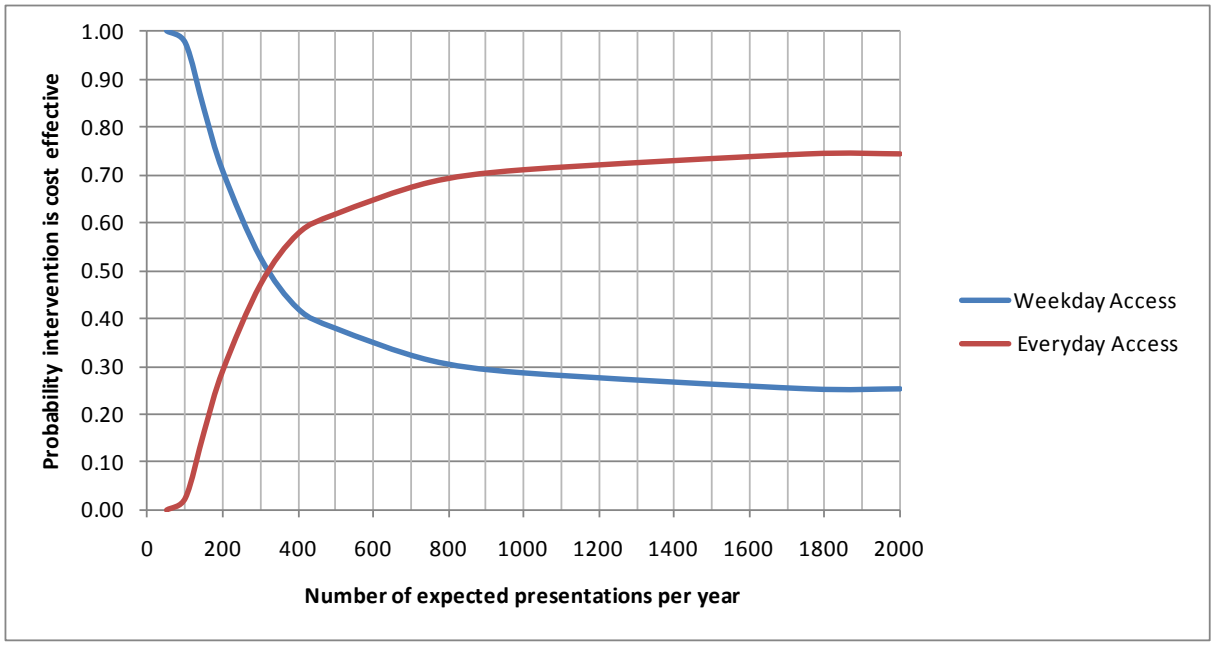
Sensitivity analyses were run probabilistically unless otherwise specified. In all analyses either the weekday or the everyday strategy was recorded as the most or second most optimal strategy. Table 30 summarises the results of these analyses. Throughout all of the sensitivity analyses, the probability that the extended everyday or the continuous access strategy being optimal was zero.

Of the sensitivity analyses that tested the robustness of the results to change in model inputs (i.e. SA1 – SA21), only changes in the number of expected presentations per year and application of the same cost for hospital stay pre and post endoscopy changed the result to the everyday strategy being most cost effective.

Figure 4 shows the probability that either the weekday or everyday strategy is cost effective, depending on the number of presentations expected per year and given base case values for the cost of hospital stay. The optimal strategy is only certain when the number of presentations per year is 50 or below. In such cases the weekday strategy is the most cost effective option. The weekday strategy is more likely to be more cost effective than the everyday strategy if a provider is expecting less than 330 presentations per year, with decreasing certainty that this is the most cost effective option as the number of presentations increase. For providers expecting more than 330 presentations per year, the everyday strategy is more likely to be optimal, with increasing certainty that this is the optimal option as the number of presentations increase.

When the same cost of hospital stay was applied for both pre and post endoscopy states the threshold of the number of presentations needed for one strategy to be more likely to be cost effective changed. If the cost of hospital stay derived from patients that had not had endoscopy was applied to all patients before and after endoscopy, the threshold for the everyday strategy to be more cost effective than the weekday strategy moved to between 150 and 200 expected presentations per year. If the average cost of hospital stay derived from patients that had endoscopy was applied to all patients before and after endoscopy, the threshold moved to between 100 and 150 expected presentations per year. Regardless of the hospital stay cost applied, the extended everyday and continuous access strategies remained dominated strategies.

Figure 168: The probability the Weekday and everyday are cost effective given a certain number of presentations per year, using base case values for cost of hospital stay



Three further sensitivity analyses were conducted to test model behaviour and structural assumptions.

The analysis SA22 explored the impact of having no mortality on results. In this scenario, only discharge rates would influence the length of stay and associated cost, a driver of the cost effectiveness. The weekday, extended everyday and continuous access strategies were dominated options. Having an endoscopy within 24 hours proved to reduce length of stay across the population to the extent where the additional implementation and endoscopy costs was offset. The probability that the Everyday strategy was most cost effective was 0.61, and the probability the weekday strategy was most cost effective was 0.39.

The analysis SA23 was conducted to explore the potential impact of increasing the time horizon. This was done as an exploratory threshold analysis, whereby we assumed a given life expectancy beyond the time horizon with no additional cost to the NHS. Table 31 details the incremental net benefit and ICER for the everyday strategy compared to the Weekday strategy if the patient could expect 5 years of life expectancy at no additional downstream cost to the NHS. In such a scenario the Everyday strategy becomes cost effective with an ICER of £463 per QALY when compared to the weekday strategy. In a threshold analysis, we determined that the patient needs to have at least 20 days of full health post the time horizon (at no additional cost to the NHS) for the everyday strategy to become cost effective with an ICER of £19,715 when compared to the weekday strategy (under the base case assumption of 300 presentations per year).

The analysis SA24 was conducted to explore the impact of adding an additional on call rota to the weekday and everyday strategies to cater for one emergency unstable patient with severe acute gastrointestinal bleed, presenting in out of hours per week. This is under the assumption that emergency endoscopy should be provided for patients with severe acute upper GI bleed and an oncall service should be available for those patients. As an oncall service is already provided in the extended everyday strategy and continuous access strategy, no change was made to these strategies in terms of implementation costs. Conservatively we did not adjust the settings to take into account any potential benefit that could arise with the addition of an oncall service to the Weekday and Everyday strategy. The base case and the analyses SA1-SA19 were rerun deterministically. Although

the cost per patient in the weekday and everyday strategies was increased in all analyses, the optimal strategy remained the same. Where the base case estimates for hospital stay cost was applied, the weekday strategy remained optimal for providers with 300 presentations or less, and the everyday strategy remained optimal for providers with 400 presentations or more.

Table 30: Results of the sensitivity analysis – probabilistic analysis

Sensitivity analysis	Mean QALYs per patient				Mean Costs per patient				Optimal strategy	Probability that strategy is optimal at 20K threshold
	Weekday	Everyday (endoscopy within 24 hrs)	Extended (endoscopy within 12 hrs)	Continuous (endoscopy within 4 hrs)	Weekday	Everyday (endoscopy within 24 hrs)	Extended (endoscopy within 12 hrs)	Continuous (endoscopy within 4 hrs)		
SA1- SA10: Number of presentations of acute upper GI bleed expected per year										
25	0.051	0.052	0.051	0.051	£10,138	£12,015	£16,497	£16,509	Weekday	1.00
50	0.051	0.052	0.051	0.051	£6,447	£7,323	£9,671	£9,684	Weekday	1.00
100	0.051	0.052	0.051	0.051	£4,601	£4,976	£6,258	£6,270	Weekday	0.97
150	0.051	0.052	0.051	0.051	£3,993	£4,201	£5,128	£5,138	Weekday	0.84
200	0.051	0.052	0.051	0.051	£3,689	£3,820	£4,570	£4,582	Weekday	0.71
300 (base case)	0.051	0.052	0.051	0.051	£3,382	£3,428	£3,999	£4,012	Weekday	0.53
400	0.051	0.052	0.051	0.051	£3,227	£3,222	£3,703	£3,714	Everyday	0.58
500	0.051	0.052	0.051	0.051	£3,134	£3,108	£3,537	£3,550	Everyday	0.62
750	0.051	0.052	0.051	0.051	£4,601	£4,976	£6,258	£3,315	Everyday	0.69
1000	0.051	0.052	0.051	0.051	£2,953	£2,880	£3,203	£3,215	Everyday	0.71
1500	0.051	0.052	0.051	0.051	£2,881	£2,788	£3,074	£3,086	Everyday	0.75
1750	0.051	0.052	0.051	0.051	£2,877	£2,780	£3,056	£3,068	Everyday	0.77
2000	0.051	0.052	0.051	0.051	£2,877	£2,769	£3,039	£3,050	Everyday	0.77
SA12 – SA13: Proportion of patients in each Rockall subgroup										
SA12: Rockall Subgroup (Uniform)	0.049	0.051	0.050	0.050	£3,477	£3,556	£4,128	£4,171	Weekday	0.59
SA13: Rockall Subgroup (low risk skew)	0.051	0.052	0.052	0.052	£3,308	£3,349	£3,915	£3,890	Weekday	0.52
SA14: Rockall Subgroup (high risk skew)	0.047	0.049	0.048	0.048	£3,659	£3,771	£4,350	£4,458	Weekday	0.62

Sensitivity analysis	Mean QALYs per patient				Mean Costs per patient				Optimal	Probability
SA1-SA16: Utility values										
SA15: Utility (full utility)	0.071	0.072	0.071	0.071	£3,374	£3,412	£3,981	£3,994	Weekday	0.53
SA16: Utility (extreme values)	0.058	0.059	0.058	0.058	£3,376	£3,420	£3,991	£4,004	Weekday	0.55
SA17-SA19: Cost of endoscopy										
SA17: Cost of endoscopy (£175)	0.051	0.052	0.051	0.051	£3,431	£3,499	£4,074	£4,087	Weekday	0.58
SA18: Cost of endoscopy (£250)	0.051	0.052	0.051	0.051	£3,479	£3,560	£4,136	£4,151	Weekday	0.61
SA19: Cost of endoscopy (£500)	0.051	0.052	0.051	0.051	£3,652	£3,802	£4,387	£4,403	Weekday	0.75
SA20-21: Cost of Length of Stay										
SA20: LOS cost pre endoscopy assumes same cost as post endoscopy basecase value	0.051	0.052	0.051	0.051	£3,567	£3,408	£3,987	£4,005	Everyday	1.00
SA21: LOS cost post endoscopy assumes same cost as pre endoscopy basecase value	0.051	0.052	0.051	0.051	£3,098	£3,009	£3,564	£3,600	Everyday	1.00
SA22: No mortality										
Base case	0.051	0.052	0.051	0.051	£3,382	£3,428	£3,999	£4,012	Weekday	0.53
SA22: No mortality	0.055	0.056	0.056	0.056	£3,713	£3,672	£4,284	£4,323	Everyday	0.61

Table 31: SA23: Exploratory threshold analysis using various time horizons.

Strategy	Proportion of population alive at end of time horizon	Cost	28 day horizon (Base case)			5 years beyond time horizon (with 3.5% discount factor applied)			20 days beyond time horizon		
			QALY	INMB vs. Weekday	ICER vs. Weekday	Mean QALY	INMB vs. weekday	ICER vs. Weekday	Mean QALY	INMB vs. Weekday	ICER vs. Weekday
Weekday	0.89	£3,382	0.051	£0		4.07	£0		0.010	£0	
Everyday	0.91	£3,428	0.052	-£21	£36,590	4.16	£1,753	£478	0.102	£1	£19,715
Extended everyday	0.90	£3,999	0.051	-£608	Dominated	4.12	£485	Dominated	0.091	-£591	Dominated
Continuous	0.89	£4,012	0.051	-£621	Dominated	4.08	-£373	Dominated	0.090	-£613	Dominated

Table 32: SA24: Adding an on call service to the Weekday and Everyday strategies, with one emergency on-call per week (deterministic). Where results have changed from the base case, deterministic base case values are provided in brackets.

Strategy	Mean per Patient		Net Monetary Benefit at threshold of:		Rank at threshold of:	
	QALY	Cost	20K	30K	£20K	£30K
Weekday	0.052	£3,591 (£3,376)	-£2,553 (-£2,338)	-£2,033 (-£1,818)	1	1
Everyday	0.053	£3,633 (£3,418)	-£2,570 (-£2,356)	-£2,039 (-£1,824)	2	2
Extended everyday	0.052	£3,989	-£2,942	-£2,418	3	3
Continuous	0.052	£4,001	-£2,955	-£2,431	4	4

I.4 Discussion

I.4.1 Summary of Results

A new cost-utility analysis was developed which compared four strategies to allow differential timing to endoscopy for patients presenting with acute upper gastrointestinal bleed. This was based on death and discharge data collected through a national audit, and outcomes were stratified by Rockall score before being aggregated to a population perspective. Costs and QALYs were considered from an NHS and personal social services perspective.

We found that for providers expecting 330 presentations per year or less, the weekday strategy was the least expensive and most cost-effective strategy. For providers expecting more than 330 presentations per year, the everyday strategy offering additional provision of services on the weekend mornings was most likely to be cost effective. The certainty of this conclusion increased as the number of expected presentations increased. The results were robust to various one-way sensitivity analyses; however, when parameters were varied simultaneously in a PSA the results were uncertain.

I.4.2 Interpretation and Limitations

The aim of this analysis was to evaluate if early endoscopy was cost effective in patients presenting with acute upper gastrointestinal bleed, given the additional implementation costs to allow early endoscopy to occur. To address this question, we assessed the cost effectiveness of having an endoscopy within 4 hours, 12 hours and 24 hours of presentation, as well as within the time period a patient could expect in a hospital that had no additional endoscopy services beyond the working week, 8am – 5pm. Each of these comparative timings to endoscopy was evaluated alongside staffing models which would make it possible to achieve the respective target time to endoscopy.

The base case analysis found that having services on the weekday only or adding additional morning lists on Saturday and Sunday could both be cost effective strategies, depending in part on the number of patients a provider expects and the likelihood that the majority of patients endoscoped early were of low risk of mortality (i.e. with Rockall score 0-2). Further, when the same cost of hospital stay was applied for time spent both pre and post endoscopy, fewer presentations were required in order for the everyday to be more likely to cost effective than the weekday strategy. This was regardless of whether the higher or lower cost estimate of hospital stay was applied. Our estimate of 330 presentations required per year for the everyday strategy to be the most likely cost effective strategy is likely to be conservative.

Disaggregated results by Rockall score demonstrate that it is in the low risk group where the greatest saving in reducing the length of stay can be realised. It is the reduced length of stay costs in the low risk patients that partly offset the cost of implementation of each of the strategies, and drives the cost effectiveness of earlier endoscopy. The quicker the endoscopy in the low risk patients, the more likely strategies to implement a strategy requiring additional staff hours will be cost effective. The higher the proportion of low risk patients in the population, the more likely strategies to implement quick endoscopies will be cost effective.

The sensitivity analyses also show that the Everyday strategy becomes more favourable with greater differences of quality of life of a patient experiences in hospital and at home after an acute gastrointestinal bleed. However, the everyday strategy is less favourable if the cost of endoscopy increases.

The results of the analysis should be interpreted with caution. As the clinical parameters were informed by observational data, this analysis has potentially serious limitations due to the possibility of confounding factors which were not controlled for i.e. factors that are related both to outcome (mortality or discharge) and time to endoscopy at a specific time. The validity of the assumption that only Rockall score and time of endoscopy could have influenced the outcome in the audit data is questionable; however, an alternative stratification system was not possible with the current evidence and data available. We recognise the possible heterogeneity within each Rockall score (with an increasing number of combinations of risk factors with the higher scores). We also acknowledge that there could be factors not contained within the Rockall score that would influence a clinician's decision to endoscope more quickly, i.e. selecting patients with additional clinical features associated with a poorer prognosis.

Given these limitations, it is possible that the increased length of stay seen with the extended everyday and continuous access strategies when compared to the everyday strategy could be a result of uncontrolled confounding in the statistical analysis of the observational data that informed the rate of death and discharge following an endoscopy at a certain time. The cost-effectiveness of these strategies offering earlier endoscopy may be underestimated. Conversely we did not assess a strategy whereby the majority of patients would be endoscoped in a time period later than 24 hours, but in less time than seen in current practice.

Assumptions regarding mortality should also be considered when interpreting the results. A lack of available data meant that survival was assumed post discharge for the full time horizon. Although the findings from the clinical review and the statistical analysis of the audit data did not suggest a significant difference in mortality in strategies comparing differential timings to endoscopy, it was felt that this evidence was not sufficient to conclude no difference in mortality would be observed in studies with a larger sample size. The number of deaths was recorded as a secondary outcome by the model, with the least deaths expected in the everyday strategy. If there is a survival benefit with early endoscopy, it is likely that the cost effectiveness of the Everyday strategy is underestimated. We also considered the potential uncaptured benefits that could accrue due to increased staffing levels but would fall outside the scope of this analysis. For example, it is likely the staff will be undertaking activity outside the endoscopy suite, especially where a low volume of patients is expected. Accounting for this benefit would favour the Everyday strategy.

Overall, this analysis is likely to be conservative in terms of the benefits of treatment and may underestimate the value of providing endoscopy within 24 hours of presentation or earlier.

I.4.3 Comparison with published studies

No published cost effectiveness studies were indentified that compared strategies of differential timing of endoscopy from a UK NHS perspective. Two studies of partial applicability and with potentially serious limitations were identified, and due to different methodologies were found to have conflicting results. Having considered the limitations in both studies, the results suggested resource savings were possible with early endoscopy in low risk stable patients, if a lead could undertake the endoscopy and facilitate early discharge of these patients. No studies were identified that looked at high risk patients.

The analysis presented in this report compared four different strategies that allowed endoscopy to occur within 4 hours, 12 hours, 24 hours of presentation or the timing observed in the current UK setting for providers without any on-call services. We considered both high and low risk groups, both of which would be found within the UK patient population. We also considered specifically the additional staffing levels that would be required to implement the strategies. The analysis is from a UK NHS perspective taking into account a range of considerations with extensive sensitivity analysis. As such it is directly applicable to the guideline and the current UK NHS setting. The results of this

analysis are in agreement with the conclusions made from looking at the published analyses, in that early endoscopy in low risk patients leads to earlier discharge and reduced length of stay.

I.5 Conclusion

I.5.1 Evidence Statement

This analysis that compared four service models that would allow endoscopy to occur within 4 hours, 12 hours, 24 hours and what is observed in UK hospitals without out of hour endoscopy service. The model found results to be highly sensitive to the number of presentations a provider would expect per year. For providers expecting fewer than 330 presentations per year, the weekday strategy was most likely to be cost effective; otherwise the everyday strategy was most likely to be cost effective. The cost effectiveness of the everyday strategy was in the main driven by the cost savings realised with reduced length of stay of the low risk patients who were scoped by 24 hours. The conclusion was robust to the majority of sensitivity analyses. However, changes in structural assumptions are most likely to favour the Everyday strategy.

This evidence has direct applicability to the guideline and the NHS setting; however, it has potentially serious limitations.

I.5.2 Implications for future research

Further research that would improve the model would include further studies to confirm the assumption that timing of endoscopy has a causal relationship to discharge, and whether or not survival is affected. If a difference in mortality is observed with differential timing to endoscopy, future evaluations would benefit from a longer time horizon for which long term health benefits and downstream costs for this population would need to be considered.

Appendix J: Time to endoscopy: statistical analysis of the UK Comparative Audit of Upper Gastrointestinal Bleeding and the use of Blood

J.1 Introduction

Many of the model inputs outlined in Appendix I, including the rates of mortality, discharge, and endoscopy, were estimated from data collected by a national prospective audit sponsored by The British Society of Gastroenterologists and the National Blood Service. The estimates used in the economic model were calculated directly from the patient-level dataset, which was provided in full. In total, details for 6750 patients were recorded, each with a Rockall score which was either assigned prospectively or retrospectively calculated by a clinician. Details of the audit population and method have been previously reported [13,22].

J.2 Methods

J.2.1 Preparation of the audit registry dataset to determine rates of endoscopy, mortality and discharge.

The rates of mortality, discharge, and endoscopy, were informed by a statistical analysis of the data provided by the national audit registry. For this analysis, the dataset was cleaned to exclude any records where the time of admission, discharge or death was incomplete or nonsensical (i.e. admission after death). If no time of death or discharge was recorded, information regarding whether the patient was still alive in hospital at 28 days was noted and then these cases are censored at 28 days. Where no endoscopy time was recorded, alternative fields such as the "number of endoscopies received" or "treatment given in first endoscopy" were cross checked to see if the missing time of endoscopy was due to missing data or if no endoscopy had been received. Records where there was no time of endoscopy recorded yet there was evidence that the patient had had an endoscopy were excluded from the analysis. Excluded records are detailed in Table 33.

Table 33: Records excluded from statistical analysis

Reason for exclusion	Number
Evidence of having an endoscopy but no time was recorded the endoscopy, so delay to endoscopy could not be calculated § ±	56
Evidence of having an endoscopy but no presentation time was recorded so delay to endoscopy could not be calculated§	123
No presentation date and no endoscopy date§	38
Endoscopy date before presentation time §	147
Discharge or death date before endoscopy date §	45
Death or discharge date before presentation date §	7
Total	**416**

Note: ± indicates records that had a sensical admission time and included in the estimation of the timing of presentation.

§ indicates records that were included in the estimation of the numbers within each Rockall score subgroup.

For the included records, time from presentation until endoscopy and time from endoscopy until death or discharge was calculated. As the audit only recorded the date (but not the time) of death

and discharge, dummy times for these variables were assigned with guidance from GDG members for clinical relevance. It was assumed that deaths occurred at midday and discharges occurred at 4pm. The exception to this rule was if a patient had died or had been discharged on the same day as admission or on the same day as their endoscopy, in which case death and discharge were assumed to both be at midnight that day.

We coded the patient records according to the the calculated time of presentation to time of endoscopy. Ten of the eleven categories to which patient records were assigned were: endoscoped in[0-4 hours (h), 4-12 h, 12-24 h, 24- 48 h, 48 – 72 h, 4- 5 days (72-120h), 6- 10 days (120-240h), 11-15 days (240h-360h), 16-20 days (360h-480h) and 21-28 days (480h-672h)]. These time periods were chosen in line with the time of the endoscopy the GDG wished to explore in the economic model. For example,the probability of being discharged in the first 4 hours in the continuous strategy would be derived from the rates calculated for the 0-4 hour time period using the data of patients who had endoscopy within this time period. Time periods in subsequent time periods were selected in consideration of the size of the remaining sample in which an event (death or discharge) could occur and were agreed by clinical members of the group. Patient records that did not have an endoscopy recorded were assigned to the eleventh category coded“no endoscopy recorded”. As there were no events occurring in any category within the first 4 hours, the patient records for 0-4 hours and 4-12 hours were combined. Note that in this statistical analysis to determine rates of death and discharge, endoscopy is not viewed as an event.

J.2.2 Dealing with confounding in the dataset.

In current practice, there are several factors that influence a doctor’s decision as to when best to provide endoscopy. For example, some high risk patients may have to be stabilised before endoscopy resulting in additional delay; or alternatively there may be a feeling of urgency for a patient that appears less well than others resulting in an earlier endoscopy time. The GDG identified the following as factors which could influence the doctor’s decision at presentation to provide earlier access to endoscopy:

Factors contained in the Rockall Score:

- History of liver disease or jaundiced look
- Age (with older patients may get scoped more quickly)
- Shock at presentation

Factors not directly contained in the Rockall Score:

- Active bleeding
- Patient presenting in intensive care
- Ongoing hypovolaemic shock despite adequate resuscitation
- Whether additional clinical support is available

It is possible that these same factors will not only influence the doctor’s decision to endoscope early but might be associated with poorer prognosis (higher risk of mortality, and longer stay in hospital). Therefore, the above are potential confounding factors in the statistical analysis of establishing differential mortality and discharge rates according to the time of endoscopy and ideally would be adjusted for.

The standard method for adjusting data for confounding variables in time to event analyses is to undertake a Cox regression. However, the assumptions implicit in this methodology were deemed as unreasonable by the GDG. For example, by using this technique we would assume:

- No interactions between factors we are adjusting for (i.e. age had the same effect in people with liver disease as people without)

- The effect of each factor within a Rockall score was the same regardless of:
  - Follow up time
  - Time to endoscopy

An alternative method is to stratify closely for a combination of confounding risk factors (i.e. those factors that influence the timing of endoscopy and the outcomes of mortality and discharge). The GDG agreed that the population in the audit registry should be stratified by Rockall score. This decision was based on the following observations:

- Each Rockall score represents a combination of risk factors, including many of those identified by the GDG as factors influencing the decision to endoscope earlier and or later (i.e. co morbidity, age, shock).
- The Rockall score is a validated predictor for mortality and no predictors currently exist for resource use in this population.
- There were complete records of Rockall score in the registry data, and therefore missing data and small number issues could be avoided in the statistical analysis.

J.2.3 Calculation of mortality and discharge rates

The data in the statistical analysis is the number of events (deaths and discharges) and the person-time at risk. Discharge and death were treated as competing risks. "Competing risks" refers to the negative correlation between discharges and mortality (if more patients are discharged, then less must die). The data was stratified for 7 different risk groups (a group with a combination of confounding factors); given by the pre endoscopy Rockall score (ranging from 0 to 7) recorded at admission for each patient. Rockall scores 6 and 7 were aggregated in a single group. For each stratum, events and time at risk were calculated for 9 time intervals post admission and 7 endoscopy states presented in Table 34.

Table 34: Codes used for time since admission in hours (h) or days (d) and endoscopy state (in hours)

i	Time since admission	K	Endoscopy state
1	0-12 h	1	pre Endoscopy
2	12-24 h	2	Endoscopy at 0-4 h
3	24- 48 h	3	Endoscopy at 4-12 h
4	48 – 72 h	4	Endoscopy at 12-24 h
5	4- 5d (72-120h)	5	Endoscopy at 24-48 h
6	6- 10 (120-240h)	6	Endoscopy at 48-72 h
7	11-15 d (240h-360h)	7	Endoscopy at 72+ h
8	16-20 d (360h-480h)		
9	21-28 d (480h-672h)		

Time at risk was allocated 'dynamically', so that time at risk PRE-endoscopy is distinguished between time at risk POST-endoscopy. At the same time, the Rockall score and the time of endoscopy were viewed as 'risk factors'. Patients therefore could contribute time at risk pre endoscopy and post endoscopy within any one time period of the statistical model. The essential comparisons are the rates of discharge and deaths between patients that have had different delays to endoscopy for a particular time period in the model. For example, for a patient who has survived 2 days post admission, the question of interest is whether the death and discharge rates for a particular time

period are higher or lower for those who had no endoscopy, had endoscopy 0-4, or had endoscopy 4-12, and so on.

The "transition" from pre to post endoscopy states was not viewed as a competing risk in the statistical model. Rather than endoscopy being viewed as an event, it was viewed as a risk factor for the discharge and death events. This was necessary as it was the role of endoscopy and its timing on outcomes which the statistical model needed to analyse. However, the dynamic allocation of time at risk in the methodology, fully allowed for the apparent "transition" from pre- to post-endoscopy states.

A joint Poisson model was devised to consider the number of events (deaths and discharges), and the person-time at risk. The model assumed constant rates within each of the time periods since admission studied.

Discharges (D) and Mortality (M) are the events of interest. We assumed that for each time post-admission *i* and endoscopy state *k,* discharges and mortalities follow a Poisson distribution with rates γ_{ik} and λ_{ik}, respectively. Because deaths and discharges are mutually exclusive events, for computational stability, we define total number of events at time post-admission *i,* for endoscopy state *k* as

$$Y_{ik} \sim \text{Poisson}\left(E_{ik}(\gamma_{ik} + \lambda_{ik})\right)$$
$$M_{ik} \sim \text{Poisson}\left(E_{ik}\gamma_{ik}\right)$$

where M_{ik} and D_{ik} are the number of deaths and discharges at time post-admission *i*, for endoscopy state *k.* Poisson likelihoods for the number of deaths and total number of events were used: with E_{ik} representing the time at risk (in hours) for all patients at time post-admission *i,* for endoscopy state *k.*

The statistical model was implemented using Markov Chain Monte Carlo (MCMC) simulation in WinBUGS. This is a Bayesian approach and therefore it combines prior beliefs with the likelihood function to give the posterior estimate of the parameter of interest. The rates of mortality and discharge were given exponential prior distributions: Exp(.001). This was chosen so that the posterior distribution for each parameter is almost identical to the likelihood distribution. A change of scale was implemented in the code to ensure that the prior distribution has only minimal effect on the posterior rates when these are very small. This does not affect the results which are converted back to rates per hour in the output tables.

Convergence of the MCMC algorithm was achieved by 20,000 iterations after which 1,000 samples from the posterior distribution were drawn from 3 independent chains. The employed rate of discharge and death for each endoscopy state for each time period in the deterministic analysis was the mean rate calculated across the 3000 values generated by the MCMC simulation.

J.3 Results

Rates of mortality and discharge, for each Rockall score, are presented for each of the nine post-admission times and for each of the seven endoscopy states in Table 35 to Table 41. These rates are also represented in Figures as the probability of survival (given not discharged), non-discharge (given alive) or being alive and not discharged, assuming that the rates are constant in a given interval (Figure 5 to Figure 7). Due to the large number of lines plotted in each graph, we have not reported the credible interval for each estimated rate, and caution should be used not to over-interpret the single rates displayed in the plots.

J.4 Interpretation and limitations

The statistical model estimated rates of mortality and discharge using the data collected by a prospective registry. The Kaplan Meier curves in Figure 169 show that there is a decreasing probability of survival as Rockall score increases. However, the Kaplan Meier curves for each Rockall score within this figure are difficult to interpret and do not suggest a clear relationship between the time of endoscopy and the probability of endoscopy across risk groups.

The Kaplan Meier curves in Figure 170 show the probability of not being discharged, with death censored. The gradient of the curve is in general steeper in the time period post admission for the lower Rockall scores than it is in the higher Rockall scores, suggesting that patients with a lower Rockall score are in general discharged more quickly across all endoscopy groups. The potential relationship between time to endoscopy and rate of discharge is clearer for the lower Rockall scores than it is for the higher Rockall scores.

For Rockall score 0 and 1, the curves show that a patient has the same or lower probability of being discharged if they have an endoscopy than if they do not, as all curves for the endoscopy group are underneath that for those who continue to wait for endoscopy (shown by the black curve). Until at least 48 hours post admission for these subgroups, those which have been endoscoped earlier, have a higher probability of being discharged.

With increasing Rockall score, there is a less clear pattern between time of endoscopy and the probability of discharge. At some points on the Kaplan Meier curves, it can be observed that the probability of being discharged is higher for patients who have been endoscoped earlier, than for those patients who have been endoscoped later, or continue to wait for endoscopy. However, the probability of being discharged after having an endoscopy at 12 or more hours after admission is higher than if still waiting for an endoscopy (shown in black) across all Rockall groups.

The Kaplan Meier curves in Figure 171 show the probability of being in hospital and alive (thereby combining the rates for mortality and discharge). In general, the same trends as seen in Figure 6 can be observed until Rockall score 5, 6 and 7. There is a higher rate of mortality in the higher Rockall scores, and this can be seen in the reduced probability of being in hospital and alive. Thus, it becomes less clear how timing of endoscopy may affect the likely length of hospital stay in the high Rockall scores.

In general, caution should be exercised when interpreting the figures presented, as uncertainty surrounding the mean rate calculated has not been depicted. Further, interpretation of the tail ends of the Kaplan Meier curves should also be done with care, as with increasing time from presentation, there is a decreasing sample to calculate the rate of mortality and discharge.

A key limitation of the statistical analysis is the simplification that only time of endoscopy and Rockall score could have influenced the outcome in the audit dataset. Even within patients with a specified Rockall score, there might still be confounding factors, i.e. factors that are both related to outcome and to the probability of endoscopy at a specific time. The counter intuitive result that in the higher Rockall scores you may be more likely to be discharged later with an early endoscopy (before 12 hours), could in part be explained by the lack of control for confounding factors, for example a doctor's selection of potentially sicker patients within a Rockall score to be endoscoped earlier. However, the potential of such confounding is a limitation of working with an observational dataset, from which it is difficult to make firm assertions of causal effect.

Table 35: Posterior mean and standard deviation (SD) for the rates of mortality, discharge and any event (mortality or discharge) by endoscopy group and time since admission for patient with Rockall = 0

Time since presentation (hours)	Endoscopy group (based on time of endoscopy post admission in hours)													
	Pre endoscopy		Post: 0-4 h		Post: 4-12 h		Post: 12-24 h		Post: 24-48 h		Post: 48-72 h		Post: 72+ h	
	mean	Sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd
Mortality														
0-12	0.000000	0.000000	0.000003	0.000003	0.000002	0.000002	NA	NA	NA	NA	NA	NA	NA	NA
12-24	0.000000	0.000000	0.000004	0.000004	0.000919	0.000030	0.000001	0.000001	NA	NA	NA	NA	NA	NA
24-48	0.000000	0.000000	0.000003	0.000003	0.000001	0.000001	0.000284	0.000009	0.000001	0.000001	NA	NA	NA	NA
48-72	0.000000	0.000000	0.000004	0.000004	0.000001	0.000001	0.000000	0.000000	0.000001	0.000001	0.000001	0.000001	NA	NA
72-120	0.000000	0.000000	0.000002	0.000002	0.000001	0.000001	0.000000	0.000000	0.000541	0.000017	0.000001	0.000001	0.000001	0.000001
120-240	0.000000	0.000000	0.000002	0.000002	0.000001	0.000001	0.000000	0.000000	0.000001	0.000001	0.000001	0.000001	0.000000	0.000000
240-360	0.000001	0.000001	0.000008	0.000008	0.000001	0.000001	0.000001	0.000001	0.000001	0.000001	0.000002	0.000002	0.000664	0.000021
360-480	0.000001	0.000001	0.000004	0.000004	0.001163	0.000038	0.000003	0.000003	0.000002	0.000002	0.000006	0.000006	0.000001	0.000001
480-672	0.000000	0.000000	0.000026	0.000027	0.000000	0.000000	0.000001	0.000001	0.000000	0.000000	0.000000	0.000000	0.000000	0.000000
Discharge														
0-12	0.005426	0.000021	0.032570	0.000304	0.002410	0.000077	NA	NA	NA	NA	NA	NA	NA	NA
12-24	0.017490	0.000045	0.033740	0.000380	0.021100	0.000147	0.004237	0.000059	NA	NA	NA	NA	NA	NA
24-48	0.011380	0.000036	0.012010	0.000191	0.017220	0.000106	0.029800	0.000093	0.023260	0.000109	NA	NA	NA	NA
48-72	0.007555	0.000041	0.007195	0.000160	0.007336	0.000082	0.017770	0.000095	0.032570	0.000130	0.015770	0.000144	NA	NA
72-120	0.005518	0.000034	0.006772	0.000128	0.012860	0.000093	0.010930	0.000067	0.014040	0.000090	0.028780	0.000145	0.021320	0.000144
120-240	0.005226	0.000035	0.012390	0.000162	0.008343	0.000071	0.011230	0.000068	0.009351	0.000069	0.013440	0.000119	0.011290	0.000062
240-360	0.007737	0.000086	0.008067	0.000256	0.001033	0.000032	0.006291	0.000088	0.002653	0.000049	0.004673	0.000104	0.010600	0.000089
360-480	0.001473	0.000046	0.000008	0.000008	0.001162	0.000066	0.005294	0.000120	0.005075	0.000091	0.012990	0.000282	0.003653	0.000067
480-672	0.000277	0.000009	0.025630	0.000817	0.000528	0.000012	0.000936	0.000029	0.000000	0.000000	0.000000	0.000000	0.000268	0.000009

Sd= Standard deviation; NA= data not available

Table 36: Posterior mean and standard deviation (SD) for the rates of mortality, discharge and any event (mortality or discharge) by endoscopy group and time since admission for patient with Rockall = 1

Time since presentation (hours)	Endoscopy group (based on time of endoscopy post admission in hours)													
	Pre endoscopy		Post: 0-4 h		Post: 4-12 h		Post: 12-24 h		Post: 24-48 h		Post: 48-72 h		Post: 72+ h	
	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd
Mortality														
0-12	0.000000	0.000000	0.000003	0.000003	0.000003	0.000003	NA	NA	NA	NA	NA	NA	NA	NA
12-24	0.000134	0.000004	0.000004	0.000004	0.000001	0.000001	0.000001	0.000001	NA	NA	NA	NA	NA	NA
24-48	0.000000	0.000000	0.000003	0.000003	0.000000	0.000000	0.000000	0.000000	0.000001	0.000000	NA	NA	NA	NA
48-72	0.000000	0.000000	0.000003	0.000003	0.000001	0.000001	0.000297	0.000009	0.000000	0.000000	0.000001	0.000001	NA	NA
72-120	0.000000	0.000000	0.000003	0.000003	0.000000	0.000000	0.000000	0.000000	0.000000	0.000000	0.000000	0.000000	0.000001	0.000001
120-240	0.000000	0.000000	0.002804	0.000090	0.000998	0.000018	0.000000	0.000000	0.000000	0.000000	0.000001	0.000001	0.000000	0.000000
240-360	0.000509	0.000016	0.000004	0.000004	0.000001	0.000001	0.000000	0.000000	0.000000	0.000000	0.000003	0.000003	0.001102	0.000020
360-480	0.000001	0.000001	0.000004	0.000004	0.000001	0.000001	0.000000	0.000000	0.000001	0.000001	0.000004	0.000004	0.000000	0.000000
480-672	0.000000	0.000000	0.022170	0.000554	0.000150	0.000005	0.000487	0.000009	0.000148	0.000005	0.009360	0.000309	0.000093	0.000003
Discharges														
0-12	0.002585	0.000016	0.010350	0.000190	0.002697	0.000085	NA	NA	NA	NA	NA	NA	NA	NA
12-24	0.005492	0.000028	0.039130	0.000405	0.005844	0.000070	0.000799	0.000026	NA	NA	NA	NA	NA	NA
24-48	0.006081	0.000027	0.005151	0.000116	0.009188	0.000067	0.016010	0.000059	0.008611	0.000067	NA	NA	NA	NA
48-72	0.002347	0.000022	0.009404	0.000176	0.007247	0.000068	0.007718	0.000049	0.016490	0.000073	0.006205	0.000088	NA	NA
72-120	0.004370	0.000027	0.019130	0.000227	0.009500	0.000063	0.009565	0.000045	0.009791	0.000052	0.021100	0.000103	0.015440	0.000106
120-240	0.004226	0.000028	0.008372	0.000198	0.006975	0.000054	0.008862	0.000038	0.006855	0.000036	0.011430	0.000082	0.013180	0.000060
240-360	0.003043	0.000046	0.000008	0.000008	0.001075	0.000024	0.002852	0.000032	0.002732	0.000033	0.005210	0.000118	0.002941	0.000043
360-480	0.005639	0.000080	0.000008	0.000008	0.004473	0.000057	0.002452	0.000035	0.003185	0.000042	0.003651	0.000117	0.002433	0.000035
480-672	0.000000	0.000000	0.000643	0.000519	0.000149	0.000008	0.000812	0.000017	0.000740	0.000012	0.009171	0.000521	0.000466	0.000008

Sd= Standard deviation; NA= data not available

Table 37: Posterior mean and standard deviation (SD) for the rates of mortality, discharge and any event (mortality or discharge) by endoscopy group and time since admission for patient with Rockall = 2

Time since presentation (hours)	Endoscopy group (based on time of endoscopy post admission in hours)													
	Pre endoscopy		Post: 0-4 h		Post: 4-12 h		Post: 12-24 h		Post: 24-48 h		Post: 48-72 h		Post: 72+ h	
	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd
Mortality														
0-12	0.000232	0.000005	0.000003	0.000003	0.000003	0.000003	NA	NA	NA	NA	NA	NA	NA	NA
12-24	0.000917	0.000012	0.002609	0.000083	0.000933	0.000030	0.000001	0.000001	NA	NA	NA	NA	NA	NA
24-48	0.000236	0.000005	0.000001	0.000001	0.000514	0.000016	0.000263	0.000008	0.000001	0.000001	NA	NA	NA	NA
48-72	0.000177	0.000006	0.000002	0.000002	0.000001	0.000001	0.000335	0.000010	0.000389	0.000013	0.000001	0.000001	NA	NA
72-120	0.000417	0.000007	0.000001	0.000001	0.000000	0.000000	0.000000	0.000000	0.000257	0.000008	0.000000	0.000000	0.000001	0.000001
120-240	0.000128	0.000004	0.000001	0.000001	0.000253	0.000008	0.000584	0.000009	0.000171	0.000005	0.000000	0.000000	0.000189	0.000006
240-360	0.000237	0.000007	0.000001	0.000001	0.000451	0.000014	0.000243	0.000008	0.000000	0.000000	0.000000	0.000000	0.000000	0.000000
360-480	0.001126	0.000021	0.000001	0.000001	0.000001	0.000001	0.000715	0.000016	0.000000	0.000000	0.000001	0.000001	0.000298	0.000009
480-672	0.000088	0.000003	0.000209	0.000007	0.000000	0.000000	0.000274	0.000005	0.000408	0.000006	0.000000	0.000000	0.000192	0.000004
Discharge														
0-12	0.001855	0.000016	0.003123	0.000098	0.004932	0.000111	NA	NA	NA	NA	NA	NA	NA	NA
12-24	0.002596	0.000026	0.002587	0.000144	0.001862	0.000059	0.000975	0.000031	NA	NA	NA	NA	NA	NA
24-48	0.003540	0.000021	0.004307	0.000082	0.006163	0.000061	0.009981	0.000052	0.007035	0.000066	NA	NA	NA	NA
48-72	0.001767	0.000019	0.001526	0.000049	0.004064	0.000050	0.007367	0.000052	0.008145	0.000058	0.007025	0.000091	NA	NA
72-120	0.002779	0.000022	0.008373	0.000089	0.005199	0.000044	0.006090	0.000035	0.006400	0.000041	0.008159	0.000056	0.014990	0.000103
120-240	0.002933	0.000020	0.004216	0.000050	0.007085	0.000044	0.006132	0.000033	0.006154	0.000034	0.005132	0.000036	0.009808	0.000045
240-360	0.001180	0.000020	0.004110	0.000065	0.004503	0.000049	0.002431	0.000027	0.002962	0.000030	0.003585	0.000038	0.002617	0.000025
360-480	0.001502	0.000038	0.000001	0.000001	0.003363	0.000054	0.002146	0.000035	0.002039	0.000028	0.001859	0.000034	0.002083	0.000029
480-672	0.000350	0.000007	0.000208	0.000011	0.000530	0.000010	0.000549	0.000010	0.000408	0.000011	0.000358	0.000007	0.000512	0.000008

Sd= Standard deviation; NA= data not available

Table 38: Posterior mean and standard deviation (SD) for the rates of mortality, discharge and any event (mortality or discharge) by endoscopy group and time since admission for patient with Rockall = 3

Time since presentation (hours)	Endoscopy group (based on time of endoscopy post admission in hours)													
	Pre endoscopy		Post: 0-4 h		Post: 4-12 h		Post: 12-24 h		Post: 24-48 h		Post: 48-72 h		Post: 72+ h	
	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd
Mortality														
0-12	0.000301	0.000006	0.000001	0.000001	0.000001	0.000001	NA	NA	NA	NA	NA	NA	NA	NA
12-24	0.001039	0.000011	0.000001	0.000001	0.003166	0.000050	0.000001	0.000001	NA	NA	NA	NA	NA	NA
24-48	0.000406	0.000006	0.000001	0.000001	0.000443	0.000014	0.000470	0.000010	0.000480	0.000015	NA	NA	NA	NA
48-72	0.000151	0.000005	0.000856	0.000027	0.000000	0.000000	0.000000	0.000000	0.000330	0.000010	0.000001	0.000001	NA	NA
72-120	0.000233	0.000005	0.000001	0.000001	0.000284	0.000009	0.000530	0.000010	0.000225	0.000007	0.000000	0.000000	0.000547	0.000018
120-240	0.000223	0.000005	0.001102	0.000020	0.000185	0.000006	0.000221	0.000005	0.000303	0.000007	0.000966	0.000015	0.000000	0.000000
240-360	0.000260	0.000008	0.000001	0.000001	0.000339	0.000011	0.000000	0.000000	0.000000	0.000000	0.000492	0.000016	0.000000	0.000000
360-480	0.000393	0.000011	0.000001	0.000001	0.001178	0.000026	0.000632	0.000014	0.000791	0.000017	0.000001	0.000001	0.000245	0.000008
480-672	0.000201	0.000005	0.000257	0.000008	0.000420	0.000009	0.000071	0.000002	0.000087	0.000003	0.000000	0.000000	0.000279	0.000004
Discharges														
0-12	0.000602	0.000011	0.000002	0.000002	0.000002	0.000002	NA	NA	NA	NA	NA	NA	NA	NA
12-24	0.002466	0.000025	0.000002	0.000002	0.002369	0.000082	0.001904	0.000043	NA	NA	NA	NA	NA	NA
24-48	0.002028	0.000017	0.002408	0.000043	0.004425	0.000050	0.010340	0.000052	0.006231	0.000060	NA	NA	NA	NA
48-72	0.003612	0.000024	0.003416	0.000066	0.003432	0.000041	0.005141	0.000039	0.010210	0.000061	0.006925	0.000083	NA	NA
72-120	0.002331	0.000018	0.004611	0.000049	0.005379	0.000041	0.005296	0.000034	0.005856	0.000037	0.007981	0.000056	0.010360	0.000080
120-240	0.003124	0.000020	0.007341	0.000060	0.005183	0.000032	0.004974	0.000025	0.006201	0.000032	0.004827	0.000040	0.006824	0.000029
240-360	0.002600	0.000029	0.002724	0.000043	0.004740	0.000043	0.004087	0.000028	0.003759	0.000031	0.002945	0.000044	0.004854	0.000028
360-480	0.000014	0.000011	0.001854	0.000042	0.002942	0.000056	0.003156	0.000038	0.001186	0.000033	0.004083	0.000053	0.003906	0.000033
480-672	0.000301	0.000008	0.000770	0.000018	0.001049	0.000020	0.000353	0.000006	0.000523	0.000008	0.000271	0.000006	0.000446	0.000008

Sd= Standard deviation; NA= data not available

Table 39: Posterior mean and standard deviation (SD) for the rates of mortality, discharge and any event (mortality or discharge) by endoscopy group and time since admission for patient with Rockall = 4

Time since presentation (hours)	Endoscopy group (based on time of endoscopy post admission in hours)													
	Pre endoscopy		Post: 0-4 h		Post: 4-12 h		Post: 12-24 h		Post: 24-48 h		Post: 48-72 h		Post: 72+ h	
	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd
Mortality														
0-12	0.000000	0.000000	0.000001	0.000001	0.001835	0.000049	NA	NA	NA	NA	NA	NA	NA	NA
12-24	0.001254	0.000012	0.001963	0.000052	0.000731	0.000023	0.000000	0.000000	NA	NA	NA	NA	NA	NA
24-48	0.000669	0.000007	0.001091	0.000035	0.001960	0.000027	0.000219	0.000007	0.000445	0.000014	NA	NA	NA	NA
48-72	0.000695	0.000009	0.001082	0.000028	0.000429	0.000014	0.000518	0.000012	0.000000	0.000000	0.000001	0.000001	NA	NA
72-120	0.000883	0.000008	0.000602	0.000019	0.000489	0.000011	0.000470	0.000009	0.000180	0.000006	0.000759	0.000017	0.000000	0.000000
120-240	0.000742	0.000006	0.001124	0.000020	0.000285	0.000006	0.000819	0.000010	0.000108	0.000003	0.001386	0.000021	0.000351	0.000006
240-360	0.001357	0.000012	0.000619	0.000019	0.000729	0.000014	0.000226	0.000007	0.001011	0.000013	0.001193	0.000026	0.000112	0.000003
360-480	0.000971	0.000013	0.000001	0.000001	0.000736	0.000016	0.000000	0.000000	0.000797	0.000014	0.000001	0.000001	0.000141	0.000004
480-672	0.000304	0.000004	0.000000	0.000000	0.000000	0.000000	0.000349	0.000006	0.000167	0.000004	0.000993	0.000016	0.000085	0.000002
Discharge														
0-12	0.000336	0.000005	0.000002	0.000002	0.000065	0.000050	NA	NA	NA	NA	NA	NA	NA	NA
12-24	0.002506	0.000023	0.000071	0.000053	0.000729	0.000040	0.000001	0.000001	NA	NA	NA	NA	NA	NA
24-48	0.001635	0.000015	0.002178	0.000069	0.002346	0.000049	0.006325	0.000039	0.002222	0.000038	NA	NA	NA	NA
48-72	0.002680	0.000020	0.000038	0.000029	0.002570	0.000038	0.005691	0.000041	0.008475	0.000049	0.001298	0.000041	NA	NA
72-120	0.002794	0.000018	0.002405	0.000047	0.003419	0.000033	0.006573	0.000034	0.005560	0.000033	0.010610	0.000070	0.005188	0.000046
120-240	0.002168	0.000014	0.005244	0.000053	0.004279	0.000026	0.005965	0.000030	0.004296	0.000022	0.006924	0.000057	0.005177	0.000023
240-360	0.002485	0.000024	0.000616	0.000033	0.003888	0.000036	0.003606	0.000030	0.002697	0.000028	0.001787	0.000049	0.003562	0.000020
360-480	0.001553	0.000025	0.004370	0.000062	0.002575	0.000037	0.003345	0.000035	0.002921	0.000035	0.001587	0.000035	0.002950	0.000022
480-672	0.000304	0.000007	0.001594	0.000022	0.000385	0.000005	0.000815	0.000013	0.000917	0.000010	0.000743	0.000026	0.000398	0.000004

Sd= Standard deviation; NA= data not available

Table 40: Posterior mean and standard deviation (SD) for the rates of mortality, discharge and any event (mortality or discharge) by endoscopy group and time since admission for patient with Rockall = 5

Time since presentation (hours)	Endoscopy group (based on time of endoscopy post admission in hours)													
	Pre endoscopy		Post: 0-4 h		Post: 4-12 h		Post: 12-24 h		Post: 24-48 h		Post: 48-72 h		Post: 72+ h	
	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd
Mortality														
0-12	0.000587	0.000009	0.000002	0.000002	0.005670	0.000107	NA	NA	NA	NA	NA	NA	NA	NA
12-24	0.002532	0.000022	0.001380	0.000036	0.002073	0.000046	0.000001	0.000001	NA	NA	NA	NA	NA	NA
24-48	0.001407	0.000014	0.001494	0.000034	0.000563	0.000018	0.002459	0.000029	0.000785	0.000020	NA	NA	NA	NA
48-72	0.001173	0.000015	0.000000	0.000000	0.000001	0.000001	0.000391	0.000012	0.000508	0.000016	0.000001	0.000001	NA	NA
72-120	0.000835	0.000011	0.000827	0.000018	0.000321	0.000010	0.000422	0.000010	0.000592	0.000013	0.000000	0.000000	0.000001	0.000001
120-240	0.001191	0.000010	0.000000	0.000000	0.000697	0.000011	0.000496	0.000008	0.000491	0.000009	0.000483	0.000011	0.000000	0.000000
240-360	0.000881	0.000011	0.000914	0.000017	0.000322	0.000010	0.000608	0.000011	0.001090	0.000017	0.000802	0.000018	0.000549	0.000012
360-480	0.001373	0.000019	0.000385	0.000012	0.000001	0.000001	0.001548	0.000022	0.000963	0.000021	0.000561	0.000018	0.000000	0.000000
480-672	0.000254	0.000005	0.001021	0.000011	0.000000	0.000000	0.000249	0.000005	0.000485	0.000008	0.000000	0.000000	0.000683	0.000007
Discharge														
0-12	0.000147	0.000014	0.003399	0.000076	0.000138	0.000106	NA	NA	NA	NA	NA	NA	NA	NA
12-24	0.000780	0.000033	0.000049	0.000037	0.001035	0.000073	0.000001	0.000001	NA	NA	NA	NA	NA	NA
24-48	0.001407	0.000024	0.002231	0.000063	0.002806	0.000047	0.002106	0.000049	0.000028	0.000021	NA	NA	NA	NA
48-72	0.001955	0.000029	0.000001	0.000001	0.001776	0.000032	0.001171	0.000028	0.003044	0.000046	0.000001	0.000001	NA	NA
72-120	0.002227	0.000023	0.002895	0.000043	0.001927	0.000028	0.003795	0.000032	0.003551	0.000037	0.004447	0.000043	0.006866	0.000098
120-240	0.001445	0.000018	0.001647	0.000018	0.003829	0.000031	0.003596	0.000024	0.003437	0.000028	0.004822	0.000037	0.004641	0.000037
240-360	0.001908	0.000023	0.003352	0.000040	0.005461	0.000044	0.002832	0.000029	0.003541	0.000039	0.002407	0.000041	0.004115	0.000037
360-480	0.003566	0.000041	0.000769	0.000024	0.003154	0.000041	0.003401	0.000045	0.003849	0.000053	0.001120	0.000035	0.003248	0.000034
480-672	0.000169	0.000008	0.000339	0.000016	0.000363	0.000007	0.000332	0.000008	0.000243	0.000012	0.001162	0.000014	0.000152	0.000011

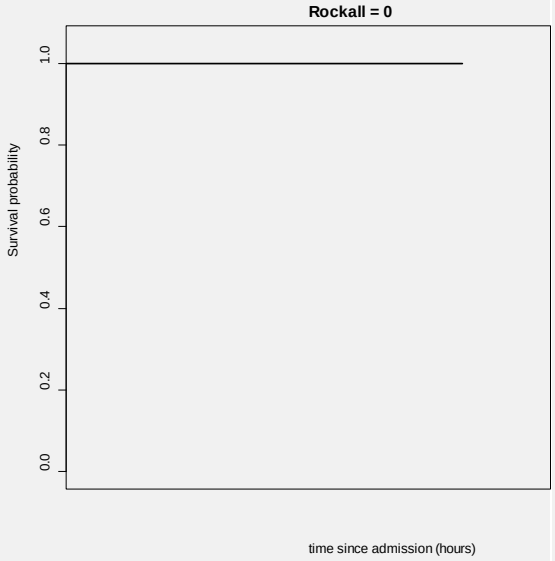
Sd= Standard deviation; NA= data not available

Table 41: Posterior mean and standard deviation (SD) for the rates of mortality, discharge and any event (mortality or discharge) by endoscopy group and time since admission for patient with Rockall = 6 or 7

Time since presentation (hours)	Endoscopy group (based on time of endoscopy post admission in hours)													
	Pre endoscopy		Post: 0-4 h		Post: 4-12 h		Post: 12-24 h		Post: 24-48 h		Post: 48-72 h		Post: 72+ h	
	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd
Mortality														
0-12	0.001400	0.000016	0.004586	0.000119	0.000002	0.000002	NA	NA	NA	NA	NA	NA	NA	NA
12-24	0.007823	0.000054	0.008290	0.000151	0.004610	0.000069	0.000001	0.000001	NA	NA	NA	NA	NA	NA
24-48	0.006236	0.000042	0.002253	0.000060	0.000802	0.000021	0.002517	0.000046	0.000001	0.000001	NA	NA	NA	NA
48-72	0.001649	0.000027	0.002398	0.000062	0.000000	0.000000	0.001856	0.000041	0.002464	0.000055	0.002744	0.000071	NA	NA
72-120	0.002054	0.000025	0.002679	0.000059	0.001837	0.000028	0.002238	0.000036	0.000001	0.000001	0.001007	0.000031	0.000003	0.000003
120-240	0.002856	0.000025	0.000705	0.000022	0.001641	0.000021	0.000624	0.000014	0.000652	0.000014	0.001147	0.000026	0.001370	0.000024
240-360	0.001865	0.000026	0.000001	0.000001	0.000854	0.000019	0.000421	0.000013	0.000000	0.000000	0.000001	0.000001	0.000556	0.000018
360-480	0.000596	0.000019	0.000001	0.000001	0.000001	0.000001	0.000562	0.000018	0.000001	0.000001	0.000001	0.000001	0.000741	0.000019
480-672	0.000899	0.000012	0.000000	0.000000	0.000430	0.000008	0.000621	0.000010	0.000594	0.000011	0.000208	0.000006	0.000571	0.000010
Discharge														
0-12	0.000022	0.000017	0.000157	0.000122	0.000004	0.000003	NA	NA	NA	NA	NA	NA	NA	NA
12-24	0.000387	0.000078	0.000202	0.000154	0.000091	0.000071	0.000003	0.000003	NA	NA	NA	NA	NA	NA
24-48	0.001132	0.000062	0.000080	0.000062	0.000029	0.000022	0.003346	0.000085	0.000002	0.000002	NA	NA	NA	NA
48-72	0.001648	0.000045	0.000083	0.000063	0.000001	0.000001	0.003705	0.000081	0.003687	0.000103	0.000096	0.000073	NA	NA
72-120	0.000882	0.000039	0.001331	0.000094	0.003670	0.000057	0.002796	0.000064	0.002108	0.000040	0.004013	0.000075	0.007146	0.000130
120-240	0.001835	0.000040	0.003514	0.000060	0.002459	0.000040	0.001246	0.000028	0.002279	0.000033	0.004008	0.000059	0.000914	0.000040
240-360	0.001490	0.000044	0.001181	0.000038	0.002557	0.000043	0.003361	0.000042	0.002280	0.000033	0.001939	0.000043	0.003882	0.000053
360-480	0.001788	0.000042	0.000001	0.000001	0.002581	0.000041	0.001120	0.000036	0.003540	0.000050	0.001091	0.000035	0.000026	0.000020
480-672	0.000359	0.000019	0.002267	0.000032	0.000287	0.000013	0.000466	0.000017	0.000396	0.000018	0.000207	0.000011	0.000572	0.000018

Sd= Standard deviation; NA= data not available

Figure 169: Probability of survival for each subgroup according to endoscopy time.



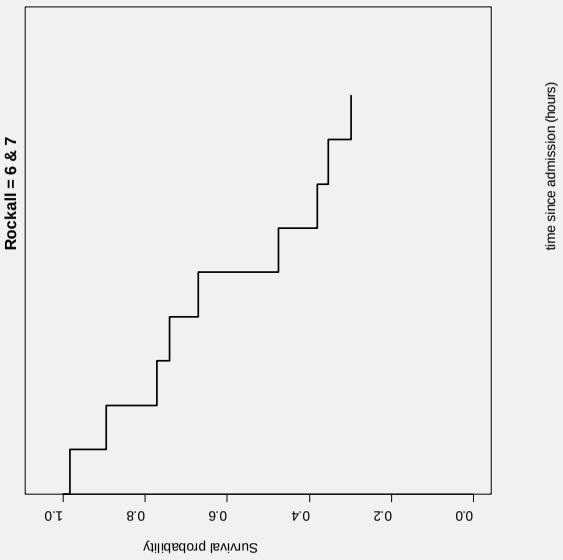
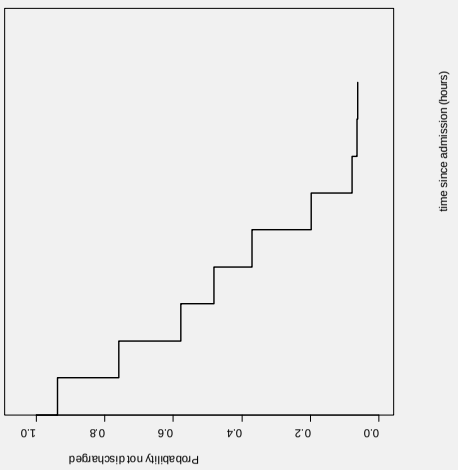

Rockall = 6 & 7
Survival probability
0.0
0.2
0.4
0.6
0.8
1.0
time since admission (hours)

Figure 170: Probability of not being discharged for each subgroup according to endoscopy time



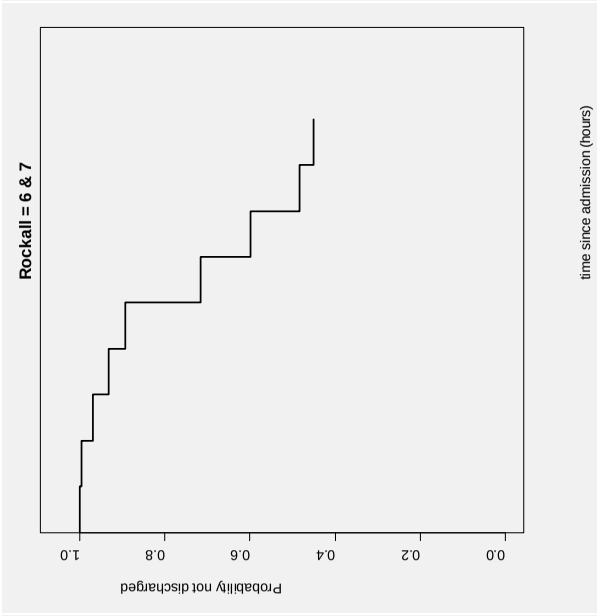
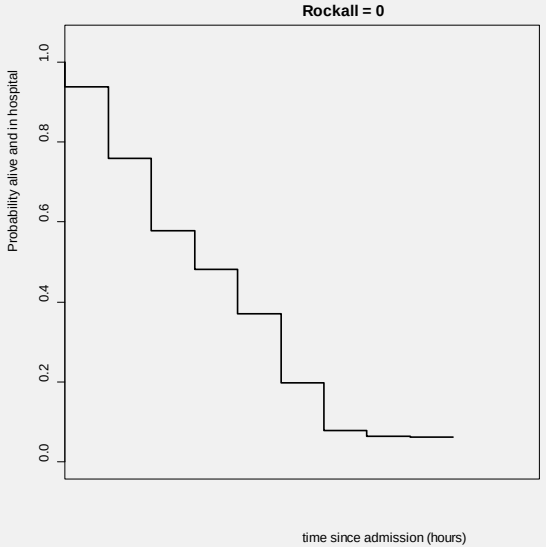
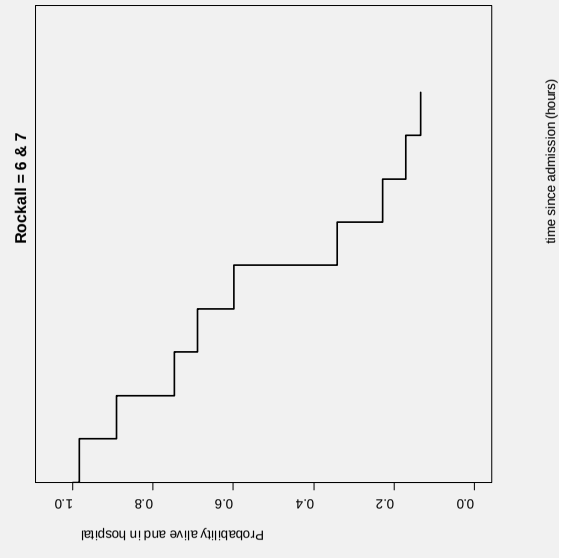

Rockall = 6 & 7
Probability not discharged
0.0
0.2
0.4
0.6
0.8
1.0
time since admission (hours)

Figure 171: Probability of staying alive and in hospital for each group in the audit according to their endoscopy time.




Rockall = 6 & 7
Probability alive and in hospital
0.0
0.2
0.4
0.6
0.8
1.0
time since admission (hours)

References for Appendix I and J

Appendix K: Excluded Studies

K.1 Initial Management

K.1.1 Blood Products

K.1.1.1 Clinical question 1

Study	Reasons for exclusion
American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. Practice guidelines for perioperative blood transfusion and adjuvant therapies: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. Anesthesiology. 2006; 105(1):198-208.	Not addressing clinical/review question
Barikbin R, Hekmatnia A, Omidifar N et al. Prediction severity of esophageal varices: a new cutoff point for Platelet count/ spleen	Not addressing clinical/review question

Study	Reasons for exclusion
diameter ratio. Minerva Gastroenterol Dietol. 2010; 56(1):1-6.	
Bellotto F, Fagiuoli S, Pavei A et al. Anemia and ischemia: myocardial injury in patients with gastrointestinal bleeding. Am J Med. 2005; 118(5):548-551.	Not addressing pre-specified population
Bracey AW, Radovancevic R, Riggs SA et al. Lowering the hemoglobin threshold for transfusion in coronary artery bypass procedures: effect on patient outcome. Transfusion (Paris). 1999; 39(10):1070-1077.	Not addressing clinical/review question
Carless PA, Henry DA, Carson JL et al. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev. 2010; 10:CD002042.	Not addressing pre-specified population
Dellinger RP, Levy MM, Carlet JM et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med. 2008; 36(1):296-327.	Not addressing clinical/review question
Elizalde JI, Moitinho E, Garcia-Pagan JC et al. Effects of increasing blood hemoglobin levels on systemic hemodynamics of acutely anemic cirrhotic patients. J Hepatol. 1998; 29(5):789-795.	Not addressing pre-specified outcomes
Hearnshaw S, Travis S, Murphy M. The role of blood transfusion in the management of upper and lower intestinal tract bleeding. [Review] [73 refs]. Best Practice & Research in Clinical Gastroenterology. 2008; 22(2):355-371.	Review article
Hebert PC, Wells G, Blajchman MA et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med. 1999; 340(6):409-417.	Not addressing pre-specified population
Jairath V, Hearnshaw S, Brunskill SJ et al. Red cell transfusion for the management of upper gastrointestinal haemorrhage. Cochrane Database Syst Rev. 2010; 9:CD006613.	Cochrane review – cross referenced in the clinical evidence summary.
Marik PE, Corwin HL. Efficacy of red blood cell transfusion in the critically ill: a systematic review of the literature. Crit Care Med. 2008; 36(9):2667-2674.	Review paper
Sihler KC, Napolitano LM. Massive transfusion: New insights. Chest. 2009; 136(6):1654-1667.	Review paper
Stainsby D, MacLennan S, Thomas D et al. Guidelines on the management of massive blood loss. Br J Haematol. 2006; 135(5):634-641.	Not addressing clinical/review question

K.1.1.2 Clinical question 2

Study	Reasons for exclusion
Lam MSH, Sims-McCallum RP. Recombinant factor VIIa in the treatment of non-hemophiliac bleeding. Ann Pharmacother. 2005; 39(5):885-891.	Case review
Mallarkey G, Brighton T, Thomson A et al. An evaluation of eptacog alfa in nonhaemophiliac conditions. [Review] [127 refs]. Drugs. 2008; 68(12):1665-1689.	Not addressing pre-specified population
Marti-Carvajal AJ, Salanti G, Marti-Carvajal PI. Human recombinant activated factor VII for upper gastrointestinal bleeding in patients with liver diseases. [Review] [45 refs]. Cochrane Database of Systematic Reviews. 2007;(1):CD004887.	Cochrane review – cross referenced
Tripodi A, Caldwell SH, Hoffman M et al. Review article: the prothrombin time test as a measure of bleeding risk and prognosis in liver disease. Aliment Pharmacol Ther. 2007; 26(2):141-148.	Not addressing clinical question/review
Vieira da Rocha EC, D'Amico EA, Caldwell SH et al. A prospective study	Review article

Study	Reasons for exclusion
of conventional and expanded coagulation indices in predicting ulcer bleeding after variceal band ligation. Clinical Gastroenterology & Hepatology. 2009; 7(9):988-993.	

K.1.2 Terlipressin

Study	Reasons for exclusion
Abid S, Jafri W, Hamid S et al. Terlipressin vs. octreotide in bleeding esophageal varices as an adjuvant therapy with endoscopic band ligation: a randomized double-blind placebo-controlled trial. Am J Gastroenterol. 2009; 104(3):617-623.	Pharmaceutical treatment as adjuvant therapy rather than direct comparison
Baik SK, Jeong PH, Ji SW et al. Acute hemodynamic effects of octreotide and terlipressin in patients with cirrhosis: a randomized comparison. Am J Gastroenterol. 2005; 100(3):631-635.	Outcomes not relevant
Bruha R, Marecek Z, Spicak J et al. Double-blind randomized, comparative multicenter study of the effect of terlipressin in the treatment of acute esophageal variceal and/or hypertensive gastropathy bleeding. Hepatogastroenterology. 2002; 49(46):1161-1166. Ref ID: 98	Time as well as doses variation
Chiu KW, Sheen IS, Liaw YF. A controlled study of glypressin versus vasopressin in the control of bleeding from oesophageal varices. Journal of Gastroenterology & Hepatology. 1990; 5(5):549-553.	Not addressing pre-specified intervention/comparison
D'Amico G, Traina M, Vizzini G et al. Terlipressin or vasopressin plus transdermal nitroglycerin in a treatment strategy for digestive bleeding in cirrhosis. A randomized clinical trial. Liver Study Group of V. Cervello Hospital. J Hepatol. 1994; 20(2):206-212.	Not addressing pre-specified intervention/comparison
Escorsell A, Ruiz del AL, Planas R et al. Multicenter randomized controlled trial of terlipressin versus sclerotherapy in the treatment of acute variceal bleeding: the TEST study. Hepatology. 2000; 32(3):471-476.	Comparison not relevant
Fort E, Sautereau D, Silvain C et al. A randomized trial of terlipressin plus nitroglycerin vs. balloon tamponade in the control of acute variceal hemorrhage. Hepatology. 1990; 11(4):678-681.	Comparison not relevant
Freeman JG, Cobden I, Lishman AH et al. Controlled trial of terlipressin ('Glypressin') versus vasopressin in the early treatment of oesophageal varices. Lancet. 1982; 2(8289):66-68.	Not addressing pre-specified intervention/comparison
Garcia-Compean D, Blanc P, Bories JM et al. Treatment of active gastroesophageal variceal bleeding with terlipressin or hemostatic balloon in patients with cirrhosis. A randomized controlled trial. Arch Med Res. 1997; 28(2):241-245.	Comparison not relevant
Gotzsche PC, Hrobjartsson A. Somatostatin analogues for acute bleeding oesophageal varices. [Review] [58 refs][Update of Cochrane Database Syst Rev. 2005;(1):CD000193; PMID: 15674868]. Cochrane Database of Systematic Reviews (3):CD000193, 2008. 2008;(3):CD000193.	Not addressing pre-specified intervention/comparison
Hafta A, Yazar A, Pata C. Comparison of terlipressin plus sclerotherapy with somatostatin plus sclerotherapy to control bleeding from esophageal varices in with Child C cirrhosis patients. Turkish Journal of Gastroenterology. 2001; 12(2):95-99.	Not addressing pre-specified intervention/comparison
Hobolth L, Krag A, Bendtsen F. The recent reduction in mortality from bleeding oesophageal varices is primarily observed from Days 1 to 5.	Case review – not clear terlipressin treatment duration

Study	Reasons for exclusion
Liver International. 2010; 30(3):455-462. Ref ID: 880	comparison
Ioannou G, Doust J, Rockey DC. Terlipressin for acute esophageal variceal hemorrhage. [Review] [39 refs][Update of Cochrane Database Syst Rev. 2003;(1):CD002147; PMID: 11279753]. Cochrane Database of Systematic Reviews (1):CD002147, 2003. 2003;(1):CD002147.	Cochrane review – used to cross reference
Kalambokis G, Economou M, Paraskevi K et al. Effects of somatostatin, terlipressin and somatostatin plus terlipressin on portal and systemic hemodynamics and renal sodium excretion in patients with cirrhosis. Journal of Gastroenterology & Hepatology. 2005; 20(7):1075-1081.	Outcomes not relevant
Kurstein P, Gluud LL, Willemann M et al. Agreement between reported use of interventions for liver diseases and research evidence in Cochrane systematic reviews. J Hepatol. 2005; 43(6):984-989.	Review article
Levacher S, Letoumelin P, Pateron D et al. Early administration of terlipressin plus glyceryl trinitrate to control active upper gastrointestinal bleeding in cirrhotic patients. Lancet. 1995; 346(8979):865-868.	Not addressing pre-specified intervention/comparison (combination treatment)
Lin HC, Yang YY, Hou MC et al. Hemodynamic effects of a combination of octreotide and terlipressin in patients with viral hepatitis related cirrhosis. Scand J Gastroenterol. 2002; 37(4):482-487.	Not pre-specified outcomes and comparison
Lo GH, Chen WC, Wang HM et al. Low-dose terlipressin plus banding ligation versus low-dose terlipressin alone in the prevention of very early rebleeding of oesophageal varices. Gut. 2009; 58(9):1275-1280.	Not pre-specified dose comparison
Pauwels A, Florent C, Desaint B et al. Terlipressin and somatostatin for controlling acute variceal bleeding. A randomized controlled trial. Gastroenterol Clin Biol. 1994; 18(4):388-389.	Not in English
Villanueva C, Planella M, Aracil C et al. Hemodynamic effects of terlipressin and high somatostatin dose during acute variceal bleeding in nonresponders to the usual somatostatin dose. Am J Gastroenterol. 2005; 100(3):624-630.	Not pre-specified outcomes
Walker S, Kreichgauer HP, Bode JC. Terlipressin (glypressin) vs. somatostatin in bleeding esophageal varices: a controlled, double-blind study. Hepatology. 1992; 15:1023-1030.	Same patients as used in the final report (included list)

K.2 Assessment of risks

Study	Reasons for exclusion
Atkinson RJ, Hurlstone DP. Usefulness of prognostic indices in upper gastrointestinal bleeding. [Review] [36 refs]. Best Practice & Research in Clinical Gastroenterology. 2008; 22(2):233-242. Ref ID: 180	Review
Church NI, Palmer KR. Relevance of the Rockall score in patients undergoing endoscopic therapy for peptic ulcer haemorrhage. European Journal of Gastroenterology & Hepatology. 2001; 13(10):1149-1152.	The sample population overlaps with Church et al. 2006
Dulai GS. Rockall redux: retracted or redacted? Gastrointest Endosc. 2006; 63(4):613-614. Ref ID: 1640	Editorial
Guglielmi A, Ruzzenente A, Sandri M et al. Risk assessment and prediction of rebleeding in bleeding gastroduodenal ulcer. Endoscopy. 2002; 34(10):778-786. Ref ID: 2812	No scoring system
Pilotto A, Addante F, D'Onofrio G et al. The Comprehensive Geriatric Assessment and the multidimensional approach. A new look at the older patient with gastroenterological disorders. Best Practice &	Index not relevant

Study	Reasons for exclusion
Research in Clinical Gastroenterology. 2009; 23(6):829-837. Ref ID: 40	
Romagnuolo J, Barkun AN, Enns R et al. Simple clinical predictors may obviate urgent endoscopy in selected patients with nonvariceal upper gastrointestinal tract bleeding. Arch Intern Med. 2007; 167(3):265-270. Ref ID: 275	Modified version of the Blatchford
Soncini M, Triossi O, Leo P et al. Management of patients with nonvariceal upper gastrointestinal hemorrhage before and after the adoption of the Rockall score, in the Italian Gastroenterology Units. European Journal of Gastroenterology & Hepatology. 2007; 19(7):543-547. Ref ID: 253	Not a validation study – audit of service provision

K.3 Timing of endoscopy

Study	Reasons for exclusion
Adamopoulos AB, Baibas NM, Efstathiou SP et al. Differentiation between patients with acute upper gastrointestinal bleeding who need early urgent upper gastrointestinal endoscopy and those who do not. A prospective study. Eur J Gastroenterol Hepatol. 2003; 15(4):381-387.	Not addressing review/clinical question
Alemayehu G, Jarnerot G. Same-day upper and lower endoscopy in patients with occult bleeding, melena, hematochezia, and/or microcytic anemia. A retrospective study of 224 patients. Scand J Gastroenterol. 1993; 28(8):667-672.	No data on early vs. late endoscopy
Anon. Hold the GI endoscopy. Emergency Medicine (00136654). 1994; 26(5):84.	Editorial
Apel D, Riemann JF. Emergency endoscopy. Can J Gastroenterol. 2000; 14(3):199-203.	Not addressing review/clinical question
Button LA, Roberts SE, Evans PA, et al. Hospitalized incidence and case fatality for upper gastrointestinal bleeding from 1999 to 2007: a record linkage study. Aliment Pharmacol Ther 2011 Jan;33:64-76.	Not addressing protocol question and retrospective case review.
Chak A, Cooper GS, Lloyd LE et al. Effectiveness of endoscopy in patients admitted to the intensive care unit with upper GI hemorrhage. Gastrointest Endosc. 2001; 53(1):6-13.	Not addressing pre-specified intervention/comparison
Cheng CL, Lee CS, Liu NJ et al. Overlooked lesions at emergency endoscopy for acute nonvariceal upper gastrointestinal bleeding. Endoscopy. 2002; 34(7):527-530.	Not addressing pre-specified intervention/comparison
Cheung J, Soo I, Bastiampillai R et al. Urgent vs. non-urgent endoscopy in stable acute variceal bleeding. Am J Gastroenterol. 2009; 104(5):1125-1129.	Retrospective case review – observational study
Cho HS, Han DS, Ahn SB et al. Comparison of the effectiveness of interventional endoscopy in bleeding peptic ulcer disease according to the timing of endoscopy. Gut and Liver. 2009; 3(4):266-270.	Survey
Choudari CP, Palmer KR. Outcome of endoscopic injection therapy for bleeding peptic ulcer in relation to the timing of the procedure. Eur J Gastroenterol Hepatol. 1993; 5(11):951-953.	Not addressing pre-specified comparison
Cipolletta L, Bianco MA, Rotondano G et al. Outpatient management for low-risk nonvariceal upper GI bleeding: a randomized controlled trial. Gastrointest Endosc. 2002; 55(1):1-5.	Not addressing pre-specified comparison
Cooper BT, Neumann CS. Upper gastrointestinal endoscopy in patients aged 80 years or more. Age & Ageing. 1986; 15(6):343-349.	Not addressing pre-specified outcomes
Cooper GS, Chak A, Connors AF, Jr. et al. The effectiveness of early	Retrospective case review –

Study	Reasons for exclusion
endoscopy for upper gastrointestinal hemorrhage: a community-based analysis. Med Care. 1998; 36(4):462-474.	observational study
Cooper GS, Chak A, Way LE et al. Early endoscopy in upper gastrointestinal hemorrhage: Associations with recurrent bleeding, surgery, and length of hospital stay. Gastrointest Endosc. 1999; 49(2):145-152.	Retrospective case review – observational study
Cooper GS, Kou TD, Wong RCK. Use and impact of early endoscopy in elderly patients with peptic ulcer hemorrhage: a population-based analysis. Gastrointest Endosc. 2009; 70(2):229-235.	Retrospective case review – observational study
da Silveira EB, Lam E, Martel M et al. The importance of process issues as predictors of time to endoscopy in patients with acute upper-GI bleeding using the RUGBE data. Gastrointest Endosc. 2006; 64(3):299-309.	Not addressing review/clinical question
Eastwood GL. Does early endoscopy benefit the patient with active upper gastrointestinal bleeding? Gastroenterology. 1977; 72(4:Pt 1):t-9.	Review
Gul YA, Jabar MF, Mo'min N et al. Appropriate utilisation of emergency upper gastrointestinal endoscopy in a tertiary referral centre. Med J Malaysia. 2004; 59(1):65-71.	Not addressing pre-specified outcomes
Gyawali P, Suri D, Barrison I et al. A discussion of the British Society of Gastroenterology survey of emergency gastroenterology workload. Clinical Medicine. 2007; 7(6):585-588.	Survey
Hearnshaw SA, Logan RF, Lowe D et al. Use of endoscopy for management of acute upper gastrointestinal bleeding in the UK: results of a nationwide audit. Gut. 2010	Audit of 'out-of-hours' services - prospective case review
Hsu YC, Chung CS, Tseng CH et al. Delayed endoscopy as a risk factor for in-hospital mortality in cirrhotic patients with acute variceal hemorrhage. Journal of Gastroenterology & Hepatology. 2009; 24(7):1294-1299.	Retrospective case review – observational study
Jensen DM. Spots and clots - Leave them or treat them? Why and how to treat. Can J Gastroenterol. 1999; 13(5):413-415.	Not addressing pre-specified comparison
Kethu SR, Davis GC, Reinert SE et al. Low utility of endoscopy for suspected upper gastrointestinal bleeding occurring in hospitalized patients. South Med J. 2005; 98(2):170-175.	Not addressing pre-specified intervention/comparison
Lim CH, Vani D, Shah SG et al. The outcome of suspected upper gastrointestinal bleeding with 24-hour access to upper gastrointestinal endoscopy: A prospective cohort study. Endoscopy. 2006; 38(6):581-585.	Not addressing pre-specified intervention/comparison
Palmer ED. The vigorous diagnostic approach to upper-gastrointestinal tract hemorrhage. A 23-year prospective study of 1,4000 patients. JAMA. 1969; 207(8):1477-1480. Ref ID: 1908	Not addressing pre-specified intervention/comparison
Parente F, Anderloni A, Bargiggia S et al. Outcome of non-variceal acute upper gastrointestinal bleeding in relation to the time of endoscopy and the experience of the endoscopist: A two-year survey. World Journal of Gastroenterology. 2005; 11(45):7122-7130.	Not addressing pre-specified intervention
Peterson WL, Barnett CC, Smith HJ. Routine early endoscopy in upper-gastrointestinal-tract bleeding. A randomized, controlled trial. N Engl J Med. 1981; 304(16):925-929.	Not addressing pre-specified comparison
Rollhauser C, Fleischer DE. Current status of endoscopic therapy for ulcer bleeding. [100 refs]. Best Practice and Research in Clinical Gastroenterology. 2000; 14(3):391-410.	Review of endoscopic treatments
Safe AF, Owens D. Upper gastrointestinal endoscopy in octogenarians.	Not addressing pre-specified

Study	Reasons for exclusion
Br J Clin Pract. 1991; 45(2):99-101.	outcomes
Sandlow LJ, Becker GH, Spellberg MA et al. A prospective randomized study of the management of upper gastrointestinal hemorrhage. Am J Gastroenterol. 1974; 61(4):282-289.	Not addressing pre-specified population
Sarin N, Monga N, Adams PC. Time to endoscopy and outcomes in upper gastrointestinal bleeding. Can J Gastroenterol. 2009; 23(7):489-493.	Retrospective case review – observational study
Schacher GM, Lesbros-Pantoflickova D, Ortner MA et al. Is early endoscopy in the emergency room beneficial in patients with bleeding peptic ulcer? A "fortuitously controlled" study. Endoscopy. 2005; 37(4):324-328.	Retrospective case review – observational study
Sperber AD, Fich A, Eidelman L et al. Open access endoscopy for hospitalized patients. Am J Gastroenterol. 1997; 92(10):1823-1826.	Not addressing pre-specified intervention/comparison
Spiegel BM, Vakil NB, Ofman JJ. Endoscopy for acute nonvariceal upper gastrointestinal tract hemorrhage: is sooner better? A systematic review. Arch Intern Med. 2001; 161(11):1393-1404.	Review paper – cross referenced
Stoltzing H, Ohmann C, Krick M et al. Diagnostic emergency endoscopy in upper gastrointestinal bleeding. Do we have any decision aids for patient selection? Hepatogastroenterology. 1991; 38(3):224-227.	Not addressing pre-specified intervention/comparison
Tai C-M, Huang S-P, Wang H-P et al. High-risk ED patients with nonvariceal upper gastrointestinal hemorrhage undergoing emergency or urgent endoscopy: a retrospective analysis. Am J Emerg Med. 2007; 25(3):273-278.	Retrospective case review – observational study
Tangmankongworakoon N, Rerknimitr R, Aekpongpaisit S et al. Results of emergency gastroscopy for acute upper gastrointestinal bleeding outside official hours at King Chulalongkorn Memorial Hospital. J Med Assoc Thai. 2003; 86:Suppl-71.	Not addressing pre-specified intervention/comparison
Targownik LE, Murthy S, Keyvani L et al. The role of rapid endoscopy for high-risk patients with acute nonvariceal upper gastrointestinal bleeding. Can J Gastroenterol. 2007; 21(7):425-429.	Retrospective case review – observational study
Thomopoulos K, Katsakoulis E, Vagianos C et al. Causes and clinical outcome of acute upper gastrointestinal bleeding: a prospective analysis of 1534 cases. Int J Clin Pract. 1998; 52(8):547-550.	No direct comparison
Triadafilopoulos G, Aslan A. Same-day upper and lower inpatient endoscopy: a trend for the future. Am J Gastroenterol. 1991; 86(8):952-955.	Not addressing pre-specified outcomes
Tsoi KK, Ma TK, Sung JJ. Endoscopy for upper gastrointestinal bleeding: how urgent is it?. [41 refs]. Nature Reviews Gastroenterology and Hepatology. 2009; 6(8):463-469.	Review paper –cross referenced
Wara P, Stodkilde H. Bleeding pattern before admission as guideline for emergency endoscopy. Scand J Gastroenterol. 1985; 20(1):72-78.	Not addressing pre-specified intervention/comparison
Whorwell PJ, Eade OE, Chapman R et al. Comparison between admission and next-day endoscopy in the management of acute upper gastrointestinal haemorrhage. Digestion. 1981; 21(1):18-20.	Outdated endoscopic procedure
Winans CS. Emergency upper gastrointestinal endoscopy: does haste make waste? Am J Dig Dis. 1977; 22(6):536-540.	Not addressing review/clinical question

K.4 Management of non-variceal bleeding

K.4.1 Combination treatments

Study	Reason for exclusion
Barkun AN, Martel M, Toubouti Y, et al. Endoscopic hemostasis in peptic ulcer bleeding for patients with high-risk lesions: a series of meta-analyses. Gastrointest Endosc 2009 Apr;69:786-99.	Meta-analysis – checked for references
Berg PL, Barina W, Born P. Endoscopic injection of fibrin glue versus polidocanol in peptic ulcer hemorrhage: a pilot study. Endoscopy 1994 Aug;26:528-30.	No combination treatments included
Bianco MA, Rotondano G, Marmo R, et al. Combined epinephrine and bipolar probe coagulation vs. bipolar probe coagulation alone for bleeding peptic ulcer: a randomized, controlled trial. Gastrointest Endosc 2004 Dec;60:910-5.	Comparison no longer in protocol
Chau CH, Siu WT, Law BK, et al. Randomized controlled trial comparing epinephrine injection plus heat probe coagulation versus epinephrine injection plus argon plasma coagulation for bleeding peptic ulcers. Gastrointest Endosc 2003;57:455-61.	Both essentially use an injection plus thermal combination which is not a comparison that is relevant
Chung SCS, Leung JWC, Leong HT, et al. Adding a sclerosant to endoscopic epinephrine injection in actively bleeding ulcers: A randomized trial. Gastrointest Endosc 1993;39:611-5.	Comparison not in protocol
Church NI, Dallal HJ, Masson J, et al. A randomized trial comparing heater probe plus thrombin with heater probe plus placebo for bleeding peptic ulcer. Gastroenterology 2003 Aug;125:396-403.	Comparison no longer included in protocol
Heldwein W, Avenhaus W, Schönekäs H, et al. Injection of fibrin tissue adhesive versus laser photocoagulation in the treatment of high-risk bleeding peptic ulcers: a controlled randomized study. Endoscopy 1996;28:756-60.	No combination treatment included
Hiele M, Rutgeerts P. Combination therapies for the endoscopic treatment of gastrointestinal bleeding. Bailliere's Best Practice and Research in Clinical Gastroenterology 2000;14:459-66.	Review – checked for references
Laine L, McQuaid KR. Endoscopic Therapy for Bleeding Ulcers: An Evidence-Based Approach Based on Meta-Analyses of Randomized Controlled Trials. Clinical Gastroenterology and Hepatology 2009;7:33-47.	Meta analysis – checked for references
Lesur G, Hour B. Discussion on a randomized trial comparing heater probe plus thrombin with heater probe plus placebo for bleeding peptic ulcer.[comment]. Gastroenterology 2004;126:939-40.	Comment
Lin HJ, Lo WC, Cheng YC, et al. Endoscopic hemoclip versus triclip placement in patients with high-risk peptic ulcer bleeding. The American Journal of Gastroenterology 2007;102:539-43.	No combination treatments investigated
Lin H-J, Perng C-L, Sun IC, et al. Endoscopic haemoclip versus heater probe thermocoagulation plus hypertonic saline-epinephrine injection for peptic ulcer bleeding. Digestive and Liver Disease 2003 Dec;35:898-902.	Comparison no longer in protocol
Llach J, Bordas JM, Salmeron JM, et al. A prospective randomized trial of heater probe thermocoagulation versus injection therapy in peptic ulcer hemorrhage. Gastrointest Endosc 1996 Feb;43:117-20.	No combination treatments investigated
Loizou LA, Bown SG. Endoscopic treatment for bleeding peptic ulcers: randomised comparison of adrenaline injection and adrenaline injection + Nd:YAG laser photocoagulation. Gut 1991 Oct;32:1100-3.	Type of treatment no longer in use
Marmo R, Rotondano G, Piscopo R, et al. Dual therapy versus	Meta-analysis – checked for

Study	Reason for exclusion
monotherapy in the endoscopic treatment of high-risk bleeding ulcers: A meta-analysis of controlled trials. Am J Gastroenterol 2007;102:279-89.	references
Rutgeerts P, Rauws E, Wara P, et al. Randomised trial of single and repeated fibrin glue compared with injection of polidocanol in treatment of bleeding peptic ulcer. Lancet 1997 Sep 6;350:692-6.	Comparison not in protocol
Saltzman JR, Strate LL, Di S, V, et al. Prospective trial of endoscopic clips versus combination therapy in upper GI bleeding (PROTECCT--UGI bleeding). Am J Gastroenterol 2005;100:1503-8.	Comparison no longer in protocol
Shimoda R, Iwakiri R, Sakata H, et al. Evaluation of endoscopic hemostasis with metallic hemoclips for bleeding gastric ulcer: comparison with endoscopic injection of absolute ethanol in a prospective, randomized study. Am J Gastroenterol 2003 Oct;98:2198-202.	No combination treatments investigated
Song SY, Chung JB, Moon YM, et al. Comparison of the hemostatic effect of endoscopic injection with fibrin glue and hypertonic saline-epinephrine for peptic ulcer bleeding: a prospective randomized trial. Endoscopy 1997;29:827-33.	No combination treatments investigated
Soon MS, Wu SS, Chen YY, et al. Monopolar coagulation versus conventional endoscopic treatment for high-risk peptic ulcer bleeding: a prospective, randomized study. Gastrointest Endosc 2003;58:323-9.	Comparison no longer in protocol
Sung JJ, Tsoi KK, Lai LH, et al. Endoscopic clipping versus injection and thermo-coagulation in the treatment of non-variceal upper gastrointestinal bleeding: a meta-analysis (Structured abstract). Gut 2007;56:1364-72.	Comparison no longer in protocol
Tekant Y, Goh P, Alexander DJ, et al. Combination therapy using adrenaline and heater probe to reduce rebleeding in patients with peptic ulcer haemorrhage: a prospective randomized trial. Br J Surg 1995;82:223-6.	No intervention comparison not in protocol
Vergara M, Calvet X, Gisbert JP. Epinephrine injection versus epinephrine injection and a second endoscopic method in high risk bleeding ulcers. Cochrane Database of Systematic Reviews 2007;Issue 2:CD005584.	Cochrane meta-analysis – cross referenced and checked for references

K.4.2 PPI

Study	Reasons for exclusion
Andriulli A, Loperfido S, Focareta R et al. High- versus low-dose proton pump inhibitors after endoscopic hemostasis in patients with peptic ulcer bleeding: a multicentre, randomized study. Am J Gastroenterol. 2008; 103(12):3011-3018. Ref ID: 89	Not addressing pre-specified comparison
Bardou M, Martin J, Barkun A. Intravenous proton pump inhibitors: an evidence-based review of their use in gastrointestinal disorders. [71 refs]. Drugs. 2009; 69(4):435-448. Ref ID: 115	Review paper
Barkun A, Sabbah S, Enns R et al. The Canadian Registry on Nonvariceal Upper Gastrointestinal Bleeding and Endoscopy (RUGBE): Endoscopic hemostasis and proton pump inhibition are associated with improved outcomes in a real-life setting. Am J Gastroenterol. 2004; 99(7):1238-1246. Ref ID: 2295	Not a randomized control trial
Cardi M, Muttillo IA, Amadori L et al. Intravenous omeprazole versus intravenous ranitidine in the treatment of bleeding duodenal ulcer: A prospective randomized trial. Ann Chir. 1997; 51(2):136-139. Ref ID:	Not in English

Study	Reasons for exclusion
2795	
Chan FK. Proton-pump inhibitors in peptic ulcer disease. Lancet. 2008; 372(9645):1198-1200. Ref ID: 88	Review paper
Cheng HC, Chang WL, Yeh YC et al. Seven-day intravenous low-dose omeprazole infusion reduces peptic ulcer rebleeding for patients with comorbidities. Gastrointest Endosc. 2009; 70(3):433-439. Ref ID: 4765	Not addressing pre-specified comparison
Cheng HC, Kao AW, Chuang CH et al. The efficacy of high- and low-dose intravenous omeprazole in preventing rebleeding for patients with bleeding peptic ulcers and comorbid illnesses. Digestive Diseases & Sciences. 2005; 50(7):1194-1201. Ref ID: 225	Not addressing pre-specified comparison
Chu XQ, Jia LS. Effects of omeprazole and ranitidine on the treatment of peptic ulcer hemorrhage [abstract]. Journal of Gastroenterology & Hepatology. 1993; 8(Suppl 2):S239. Ref ID: 2809	Abstract
Colin R, Michel P, Sallerin V. Comparison of the efficacy of lansoprazole and ranitidine in the prevention of early relapse in people with upper gastrointestinal ulcerative haemorrhage with a high risk of early recurrence of rebleeding. A double blind multi-centre study. Gastroenterolgie Clinique et Biologique. 1993; 17:A105. Ref ID: 4764	French abstract
Felder LR, Barkin JS. A comparison of omeprazole and placebo for bleeding peptic ulcer. Gastrointest Endosc. 1998; 47(5):428-429. Ref ID: 433	Review of another included reference
Hsu YC, Perng CL, Yang TH et al. A randomized controlled trial comparing two different dosages of infusional pantoprazole in peptic ulcer bleeding. Br J Clin Pharmacol. 2010; 69(3):245-251. Ref ID: 17	Not addressing pre-specified comparison
Hulagu S, Demirturk L, Gul S et al. The effect of omeprazole or ranitidine intravenous on upper gastrointestinal bleeding.[abstract]. Endoscopy. 1994; 26(4):404. Ref ID: 2866	Insufficient information (abstract only)
Hulagu S, Demorturk L, Gul S et al. The effect of omeprazole or ranitidine intravenous on upper gastrointestinal bleeding. Endoskopi Journal. 1995; 2:35-43. Ref ID: 4762	Not in English
Keyvani L, Murthy S, Leeson S et al. Pre-endoscopic proton pump inhibitor therapy reduces recurrent adverse gastrointestinal outcomes in patients with acute non-variceal upper gastrointestinal bleeding. Aliment Pharmacol Ther. 2006; 24(8):1247-1255. Ref ID: 3024	Not a randomized control trial
Kim JI, Cheung DY, Cho SH et al. Oral proton pump inhibitors are as effective as endoscopic treatment for bleeding peptic ulcer: a prospective, randomized, controlled trial. Dig Dis Sci. 2007; 52(12):3371-3376. Ref ID: 110	Not addressing pre-specified comparison
Lang ES. Intravenous proton pump inhibitors prior to endoscopy in suspected upper gastrointestinal bleeding. Canadian Journal of Emergency Medicine. 2008; 10(3):244-246. Ref ID: 4772	Journal Club
Leontiadis GI, Howden CW. The role of proton pump inhibitors in the management of upper gastrointestinal bleeding. [59 refs]. Gastroenterol Clin North Am. 2009; 38(2):199-213. Ref ID: 118	Meta Analysis – cross-referenced
Leontiadis GI, Sharma VK, Howden CW. Proton pump inhibitor therapy for peptic ulcer bleeding: Cochrane collaboration meta-analysis of randomized controlled trials.[see comment]. Mayo Clin Proc. 2007; 82(3):286-296. Ref ID: 287	Meta analysis – used to cross-reference and many of the same study data was included in NCGC new meta analysis (and updated)
Leontiadis GI, Sreedharan A, Dorward S et al. Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding. Health Technol Assess. 2007; 11(51):iii-126. Ref ID: 3186	Health Technology Assessment - additional source of cross-reference for new NCGC meta analysis

Study	Reasons for exclusion
Liang XY, Gao Q, Gong NP et al. Comparison of esomeprazole enteric-coated capsules vs esomeprazole magnesium in the treatment of active duodenal ulcer: a randomized, double-blind, controlled study. World Journal of Gastroenterology. 2008; 14(12):1941-1945. Ref ID: 4768	Not addressing pre-specified comparison
Mesihovic R, Vanis N, Mehmedovic A et al. Proton pump inhibitors after endoscopic hemostasis in patients with peptic ulcer bleeding. Med Arh. 2009; 63(6):323-327. Ref ID: 25	Not addressing pre-specified comparison
Michel P, Duhamel C, Bazin B et al. Prevention of early rebleeding from gastric and duodenal peptic ulcer with lansoprazole or ranitidine. Randomized multicentre trial. Gastroenterologie Clinique Et Biologique. 1994; 18(12):1102-1105. Ref ID: 2943	Not in English
Munkel L, French L. Treatment of bleeding peptic ulcers with omeprazole. J Fam Pract. 1997; 45(1):20-21. Ref ID: 450	Journal Club
Murthy S, Keyvani L, Leeson S et al. Intravenous versus high-dose oral proton pump inhibitor therapy after endoscopic hemostasis of high-risk lesions in patients with acute nonvariceal upper gastrointestinal bleeding. Dig Dis Sci. 2007; 52(7):1685-1690. Ref ID: 3424	Not a randomized control trial
Nehme O, Barkin JS. Recurrent ulcer bleeding: is intravenous omeprazole the solution? Am J Gastroenterol. 2001; 96(2):594-595. Ref ID: 382	Comment / review of an included study
Perez FR, Garcia Molinero MJ, Herrero QC et al. [The treatment of upper digestive hemorrhage of peptic origin: intravenous ranitidine versus intravenous omeprazole]. Rev Esp Enferm Dig. 1994; 86(3):637-641. Ref ID: 4780	Article in Spanish – English abstract (insufficient information)
Plevris JN. Intravenous administration of proton pump inhibitors in upper gastrointestinal bleeding. Journal of the Royal College of Physicians of Edinburgh. 2008; 38(4):326-327. Ref ID: 672	Not an RCT
Savides TJ, Pratha V. Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. Gastrointest Endosc. 2001; 54(1):130-132. Ref ID: 370	Comment on Lau et al. reference
Sreedharan A, Martin J, Leontiadis GI et al. Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding. [71 refs]. Cochrane Database of Systematic Reviews. 2006;(4):CD005415. Ref ID: 316	Cochrane review
Sung JJ, Chan FK, Lau JY et al. The effect of endoscopic therapy in patients receiving omeprazole for bleeding ulcers with nonbleeding visible vessels or adherent clots: a randomized comparison. Ann Intern Med. 2003; 139(4):237-243. Ref ID: 297	Not addressing pre-specified comparison
Sung JJ, Mössner J, Barkun A et al. Intravenous esomeprazole for prevention of peptic ulcer re-bleeding: rationale/design of Peptic Ulcer Bleed study. Alimentary pharmacology & therapeutics. 2008; 27(8):666-677. Ref ID: 79	Protocol
Tai CK, Graham CA. Use of intravenous omeprazole in gastrointestinal patients before endoscopy. Emergency Medicine Journal. 2008; 25(11):765. Ref ID: 4771	Protocol
Tajima A, Koizumi K, Suzuki K et al. Proton pump inhibitors and recurrent bleeding in peptic ulcer disease. [44 refs]. J Gastroenterol Hepatol. 2008; 23 Suppl 2:S237-S241. Ref ID: 135	Not a randomized control trial
Thomson ABR. Intravenous esomeprazole for prevention of recurrent peptic ulcer bleeding. Current Gastroenterology Reports. 2009; 11(5):339-341. Ref ID: 670	Review of included reference
Tsibouris P, Zintzaras E, Lappas C et al. High-dose pantoprazole	Not addressing pre-specified

Study	Reasons for exclusion
continuous infusion is superior to somatostatin after endoscopic hemostasis in patients with peptic ulcer bleeding. Am J Gastroenterol. 2007; 102(6):1192-1199. Ref ID: 3998	comparison
Udd M, Toyry J, Miettinen P et al. The effect of regular and high doses of omeprazole on the intragastric acidity in patients with bleeding peptic ulcer treated endoscopically: A clinical trial with continuous intragastric pH monitoring. Eur J Gastroenterol Hepatol. 2005; 17(12):1351-1356. Ref ID: 4007	Not addressing pre-specified intervention/comparison
Walt RP, Cottrell J, Mann SG et al. Continuous intravenous famotidine for haemorrhage from peptic ulcer. Lancet. 1992; 340(8827):1058-1062. Ref ID: 595	Not addressing pre-specified intervention/comparison
Wang CH, Ma MH, Chou HC et al. High-dose vs non-high-dose proton pump inhibitors after endoscopic treatment in patients with bleeding peptic ulcer: a systematic review and meta-analysis of randomized controlled trials. Arch Intern Med. 2010; 170(9):751-758. Ref ID: 9	Not addressing pre-specified comparison
Xuan JL. Loseco compared with famotidine in the treatment of upper gastrointestinal bleeding: clinical analysis of 90 cases. Guangxi Medical Journal. 2003; 25(4):529-531. Ref ID: 3045	Not in English
Yuksel I, Ataseven H, Koklu S et al. Intermittent versus continuous pantoprazole infusion in peptic ulcer bleeding: A prospective randomized study. Digestion. 2008; 78(1):39-43. Ref ID: 4174	Not addressing pre-specified intervention/comparison

K.4.3 Treatment options after first/failed endoscopy

Study	Reasons for exclusion
Brullet E, Campo R, Calvet X et al. Factors related to the failure of endoscopic injection therapy for bleeding gastric ulcer. Gut. 1996; 39(2):155-158.	Not addressing clinical/review question
Busch ORC, van D, Gouma DJ. Therapeutic options for endoscopic haemostatic failures: the place of the surgeon and radiologist in gastrointestinal tract bleeding. Best Practice and Research in Clinical Gastroenterology. 2008; 22(2):341-354.	Review
Chung SCS, Leung JWC, Leong HT et al. Adding a sclerosant to endoscopic epinephrine injection in actively bleeding ulcers: A randomized trial. Gastrointest Endosc. 1993; 39(5):611-615.	Not addressing clinical/review question
Defreyne L, De S, I, Decruyenaere J et al. Therapeutic decision-making in endoscopically unmanageable nonvariceal upper gastrointestinal hemorrhage. Cardiovasc Intervent Radiol. 2008; 31(5):897-905.	Not addressing clinical/review question
Lang EV, Picus D, Marx MV et al. Massive arterial hemorrhage from the stomach and lower esophagus: impact of embolotherapy on survival. Radiology. 1990; 177(1):249-252.	Only 3 patients received surgery
Lin HJ, Perng CL, Lee FY et al. Clinical courses and predictors for rebleeding in patients with peptic ulcers and non-bleeding visible vessels: a prospective study. Gut. 1994; 35(10):1389-1393.	Not addressing clinical/review question
Loffroy R, Rao P, Ota S et al. Embolization of acute nonvariceal upper gastrointestinal hemorrhage resistant to endoscopic treatment: results and predictors of recurrent bleeding. Cardiovasc Intervent Radiol. 2010; 33(6):1088-1100.	Review – cross checked for references
Mahadeva S, Linch M, Hull MA. Variable use of endoscopic haemostasis in the management of bleeding peptic ulcers. Postgrad Med J. 2002; 78(920):347-351.	Retrospective review of cases with comparisons starting from different points (injection vs. combination)

Study	Reasons for exclusion
Romagnuolo J. Routine second look endoscopy: Ineffective, costly and potentially misleading. Can J Gastroenterol. 2004; 18(6):401-404.	Review of RCTs without meta-analysis
Saeed ZA, Michaletz PA, Winchester CB et al. Endoscopic variceal ligation in patients who have failed endoscopic sclerotherapy. Gastrointest Endosc. 1990; 36(6):572-574.	No group comparison
Spiegel BMR, Ofman JJ, Woods K et al. Minimizing recurrent peptic ulcer hemorrhage after endoscopic hemostasis: the cost-effectiveness of competing strategies. Am J Gastroenterol. 2003; 98(1):86-97.	Economic analysis – checked for relevant papers
Trap R, Skarbye M, Rosenberg J. Planned second look endoscopy in patients with bleeding duodenal or gastric ulcers. Dan Med Bull. 2000; 47(3):220-223.	No group comparison

K.5 Control of bleeding and prevention of rebleeding

Study	Reason for exclusion
Anon. Summaries for patients. Benefits and risks of continuing aspirin in patients with peptic ulcer bleeding.[Original report in Ann Intern Med. 2010 Jan 5;152(1):1-9; PMID: 19949136]. Ann Intern Med. 2010; 152(1):I-20.	Not addressing clinical/review question.
Bhatt DL, Scheiman J, Abraham NS et al. ACCF/ACG/AHA 2008 Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use. A Report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol. 2008; 52(18):1502-1517.	Recommendation
Garrett MM, Feiler MJ. Managing Anti-Coagulation for Endoscopic Procedures. Techniques in Gastrointestinal Endoscopy. 2007; 9(2):68-73.	Review
Kimchi NA, Broide E, Scapa E et al. Antiplatelet therapy and the risk of bleeding induced by gastrointestinal endoscopic procedures. A systematic review of the literature and recommendations. [Review] [52 refs]. Digestion. 2007; 75(1):36-45.	Review and recommendation
Komatsu T, Tamai Y, Takami H et al. Study for determination of the optimal cessation period of therapy with anti-platelet agents prior to invasive endoscopic procedures. J Gastroenterol. 2005; 40(7):698-707.	Not addressing pre-specified comparison
Kwok A, Faigel DO. Management of anticoagulation before and after gastrointestinal endoscopy. [Review] [117 refs]. Am J Gastroenterol. 2009; 104(12):3085-3097.	Review
Laine L, Curtis SP, Cryer B et al. Risk factors for NSAID-associated upper GI clinical events in a long-term prospective study of 34 701 arthritis patients. Alimentary pharmacology & therapeutics. 2010; 32(10):1240-1248.	Risk factor analysis – not addressing clinical/review question.
Malagelada JR, ED, guez de la Serna et al. Sucralfate therapy in NSAID bleeding gastropathy. Clinical Gastroenterology & Hepatology. 2003; 1(1):51-56.	Not addressing pre-specified comparison
Ng FH, Wong BC, Wong SY et al. Clopidogrel plus omeprazole compared with aspirin plus omeprazole for aspirin-induced symptomatic peptic ulcers/erosions with low to moderate bleeding/re-bleeding risk -- a single-blind, randomized controlled study. Alimentary pharmacology & therapeutics. 2004; 19(3):359-365.	Not addressing pre-specified comparison

Study	Reason for exclusion
Scheiman JM. Prevention of NSAID-induced ulcers. Current Treatment Options in Gastroenterology. 2008; 11(2):125-134.	Review
Shiffman ML, Farrel MT, Yee YS. Risk of bleeding after endoscopic biopsy or polypectomy in patients taking aspirin or other NSAIDS. Gastrointest Endosc. 1994; 40(4):458-462.	Risk factor analysis – not addressing clinical/review question.
Thomopoulos KC, Mimidis KP, Theocharis GJ et al. Acute upper gastrointestinal bleeding in patients on long-term oral anticoagulation therapy: Endoscopic findings, clinical management and outcome. World Journal of Gastroenterology. 2005; 11(9):1365-1368.	Not addressing pre-specified intervention/comparison
Veitch AM, Baglin TP, Gershlick AH et al. Guidelines for the management of anticoagulant and antiplatelet therapy in patients undergoing endoscopic procedures. Gut. 2008; 57(9):1322-1329.	Paper on Guideline recommendations – not relevant to clinical question
Wolf AT, Wasan SK, Saltzman JR. Impact of anticoagulation on rebleeding following endoscopic therapy for nonvariceal upper gastrointestinal hemorrhage. Am J Gastroenterol. 2007; 102(2):290-296.	Not addressing pre-specified intervention

K.6 Primary prophylaxis

Study	Reason for exclusion
Calvet X, Baigorri F, Duarte M et al. Effect of ranitidine on gastric intramucosal pH in critically ill patients. Intensive Care Med. 1998; 24(1):12-17.	Not addressing pre-specified outcomes
Cheadle WG, Vitale GC, Mackie CR et al. Prophylactic postoperative nasogastric decompression. A prospective study of its requirement and the influence of cimetidine in 200 patients. Ann Surg. 1985; 202(3):361-366. Ref ID: 5261	Patient criteria not clearly specified
Cloud ML, Offen W. Continuous infusions of nizatidine are safe and effective in the treatment of intensive care unit patients at risk for stress gastritis. The Nizatidine Intensive Care Unit Study Group. Scandinavian Journal of Gastroenterology - Supplement. 1994; 206:29-34. Ref ID: 85	Not addressing pre-specified intervention/comparison
George AT, Tharyan P, Peter J, V et al. Interventions for preventing upper gastrointestinal bleeding in people admitted to intensive care units. Cochrane Database of Systematic Reviews. 2010;(Tharyan Prathap) Ref ID: 1278	Cochrane protocol - cross checked prior to protocol completion
Lin PC, Chang CH, Hsu PI et al. The efficacy and safety of proton pump inhibitors vs histamine-2 receptor antagonists for stress ulcer bleeding prophylaxis among critical care patients: a meta-analysis. Crit Care Med. 2010; 38(4):1197-1205. Ref ID: 34	Meta analysis – cross checked for references
Muller T, Barkun AN, Martel M et al. Non-variceal upper GI bleeding in patients already hospitalized for another condition. Am J Gastroenterol. 2009; 104(2):330-339. Ref ID: 569	Review
Peura DA et al. Cimetidine for prevention and treatment of gastroduodenal mucosal lesions in patients in an	Not addressing pre-specified population

Study	Reason for exclusion
intensive care unit. Ann Intern Med 1985; 103: 173-177.	
Powell HM. Inhibition of gastric acid secretion in the intensive care unit after coronary artery bypass graft. A pilot control study of intravenous omeprazole by bolus and infusion, ranitidine and placebo. Theoretical Surgery. 1993; 8(3):125-130. Ref ID: 5216	Patient group not in protocol. Elective surgery.
Quenot JP, Thiery N, Barbar S. When should stress ulcer prophylaxis be used in the ICU?. [Review] [50 refs]. Current Opinion in Critical Care. 2009; 15(2):139-143. Ref ID: 60	Review
Rixen D, Livingston DH, Loder P et al. Ranitidine improves lymphocyte function after severe head injury: results of a randomized, double-blind study. Crit Care Med. 1996; 24(11):1787-1792. Ref ID: 61	Same participants as in another included study (Metz 1993
Zach GA, Gyr KE, von AE et al. A double-blind randomized, controlled study to investigate the efficacy of cimetidine given in addition to conventional therapy in the prevention of stress ulceration and haemorrhage in patients with acute spinal injury. Digestion. 1984; 29(4):214-222. Ref ID: 5258	Wrong patient group

K.7 Management of variceal bleeding

K.7.1 TIPS

K.7.1.1 Clinical question 1

Study	Reason for exclusion
Boyer TD, Henderson JM, Heerey AM et al. Cost of preventing variceal rebleeding with transjugular intrahepatic portal systemic shunt and distal splenorenal shunt. J Hepatol. 2008; 48(3):407-414.	Distal splenorenal shunts not in protocol
Cabrera J, Maynar M, Granados R et al. Transjugular intrahepatic portosystemic shunt versus sclerotherapy in the elective treatment of variceal hemorrhage. Gastroenterology. 1996; 110(3):832-839.	Not addressing pre-specified intervention
Cello JP, Grendell JH, Crass RA et al. Endoscopic sclerotherapy versus portacaval shunt in patients with severe cirrhosis and variceal hemorrhage. N Engl J Med. 1984; 311(25):1589-1594.	Portacaval shunts not in protocol
Cello JP, Grendell JH, Crass RA et al. Endoscopic sclerotherapy versus portacaval shunt in patient with severe cirrhosis and acute variceal hemorrhage. Long-term follow-up. N Engl J Med. 1987; 316(1):11-15.	Portacaval shunts not in protocol
Garcia-Pagan JC, Caca K, Bureau C et al. Early use of TIPS in patients with cirrhosis and variceal bleeding. N Engl J Med. 2010; 362(25):2370-2379.	Not addressing pre-specified intervention
Garcia-Villarreal L, Martinez-Lagares F, Sierra A et al. Transjugular intrahepatic portosystemic shunt versus endoscopic sclerotherapy for the prevention of variceal rebleeding after recent variceal hemorrhage. Hepatology. 1999; 29(1):27-32. Ref ID: 199	Not addressing pre-specified intervention

Study	Reason for exclusion
Gulberg V, Schepke M, Geigenberger G et al. Transjugular intrahepatic portosystemic shunting is not superior to endoscopic variceal band ligation for prevention of variceal rebleeding in cirrhotic patients: A randomized, controlled trial. Scand J Gastroenterol. 2002; 37(3):338-343. Ref ID: 5269	Not addressing pre-specified intervention
Henderson JM, Kutner MH, Millikan WJ, Jr. et al. Endoscopic variceal sclerosis compared with distal splenorenal shunt to prevent recurrent variceal bleeding in cirrhosis. A prospective, randomized trial. Ann Intern Med. 1990; 112(4):262-269. Ref ID: 247	Distal splenorenal shunts not in protocol
Jalan R, Forrest EH, Stanley AJ et al. A randomized trial comparing transjugular intrahepatic portosystemic stent-shunt with variceal band ligation in the prevention of rebleeding from esophageal varices. Hepatology. 1997; 26(5):1115-1122. Ref ID: 665	Not addressing pre-specified intervention
Khan S, Tudur SC, Williamson P et al. Portosystemic shunts versus endoscopic therapy for variceal rebleeding in patients with cirrhosis. Cochrane Database Syst Rev. 2006;(4):CD000553. Ref ID: 5206	Cochrane review – cross checked for references
Meddi P, Merli M, Lionetti R et al. Cost analysis for the prevention of variceal rebleeding: a comparison between transjugular intrahepatic portosystemic shunt and endoscopic sclerotherapy in a selected group of Italian cirrhotic patients. Hepatology. 1999; 29(4):1074-1077. Ref ID: 406	Not addressing pre-specified intervention and the study population is a subgroup of patients in the study below by Merli et al. 1998
Merli M, Salerno F, Riggio O et al. Transjugular intrahepatic portosystemic shunt versus endoscopic sclerotherapy for the prevention of variceal bleeding in cirrhosis: A randomized multicenter trial. Hepatology. 1998; 27(1):48-53. Ref ID: 5272	Not addressing pre-specified intervention
Narahara Y, Kanazawa H, Kawamata H et al. A randomized clinical trial comparing transjugular intrahepatic portosystemic shunt with endoscopic sclerotherapy in the long-term management of patients with cirrhosis after recent variceal hemorrhage. Hepatology Research. 2001; 21(3):189-198. Ref ID: 437	Not addressing pre-specified intervention
Ochs A. Transjugular intrahepatic portosystemic shunt. Dig Dis. 2005; 23(1):56-64. Ref ID: 446	Review – cross checked for references
Orloff MJ, Isenberg JI, Wheeler HO et al. Emergency portacaval shunt versus rescue portacaval shunt in a randomized controlled trial of emergency treatment of acutely bleeding esophageal varices in cirrhosis--part 3. J Gastrointest Surg. 2010; 14(11):1782-1795. Ref ID: 5276	Portacaval shunts not in protocol
Orloff MJ, Isenberg JI, Wheeler HO et al. Randomized trial of emergency endoscopic sclerotherapy versus emergency portacaval shunt for acutely bleeding esophageal varices in cirrhosis. J Am Coll Surg. 2009; 209(1):25-40. Ref ID: 5275	Portacaval shunt not in protocol
Pera C, Visa J, Garcia-Valdecasas JC et al. The modified distal splenorenal shunt in the elective treatment of variceal hemorrhage. Hepatogastroenterology. 1991; 38 Suppl 1:12-15. Ref ID: 5277	Distal splenorenal shunts not in protocol

Study	Reason for exclusion
Planas R, Boix J, Broggi M et al. Portacaval shunt versus endoscopic sclerotherapy in the elective treatment of variceal hemorrhage. Gastroenterology. 1991; 100(4):1078-1086.	Portacaval shunts not in protocol
Pomier-Layrargues G, Villeneuve JP, Deschenes M et al. Transjugular intrahepatic portosystemic shunt (TIPS) versus endoscopic variceal ligation in the prevention of variceal rebleeding in patients with cirrhosis: A randomised trial. Gut. 2001; 48(3):390-396. Ref ID: 5278	Unclear variceal bleeding,
Rikkers LF, Jin G, Burnett DA et al. Shunt surgery versus endoscopic sclerotherapy for variceal hemorrhage: late results of a randomized trial. Am J Surg. 1993; 165(1):27-32. Ref ID: 5279	Shunt surgery not in protocol
Sauer P, Hansmann J, Richter GM et al. Endoscopic variceal ligation plus propranolol vs. transjugular intrahepatic portosystemic stent shunt: a long-term randomized trial. Endoscopy. 2002; 34(9):690-697. Ref ID: 265	Not addressing pre-specified intervention
Sauer P, Theilmann L, Stremmel W et al. Transjugular intrahepatic portosystemic stent shunt versus sclerotherapy plus propranolol for variceal rebleeding. Gastroenterology. 1997; 113(5):1623-1631. Ref ID: 575	Not addressing pre-specified intervention
Zheng M, Chen Y, Bai J et al. Transjugular intrahepatic portosystemic shunt versus endoscopic therapy in the secondary prophylaxis of variceal rebleeding in cirrhotic patients: Meta-analysis update. J Clin Gastroenterol. 2008; 42(5):507-516.	Meta-analysis – cross checked for references

K.7.1.2 Clinical question 2

Study	Reason for exclusion
Azoulay D, Castaing D, Majno P et al. Salvage transjugular intrahepatic portosystemic shunt for uncontrolled variceal bleeding in patients with decompensated cirrhosis. J Hepatol. 2001; 35(5):590-597. Ref ID: 5289	No comparison
Banares R, Casado M, Rodriguez-Laiz JM et al. Urgent transjugular intrahepatic portosystemic shunt for control of acute variceal bleeding. Am J Gastroenterol. 1998; 93(1):75-79. Ref ID: 5283	No comparison
Chau TN, Patch D, Chan YW et al. "Salvage" transjugular intrahepatic portosystemic shunts: gastric fundal compared with esophageal variceal bleeding. Gastroenterology. 1998; 114(5):981-987. Ref ID: 5281	Not addressing pre-specified comparison
Gerbes AL, Gulberg V, Waggershauser T et al. Transjugular intrahepatic portosystemic shunt (TIPS) for variceal bleeding in portal hypertension: comparison of emergency and elective interventions. Dig Dis Sci. 1998; 43(11):2463-2469. Ref ID: 5284	Not addressing pre-specified comparison/intervention
Jalan R, Hayes PC. UK guidelines on the management of variceal haemorrhage in cirrhotic patients. British Society of Gastroenterology.[see comment]. Gut. 2000; 46 Suppl 3-4:III1-III15. Ref ID: 67	Guideline document
Jalan R, John TG, Redhead DN et al. A comparative study	Not addressing pre-specified comparison

Study	Reason for exclusion
of emergency transjugular intrahepatic portosystemic stent-shunt and esophageal transection in the management of uncontrolled variceal hemorrhage. Am J Gastroenterol. 1995; 90(11):1932-1937. Ref ID: 5282	
McCormick PA, Dick R, Panagou EB et al. Emergency transjugular intrahepatic portasystemic stent shunting as salvage treatment for uncontrolled variceal bleeding. Br J Surg. 1994; 81(9):1324-1327. Ref ID: 5285	No comparison
Patch D, Dagher L. Acute variceal bleeding: general management. World J Gastroenterol. 2001; 7(4):466-475. Ref ID: 5287	Review
Sanyal AJ, Freedman AM, Luketic VA et al. Transjugular intrahepatic portosystemic shunts for patients with active variceal hemorrhage unresponsive to sclerotherapy. Gastroenterology. 1996; 111(1):138-146. Ref ID: 5286	No comparison
Spina GP, Santambrogio R, Opocher E et al. Emergency portosystemic shunt in patients with variceal bleeding. Surgery, Gynecology & Obstetrics. 1990; 171(6):456-464. Ref ID: 421	No comparison

K.7.2 Antibiotics

Study	Reason for exclusion
Chavez-Tapia NC, Barrientos-Gutierrez T, Tellez-Avila FI, et al. Antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding. Cochrane Database of Systematic Reviews 2010;CD002907.	Cochrane review – cross-checked for references
Coffin B, Pocard M, Panis Y, et al. Erythromycin improves the quality of EGD in patients with acute upper GI bleeding: a randomized controlled study. Gastrointest Endosc 2002 Aug;56:174-9.	Mixed variceal / non-variceal population of patients and outcomes not relevant
Fernandez J, Ruiz del AL, Gomez C, et al. Norfloxacin vs ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage. Gastroenterology 2006 Oct;131:1049-56.	Not addressing pre-specified comparisons.
Gulberg V, Deibert P, Ochs A, et al. Prevention of infectious complications after transjugular intrahepatic portosystemic shunt in cirrhotic patients with a single dose of ceftriaxone. Hepatogastroenterology 1999 Mar;46:1126-30. Ref ID: 5292	Not addressing pre-specified comparisons.
Kim BI, Kim HJ, Park JH, et al. Increased intestinal permeability as a predictor of bacterial infections in patients with decompensated liver cirrhosis and hemorrhage. J Gastroenterol Hepatol 2011;26:550-7. Ref ID: 173	Not addressing pre-specified comparisons.
Lata J, Jurankova J, Husova L, et al. Variceal bleeding in portal hypertension: bacterial infection and comparison of efficacy of intravenous and per-oral application of antibiotics--a randomized trial. European Journal of Gastroenterology & Hepatology 2005 Oct;17:1105-10. Ref ID: 58	Not addressing pre-specified comparisons.
Panchavati PK, Chesebro MJ. Should antibiotic prophylaxis	Editorial comment

Study	Reason for exclusion
be used for cirrhotic patients hospitalized with gastrointestinal bleeding? Evidence-Based Practice 2010;13:9. Ref ID: 258	
Pulanic R, Vrhovac B, Jereb B, et al. Controlled trial of the prophylactic administration of antibiotics in sclerotherapy of esophageal varices. J Chemother 1989;1:261-5. Ref ID: 279	Outcomes not relevant
Rimola A, Bory F, Teres J, et al. Oral, nonabsorbable antibiotics prevent infection in cirrhotics with gastrointestinal hemorrhage. Hepatology 1985 May;5:463-7. Ref ID: 5295	Not addressing pre-specified comparisons (focus on a particular type of antibiotic)
Sabat M, Kolle L, Soriano G, et al. Parenteral antibiotic prophylaxis of bacterial infections does not improve cost-efficacy of oral norfloxacin in cirrhotic patients with gastrointestinal bleeding. Am J Gastroenterol 1998;93:2457-62. Ref ID: 440	Not addressing pre-specified comparisons.
Yun JW, Kim BI, Park JH, et al. Ciprofloxacin vs. ceftriaxone in the prevention of bacterial Infection in patients with advanced cirrhosis and gastrointestinal hemorrhage. J Hepatol 2008;48:S125. Ref ID: 5303	Abstract

K.7.3 Band ligation

Study	Reason for exclusion
Avgerinos A, Armonis A, Manolakopoulos S et al. Endoscopic sclerotherapy plus propranolol versus propranolol alone in the primary prevention of bleeding in high risk cirrhotic patients with esophageal varices: a prospective multicenter randomized trial. Gastrointest Endosc. 2000; 51(6):652-658. Ref	Comparison not in protocol
Avgerinos A, Armonis A, Manolakopoulos S, Poulianos G, Rekoumis G, Sgourou A, Gouma P, Raptis S. Endoscopic sclerotherapy versus variceal ligation in the long-term management of patients with cirrhosis after variceal bleeding – a prospective randomised study. Journal of hepatology 1997; 26:1034-1041.	Not addressing pre-specified intervention/comparison
Baroncini D, Piemontese A, Milandri G et al. Variceal ligation compared with sclerotherapy in elective treatment: Preliminary results of a prospective randomized study. Giornale Italiano di Endoscopia Digestiva. 1996; 19(1):39-45.	Article in Italian
Berner JS, Gaing AA, Sharma R, Almenoff PL, Muhlfelder T, Korsten MA. Sequelae after esophageal variceal ligation and sclerotherapy: a prospective randomised study. The American Journal of Gastroenterology. 1994; 89: 852-858	No relevant outcomes
Cipolletta L, Bianco MA, Rotondano G et al. Endoscopic ligation vs sclerotherapy for bleeding oesophageal varices: A prospective, randomized study. Giornale Italiano di Endoscopia Digestiva. 1997; 20(2):67-70.	Article in Italian
De BK, Ghoshal UD, Das T, Santra A, Biswas PK.	Not addressing pre-specified

Study	Reason for exclusion
Endoscopic variceal ligation for primary prophylaxis of oesophageal variceal bleed: preliminary report of a randomised controlled trial. Journal of gastroenterology and hepatology 1999; 14: 220-224	intervention/comparison
De La Pena J, Brullet E, Sanchez-Hernandez E et al. Variceal ligation plus nadolol compared with ligation for prophylaxis of variceal rebleeding: A multicenter trial. Hepatology. 2005; 41(3):572-578.	Not addressing pre-specified comparison
Elsherbiny A, Assal HS, Abd EM et al. Gastro-esophageal varices: Endoscopic band ligation, alcohol injection and cyanoacrylate injection. Journal of Medical Sciences. 2006; 6(2):164-168.	Not an RCT
Gilbert DA, Buelow RG, Chung RSK et al. Technology assessment status evaluation: Endoscopic band ligation of varices. Gastrointest Endosc. 1991; 37(6):670-672.	Not an RCT – cross-checked for references
Gotoh Y, Iwakari R, Yasushi S et al. Evaluation of endoscopic variceal ligation in prophylactic therapy for bleeding of oesophageal varices: a prospective controlled trial compared with endoscopic injection sclerotherapy. Journal of Gastroenterology and Hepatology 1999; 14: 241-244	Prophylactic study: patients were not actively bleeding at inception of study
Hashizume M, Ohta M, Ueno K, Tanoue K, Kitano S, Sugimachi K. Endoscopic ligation of esophageal varices compared with injection sclerotherapy: a prospective randomised trial. Gastrointestinal endoscopy 1993; 39: 123- 126	Prophylactic study: patients were not actively bleeding at inception of study
Hou MC, Lin HC, Kuo BIT, Lee FY, Chang FY, Lee SD. The re-bleeding course and long-term outcome of esophageal variceal hemorrhage after ligation: comparison with sclerotherapy. Scan J Gastroenterol 1999; 34: 1071-1076	Overlapping patients with Hou 2000
Imazu H, Matsui T, Noguchi R, Asada K, Miyamoto Y, Kawata M, Nakayama M, Matsuo N, Matsumura M, Fukui H. Magnetic resonance angiography for monitoring prophylactic endoscopic treatment of high risk esophageal varices. Endoscopy 2000; 32: 766-772	Prophylactic study: patients were not actively bleeding at inception of study
Imperiale TF, Chalasani N. A meta-analysis of endoscopic variceal ligation for primary prophylaxis of esophageal variceal bleeding. Hepatology. 2001; 33(4):802-807.	Meta – analysis (cross referenced)
Laine L, Cook D. Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding – a meta-analysis. Ann Intern med 1995: 123: 280-287	Review article – cross checked for references
Lo G-H, Chen W-C, Chan H-H et al. A randomized, controlled trial of banding ligation plus drug therapy versus drug therapy alone in the prevention of esophageal variceal rebleeding. J Gastroenterol Hepatol. 2009; 24(6):982-987.	Not addressing pre-specified comparison
Lo GH, Lai KH, Cheng JS et al. A prospective, randomized trial of butyl cyanoacrylate injection versus band ligation in the management of bleeding gastric varices. Hepatology. 2001; 33(5):1060-1064.	Restricted to gastric varices (not in protocol)
Lo GH, Lai KH, Cheng JS, Hwu JH, Chang CF, Chen SM, Chiang HT. A prospective randomised trial of	Overlapping patients with Lo 1994

Study	Reason for exclusion
sclerotherapy versus ligation in the management of bleeding esophageal varices. 1995; 22:466-471.	
Lo G-H. Management of Acute Esophageal Variceal Hemorrhage. Kaohsiung Journal of Medical Sciences. 2010; 26(2):55-67.	Review article – cross checked for references
Masumoto H, Toyonaga A, Oho K et al. Ligation plus low-volume sclerotherapy for high-risk esophageal varices: comparisons with ligation therapy or sclerotherapy alone. J Gastroenterol. 1998; 33(1):1-5.	Prophylactic study: patients were not actively bleeding at inception of study
Mohamed AR, Gadour M, Ghandour Z, Al Karawi M. Endoscopic management for bleeding esophageal varices: sclerotherapy versus sclerotherapy plus band ligation versus band ligation alone. One year experience at a main hospital in Saudi Arabia. Hepato-Gastroenterology 1999; 46: 967-970	Observational study
Nakase H, Kawasaki T, Komori H et al. Endoscopic variceal ligation versus endoscopic injection sclerotherapy: comparison of hepatic and renal function. Am J Gastroenterol. 1996; 91(10):2170	No relevant outcomes
Pereira SP, Wilkinson ML. Prospective randomized trial of endoscopic sclerotherapy versus variceal band ligation for esophageal varices: influence on gastropathy, gastric varices and variceal recurrence. Gastrointest Endosc. 1997; 46(4):384	Comment on an included trial
Sauer P, Hansmann J, Richter GM et al. Endoscopic variceal ligation plus propranolol vs. transjugular intrahepatic portosystemic stent shunt: a long	Comparison not in protocol
Sheikh RA, Trudeau WL. Evaluation of endoscopic variceal ligation in prophylactic therapy for bleeding of oesophageal varices: a prospective, controlled trial compared with endoscopic injection sclerotherapy. Gastrointest Endosc. 2000; 51(2):245	Comment on an included trial
Siqueira ES, Rohr MRDS, Libera ED, Castro RRO, Ferrari AP. Band ligation or sclerotherapy as endoscopic treatment for oesophageal varices in schistosomotic patients: results of a randomised study. HPB Surgery 1998; 11: 27-32	Prophylactic study: patients were not actively bleeding at inception of study
Svoboda P, Kantorova I, Ochmann J, Kozumplik L, Marsova J. A prospective randomised controlled trial of sclerotherapy vs ligation in the prophylactic treatment of high risk esophageal varices. Surg Endosc 1999; 13: 580-584	Prophylactic study: patients were not actively bleeding at inception of study
Triantos CK, Goulis J, Patch D, Papatheodoridis GV, Leandro G, Samonakis D, Cholongitas E, Burroughs AK. An evaluation of emergency sclerotherapy of varices in randomised trials: looking the needle in the eye. Endoscopy 2006; 38: 797-808	Review article – cross checked for references
Villanueva C, Minana J, Ortiz J et al. Endoscopic ligation compared with combined treatment with nadolol and isosorbide mononitrate to prevent recurrent variceal bleeding. N Engl J Med. 2001; 345(9):647	Not addressing pre-specified comparison
Avgerinos A, Armonis A, Manolakopoulos S et al. Endoscopic sclerotherapy plus propranolol versus propranolol alone in the primary prevention of bleeding in	Comparison not in protocol

Study	Reason for exclusion
high risk cirrhotic patients with esophageal varices: a prospective multicenter randomized trial. Gastrointest Endosc. 2000; 51(6):652-658. Ref	
Avgerinos A, Armonis A, Manolakopoulos S, Poulianos G, Rekoumis G, Sgourou A, Gouma P, Raptis S. Endoscopic sclerotherapy versus variceal ligation in the long-term management of patients with cirrhosis after variceal bleeding – a prospective randomised study. Journal of hepatology 1997; 26:1034-1041.	Not addressing pre-specified intervention/comparison
Baroncini D, Piemontese A, Milandri G et al. Variceal ligation compared with sclerotherapy in elective treatment: Preliminary results of a prospective randomized study. Giornale Italiano di Endoscopia Digestiva. 1996; 19(1):39-45.	Article in Italian
Berner JS, Gaing AA, Sharma R, Almenoff PL, Muhlfelder T, Korsten MA. Sequelae after esophageal variceal ligation and sclerotherapy: a prospective randomised study. The American Journal of Gastroenterology. 1994; 89: 852-858	No relevant outcomes
Cipolletta L, Bianco MA, Rotondano G et al. Endoscopic ligation vs sclerotherapy for bleeding oesophageal varices: A prospective, randomized study. Giornale Italiano di Endoscopia Digestiva. 1997; 20(2):67-70.	Article in Italian
De BK, Ghoshal UD, Das T, Santra A, Biswas PK. Endoscopic variceal ligation for primary prophylaxis of oesophageal variceal bleed: preliminary report of a randomised controlled trial. Journal of gastroenterology and hepatology 1999; 14: 220-224	Not addressing pre-specified intervention/comparison
De La Pena J, Brullet E, Sanchez-Hernandez E et al. Variceal ligation plus nadolol compared with ligation for prophylaxis of variceal rebleeding: A multicenter trial. Hepatology. 2005; 41(3):572-578.	Not addressing pre-specified comparison
Elsherbiny A, Assal HS, Abd EM et al. Gastro-esophageal varices: Endoscopic band ligation, alcohol injection and cyanoacrylate injection. Journal of Medical Sciences. 2006; 6(2):164-168.	Not an RCT
Gilbert DA, Buelow RG, Chung RSK et al. Technology assessment status evaluation: Endoscopic band ligation of varices. Gastrointest Endosc. 1991; 37(6):670-672.	Not an RCT – cross-checked for references
Gotoh Y, Iwakari R, Yasushi S et al. Evaluation of endoscopic variceal ligation in prophylactic therapy for bleeding of oesophageal varices: a prospective controlled trial compared with endoscopic injection sclerotherapy. Journal of Gastroenterology and Hepatology 1999; 14: 241-244	Prophylactic study: patients were not actively bleeding at inception of study
Hashizume M, Ohta M, Ueno K, Tanoue K, Kitano S, Sugimachi K. Endoscopic ligation of esophageal varices compared with injection sclerotherapy: a prospective randomised trial. Gastrointestinal endoscopy 1993; 39: 123- 126	Prophylactic study: patients were not actively bleeding at inception of study
Hou MC, Lin HC, Kuo BIT, Lee FY, Chang FY, Lee SD. The re-bleeding course and long-term outcome of esophageal variceal hemorrhage after ligation: comparison with sclerotherapy. Scan J Gastroenterol 1999; 34: 1071-1076	Overlapping patients with Hou 2000

Study	Reason for exclusion
Imazu H, Matsui T, Noguchi R, Asada K, Miyamoto Y, Kawata M, Nakayama M, Matsuo N, Matsumura M, Fukui H. Magnetic resonance angiography for monitoring prophylactic endoscopic treatment of high risk esophageal varices. Endoscopy 2000; 32: 766-772	Prophylactic study: patients were not actively bleeding at inception of study
Imperiale TF, Chalasani N. A meta-analysis of endoscopic variceal ligation for primary prophylaxis of esophageal variceal bleeding. Hepatology. 2001; 33(4):802-807.	Meta – analysis (cross referenced)
Laine L, Cook D. Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding – a meta-analysis. Ann Intern med 1995: 123: 280-287	Review article – cross checked for references
Lo G-H, Chen W-C, Chan H-H et al. A randomized, controlled trial of banding ligation plus drug therapy versus drug therapy alone in the prevention of esophageal variceal rebleeding. J Gastroenterol Hepatol. 2009; 24(6):982-987.	Not addressing pre-specified comparison
Lo GH, Lai KH, Cheng JS et al. A prospective, randomized trial of butyl cyanoacrylate injection versus band ligation in the management of bleeding gastric varices. Hepatology. 2001; 33(5):1060-1064.	Restricted to gastric varices (not in protocol)
Lo GH, Lai KH, Cheng JS, Hwu JH, Chang CF, Chen SM, Chiang HT. A prospective randomised trial of sclerotherapy versus ligation in the management of bleeding esophageal varices. 1995; 22:466-471.	Overlapping patients with Lo 1994
Lo G-H. Management of Acute Esophageal Variceal Hemorrhage. Kaohsiung Journal of Medical Sciences. 2010; 26(2):55-67.	Review article – cross checked for references
Masumoto H, Toyonaga A, Oho K et al. Ligation plus low-volume sclerotherapy for high-risk esophageal varices: comparisons with ligation therapy or sclerotherapy alone. J Gastroenterol. 1998; 33(1):1-5.	Prophylactic study: patients were not actively bleeding at inception of study
Mohamed AR, Gadour M, Ghandour Z, Al Karawi M. Endoscopic management for bleeding esophageal varices: sclerotherapy versus sclerotherapy plus band ligation versus band ligation alone. One year experience at a main hospital in Saudi Arabia. Hepato-Gastroenterology 1999; 46: 967-970	Observational study
Nakase H, Kawasaki T, Komori H et al. Endoscopic variceal ligation versus endoscopic injection sclerotherapy: comparison of hepatic and renal function. Am J Gastroenterol. 1996; 91(10):2170	No relevant outcomes
Pereira SP, Wilkinson ML. Prospective randomized trial of endoscopic sclerotherapy versus variceal band ligation for esophageal varices: influence on gastropathy, gastric varices and variceal recurrence. Gastrointest Endosc. 1997; 46(4):384	Comment on an included trial
Sauer P, Hansmann J, Richter GM et al. Endoscopic variceal ligation plus propranolol vs. transjugular intrahepatic portosystemic stent shunt: a long	Comparison not in protocol
Sheikh RA, Trudeau WL. Evaluation of endoscopic variceal ligation in prophylactic therapy for bleeding of oesophageal varices: a prospective, controlled trial	Comment on an included trial

Study	Reason for exclusion
compared with endoscopic injection sclerotherapy. Gastrointest Endosc. 2000; 51(2):245	
Siqueira ES, Rohr MRDS, Libera ED, Castro RRO, Ferrari AP. Band ligation or sclerotherapy as endoscopic treatment for oesophageal varices in schistosomotic patients: results of a randomised study. HPB Surgery 1998; 11: 27-32	Prophylactic study: patients were not actively bleeding at inception of study
Svoboda P, Kantorova I, Ochmann J, Kozumplik L, Marsova J. A prospective randomised controlled trial of sclerotherapy vs ligation in the prophylactic treatment of high risk esophageal varices. Surg Endosc 1999; 13: 580-584	Prophylactic study: patients were not actively bleeding at inception of study
Triantos CK, Goulis J, Patch D, Papatheodoridis GV, Leandro G, Samonakis D, Cholongitas E, Burroughs AK. An evaluation of emergency sclerotherapy of varices in randomised trials: looking the needle in the eye. Endoscopy 2006; 38: 797-808	Review article – cross checked for references
Villanueva C, Minana J, Ortiz J et al. Endoscopic ligation compared with combined treatment with nadolol and isosorbide mononitrate to prevent recurrent variceal bleeding. N Engl J Med. 2001; 345(9):647	Not addressing pre-specified comparison

K.7.4 Patient information

Study	Reason for exclusion
Cullen G, Kelly E, Murray FE. Patients' knowledge of adverse reactions to current medications. Br J Clin Pharmacol 2006 Aug;62:232-6.	Not addressing pre-specified population
Drossman DA, Brandt LJ, Sears C, et al. A preliminary study of patients' concerns related to GI endoscopy. Am J Gastroenterol 1996 Feb;91:287-91.	Not addressing pre-specified population
Lin H-J, Perng C-L, Sun IC, et al. Endoscopic haemoclip versus heater probe thermocoagulation plus hypertonic saline-epinephrine injection for peptic ulcer bleeding. Digestive and Liver Disease 2003 Dec;35:898-902.	Not addressing pre-specified population
Mahajan RJ, Johnson JC, Marshall JB. Predictors of patient cooperation during gastrointestinal endoscopy. J Clin Gastroenterol 1997 Jun;24:220-3.	Not addressing pre-specified population
Romagnuolo J, Flemons WW, Perkins L, et al. Post-endoscopy checklist reduces length of stay for non-variceal upper gastrointestinal bleeding. Int J Qual Health Care 2005 Jun;17:249-54.	Not addressing pre-specified population
Schwartz LM, Woloshin S, Welch HG. Using a drug facts box to communicate drug benefits and harms: Two randomized trials. Ann Intern Med 2009;150:516-27.	Not addressing pre-specified population
Shipley RH, Butt JH, Farbry JE, et al. Psychological preparation for endoscopy. Physiological and behavioral changes in patients with differing coping styles for stress. Gastrointest Endosc 1977 Aug;24:9-13.	Not addressing pre-specified population

Study	Reason for exclusion
Summaries for patients. Benefits and risks of continuing aspirin in patients with peptic ulcer bleeding.[Original report in Ann Intern Med. 2010 Jan 5;152(1):1-9; PMID: 19949136]. Ann Intern Med 2010 Jan 5;152:I-20.	Not addressing pre-specified population

Appendix L: Details of Risk scoring analysis and diagnostic meta-analysis plots

Diagnostic meta-analysis was conducted where 5 or more similar studies were identified that compared the index test to the reference standard. The test accuracy for the studies was pooled using the bivariate method modelled in Winbugs® by; the advantage of this approach is that it produces summary estimates of sensitivity and specificity that account for the correlation between the two. Other advantages of this method have been described elsewhere [39-41]

Analysis

The bivariate method utilises a logistic regression on the true positives, true negatives, false positives and false negatives reported in the sudies and is parameterised as follow:

Where:

and represent the true positives, true negatives, false positives and false negatives, respectively, reported in study i.

and represent the sensitivity and specificity calculated from the results of study i on the log odds scale.

and represent the mean pooled sensitivity and specificity on the log odds scale, i.e. the results of the meta analysis.

represents the variance-covariance matrix of the pooled sensitivity and specificity on the log odds scale.

and represent the pooled sensitivity and specificity on the natural scale; these are the final summary estimates of interest.

The model above was fitted in WinBUGS®. Using the output from WinBUGS®, we constructed and plotted confidence regions and, where appropriate ROC curves, using methods outlined by Novelli et al [42] in Microsoft Excel®.

As it was a Bayesian analysis, the evidence distribution is weighted by a distribution of prior beliefs. Vague non-informative priors were used for all parameters. For each analysis, a series of 50,000 burn-in simulations were run to allow convergence and then a further 50,000 simulations were run to produce the outputs. Convergence was assessed by investigating density plots, auto correlation plots and history plots for parameters of interest.

In cases where cell counts were 0, 1 was added to each category (true positives, false positives, true negatives, false negatives) to ensure the model was able to run, whilst not significantly distorting the results.

WinBUGS code

Model

```
{
for (i in 1:NS)
        {
        TotP[i]<-TP[i] + FN[i]
        TotN[i]<-FP[i] + TN[i]
        TP[i] ~ dbin(p[i , 1] , TotP[i])
        TN[i] ~ dbin(p[i , 2]  , TotN[i])
```

```
                for (j in 1:2)

                {
                logit(p[i , j]) <- MeanS[i , j]
                }
        MeanS[i , 1:2] ~ dmnorm(md[] , sigma[,])

        }
        sigma[1:2,1:2]~dwish(R[,] , 2)
        Sigma.sq[1:2,1:2] <- inverse(sigma[,])

                for (i in 1:2)
                        {
                        parms[i] <- exp(md[i])/(1+exp(md[i]))
                        }

        sens <- parms[1]
        spec<- parms[2]


                for (i in 1:2)
                        {
                        md[i] ~ dnorm(0 , 0.001)
                        }

                sensitivity.bar <- exp(md[1])/(1+ exp(md[1]))
        specificity.bar <- exp(md[2])/(1+exp(md[2]))


    }


}
```

Data

```
list(NS= Number of studies goes here)

list(R = structure(
        .Data = c(1, 0,
              0, 1), .
        Dim = c(2, 2))
```

Cell Counts for each strategy are entered below, in place of the ni values

```
TP=True positives
FP=False positives
FN=False negatives
TN=True negatives

TP[]    FP[]    FN[]    TN[]
n1      n2      n3      n4
END
```

Initial conditions

```
list(md=c(0,0))
```

Data sets

The following are the data entered into the WinBUGS® code with sensitivity and specificty (plus 95% CIs) plotted in RevMan5 plus the corresponding ROC graphs plotted from the diagnostic meta-analysis in EXCEL. As can be seen in 6 out of 7 studies that used the Blatchford scoring system 100% sensitivity was reported. However the 0 false negative cases resulted in non-convergence of the model and therefore 1 false positive was added leading to more conservative estimated (to keep the the total patient number the same one patient was deducted from the total positive events to keep the original proportion of overall events the same) .

Figure 172: Data for the clinical Rockall diagnostic meta analysis (plotted with 95% CI) for all outcomes combined

Figure 173: Diaganostic test accuracy plot for the pre endoscopy Rockall for all outcomes combined (need for intervention, mortality and rebleeding). See legend for the different aspects of the graph. Sensitivity and specificity summary statistics are presented in the box below the legend.

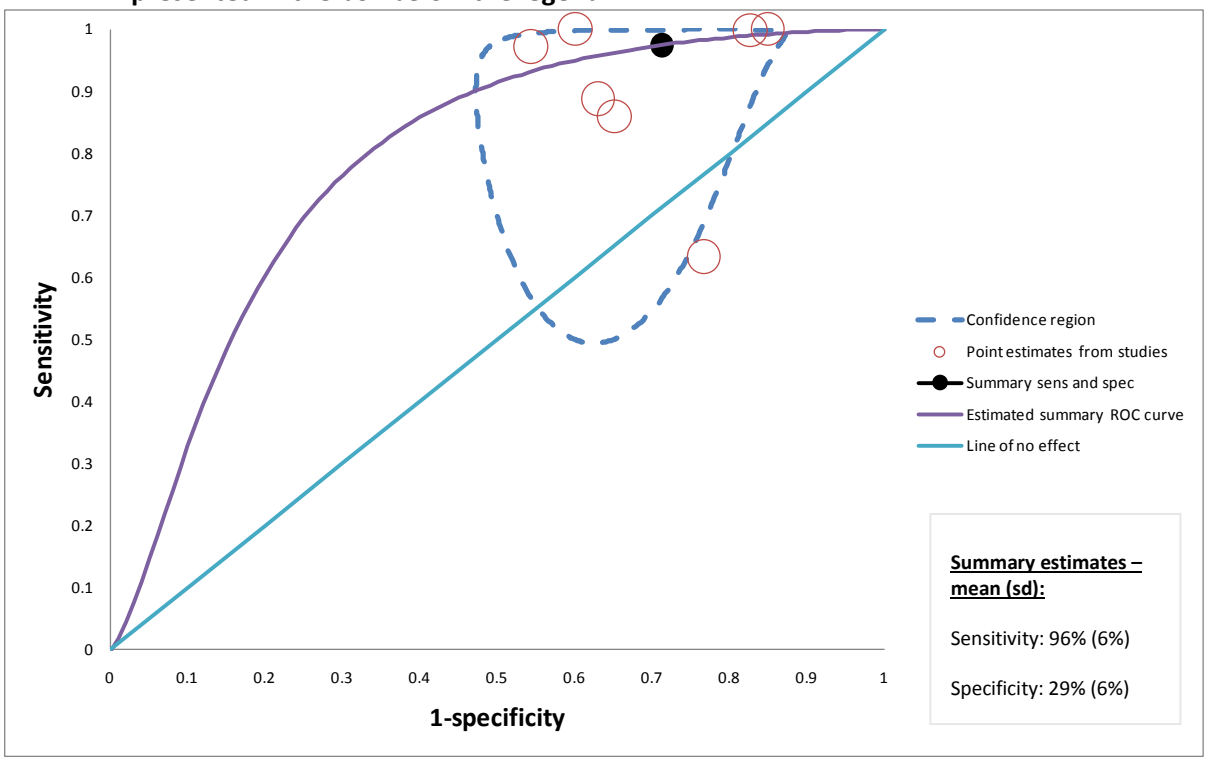
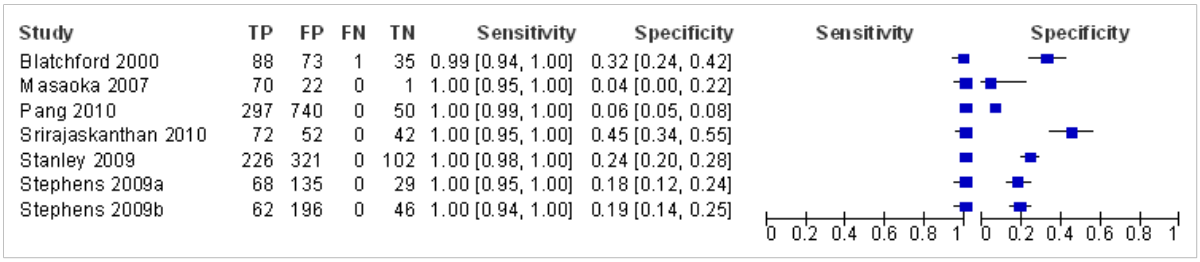


Figure 174: Data for the Blatchford diagnostic meta analysis (plotted with 95% CI)



Study	TP	FP	FN	TN	Sensitivity	Specificity
Blatchford 2000	88	73	1	35	0.99 [0.94, 1.00]	0.32 [0.24, 0.42]
Masaoka 2007	70	22	0	1	1.00 [0.95, 1.00]	0.04 [0.00, 0.22]
Pang 2010	297	740	0	50	1.00 [0.99, 1.00]	0.06 [0.05, 0.08]
Srirajaskanthan 2010	72	52	0	42	1.00 [0.95, 1.00]	0.45 [0.34, 0.55]
Stanley 2009	226	321	0	102	1.00 [0.98, 1.00]	0.24 [0.20, 0.28]
Stephens 2009a	68	135	0	29	1.00 [0.95, 1.00]	0.18 [0.12, 0.24]
Stephens 2009b	62	196	0	46	1.00 [0.94, 1.00]	0.19 [0.14, 0.25]

Figure 175: Diaganostic test accuracy plot for the Blatchford scale for need for intervention. See legend for the different aspects of the graph. Sensitivity and specificity summary statistics are presented in the box below the legend.

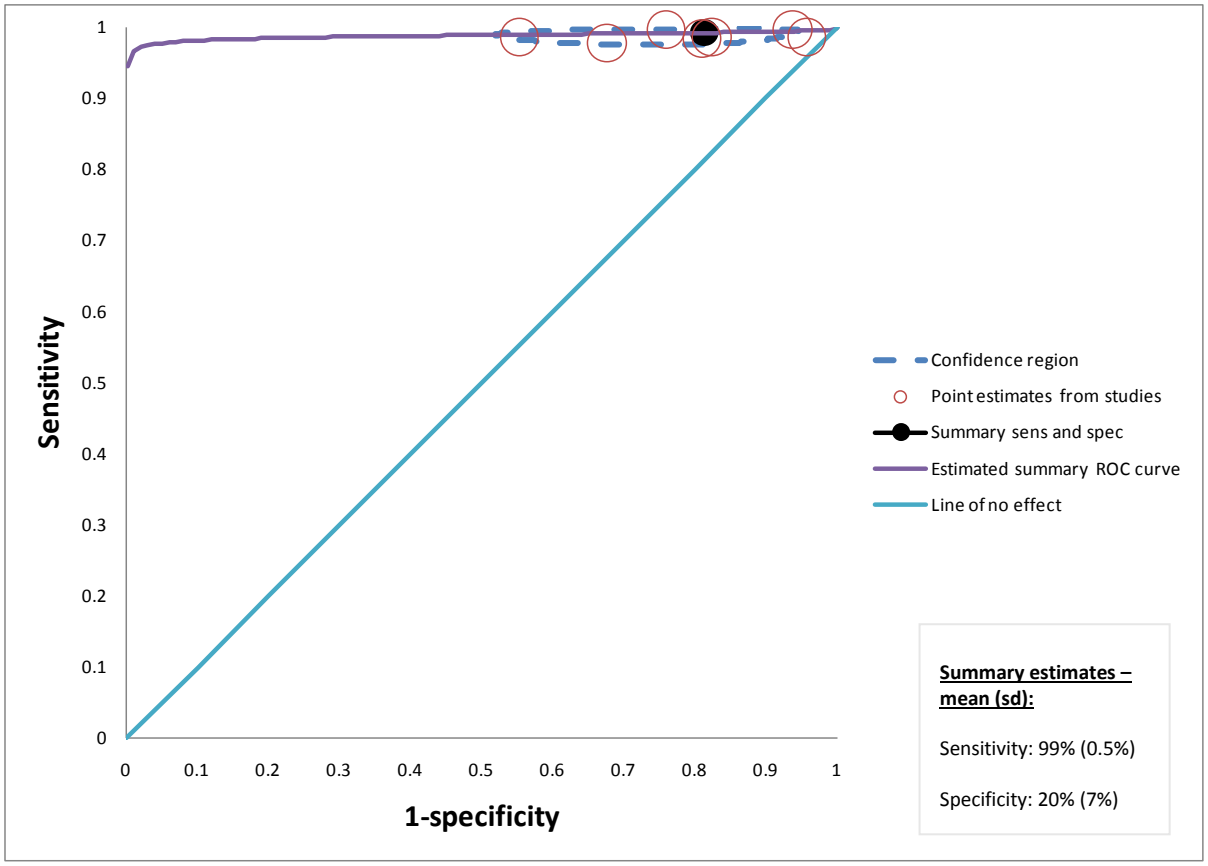


Figure 176: Data for full (post endoscopy) Rockall diagnostic meta analysis for rebleeding (plotted with 95% CI)

Figure 177: Diaganostic test accuracy plot for the post endoscopy Rockall scale for rebleeding. See legend for the different aspects of the graph. Sensitivity and specificity summary statistics are presented in the box below the legend.

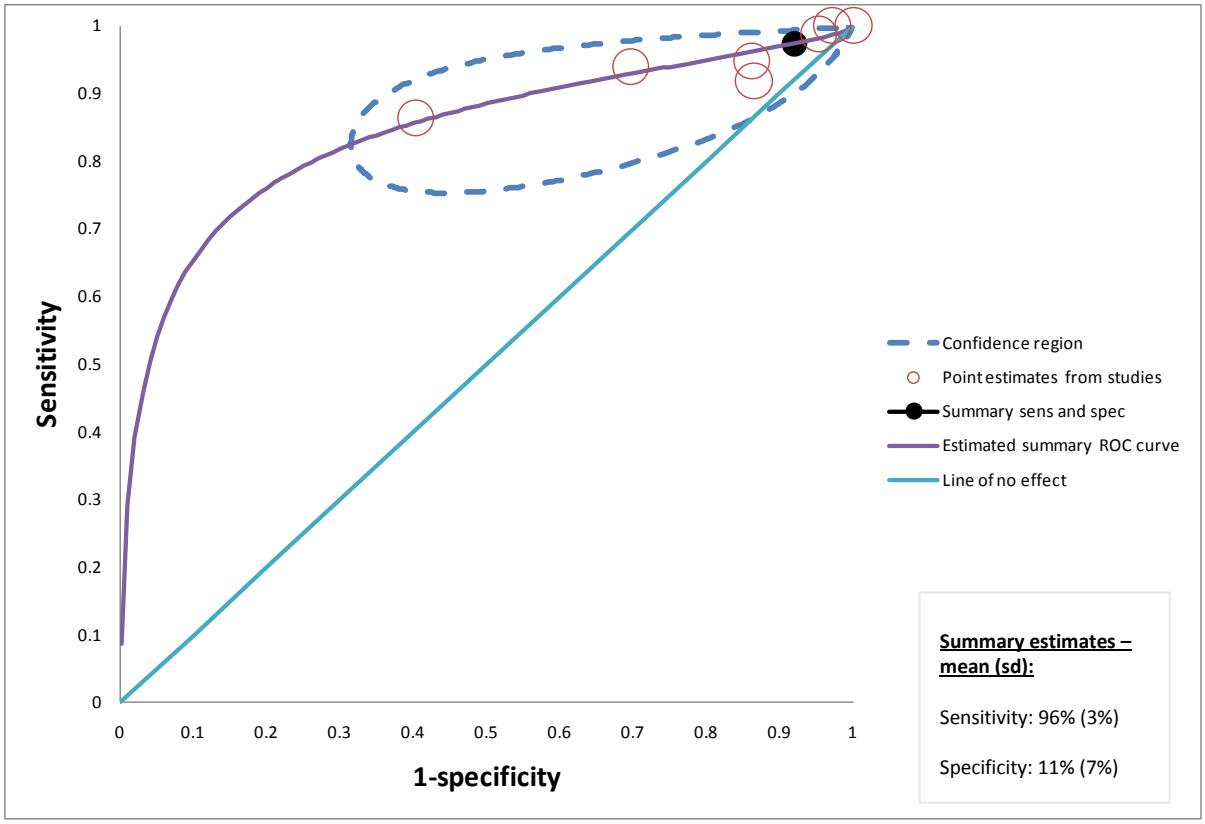
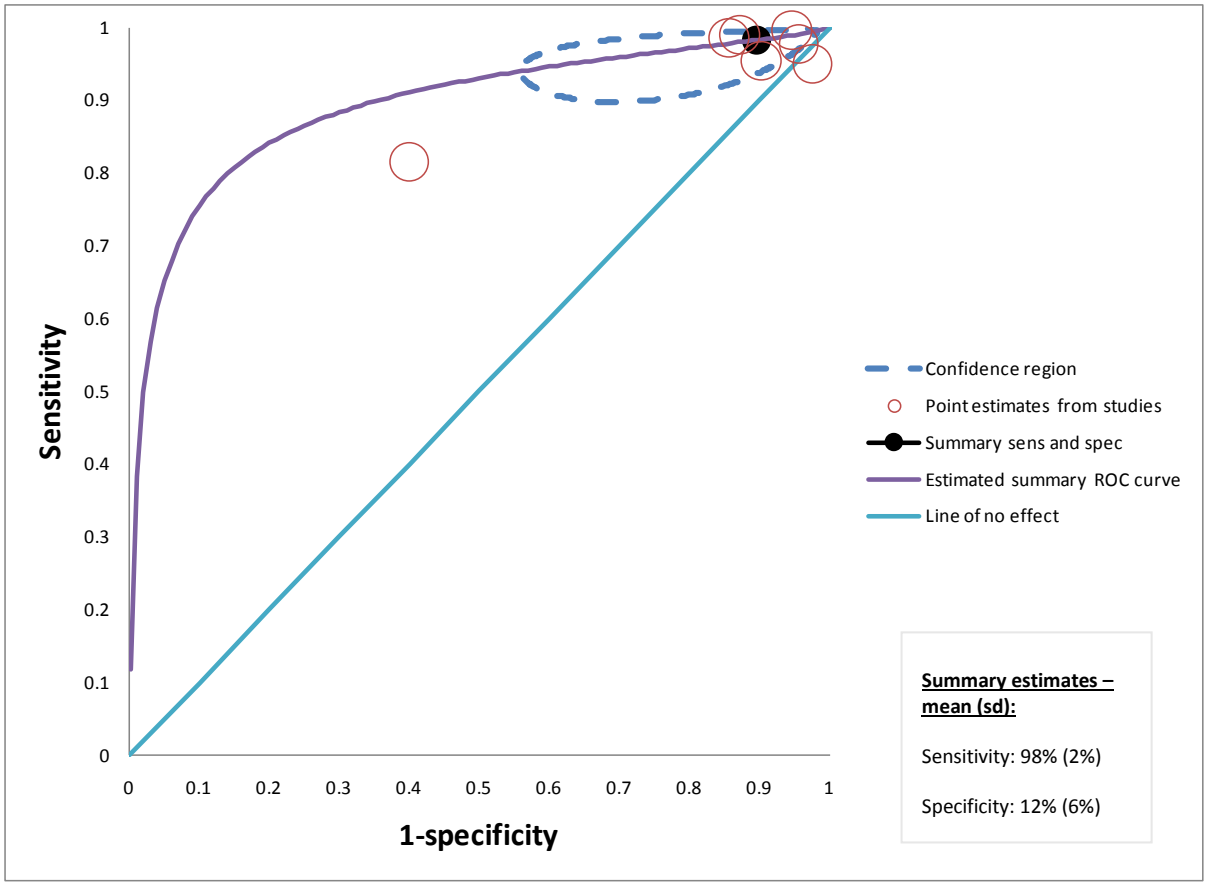


Figure 178: Data for full (post endoscopy) Rockall diagnostic meta analysis for mortality (plotted with 95% CI)

Figure 179: Diaganostic test accuracy plot for the post endoscopy Rockall scale for mortality. See legend for the different aspects of the graph. Sensitivity and specificity summary statistics are presented in the box below the legend.



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